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PREVALENCE, CLINICAL FEATURES, AND PROGNOSIS OF THE PSYCHOSOMATIC PATHOLOGY IN CHILDREN WITH PSYCHOPHYSICAL DEVELOPMENTAL DISORDERS

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The article presents the results of the clinical and epidemiological study on the prevalence of psychosomatic pathology (PSP) in Ukraine in children with psychophysical developmental disorders (PPDD). It was found that the prevalence of PSP in children with PPDD did not significantly differ from that in patients without PPDD and was estimated 89 and 86 children per 1000 of child population, respectively. The predominant psychosomatic diseases in children with and without PPDD were bronchial asthma (BA) and duodenal ulcer (DU). In patients with PPDD, the highest prevalence of duodenal ulcer (56%), and bronchial asthma (26%) was observed, while on the contrary in children without PPDD the prevalence of duodenal ulcer was estimated 12% and of bronchial asthma 68%. In children with PSP and PPDD, earlier onset of duodenal ulcer was revealed, as compared to children without PPDD (10.5±0.7 years and 14.2±0.5, respectively). Clinical features of the course of duodenal ulcer in children without PPDD were the prevalence of minor and asymptomatic forms (29.0%) with detection of the first clinical signs of the disease in the form of complications (gastrointestinal bleeding, scar-and-ulcer deformity of duodenum) (8.1%). The same pattern was observed in children with PPDD, however, the frequency of complications in them was significantly higher (14.7%) with longer duration (73.0%) and severity (53.8%) of the disease, as compared to 46.6% and 16.7% in patients without PPDD. Pivotal complex psychological markers of the development of PSP in children with and without PPDD were high levels of personal and reactive anxiety, emotional lability and deviation from autogenous norm, low indicators of self-esteem and poor performance, which required differentiated medical and psychological support.

Key words: psychosomatic pathology, psychophysical disorders, children, adolescents, risk factors.

The work is a fragment of the research project "Clinical-pathogenetic and psychological features of somatic pathology formation in children and adolescents and improvement of therapeutic and preventive measures", state registration No. 0119U100944.

The problem of psychosomatic pathology (PSP) in a broad sense is the problem of human existence [1, 2, 4]. In particular, psychosomatic diseases are so-called adaptation diseases that combine somatic and psychological aspects [4, 6]. Traditionally, PSP include hypertension (BH), bronchial asthma (BA), ulcerative colitis (UC), diabetes mellitus (DM), rheumatoid arthritis (RA), gastric (GU) and duodenal ulcers (DU), diseases that have a progressive course, greatly deteriorating the quality of human life [1, 2, 5, 6-8]. Psycho-somatic relationship is one of the most complex issues of modern medicine and psychology, despite the fact that close connection between the mental and the somatic components has been established a long time ago and has been studied since the days of Hippocrates, Plato and Aristotle. In the process of the development of medicine, the issues of the psyche influence on the course of somatic disease was almost not considered. However, nowadays, at a time of rapid increase in information flow, with significant reduction in motor activity and global impact of adverse environmental factors, it becomes relevant to consider issues of mental and physical health in unity – that is, in a frame of psychosomatics [2, 3, 4, 6].

PSP, as a general pathological process, is characterized by the following features: it is developed only in humans, since psyche acts as a significant component of objective impairment of life; it is characterized by a non-stereotypical response to an action of causally significant factors and differs in the absence of genetically determined unified protective adaptive mechanisms [3].

Thus, it is obvious that there are two main components that play leading role in the emergence of PSP: a psychotraumatic factor and a state of a subject, influenced by it. In this case, the deciding aspect is the a behavioral pattern of personality in various adverse situations. Therefore, in presence of a high level of creativity, a person is much more likely to be identified in interaction with the world and social environment. That is why orientation of patient to his creative implementation is of a great importance in the prevention and treatment of PSP.

In this respect, a special place was given to children with disorders of psychophysical development (PPDD), since the prevalence, peculiarities of clinical manifestations of PSP, and risk factors of their formation

have not been investigated in these children so far. Recent studies have shown that developmental disorder is a universal form of reaction of the organism to any negative impact not only biological but also unfavorable sociopsychological factors.

There are many different terms that have been used in the domestic literature for defining the violations of development in children: "developmental abnormalities", "children with special needs", "children with special educational needs", "children with peculiarities of psychophysical development (PPD)", etc. All of these concepts reflect various aspects of the manifestations of disturbed development, but their most common features are characterized by the term "disontogenesis", proposed by E. Schwalbe in 1927. At present, under this concept are understood different forms of disorders of ontogenesis, especially the nervous system (NS), which cover the period of early childhood (up to 3 years), when morphological systems of an organism have not yet reached maturity.

Nervous system disorders are usually caused by biological and social factors that can act separately and in combination, predominantly during the period of intense cellular differentiation of the brain structures, that is, at the early stages of embryogenesis.

It is known that the development of a child with violations of the PPD has a number of its own laws. The complexity of the structure of abnormal development is determined by the presence of the primary defect caused by the biological factor and secondary disorders that arise in the process of further abnormal development. The farther in time, the root causes (the primary defect of biological origin) and the secondary symptom (violation in the development of mental processes) are "separated" among themselves, the more opportunities are opened for correction and compensation of the latter with the help of a rational system of medical and psychological influences, education and upbringing. However, data on the prevalence, structure, peculiarities of the clinical course and risk factors for the formation of PSP in children with PPDD were not found in available literature [1].

The purpose of the study was to investigate the prevalence, peculiarities of the clinical manifestations, risk factors for the emergence and progression of the psychosomatic pathology in children and adolescents with and without psychophysical disorders.

Materials and methods. 209 children aged between 7 and 17 years old with PSP were examined, among them 111 were without PPDD (Group I) and 98 with PPDD (Group II). Diagnosis was verified according to ICD-10. The study of the prevalence of PSP in children and adolescents with and without psychophysiological disorders was performed using the cohort-epidemiological method.

The socio-demographic method was used to analyze the factors that influenced the formation of PSP. By questioning in accordance to the questionnaire developed by us, we collected information about a child himself, his family, living conditions, state of health, hereditary burden, bad habits, the presence of conflict and other psychogenic situations, and the success and nature of interpersonal relationships. Clinical-psychological method was used to study the psychopathological characteristics of children and adolescents with PSP. The research was carried out using the following methods: the level of anxiety as a constitutional feature of a patient or as a consequence of a person's illness / reaction to stress was determined using the Ch. D. Spielberger-Yu.L.Khanin (1978) scale of personal and reactive anxiety; the method of R. Cattell allowed to identify peculiarities of the individual in terms of his integrity; to determine the general psychoemotional state of children, the invented by us "method of diagnosing persistent stereotypes of psychoemotional response of children and adolescents" was used, the priority of which was confirmed by the patent of Ukraine to utility model No. 22346, 22347 dated September 25, 2009. Comprehensive neurophysiological diagnostics was carried out using topographic mapping of the spectral power of the main rhythms of electroencephalogram (EEG) with its spectral analysis. Instrumental methods of investigation included ultrasound of the organs of the abdominal cavity, thyroid gland, kidneys, fibroezofagogastroduodenoscopy (FEGDS), if necessary, sight biopsy with further histological examination of biopsy specimens, intragastric pH-metry, and spirography. General clinical, biochemical, immunoenzymatic examinations for verifying diagnoses according to ICD-10 were conducted as well.

Statistical processing of the obtained data was performed using mathematical statistical method on PC using SPSS and Excel software from the Microsoft Office 2003, STATISTIKA 8.0, and EPIINFO 5.0 packages. During the formation of representative samples, a STATCALC program from the EPIINFO package, V.5.0, was used to calculate the sufficient number of examined individuals.

Results of the study and their discussion. The performed study permitted to reveal the prevalence of PSP among children with and without PPDD, as well as to identify the main risk factors for the formation and progression of PSP. The prevalence of PSP among children with PPDD was: bronchial asthma (68%), duodenal ulcer (12%), diabetes mellitus (5%), rheumatoid arthritis (4%) and total PSP (89%). The

prevalence of PSP among children without PPDD was: duodenal ulcer (56%), bronchial asthma (26%), ulcerative colitis (3%), diabetes mellitus (1%) and total PSP (86%).

As it can be seen from the data, the prevalence of PSP among children with and without PPDD did not have significant differences and was 86% and 89%, respectively ($p>0.05$). In the PSP structure in both groups the most significant nosologies were BA and DU. Particularly, in children without PPDD, the prevalence of bronchial asthma (68%) was significantly higher than that of duodenal ulcer (12%) ($p<0.001$), which, according to F. Alexander (2002), was considered "the queen of psychosomatics". On the contrary, in children with PPDD statistically significant prevalence of duodenal ulcer (56%) as compared to bronchial asthma (26%) was observed ($p<0.001$).

Correlation of girls and boys in the 1st and 2nd groups was 1:1. The vast majority of patients in both groups (62.2% and 73.0% respectively) were between 11 and 17 years old. Probably, this is because in most sick children, the onset of disease occurs at the junior school age (7-10 years), and it usually takes 2-4 years for the formation of chronic pathology. At the same time, the risk of chronic disease increases significantly in the pre- and puberty period, which is explained by the peculiarities of functioning of a child's organism during these periods. Heterochronous formation of regulation processes of various physiological functions determine so-called critical periods of a child's organism development, which are basic for increased sensitivity to environmental influences and the development of desynchronosis- one of the first nonspecific manifestations of many pathological conditions. Distribution of risk factors (FR) in the examined patients is presented in table 1.

Table 1

Prognostic table of risk assessment for the formation of psychosomatic pathology in children with psychophysical defects

Risk factors and anti-risk factors	DK	J
Risk factors		
Conflicts in family (between parents)	10.48	2.45
Bad or missing search activity	9.48	2.45
Malnutrition	8.34	1.42
Conflicts in family (children-parents)	8.23	1.33
Alexithymia	7.24	1.12
Low social status of parents	3.77	0.68
Head and spine injuries in anamnesis	3.67	0.57
Meteosensitivity	3.46	0.51
Death of parents	2.28	0.41
Incomplete family	2.25	0.39
Pathology of childbirth	2.24	1.23
Not participating in creative circles	2.23	0.36
Not engaged in sports activities	2.03	0.34
Presence of chronic somatic diseases in family	1.86	0.32
Presence of birth defects in family	1.82	0.31
Mother's disease during pregnancy	1.76	0.28
Poor progress at school	1.66	0.28
Conflicts at school	1.56	0.22
Perinatal lesion of central nervous system	1.54	0.17
Frequent acute respiratory infections (ARIs) in medical history	1.12	0.02
Accidents and catastrophes in anamnesis	1.12	0.02
One in family	1.11	0.01
No risk		
Harmonious relationships in family	-5.95	0.95
Search activity (creativity)	-4.68	0.64
Rational nutrition	-3.66	0.54
Full family	-3.54	0.45
Satisfactory parents' social status	-1.08	0.24
Classes in creative circles	-0.98	0.19
Absence of hereditary diseases	-0.89	0.18

Analysis of risk factors (RF) affecting the formation of PSP, considering their versatility and multifactoriality, substantiates a need of identification of their statistically significant combinations. This will allow to predict further course of a disease on its early stages.

When conducting cohort-epidemiological analysis, data on the presence / absence of pathological symptoms for comparative analysis with assessment of the frequency of signs and calculation of the values

of diagnostic coefficients and measures of informativeness were digitized. Numerical expression of symptoms was carried out through calculations of the integral index of intensity of symptoms, depending on the degree of their severity and frequency of occurrence. For each child, a questionnaire with a list of different RFs was completed. These questionnaires were summarized in a protocol. The conducted comprehensive research made it possible to create a prognostic table (table 1) for assessing risks of developing PSP in children. In this table, all statistically significant factors were arranged and located in order of decreasing of the modules of their diagnostic coefficients (that is, in order of decreasing their "predictive power"). Risk assessment using the developed tables was carried out by using the Wald's sequential procedure (modified by E. Gubler) [3].

The essence of this procedure was that the diagnostic coefficients (DK) of the characteristics of each person were added to each other until the recommended level of reliability of the forecast was achieved. For example, reliability of the forecast at the level $p<0.05$ corresponds to the value of the sum of the diagnostic coefficients $\sum_{DK} > 13$, at the level of $p<0.01$ – $\sum_{DK} > 20$, and at the level $p<0.001$ – $\sum_{DK} > 30$. Thus, it becomes clear that none of the established RFs is self-sufficient for a probable forecast (for all the factors presented in the table DK<13), and therefore a plausible forecast is possible only in case of their cumulative use.

In this study, seven anti-risk factors for the formation of PSPs were also identified. Their significance varies from a small (absence of hereditary diseases - DK = -0.89 at J = 0.18) to moderate (harmonic relationships in family - DK = -5.95 at J = 0.92). Nevertheless, anti-risk factors listed in table. 2 together provide reliability of the prediction of no risk of the PSP formation at the level of $p<0.01$, since in this combination of factors the module $\sum_{DK} = -20.77$, that is, more than 20 – is the limit value for this level of reliability. Clinical and paraclinical features of PSP in children with and without PPDD were determined, and the main clinical and pathological tendencies in their psychological and neurophysiological status, which can be diagnosed in the early stages of the formation of the disease were estimated (table 2 and table 3).

Clinical picture of PSP in children with and without PPDD was characterized by polymorphism of complaints and clinical syndromes. In patients with duodenal ulcer abdominal pain (93.8% and 91.7%), dyspeptic (65.2% and 58.4%) and chronic intoxication syndrome (38.8% and 38.7%, respectively) were found and were not significantly different in both groups ($p >0.05$).

Table 2

Distribution of patients by duration of PAP (n = 194)

Groups of children	Nosological form	Duration of the disease, years			Total
		1-2 years	< 5 years	> 5 years	
		abs. n. (%)	abs. n. (%)	abs. n. (%)	abs. n. (%)
I group (n = 93)	bronchial asthma	4(4.3)	16(17.2)	10(10.7)	30(32.5)
	peptic ulcer disease	21(22.6)	23(24.7)	19(20.4)	63(67.5)*
Total		25(26.9)	39(41.9)^	29(31.1)+	93(100.0)
II group (n = 101)	bronchial asthma	45(44.6)	23(22.8)	16(15.8)*	84(83.2).*
	peptic ulcer disease	9(8.8)	7(7.1)	1(0.9)	17(16.8)
Total		54(53.4)#	30(29.9)	17(16.7)	101(100.0)

Note: * - the difference is significant ($p <0.05$) between patients with asthma and BH of the duodenum; # -between PSP duration 1-2 years; ^ - up to 5 years; + - more than 5 years.

Table 3

Distribution of patients with severity of PSP (n = 194)

Groups of children	Nosological form	Severity of the disease			Total
		Light	moderate	severe	
		abs. n.(%)	abs. n.(%)	abs. n.(%)	abs. n.(%)
I group (n = 93)	bronchial asthma	2(6.7)*	10(33.3)*	18(60.0)*	30(100.0)
	duodenal ulcer	8(12.7)*	23(36.5)*	32(50.8)*	63(100.0)
Total		10(10.8)*	33(35.4)	50(53.8)*	93(100.0)
II group (n = 101)	bronchial asthma	45(44.6)	23(22.8)	16(15.8)	84(100.0)
	duodenal ulcer	9(8.8)	7(7.1)	1(0.9)	17(16.8)
Total		54(53.4)	30(29.9)	17(16.7)	101(100.0)

Note: * - the difference is significant ($p <0.05$) between the 1st and 2nd groups

Regarding the asthenoneurotic syndrome, it was significantly more prevalent in children with PSP and PPDD (95.9% and 52.1%) ($p <0.001$). The same tendency was observed among children with bronchial asthma. In children without psychophysical developmental disorders (group II), short duration of disease (1-2 years) was observed in more than half of cases (53.4%), up to 5 years - in 29.9%, more than 5 years - in 16.7%. On the other hand, in patients with PPDD (Group I), a significant increase in the duration of disease was found, that is: duration of 1-2 years - only in 26.9% of patients, up to 5 years - 41.9% and more than 5 years 31.1% of children ($p <0.05$).

In the age structure of PSP in children with PPDD a significantly earlier onset of duodenal ulcer was found in comparison to children without psychophysical developmental defects (10.5 ± 0.7 and 14.2 ± 0.5 years old, respectively ($p < 0.05$)). Also, more severe course of PSP was detected in the vast majority (53.8%) of patients with PPDD vs. 16.7% in children without PPDD ($p < 0.001$) (Table 6). Psychological markers for the formation of PSP in children with PPDD are given in table 4.

Table 4

Prognostic table of risk markers - absence of risk of formation of psychosomatic pathology (psychological study)

Test	Feature	Range of feature	DK	J
Risk markers				
Test of Spielberger-Khanin	high personal anxiety	> 50 points	**4.53**	**0.21**
		46-50 points	**7.84**	**0.13**
	high reactive anxiety	> 45 points	**2.33**	**0.07**
		36-45 points	**7.30**	**0.21**
Method of R. Cattell	low self-esteem	≤ 3.0 points	**0.57**	**0.01**
		3.1-5.0 points	**7.34**	**0.45**
	low emotional constancy	≤ 3.0 points	**0.68**	**0.14**
		3.1-5.0 points	**6.70**	**1.38**
	high anxiety	6.0-7.0 points	**1.95**	**0.12**
		8.0-9.0 points	**7.35**	**0.31**
projective test "good" and "evil" with a choice of color	Poor performance	30-45 points	**7.40**	**0.23**
	Poor performance	46-50 points	**2.84**	**0.18**
	deviation from autogenous N	30-45 points	**4.71**	**0.27**
	deviation from autogenous N	46-50 points	**6.30**	**0.11**
risk-free markers				
Test of Spielberger-Khanin	low personal anxiety	< 36 points	**-1.68**	**0.27**
		36-40 points	**-4.38**	**0.42**
	Low reactive anxiety	< 26 points	**-0.73**	**0.07**
		26-30 points	**-3.71**	**0.47**
Method of R. Cattell	High self-esteem	> 7.0 points	**-0.57**	**0.01**
		6.0-7.0 points	**-7.91**	**0.46**
	high emotional constancy	> 7.0 points	**-0.68**	**0.05**
		6.0-7.0 points	**-1.02**	**0.02**
Projective test	High performance	≥ 50-60 points	**-1.07**	**0.16**

Determination of a psychological status can be considered as an integral component of a child's health, since the problems that we were planning to identify in the process of diagnosis were entirely focused on personal level. Apart from the objective situation of each person (life circumstances, the real state of health), it was essential to determine their subjective attitude to this situation, as well as to assess their own reactions to life difficulties, individual resources of resistance and development. It is known that lack of protection mechanisms complicates the processes of recognition and expression of emotions, reduces the child's ability to psychologically transform stress, reduces the possibility of managing intense negative experiences. The latter usually serve as a basis for further formation of various psychosomatic disorders, which can be considered as a separate personal way of responding [4].

Analysis of the data of psychological research allowed to establish 7 markers of susceptibility to PSP, namely: high levels of personal and reactive anxiety (according to the Spielberger-Khanin test), low self-esteem and high indices of anxiety and emotional lability (by R. Cattell's test), poor performance and high rates of deviation from the autogenous norm (according to the projective test "good" and "evil" with the choice of color).

As can be seen from Table. 4, some of the established markers, such as high personal and reactive anxiety according to the Spielberger-Khanin test, and poor performance and deviation from the autogenous norm according to the projective test "good" and "evil" with choice of color are self-sufficient for the probable risk assessment or absence of risk because their DK is high enough but lower than the threshold number of 13, which ensures the accuracy of the diagnostic conclusion at the level of $p<0.05$. Therefore, they provide the necessary reliability of diagnostic findings only when combined with others.

Conclusions

1. The prevalence of PSP in children with PPDD was not significantly different from that in patients without PPDD and was estimated 89 and 86 per 1.000 children, respectively.

2. In the structure of PSP in children with and without PPDD two nosological forms – bronchial asthma and duodenal ulcer were predominant. However, in patients with PPDD, the most prevalent were duodenal ulcer, found at 56% of cases, bronchial asthma – 26%, and diabetes mellitus and ulcerative colitis – 1% and 3%, respectively. In the absence of PPDD, a reverse trend was observed – bronchial asthma was observed in 68% of cases, duodenal ulcer in 12%, diabetes mellitus in 5% and rheumatoid arthritis in 4% patients.

3. In the age structure of children with PSP and PPDD a significantly earlier onset of duodenal ulcer disease was observed as compared to children without psychophysical developmental defects (10.5±0.7 years and 14.2±0.5, respectively).

4. Clinical peculiarities of duodenal ulcer disease in 29.0% of children without PPDD were light and asymptomatic clinical forms and detection of the first clinical signs of the disease in the form of complications (gastro-intestinal bleeding, scar-and-ulcer deformation of the duodenal mucosa) (8.1%). The same pattern has been observed in children with PPDD. However, in them the frequency of detection of complicated forms of the disease was significantly higher (14.7%).

5. The peculiarities of the clinical course of PSP in children with PPDD were their longer duration (73.0%) and severity (53.8%) vs. 46.6% and 16.7% in patients without PPDD.

6. Pivotal complex psychological markers for the development of PSP in children with and without PPDD were high levels of personal and reactive anxiety, emotional lability and deviation from autogenous norm, low self-esteem and poor performance indicators, which required differentiated medical and psychological support.

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Реферати

РОЗПОВСЮДЖЕНІСТЬ, КЛІНІЧНІ ОСОБЛИВОСТІ ТА ПРОГНОЗУВАННЯ ПЕРЕБІГУ ПСИХОСОМАТИЧНОЇ ПАТОЛОГІЇ У ДІТЕЙ З ПОРУШЕННЯМИ ПСИХОФІЗИЧНОГО РОЗВИТКУ

Бекетова Г.В., Мозгова Г.П., Солдатова О.В., Нехаєнко М.І., Горячева І.П., Алексєєнко Н.В., Квашніна Л.В., Бекетова Н.В.

У статті представлені результати клінічного та епідеміологічного дослідження щодо поширеності психосоматичної патології (ПСП) в Україні у дітей з порушеннями психофізичного розвитку (ППФР). Було встановлено, що поширеність ПСП у дітей з ППФР суттєво не відрізняється від долі пацієнтів без ППФР і оцінювались відповідно 89 та 86 дітей на 1000 дитячого населення. Переважаючими психосоматичними захворюваннями у дітей з та без ППФР були бронхіальна астма (БА) та виразка дванадцятипалої кишки (ВДК). У пацієнтів з ППФР спостерігалася найвища поширеність виразки дванадцятипалої кишки (56%) та бронхіальної астми (26%), тоді як, навпаки, у дітей без ППФР поширеність виразки дванадцятипалої кишки оцінювали 12%, а бронхіальної астми - 68%. У дітей із ПСП та ППФР виявлено раніше виникнення виразки дванадцятипалої кишки порівняно з дітьми без ППФР (10,5 ± 0,7 років та 14,2 ± 0,5 відповідно). Клінічними особливостями перебігу виразки дванадцятипалої

РАСПРОСТРАНЕННОСТЬ, КЛИНИЧЕСКИЕ ОСОБЕННОСТИ И ПРОГНОЗИРОВАНИЕ ТЕЧЕНИЯ ПСИХОСОМАТИЧЕСКОЙ ПАТОЛОГИИ У ДЕТЕЙ С НАРУШЕНИЯМИ ПСИХОФИЗИЧЕСКОГО РАЗВИТИЯ

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В статье представлены результаты клинико-эпидемиологического исследования распространенности психосоматической патологии (ПСП) в Украине у детей с психофизическими нарушениями развития (ПФНР). Было установлено, что распространенность ПСП у детей с ПФНР существенно не отличалась от таковой у пациентов без ПФНР и составила 89 и 86 детей на 1000 детей, соответственно. Преобладающими психосоматическими заболеваниями у детей с и без ПФНР были бронхиальная астма (БА) и язва двенадцатиперстной кишки (ЯДК). У пациентов с ПФНР наблюдалась наибольшая распространенность язвенной болезни двенадцатиперстной кишки (56%) и бронхиальной астмы (26%), в то время как у детей без ПФНР распространенность язвенной болезни двенадцатиперстной кишки оценивалась в 12% и бронхиальной астмы 68%. У детей с ПСП и ПФНР было выявлено более раннее начало язвенной болезни двенадцатиперстной кишки по сравнению с детьми без ПФНР (10,5±0,7 года и 14,2±0,5 соответственно). Клиническими признаками течения язвенной болезни

кишки у дітей без ППФР були поширеність незначних та безсимптомних форм (29,0%) з виявленням перших клінічних ознак захворювання у вигляді ускладнень (шлунково-кишкова кровотеча, рубцево-виразкова деформація дванадцятипалої кишки) (8,1%). Така ж картина спостерігалася і у дітей з ППФР, проте частота ускладнень у них була значно вищою (14,7%) при більшій тривалості (73,0%) та тяжкості (53,8%) захворювання порівняно з 46,6% та 16,7% у пацієнтів без ППФР. Основними комплексними психологічними маркерами розвитку ПСП у дітей з та без ППФР були високий рівень особистісної та реактивної тривожності, емоційна лабільність та відхилення від аутогенної норми, низькі показники самооцінки та низька працездатність, що вимагало диференційованої медико-психологічної підтримки.

Ключові слова: психосоматична патологія, психофізичні розлади, діти, підлітки, фактори ризику.

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двенадцатиперстной кишки у детей без ПФНР являлись распространенность малых и бессимптомных форм (29,0%) с выявлением первых клинических признаков заболевания в виде осложнений (желудочно-кишечные кровотечения, рубцово-язвенная деформация двенадцатиперстной кишки) (8,1%). Такая же картина наблюдалась у детей с ПФНР, однако частота осложнений у них была достоверно выше (14,7%) при более длительной (73,0%) и тяжести (53,8%) заболевания по сравнению с 46,6% и 16,7% у пациентов без ПФНР. Ключевым комплексом психологических маркеров развития ПСП у детей с и без ПФНР являлись высокий уровень личной и реактивной тревоги, эмоциональная лабильность и отклонение от аутогенной нормы, низкие показатели самооценки и плохая успеваемость, что требовало дифференцированной медицинской и психологической поддержки.

Ключевые слова: психосоматическая патология, психофизические расстройства, дети, подростки, факторы риска.

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TREATMENT OF ARTERIAL HYPERTENSION IN YOUNG MALES WITH CLINICAL SIGNS OF AUTONOMIC DYSFUNCTION

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The aim of the study was to improve the effectiveness of the treatment of arterial hypertension (AH) in young patients with clinical signs of autonomic dysfunction. We examined 65 male patients with AH (mean age 35.6 ± 4.3 years) and clinical signs of autonomic dysfunction. Basic therapy was administered to 30 of them (group 1), and ethylmethylhydroxypyridine succinate (EMS) was additionally administered to 35 patients (group 2) for 4 weeks. After treatment, BP correction to target values was achieved in 76.7% of the patients in group 1 and in 88.6% in group 2. On the background of therapy with EMS, a more pronounced increase in total HRV, decreased activity of the sympathetic division of the autonomic nervous system and restoration of the vegetative balance according to the temporal HRV indicators, as well as the significant positive changes in state and trait anxiety were observed. Thus, the inclusion of EMS in the complex treatment of young males with AH and clinical signs of autonomic dysfunction has a positive effect on clinical symptoms, contributes to the restoration of the autonomic balance and correction of psycho-emotional state.

Key words: arterial hypertension in young, autonomic dysfunction, heart rate variability, anxiety, ethylmethylhydroxypyridine succinate.

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Hypertension is one of the major health maintenance problems due to the high prevalence of AH and the fact that this condition is one of the main risk factors for cardiovascular diseases and their complications, disability and mortality [10]. Vegetative dysfunction is the most widespread and unpredictable disorder of the young by the variety of its manifestations and results [8]. In the early stages of the AH development in case of absence of complaints from patients, an imbalance in the system of autonomic regulation of cardiac rhythm already appears [4], and in case of a pronounced clinical picture of AH, it is possible to prevent the most frequent complications arising from the traumas of target organs by means of the evaluation of the autonomic status. Clinicians face the difficult task of choice of the optimal therapy in each case, based not only on the BP indicators, but also on the nature of the functioning of the nervous system, which is directly related to the regulation of blood circulation.

Ethylmethylhydroxypyridine succinate (EMS) is an antioxidant drug with a wide spectrum of clinical activity, induced by its polyvalent mechanism of action: antioxidant (inhibits the processes of free radical oxidation, lipid peroxidation, activates superoxide dismutase what leads to an increase of the activity of the physiological antioxidant system as a whole); anxiolytic (due to modeling effect on GABA-receptor complex), antihypoxic (intrinsic antioxidant properties provided by the influence on endogenic respiration of mitochondria and activation of succinate oxidation pathway contributes to an increase of the

resistance of brain cells to oxygen deficiency), and also nootropic (increases the activity of neurotransmitters, improves synaptic transmission and interrelation of brain structures). [1].

The purpose of our study was to increase the efficacy of hypertension treatment in young adults with clinical signs of autonomic dysfunction.

Materials and methods. The study included 65 male patients with AH, aged 30 - 40 years old (mean age 35.6 ± 4.3 years). The average duration of AH was (2.9 ± 2.1) years. 32.3% of patients had AH of the 1st degree, 67.7% – of the 2nd degree. The diagnosis of AH was established in accordance with the recommendations of the European Society of Hypertension and the European Society of Cardiology (ESH / ESC, 2013). The control group consisted of 20 practically healthy males aged 30 - 40 years (mean age 35.3 ± 3.9 years). All the surveyed persons underwent general clinical examination, biochemical analysis of blood with determination of indicators of lipid metabolism, glucose, creatinine, neuro-ophthalmic examination, ECG registration in 12 standard leads. Ambulatory Blood Pressure Monitoring (ABPM) was performed with device "ABPM-02" (Meditech, Hungary). The following indicators were determined: daytime, nighttime, average daily (24 hours) SBP and DBP, HR. To detect vegetative dysfunction, "Screening questionnaire for revealing the signs of vegetative changes" (Wein A.M., 2003) was used. With a score greater than 15, vegetative dysfunction is assumed. In the examined patients with AH and autonomic dysfunction, the mean score was 47.3 ± 1.7, in the control group - 12.9 ± 1.5 points ($p<0.001$).

To assess state and trait anxiety, the State-Trait Anxiety Inventory by Charles D. Spielberger (1973) was used. It was adapted by Yu. L. Khanin and contains 40 questions. The result was evaluated as follows: up to 30 – low anxiety, 31 - 45 – moderate anxiety, 46 and more – high anxiety.

Nonspecific changes in the functional state of the central nervous system were studied by the method of indirect recording of heart rate variability on the cardiographic complex of Holter ECG monitoring "Cardiosense" ("KhAI Medica", Ukraine). Registration and automated processing of ECG signals were performed with the calculation of the parameters of temporal and spectral analysis, as well as the indices obtained on their ground and proposed by R.M. Bayevsky [7]. The following parameters were used for the analysis of vegetative regulation:

– TI is the tension index of the regulatory systems, calculated as TI = AMo / 2 × BP × Mo

where AMo is the mode amplitude – the number of cardio intervals corresponding to the mode range (in %); VR – variation range – the difference between the maximum and minimum values of RR; Mo (mode) is the most commonly recorded RR value.

– SDNN – standard deviation of the duration of normal R–R intervals;

– pNN 50 – percent of all analyzed cardio intervals;

– RMSSD – the square root of the mean squared difference between complementary RR intervals. Indicator of activity of parasympathetic link of vegetative regulation. The higher the RMSSD value, the more active is the link of parasympathetic regulation [9].

– LF / HF – index of vagosympathetic interaction, the ratio of high-frequency and low-frequency component of oscillations of heart rhythm. Indicates a shift of the vegetative balance toward the sympathetic or parasympathetic division.

After registration of the baseline data, the patients were randomly divided into 2 groups. Basic antihypertensive therapy was administered to 30 patients (group 1), and included an ACE inhibitor (Lisinopril 10-20 mg/day). The second group consisted of 35 patients who were prescribed complex therapy, which included an ACE inhibitor (Lisinopril 10-20 mg/day) and ethylmethylhydroxypyridine succinate (Mexiprim, Stada, Germany) 125 mg t.i.d. for 4 weeks. Indapamide 2.5 mg/day was added when necessary. Before the study initiation, the patients in both groups were compared by age, AH duration, levels of office BP, ABMP indices and HRV parameters (all $p> 0.05$).

All patients successfully completed the study according to the protocol. A revive study was performed after 4 weeks of treatment. Side and adverse effects have not been reported for this period.

Statistical processing of the study results was performed using the software Statistica 6.0 for Windows. During analysis, mean values (Me) were calculated and the interquartile interval (II) was recorded. Comparison of qualitative parameters was performed using Fisher's exact two-tailed test, and a comparison of quantitative indicators in the study groups was performed using the Mann-Whitney U test. Differences at $p<0.05$ were considered statistically significant.

Results of the study and their discussion. In our study, baseline investigation of vegetative balance allowed us to establish that in patients with AH and clinical signs of autonomic dysfunction sympathicotonia was revealed in 42 patients (64.6%), vagotonia – in 20 (30.8%) and amphotonia in 3 (4, 6%) patients. The state of eutonia was not found. Since the activity of both departments of the autonomic nervous system is organized synergistically, the behavior of autonomic regulation during AH is evaluated

in terms of shifts in the activity of both sympathetic and parasympathetic links simultaneously [4]. HRV testing is often used to implement such control of autonomic nerve regulation. However, the results of HRV assessment in case of AH are often controversial. Some authors noted an increase in sympathetic activity, while others received directly opposite data [6].

Analysis of HRV indicators at baseline indicates the presence of vegetative disorders in the examined patients with AH and clinical signs of autonomic dysfunction (table 1).

Table 1

Dynamics of HRV parameters in patients with AH and clinical signs of autonomic dysfunction (M±m)

Index	Group of healthy persons (n = 20)	Group 1 (n = 30)		Group 2 (n = 35)	
		Baseline data	After treatment	Baseline data	After treatment
Mo, s	0.81±0.03	0.60±0.05	0.82±0.04***	0.63±0.04	0.83±0.01***
VR, s	0.20±0.02	0.14±0.01	0.18±0.01**	0.14±0.03	0.24±0.02**
AMo, %	31.8±1.5	62.7±2.5	53.3±2.5**	63.2±2.2	42.8±2.6***
TI, RU	97.6±3.1	349	176 ***	348±7	111±11***
SDNN, ms	82.1±3.1	63.1±3.1	68.7±3.3	63.6±3.3	79.8±3.9**
pNN 50, %	29.9±1.3	24.9±1.2	27.8±1.5	24.1±1.3	29.3±1.6**
RMSSD, ms	61.4±3.5	47.5±3.5	51.7±3.7	47.9±3.3	60.7±3.7*
LF/HF, RU	1.56±0.3	2.17±0.3	1.87±0.2	2.31±0.3	1.59±0.1

Notes: 1. * - reliability of differences compared to the original data; 2. * - p <0.05; 3. ** - p <0.01; 4. *** - p <0.001.

At baseline, the evaluation of HRV indices in patients with AH and clinical signs of autonomic dysfunction revealed that the mode amplitude exceeded the results of healthy individuals by 1.9 times, the tension index by 3.6 times, the variational range was reduced by 1.4 times, indicating prevalence of activity of the sympathetic division of the autonomic nervous system (table 1). In addition, compared with the control group in patients with AH and clinical signs of autonomic dysfunction, a significant decrease in general heart rate variability (SDNN) by 1.3 times and a decrease in the parasympathetic component of heart rate regulation (RMSSD) by 1.3 times were registered. During the correlation analysis of BP level and HRV indicators in all patients with AH strong negative correlations of SBP level with SDNN (r = -0.70; p <0,01) and RMSSD indicators (r = -0.73; p <0.01) were registered, correlations of these HRV indicators with DBP level were weaker with SDNN (r = -0.43; p <0.05) and RMSSD indicators (r = -0.41; p <0.05).

After the course of treatment, BP correction to the target values was achieved in 23 (76.7%) patients in group 1 and in 31 (88.6%) in the second group. The dynamics of average indicators of office BP is presented in table 2. After 4 weeks of treatment there was a significant and equally pronounced decrease in SBP (p <0.001) and DBP (p <0.05).

An analysis of DMBP indicators after 4 weeks showed high antihypertensive efficacy of both treatment regimens (table 2).

Table 2

Change of office BP and DMBP indices in the treatment time course of patients with AH and clinical signs of autonomic dysfunction (M±m)

Index	Group 1 (n = 30)		Group 2 (n = 35)	
	Baseline data	After 4 weeks	Baseline data	After 4 weeks
Sphygmomanometry: SBP, mm Hg	158.1±4.6	133.3±3.9***	158.9±4.8	131.7±3.7***
DBP, mm Hg	95.2±4.3	83.6±3.8*	95.9±4.1	81.4±3.9*
DMBP: 24 hrs				
SBP, mm Hg	147.1±4.1	127.3±3.8***	149.3±4.5	128.1±4.6***
DBP, mm Hg	94.5±4.3	78.8±3.5**	94.9±4.1	79.1±3.8**
TI SBP, %	69.6±7.4	18.3±6.7***	68.9±7.5	15.1±6.3***
TI DBP, %	58.7±7.3	16.3±6.4***	59.1±7.1	11.7±5.8***
Day				
SBP, mm Hg	153.1±4.6	123.1±4.1***	154.3±4.7	127.5±4.1***
DBP, mm Hg	97.3±4.6	81.4±4.1**	97.1±4.8	78.7±4.3**
TI SBP, %	67.6±6.3	27.6±6.9***	66.3±7.8	24.7±7.1***
TI DBP, %	58.1±7.9	19.9±7.5***	58.3±8.3	15.3±8.7***
Night				
SBP, mm Hg	140.7±4.6	118.4±6.3***	141.8±4.7	110.7±6.1***
DBP, mm Hg	86.7±4.3	73.1±3.9*	86.3±5.1	68.4±4.3*
TI SBP, %	72.3±8.7	17.9±9.4***	73.1±9.3	15.7±8.1***
TI DBP, %	52.1±8.3	12.4±8.7***	53.5±8.5	10.1±9.1***

Notes: 1. * - reliability of differences compared to the original data; 2. * - p <0.05; 3. ** - p <0.01; 4. *** - p <0.001.

During evaluation of HRV indicators (table 1), it was found that the patients of the 1st and 2nd groups had a decrease in sympathetic activity on the background of therapy. Thus, there was a decrease in the tension index in the 1st group by 49.6% (p <0.001) and in the 2nd group by 68.1% (p <0.001); mode amplitude index – by 15% (p <0.01) and 32.3% (p <0.001); an increase in the variation range by 28.6% (p <0.01) and 71.4% (p <0.001) respectively, indicating an improvement in vegetative tone, and in the 2nd group – restoration of vegetative balance. In patients with AH and clinical signs of autonomic dysfunction, which additionally received EMS, a significantly better result was observed contrary to the comparison group according to the tension index (36.9%; p <0.001) and the variation range (55.6%; p < 0.01). Therefore, in the group which received additional EMS, harmonization of autonomic nervous system function was registered.

At the same time, total HRV according to SDNN data and parasympathetic component of regulation of the cardiovascular system according to the RMSSD indicator increased. In particular, the SDNN index, reflecting the cooperative effect of the autonomic regulation of blood circulation, increased by 8.9% (p> 0.05), and in group 2 – by 25.5% (p <0, 01) respectively (table 1) in patients of group 1; RMSSD index, which indicates the activity of the parasympathetic link of autonomic regulation in the 1st group increased by 8.84% (p> 0.05) and in the 2nd group - by 26.7% (p <0.01) respectively; pHN 50 index – a predominance degree of parasympathetic regulation link in the 1st group increased by 11.6% (p> 0.05) and in the 2nd group – by 21.6% (p <0.01), respectively. Thus, in patients with hypertension and clinical signs of autonomic dysfunction, complex therapy with addition of EMS resulted in more pronounced increase in total HRV, decreased activity of the sympathetic division of the autonomic nervous system and restoration of the autonomic balance according to the temporary HRV indicators.

Analysis of the psycho-emotional state at baseline showed that in the examined patients with AH and clinical signs of autonomic dysfunction increased levels of anxiety on the scale by Ch.D. Spielberg-Y. L. Khanin were noted. It is explained by the specifics of the patients' response to the disease and the changes in psychological status related to it, as well as premorbid characteristics of the patients' personalities. Thus, the degree of reactive and trait anxiety made (48.3±1.9) and (47.0±1.5) in the 1st group and (49.1±1.4) and (48.9±1.6) in the 2nd group respectively. Most patients with AH showed high and moderate levels of reactive and trait anxiety (table 3).

Table 3

Indicator changes in reactive and trait anxiety in patients with AH and clinical signs of autonomic dysfunction (M±m)

Indicator	Level	Group	Baseline data	After treatment
Reactive anxiety	low	1	28.6±1.5 (n = 2)	28.9±1.4 (n = 5)
		2	28.2±1.3 (n = 2)	28.1±1.2 (n =22)
	moderate	1	39.7±1.6 (n = 12)	36.3±1.5 (n = 13)
		2	41.5±0.8 (n = 12)	34.1±0.9* (n = 11)
	high	1	56.3±2.3 (n = 16)	52.0±2.1 (n = 17)
		2	56.1±1.3 (n = 16)	46.3±0.5* (n = 2)
Trait anxiety	low	1	28.2±1.2 (n = 3)	28.6±1.1 (n = 5)
		2	28.6±1.3 (n = 3)	28.1±1.5 (n = 22)
	moderate	1	41.6±1.2 (n = 14)	39.6±1.5 (n = 18)
		2	43.7±1.1 (n = 13)	33.5±0.7* (n = 6)
	high	1	55.3±1.7 (n = 13)	53.6±2.1 (n = 12)
		2	55.9±1.3 (n = 14)	47.1±0.5* (n = 2)

Notes: 1. * - reliability of differences compared to the original data; 2. * - p <0.05.

The results of the study allowed us to establish that the patients of group 1 with low, moderate and high levels of reactive and trait anxiety at baseline after the treatment did not have any significant changes (table. 3). At the same time, after the course of complex therapy with the addition of EMS a pronounced decrease of the level of reactive anxiety by 41% (p <0.001) and trait anxiety by 37.8% (p <0.001) was present. Moreover, EMS proved to be the most effective in the high and moderate anxiety group what was proved by the change of 17 patients to low level of reactive and trait anxiety respectively (table 3). However, in patients with low anxiety at baseline, there were no significant changes of this indicator.

It should be noted that the time course difference of the level of state and trait anxiety during complex therapy with the addition of EMS was statistically significant (48.4%, p <0.01) and (37.8%, p <0.05) respectively in the comparison group. The data obtained demonstrates an increase of the specific influence on the cortical excitation and subcortical formations, what modulates psycho-emotional processes in the body. Therefore, in young males with AH and clinical signs of autonomic dysfunction on

the background of complex treatment with addition of EMS a positive time course of state and trait anxiety was noted, suggesting the improvement of patients' emotional state.

In the pathogenesis of hypertension, activation of the sympathetic nervous system plays an important role, especially at the initial stages [3]. A high level of anxiety is accompanied by an increase of sympathetic influences on cardiac activity and leads to the tension in regulatory systems. However, the features and patterns of manifestation of psychosomatic disorders during AH in young people with clinical signs of autonomic dysfunction require further study. In our study, the analysis of the daily BP profile and condition of the autonomic nervous system in young men with AH, despite a short history of the disease, revealed abnormalities in the circadian rhythms of BP associated with impaired autonomic regulation of the cardiovascular system in the form of a relative increase of sympathetic influences and weakening of parasympathetic ones, what corresponds to the previous studies [5]. In the examined patients with AH and autonomic dysfunction, a decrease in the level of psychological health was revealed, what was expressed in an increase of the number of patients with high and moderate levels of reactive and personal anxiety. Complex antihypertensive therapy with addition of EMS significantly improved HRV parameters, what was expressed in a decrease of the stress index and restoration of the autonomic balance according to temporal indicators of heart rate variability. It was noted that EMS has a pronounced tranquilizing and anti-stress effect, an ability to eliminate anxiety, fear, tension, anxiety [2]. In our study, it was found that the addition of EMS to the antihypertensive therapy can reduce the level of reactive anxiety, what allows to increase the body's functional capacities secondary to the improvement of the psychoemotional state.

Conclusion

Thus, the inclusion of EMS in the complex treatment of young males with AH and clinical signs of autonomic dysfunction has a positive effect on clinical symptoms, contributes to the restoration of vegetative balance and correction of psycho-emotional state.

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Реферати

ЛІКУВАННЯ АРТЕРІАЛЬНОЇ ГІПЕРТЕНЗІЇ У ЧОЛОВІКІВ МОЛОДОГО ВІКУ З КЛІНІЧНИМИ ОЗНАКАМИ ВЕГЕТАТИВНОЇ ДИСФУНКЦІЇ

Біловол О.М., Князькова І.І., Богун М.В., Луценко Р.В.

Метою дослідження було підвищення ефективності лікування артеріальної гіпертензії (АГ) у осіб молодого віку з клінічними ознаками вегетативної дисфункції. Обстежено 65 хворих АГ чоловічої статі (середній вік 35,6 ± 4,3 років) з клінічними ознаками вегетативної дисфункції, яких 30 (1 група) призначалась базисна терапія і 35 пацієнтам (2 група) додатково призначали етилметилгідроксипіридина сукцинат (ЕМС) протягом 4 тижнів. Після лікування корекція АТ до цільових значень була досягнута 76,7 % пацієнта 1-ї групи і 88,6 % 2-ої груп. На фоні терапії ЕМС, спостерігався більш виражене зростання загальної ВРС, зниження активності симпатичного відділу вегетативної

ЛЕЧЕНИЕ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ У МОЛОДЫХ МУЖЧИН С КЛИНИЧЕСКИМИ ПРИЗНАКАМИ ВЕГЕТАТИВНОЙ ДИСФУНКЦИИ

Беловол А.Н., Князькова И.И., Богун М.В., Луценко Р.В.

Цель работы - повышение эффективности лечения артериальной гипертензии (АГ) у лиц молодого возраста с клиническими признаками вегетативной дисфункции. Обследовано 65 мужчин с АГ (средний возраст 35,6 ± 4,3 лет) с клиническими признаками вегетативной дисфункции, из которых 30 (1 группа) назначалась базисная терапия и 35 пациентам (2 группа) дополнительно назначали этилметилгидроксипиридина сукцинат (ЭМС) в течение 4 недель. После проведенного лечения коррекция АД до целевых значений была достигнута у 76,7% пациентов 1-й группы и 88,6% - второй групп. На фоне терапии ЭМС, наблюдался более выраженный рост общей ВРС, подавление активности симпатического отдела вегетативной нервной

нервової системи і відновленню вегетативного балансу згідно даних тимчасових показників ВРС, а також суттєва позитивна динаміка ситуативної та особистої тривожності. Таким чином, включення ЕМС у комплексну терапію лікування чоловіків молодого віку з АГ і клінічними ознаками вегетативної дисфункції позитивно впливає на клінічну симптоматику, сприяє відновленню вегетативного балансу і корекції психоемоційного стану.

Ключові слова: артеріальна гіпертензія у молодих, вегетативна дисфункція, варіабельність ритму серця, тривога, етилметилгідроксипіридина сукцинат.

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системы и восстановление вегетативного баланса по данным временных показателей ВРС, а также существенная положительная динамика ситуативной и личной тревожности. Таким образом, включение ЭМС в комплексную терапию лечения мужчин молодого возраста с АГ и клиническими признаками вегетативной дисфункции положительно влияет на клиническую симптоматику, способствует восстановлению вегетативного баланса и коррекции психоэмоционального состояния.

Ключевые слова: артериальная гипертензия у молодых, вегетативная дисфункция. вариабельность сердечного ритма, тревога, этилметилгидроксипиридина сукцинат.

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TREATMENT OF HEART FAILURE IN PATIENTS WITH DIABETES MELLITUS

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The purpose of the work was to study the effect of fixed combination of meldonium dihydrate and γ-butyrobetaine dihydrate (MD+γ-BD) on clinical, hemodynamic and glucometabolic parameters, as well as indicators of oxidant-antioxidant status in patients (pts) with heart failure (HF) and type 2 diabetes mellitus (DM). The total of 62 patients with HF and DM were examined. After registration of the baseline data, baseline therapy was prescribed to all patients, 30 of them (group 1) obtained an additional fixed combination of MD+γ-BD 2 capsules three times a day for 3 months and 32 patients were included in the comparison group (group 2). After treatment in group 1, the increase of the distance walked was determined according to the 6-minute walk test by 31.2% versus 12.7% in group 2 ($p < 0.05$). There was an increase in left ventricular (LV) ejection fraction by 4.5% in group 1 versus 1.9% in group 2 ($p < 0.05$). Positive changes in glucometabolic parameters were observed. A decrease of the activity of lipid peroxidation processes according to the level of malondialdehyde (Δ-22.3% in patients of group 1 versus Δ-11.2% in group 2, $p < 0.05$) and an increase in the activity of erythrocyte superoxide dismutase (respectively Δ29.5% vs. 8.1%, $p < 0.05$) were found. Thus, an addition of a fixed combination of MD+γ-BD in the complex therapy of pts with HF and type 2 DM improves clinical symptoms in patients, has a positive effect on the structural and functional parameters of the left ventricle, glucometabolic parameters and imbalance of the oxidant-antioxidant system by increasing the activity of intracellular antioxidant enzymes.

Key words: heart failure, type 2 diabetes mellitus, structural and functional changes of the left ventricle, lipid peroxidation, fixed combination of meldonium dihydrate and γ-butyrobetaine dihydrate.

The work is a fragment of the research project "Optimization of diagnosis and treatment of comorbid pathology (hypertension and type 2 diabetes mellitus) based on the assessment of cardiohemodynamics, metabolism and pharmacogenetic analysis", state registration No.0116U004983.

Heart failure (HF) is a rapidly growing disease of the clinical cardiology in many countries [2]. Despite significant advances in the study of pathogenesis, clinical findings and treatment, this pathology remains widespread with dismal course and prognosis. Patients with HF of ischemic etiology are characterized by the involvement of target organs, behind which lie hypoxia processes caused by impaired macro- and microcirculation [4].

Type 2 diabetes mellitus (DM) is also a rapidly growing medical and social problem in all industrially developed countries. It is particularly disturbing that the prevalence and incidence of type 2 DM in recent years have tendency to increase in young age groups [12]. More than 50% of patients with type 2 DM do not even suspect that they have this disease because it can be asymptomatic for many years [3]. The presence of type 2 DM in patients contributes to the formation of additional hemodynamic and metabolic damage to the heart and the blood stream [6].

Predictably poor and even fatal effect of DM on the prognosis of HF have been established in numerous clinical studies; diabetes mellitus was not only associated with an increase in mortality but was also recognized as an independent predictor in HF patients [10, 13]. The problem of optimization and individualization of pharmacotherapeutic approaches in this category of patients is extremely urgent. Therefore, it is important to optimize the treatment of patients with HF in combination with type 2 DM, taking into account clinical features found in this category of patients.

In therapeutic practice, 3- (2,2,2-trimethylhydrazinium) propionate dihydrate (meldonium dihydrate) has been widely used, the action of which is to optimize intracellular mitochondrial energy

metabolism, to reduce cell oxygen demand by shifting energy metabolism to oxidation of fatty acids to the dominating utilization of glucose. Antioxidant properties of meldonium have been established, which are able to influence the manifestations of insulin resistance and lipid metabolism [9].

Gamma-butyrobetaine dihydrate affects the induction of biosynthesis of nitric oxide (NO), protects cells from the toxic effects of free radicals, normalizes oxidative homeostasis at the cellular level, has a positive effect on endothelial function, inhibits aggregation and adhesion of thrombocytes, neutrophil adhesion to the endothelium, migration of monocytes [11].

The purpose of the work was to study the effect of fixed combination of meldonium dihydrate and γ-butyrobetaine dihydrate on the clinical, hemodynamic and glucometabolic parameters, as well as the indicators of oxidant-antioxidant status in patients with HF and type 2 DM.

Materials and methods. We examined 62 patients (18 women and 44 men, mean age 60.3 ± 1.6 years) with HF stage II A, NYHA class II and III of ischemic etiology and type 2 DM (moderate severity, subcompensation stage). The diagnosis of HF was established in accordance with the recommendations of the European Society of Cardiology for the diagnosis and treatment of acute and chronic heart failure (ESC, 2016), as well as the Ukrainian Association of Cardiology for the diagnosis and treatment of chronic heart failure (2017). Diagnosis of type 2 DM was established according to the general recommendations of the European Association for the Study of Diabetes (EASD, 2013).

All examined patients underwent general clinical examination, physical examination, anthropometric measurements, measurements of office blood pressure (BP), heart rate (HR), 6-minute walk test (6MWT), general blood test and urinalysis, biochemical analysis of blood with determination of glucose concentration in fasting blood serum (FBS), levels of glycosylated hemoglobin (HbA1c) in whole blood, insulin, lipid profile indices. Insulin resistance was evaluated by the NOMA-IR index. The content of malondialdehyde (MDA) was determined by reaction with thiobarbituric acid (TBA), which at high temperature (100 ° C) in acid medium proceeds with the formation of the stained trimethyl complex. The activity of superoxide dismutase (SOD) was determined by the level of enzyme inhibition of reduction of nitrotetrazolium blue with the participation of reduced nicotinamide adenine dinucleotide (NADH) and phenazin metasulfate.

Structural and functional parameters of the heart were accessed by echocardiography using the diagnostic system "GE Medical Systems" (Germany) by a phased array transducer with a modulated frequency of 2.25-3 MHz in M- and B-modes in accordance with the recommendations of the American Society of Echocardiography (ASE, 2016). The study included an assessment of the linear dimensions of the heart cavities (anterior-posterior size of the left atrium, end-systolic and end-diastolic dimensions of the left ventricle (ESD and EDD LV)), thickness of the interventricular septum and posterior wall of the LV. The mass of the left ventricular (MLV) (by the formula Devereux R.B. et al.) and the MLV index (IMLV) were calculated relative to the body surface and the LV systolic function was evaluated.

After registration of baseline data, basic therapy for HF (Lisinopril, Carvedilol, Eplerenone in individually selected dosages) and a fixed combination of meldonium dihydrate and γ-butyrobetaine dihydrate ("Kapikor", Olainfarm, Latvia) 2 capsules three times a day for 3 months were administered to 30 patients of the main group (group 1). The comparison group (group 2) consisted of 32 patients whom basic HF therapy was administered. Patients in both groups also received antiplatelet therapy (metformin + gliclazide), statins, antiplatelet therapy. These groups of patients were comparable by age, sex, disease severity, main clinical and hemodynamic parameters, as well as the administered doses of standard therapy for HF. The second study was performed after 3 months of treatment. Side and undesirable effects during this period have not been reported.

The mathematical computer processing of the results of the study was carried out using the software package "Statistica 8.0" (StatSoft Inc, USA). Mean value (M), variance, standard deviation, median (m), probability and significance level (p) were calculated. Differences were considered significant at the level of statistical significance $p < 0.05$. To evaluate the relationship between the indicators the method of correlation analysis with the calculation of the Pearson correlation coefficients (at normal distribution) and Spearman correlation coefficients (at the distribution different from normal) was used.

The mathematical computer processing of the results of the study was made using the software package "Statistica 8.0" (StatSoft Inc, USA). Mean value (M), variance, standard deviation, median (m), probability and significance level (p) were calculated. Differences were considered significant at the level of statistical significance $p < 0.05$. To evaluate the relationship between the indicators the method of correlation analysis with the calculation of the Pearson correlation coefficients (at normal distribution) and Spearman correlation coefficients (at the distribution different from normal) was used.

Results of the study and their discussion. Reduction of HF class (NYHA) was found in patients of group 1 by 12.5% (from 2.4 ± 0.5 to 2.1 ± 0.3) compared to group 2, where this index remained practically unchanged (2.4 ± 0.5 at baseline and 2.3 ± 0.3 after 3 months of treatment). In addition, according to 6MWT after treatment, the distance traveled increased significantly in patients in group 1 by 31.2% versus 12.7% in group 2 ($p<0.05$).

Analysis of the structural and functional parameters of the heart after the course of treatment showed that no significant changes in the end-diastolic and end-systolic dimensions of the left ventricle (LV) occurred (table 1). An increase in the LV ejection fraction by 4.5% in the group of patients, in addition to baseline therapy, receiving a fixed combination of meldonium dihydrate and γ-butyrobetaine dihydrate, versus 1.9% in the comparison group ($p<0.05$). The tendency to decrease the LV myocardial mass index (LVMI) was determined by 6.2% in patients of group 1 and 2.0% in the comparison group.

Table 1

Changes in biochemical parameters in the course of treatment of patients with CHF and type 2 DM (M ± m)

Indicators	Group 1 (n = 30)		Group 2 (n = 32)	
	Before treatment	After treatment	Before treatment	After treatment
EDD, cm	5.42±0.05	5.37±0.05	5.47±0.08	5.46±0.07
ESD, cm	3.92±0.04	3.67±0.04	3.90±0.06	3.75±0.06
EF LV, %	47.0±0.4	49.1±0.3*	46±0.6	46.9±0.5
IMLV, g/m^2	147.16±6.62	138.04±4.23	149.14±7.74	146.13±4.19

Note: * - significance of differences in comparison to the original data.

There was an improvement in carbohydrate metabolism indices, a decrease in the insulin resistance index HOMA ($p>0.05$) and lipidograms, but significant changes were found between the groups only for triglyceride levels (Δ -15.1% vs. Δ -3.9%, p <0, 05, respectively). Previous studies have also mentioned the positive effect of meldonium on lipid metabolism in patients with type 2 DM [8]. Analysis of the effect of treatment on lipid peroxidation (LPO) and antioxidant status (table 2) showed that in group 1 there was a significant decrease of MDA by -22.3% ($p<0.05$), indicating a decrease in free- radical processes. Determination of SOD content was used as indicators of antioxidant protection, which, being a key enzyme of antioxidant protection, interrupts the chain of free radical processes at the beginning of its origin. An increase in SOD activity by 29.5% ($p<0.05$) was observed, which indicates activation of antioxidant protection of the body. In group 2, the dynamics of LPO and antioxidant protection were significant, but much ($p<0.05$) lower than in the main group: reduction of MDA by -11.2% and increase in SOD activity by 8.1%, $p < 0.05$).

Table 2

Change of lipid peroxidation (LPO) and antioxidant status during therapy

Indicator	Group	Baseline data	After treatment
MDA, mmol/l	1 (n = 30)	7.70±0.20	5.98±0.18*
	2 (n = 32)	7.52±0.21	6.68±0.15*
SOD erythr., %	1 (n = 30)	37.0±1.3	47.9±1.1
	2 (n = 32)	37.3±1.1	40.32±1.0*

Note: * - significance of differences compared to baseline data ($p<0.05$).

The combination of HF with type 2 DM is accompanied by the development of hypoxia as a universal pathological process associated with an injury of target organs in case of comorbid pathology and the development of mitochondrial oxidative phosphorylation disorders in any cell. In this case, the violation of oxidative processes with insufficient antioxidant protection system contributes to the development of oxidative stress. Disruption of mitochondrial oxidation leads to the suppression of conjugated phosphorylation and causes a progressive deficit of ATP, a universal energy source. A promising trend in the treatment of HF is cytoprotective therapy aimed at improvement of the efficiency of myocardium by optimization of the synthesis of adenosine triphosphate in cardiomyocyte mitochondria with lower oxygen consumption [7].

Clinical studies [5] have shown the efficacy and safety of therapy with the addition of meldonium in the treatment of HF. It has been noted that meldonium cytoprotector, which inhibits β - fatty acid oxidation and activates glucose oxidation (aerobic glycolysis) in ischemic myocardium, contributes to the improvement of tissue microcirculation [1].

In our study, it was found that in addition to basic therapy a fixed combination of meldonium dihydrate and γ-butyrobetaine dihydrate contributes to slowing of the progression of HF. Thus, more pronounced positive changes in clinical status and physical activity were observed during the therapy, which included a fixed combination of meldonium dihydrate and γ-butyrobetaine dihydrate.

Metabolic disorders during oxidative stress (activation of the polyol pathway, impaired free fatty acid metabolism, development of hypertriglyceridemia, endothelial dysfunction) lead to the occurrence of metabolic remodeling of the myocardium and impaired function of the left ventricle [1].

Therefore, additional administration of a fixed combination of meldonium dihydrate and γ-butyrobetaine dihydrate has a positive effect on both the oxidant and antioxidant systems, what is manifested in the inhibition of lipid peroxidation and activation of the compensatory processes that provide retention of free radicals to keep the normal level for metabolic processes in the cell.

Conclusion

Thus, 3-month therapy with fixed combination of meldonium dihydrate and γ-butyrobetaine dihydrate as a part of complex therapy of patients with chronic heart failure and type 2 DM improves clinical symptoms of patients, has a positive effect on the structural and functional parameters of left ventricle, glucometabolic parameters and imbalance of the oxidant-antioxidant system by increasing the activity of intracellular antioxidant enzymes.

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Реферати

ЛІКУВАННЯ ХРОНІЧНОЇ СЕРЦЕВОЇ НЕДОСТАТНОСТІ У ПАЦІЄНТІВ З ЦУКРОВИМ ДІАБЕТОМ 2-ГО ТИПУ

Біловол О.М., Князькова І.І., Богун М.В., Кузьмінова Н.В., Осовська Н.Ю.

Метою дослідження було вивчення впливу фіксованої комбінації мельдонію дигідрату та γ-бутиробетаїну дигідрату (МД+γ-БД) на клініко-гемодинамічні та глюкометаболічні параметри, а також показники оксидантно-антиоксидантнлого статусу у пацієнтів з хронічною серцевою недостатністю (ХСН) та цукровим діабетом (ЦД) 2 типу. Обстежено 62 хворих з ХСН та ЦД 2 типу. Після реєстрації вихідних даних усім пацієнтам призначали базисну терапію, з них 30 (1 група) додатково фіксовану комбінацію МД+γ-БД по 2 капсули тричі на добу протягом 3 місяців та 32 пацієнта увійшли у групу порівняння (2 група). Після лікування в 1 групі визначалось збільшення пройденої дистанції за даними теста 6-хвилинної ходьби на 31,2% і 1,9% ($p<0,05$) відповідно. Спостерігалось позитивні зміни глюкометаболічних показників. Відзначено зменшення активності процесів перекісного окислення ліпідів за рівнем малонового діальдегіду (Δ-22,3% у 1 групі, проти Δ-11,2% у 2 групі, $p<0,05$) і підвищення активності супероксиддисмутази еритроцитів (відповідно Δ29,5%

ЛЕЧЕНИЕ ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ У ПАЦИЕНТОВ С САХАРНЫМ ДИАБЕТОМ 2-ГО ТИПА

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Целью исследования было изучение влияния фиксированной комбинации мельдония дигидрата и γ-бутиробетаина дигидрата (МД+γ-БД) на клинико-гемодинамические и глюкометаболические параметры, а также показатели оксидантно-антиоксидантнлого статуса у пациентов с хронической сердечной недостаточностью (ХСН) и сахарным диабетом (СД) 2-го типа. Обследовано 62 больных с ХСН и СД 2 типа. После регистрации исходных данных всем пациентам назначали базисную терапию, из них 30 (1 группа) дополнительно МД+γ-БД по 2 капсулы три раза в сутки в течение 3 месяцев, и 32 пациента составили группу сравнения (2 группа). После лечения отмечено увеличение пройденной дистанции по данным теста 6-минутной ходьбы на 31,2% в 1-й против 12,7% во 2 группе ($p<0,05$) и фракции выброса левого желудочка (ЛЖ) на 4,5% против 1,9% ($p<0,05$), соответственно. Наблюдалось положительные изменения глюкометаболических показателей, уменьшение уровня малонового диальдегида (в 1 группе Δ-22,3% против Δ-11,2% во 2 группе, $p<0,05$) и повышение активности супероксиддисмутазы эритроцитов (соответственно Δ29,5%

проти 8,1%, p<0,05). Таким чином, додавання МД+γ-БД до комплексної терапії пацієнтів з ХСН та ЦД 2 типу покращує клініко-гемодинамічні і глюкометаболічні показники та коригує дисбаланс оксидантно-антиоксидантної системи.

Ключові слова: хронічна серцева недостатність, цукровий діабет 2 типу, структурно-функціональні зміни лівого шлуночка, перекісне окислення ліпідів, фіксована комбінація мельдонію дигідрату та γ-бутиробетаїну дигідрату.

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против 8,1%, p <0,05). Таким образом, добавление МД+γ-БД в составе комплексной терапии пациентов с ХСН и СД 2 типа улучшает клинико-гемодинамические и глюкометаболические параметры и корригирует дисбаланс оксидантно-антиоксидантной системы.

Ключевые слова: хроническая сердечная недостаточность, сахарный диабет 2 типа, структурно-функциональные изменения левого желудочка, перекисное окисление липидов, фиксированная комбинация мельдония дигидрата и γ-бутиробетаина дигидрата.

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INFLUENCE OF EXCESSIVE NIGHTTIME ACTIVITY ON THE RISK OF ISCHEMIC CEREBRAL STROKE EVENT AND ITS COURSE FEATURES

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Clinical neurological and neuroimaging examination of 300 patients with ischemic stroke was performed. The control group included 40 patients without signs of acute cerebral stroke (men - 21, women - 19) aged 46 to 76 years (mean age being 62.6 ± 10.2 years). The data obtained confirmed that the important role of excessive nighttime activity (ENA) is characteristic of all groups of patients, but 100% correlation is observed in patients with nocturnal strokes. In patients with ENA there are two peaks of blood pressure increase: - 9:00 and 21:00. Patterns of blood pressure disorders at night were as follows: 68.4% (n = 13) - night peaker, 26.3% (n = 5) - non dipper, 5.2% (n = 1) - dipper subtype. Against the background of an optimized stroke prevention program, the incidence of recurrent ischemic strokes was by 2.09 times lower than in the control group within 2 years. The present study results show the importance of ENA for the diagnosis and pathogenesis of acute ischemic stroke.

Key words: stroke, excessive nighttime activity, onset time, stroke risk, prevention.

The study is a fragment of the research project "Development and improvement of diagnostic and therapeutic tactics in patients with acute diseases of the abdominal cavity complicated by peritonitis", state registration No. 0118U001029.

The problem of acute ischemic stroke remains one of the main issues in modern medicine, being one of the main causes of disability and mortality of people in Ukraine and in the world. The issue of ischemic stroke treatment, regardless of the economic status of the country, remains expensive, therefore, the world's organizations focus on the therapeutic strategy to combat ischemic stroke, precisely on the prevention of this disease [6].

Importance of the ischemic stroke prevention brings to the forefront identification and unifying the whole variety of risk factors for cerebral ischemia [1]. However, at this stage, researchers have only agreed concerning unmodified (age, gender, race, etc.) and "internal" modified risk factors for cerebrovascular catastrophe (arterial hypertension, hypercholesterolemia, diabetes, etc.) [1, 2]. As for the "external" risk factors, researchers have not yet come to a single conclusion, separately identifying only the factors of bad habits [3, 5].

One of the important predictors of cerebral ischemia, which, however, is poorly described in modern literature, remains excessive nighttime activity (ENA). Excessive nighttime activity is a habitual permanent deformation of the day regime (social risk groups are doctors, taxi drivers, night shift workers). This factor plays a significant social role in many people's lives and can seriously affect the incidence of cerebrovascular pathology in many groups of population [4]. Studies have already confirmed that excessive nighttime activity shows a pronounced association with cardiovascular disease [7], diabetes mellitus and cancer, but the question of the impact on patients with acute ischemic stroke remains understudied [9].

The purpose of the work was to determine the extent and nature of the excessive nighttime activity factor's influence on the incidence of ischemic stroke and to study the efficacy of ENA prevention in association with the recurrent ischemic strokes incidence.

Materials and methods. To achieve this purpose, we performed a clinical neurological and neuroimaging examination of 300 patients who had acute ischemic stroke (men - 196, women - 104) aged 42 to 84 years (mean age - 65.2 ± 8.7 years). The inclusion criteria for this study were: the patients' age from 40 to 85 years; ischemic stroke focus verified by MRI; consent of the patient or his legal representative.

The control group consisted of 40 patients with no signs of acute stroke (men - 21, women - 19) aged 46 to 76 years (mean age being 62.6 ± 10.2 years) who were enrolled in the study to develop a social risk assessment scale for the cerebral stroke onset.

To assess the risk of a patient with acute ischemic stroke, preference was given to clinical examination methods directly at the patient's bedside. In this case, the patient with acute stroke (or his relatives in case of inability to contact) subject to a detailed survey and collection of premorbid anamnesis, followed by the use of the stroke social risk scale, which presents the severity of such cerebrovascular ischemia social risk factors in the patient as sleep disturbance, stress inducing environment, excessive nighttime activity, prolonged work with monitors, low physical activity, poor nutrition, bad habits (alcohol, tobacco smoking).

Assessment of the excessive nighttime activity severity was performed by collecting information on the nature and timing of the patient's work and rest according to the following criteria:

• 3 points - one or more of the following symptoms are observed: permanent work at night shift or work ending later than 3:00; severe nocturnal physical or mental activity more than 3 nights per week.

• 2 points - one or more of the following symptoms are observed: periodic work at night shift or end of work ending after 00:00; severe nocturnal physical or mental activity more than 1 night per week.

• 1 point - one or more of the following symptoms are observed: rarely work at night shift or end of work after 9:00 pm; severe nocturnal physical or mental activity more than 1 night per month.

• 0 points - work ends no later than 6:00 pm, severe nocturnal physical or mental activity is observed less frequently than 1 night per month.

According to the severity of one or another factor, each predictor is scored in points, denoting the highest grade of the score being 3 points, complete absence - 0 points. In the case of several signs indicating different degrees of the factor severity, the one considered to be of the highest risk is taken into account.

Statistical analysis was performed using Microsoft Excel. Average values (M) were calculated to provide adequate evaluation of the data. Statistical processing of absolute values was carried out according to conventional methods with the calculation of intensive and extensive indicators. The relationship between qualitative variables was determined using the Fisher's exact test, the difference between the average values was estimated using the non-parametric Mann-Whitney U-test. The difference at $p < 0.05$ was considered statistically significant (using the Bonferroni amendment).

Results of the study and their discussion. To identify the most important risk factors for ischemic stroke and the place of ENA among them, we analyzed the occurrence frequency of the most common stroke predictors not only among the main A1 group patients (n = 300) but also among the A2 control group (n = 40), which representatives had no ischemic stroke (table 1).

Table 1

Social risk factors and their incidence in patients with and without acute cerebral stroke (%)

Social factors	Patient groups	
	A1 n=300) %	A2 (n=40 %
Stress inducing environment	98.3*	10
Sleep disturbance	96.0*	5
Low physical activity	86.0*	11
Excessive nighttime activity	83.3*	5
Prolonged work with monitors	80.0*	35
Poor and irregular food intake	75.0*	5
Bad habits (alcohol, tobacco smoking)	71.0*	10
Marital status	70	84
Physical overload	62	45
Hyperthermia	57	40
Past lung infection	55	58
Unsystematic intake of antihypertensive drugs	54	39
Frequent voyages by train, air travels	46	23
Absence of sexual activity	37	18
Depression	18	10

* - statistically significant difference ($p < 0.05$).

The results of the analysis indicate a high diagnostic value of such a predictor as ENA, which ranked fourth (83.3%) in the list of the most frequently diagnosed risk factors for cerebral ischemia, while among the representatives of the control group the frequency of this factor detection did not exceed 5% ($p < 0.05$).

The mean ENA severity among the patients in the main group who showed this risk factor (n = 249) was 2.22 ± 0.16 points.

Having obtained confirmation of the ENA factor diagnostic value, we continued studying the effect of this predictor on the ischemic stroke course. In particular, we analyzed variants of the cerebral ischemia onset time against the background of excessive nighttime activity detected in patients of the main group (table 2). To optimize the analysis of the data obtained, all patients were divided into 3 groups according to the of day when the ischemic stroke occurred:

- group 1, which patients suffered from cerebral ischemia during the day (8: 00-14: 59);
- group 2, which patients had a stroke in the evening (15: 00-21: 59);
- group 3, which patients underwent ischemic stroke at night (22: 00-7: 59).

Table 2

Influence of ENA on the daytime period of ischemic stroke onset

Index	Patient groups		
	Daytime stroke (n=146)	Evening stroke (n=107)	Nocturnal stroke (n=47)
Excessive nighttime activity	123 (84.2 %)	80 (74.7 %)	47 (100 %)

The data obtained confirmed that excessive nighttime activity played an important role in all patient groups, however, there was a 100% correlation for patients with nocturnal strokes.

Based on the above information, we analyzed the ENA influence on the patterns of blood pressure (BP) fluctuations in patients within the day and night periods (fig. 1).

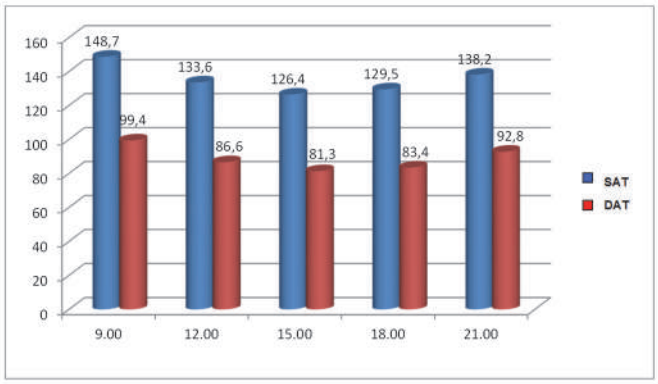

Fig. 1. Characteristics of systolic (SAT) and diastolic blood pressure (DAT) fluctuations among patients with acute ischemic stroke in whom ENA was observed.

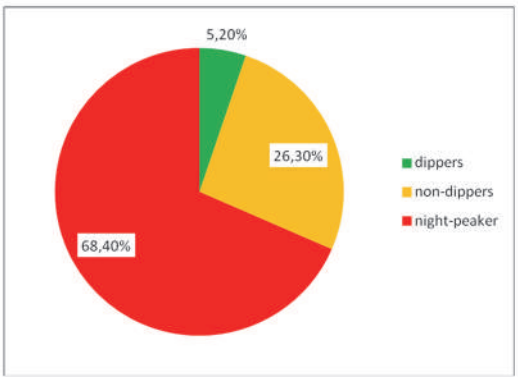

Fig. 2. Variability of nocturnal of blood pressure oscillation in patients with stroke that occurred against the ENA background (22: 00-7: 59)

The features of the blood pressure dynamics in patients with ENA lied in the fact that such patients had two peaks of blood pressure increase - 9:00 and 21:00 respectively. It is noteworthy, that such a model of blood pressure variability, according to our observations, is largely associated with the disturbance of the sympathetic system circadian activity and its forced stimulation in the night period due to excessive night activity, sleep disorders and active night consumption of alcohol in the history of the ischemic stroke social risk. Such a shift leads to a high risk of increased blood pressure during sleep and causes a pathological background for the cerebrovascular catastrophe onset during the night period.

Observation of nocturnal blood pressure oscillation in such patients only confirms our findings, since the spectrum of blood pressure oscillation patterns was as follows: 68.4% (n = 13) - night-peaker, 26.3% (n = 5) - non- dipper, 5.2% (n = 1) - dipper subtype (fig. 2).

The obtained data permit to conclude that for patients with ENA, in whom stroke was mostly observed at night, the main internal risk factor for the cerebral ischemia onset is arterial hypertension, which is confirmed by the results of the study on the influence of circadian rhythm disturbance on heart disease risk performed by Shanmugam V. with co-authors [7].

However, it should be emphasized that the peak of blood pressure in such patients occur during the night period, which contradicts the standard daily blood pressure fluctuations and, most likely, are associated with patients' lifestyle, which requires them to be excessively active during the night time of day (security, night duty, dispatcher's service, active nightlife, etc.) and thus causes the body to maintain a sufficient level of vigor and functionality due to chronic unnatural stimulation of the sympatho-adrenal system.

Important is the fact that, even after a person returns to normal daytime work and activity, such a pathological pattern of BP fluctuation continues to persist for a long time and, as a result, can lead to the

ischemic stroke onset at night. Similar trends are consistent with the findings of a research team led by Yadegarfar G., although the focus of their study was related to cardiovascular rather than cerebrovascular diseases [9].

Given the identified trends in the ENA impact on the ischemic stroke course, the following algorithm for the ischemic stroke prevention is possible for the following patients:

1) Antihypertensive therapy with assignment of complex (2 or more drugs) therapeutic regimens according to individual features. Given the subtype of "night-peaker" daily BP fluctuation, evening antihypertensive medication is mandatory and the main thing is that the drugs are given at a high dose before bedtime. In the absence of counterindications, the calcium antagonist group is preferred;

2) Continuous control over the patient's own heart rate;

3) Adequate antiplatelet therapy (100 mg of protected acetylsalicylic acid form in the evening after meals);

4) Prescription of statins in standard (20 mg) dosage according to the scheme "1 month of admission - 1 month without drug" under the control of liver sampling;

5) Use of drug-free (autotraining, exercise, meditation, swimming) and medicamentous (antidepressants, anxiolytics, sedatives) methods of stress relief, avoidance or elimination of stress inducing environmental elements;

6) Adequate oxygenation of the office space where the office equipment is located. Periodic breaks every 45 minutes (it is advisable to do exercises to remove the spasm of accommodation or just staying with eyes closed). During breaks it is necessary to perform a set of exercises for the neck;

7) Changing working conditions to adapt to the usual biorhythm with daytime activity and nighttime sleep, reducing episodes of nighttime activity, and a mandatory after-work rehabilitation period. Avoiding the use of stimulants to enhance activity at night;

8) Complete refusal of alcohol intake or a significant restriction on its consumption. It is permissible to consume alcohol in small or moderate amounts, which makes - 2 units of alcohol per day for men and - 1 unit for nonpregnant women;

9) Prevention of night hypoxia by room ventilation or oxygen therapy. Removal of the elements that can excite the nervous system at bedtime (stimulants, alcohol, videos, etc.). Normalization of sleep by physical methods (gymnastics, warm baths, autotraining) and medication (sleeping pills, sedatives). It is recommended to administer melatonin as a hypnotic and neuroprotective drug at the dose of 1-2 mg before going to bed with a gradual transition to the dose of 3-6 mg in case of failure in the circadian rhythms normalization.

Considering the ability of melatonin (N-acetyl-5-methoxytryptamine) and its metabolites to absorb a wide range of free radicals, researchers consider this compound as one of the most important antioxidants in the body. Acting as the mechanism of direct acceptor, this neurohormone is able to neutralize the effect of free radicals on the cell wall of neurons [8].

Assessment of the described prevention scheme efficacy in patients with stroke, which occurred against the background of the ENA, was performed according to a comparative data assessment of the main group, which included 24 patients with stroke against the ENA background, aged 52 to 83 years (mean age – 63. 6±1.3 years), who received prevention treatment according to the algorithm described above.

To control the prophylactic treatment efficacy, the control group was also formed including 23 patients with acute stroke, which also occurred in association with ENA, aged 51 to 84 years (mean age 64.1±1.5 years), but who were assigned a standard prophylactic regimen.

The efficacy of the presented preventive regimen was studied during the observation period of 2 years. During this period, only 2 recurrent cerebrovascular catastrophes occurred in the main group (8.3%). However, in the control group the situation with recurrent episodes of ischemia was worse - 4 cases (17.4%). Thus, in this case, the specialized scheme had a positive effect in reducing the incidence of recurrent ischemic strokes by 2.09 times compared to the control group, which confirms the results obtained by Wirtz P.H. and co-authors concerning the positive effect of melatonin use on blood coagulation properties [8] and the respective prevention of thrombosis.

In general, the results of our study are concordant with the general scientific trends outlined in the work of Douma et al. [3], but our data indicate a more pronounced dependence of daily fluctuations in blood pressure both on the complex effects of internal risk factors and excessive nighttime activity, which also was reflected in our other scientific works [1].

At the same time, a data from Fodor et al. [4] supports our findings that excessive nighttime activity has a particularly pronounced negative impact on the nocturnal time of onset of ischemic stroke, which has a more severe clinical course and a special nature of complications [1].

Conclusion

The results of the presented study indicate that ENA has significant diagnostic and informational value for determining the risk of ischemic stroke. The study of the excessive nighttime activity effect on the ischemic stroke course showed that this risk factor had a pronounced association with the stroke onset at night and led to a characteristic disturbance of blood pressure daily fluctuations patterns in patients with ischemic stroke. Preventive measures that included ENA correction resulted in a decrease of the recurrent ischemic strokes incidence by 2.09 times compared to the control group.

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Реферати

ВПЛИВ НАДМІРНОЇ НІЧНОЇ АКТИВНОСТІ НА РИЗИК ВИНИКНЕННЯ ТА ОСОБЛИВОСТІ ПЕРЕБІГУ ІШЕМІЧНОГО МОЗКОВОГО ІНСУЛЬТУ

Волосовець А.О., Зозуля І.С., Волосовець О.П., Савченко Д.С., Крамарева О.Г.

Проведено клініко-неврологічне та нейровізуалізаційне обстеження 300 хворих, що перенесли ішемічний інсульт. Контрольну групу склали 40 пацієнтів без ознак гострого мозкового інсульту (чоловіків - 21, жінок - 19) у віці від 46 до 76 років (середній вік 62,6 ± 10,2 року). Отримані дані підтвердили, що важлива роль надмірної нічної активності характерна для всіх груп пацієнтів, однак для пацієнтів з нічними інсультами спостерігається кореляція 100 %. У пацієнтів з ННА спостерігається два піки підвищення АТ - 9:00 і 21:00. Паттерни порушення артеріального тиску в нічний час виглядали наступним чином: 68,4% (n = 13) – night peaker, 26,3% (n = 5) – non dipper, 5,2% (n = 1) - підтип dipper. На тлі оптимізованої програми профілактики інсульту протягом 2 років серед пацієнтів у основній групі спостерігалося зменшення частоти повторних ішемічних інсультів у 2,09 рази в порівнянні з контрольною групою. Результати представленого дослідження показують важливість ННА для діагностики та патогенезу гострого ішемічного інсульту.

Ключові слова: інсульт, надмірна нічна активність, час початку, ризик інсульту, профілактика.

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ВЛИЯНИЕ ЧРЕЗМЕРНОЙ НОЧНОЙ АКТИВНОСТИ НА РИСК ВОЗНИКНОВЕНИЯ И ОСОБЕННОСТИ ТЕЧЕНИЯ ИШЕМИЧЕСКОГО МОЗГОВОГО ИНСУЛЬТА

Волосовец А.А., Зозуля И.С., Волосовец О.П., Савченко Д.С., Крамарева О.Г.

Проведены клинико-неврологическое и нейровизуализационное обследования 300 больных, перенесших ишемический инсульт. Контрольную группу составили 40 пациентов без признаков острого мозгового инсульта (мужчин - 21, женщин - 19) в возрасте от 46 до 76 лет (средний возраст 62,6 ± 10,2 года). Полученные данные подтвердили, что важная роль чрезмерной ночной активности характерна для всех групп пациентов, однако для пациентов с ночными инсультами наблюдается корреляция 100%. У пациентов с чрезмерной ночной активностью (ЧНА) наблюдается два пика повышения АД - 9:00 и 21:00. Паттерны нарушения артериального давления в ночное время выглядели следующим образом: 68,4% (n = 13) - night peaker, 26,3% (n = 5) - non dipper, 5,2% (n = 1) - подтип dipper. На фоне оптимизированной программы профилактики инсульта в течение 2 лет среди пациентов в основной группе наблюдалось уменьшение частоты повторных ишемических инсультов в 2,09 раза по сравнению с контрольной группой. Результаты представленного исследования показывают важность ЧНА для диагностики и патогенеза острого ишемического инсульта.

Ключевые слова: инсульт, чрезмерная ночная активность, время начала, риск инсульта, профилактика.

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IMPROVEMENT OF THE MEDICAL THERAPY REGIMENS FOR PATIENTS WITH II DEGREE GENERALIZED PERIODONTITIS AT THE STAGES OF CLOSED CURETTAGE AND COMPARISON OF THEIR EFFICACY

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Unmotivated use of antibiotics leads to the emergence of periodontopathogenic microorganisms strains resistant to them. It is necessary to develop modern regimens of drug therapy for treatment of inflammatory and dystrophic-inflammatory periodontal tissues diseases, which would not involve the local use of antibiotics. For medical treatment of patients with generalized II degree periodontitis, two regimens of drug therapy were suggested, one of which (No. 1) included local administration of an antibiotic and a non-steroidal anti-inflammatory drug in combination with oral administration of a proteolytic enzyme (serratiopeptidase) and the second regimen (No. 2) included only non-steroidal anti-inflammatory drug in combination with oral administration of a proteolytic enzyme. The regimens efficacy was assessed by the dynamics of hygienic and periodontal indices, as well as by the quantitative index dynamics of gum fluid and the presence of histamine and serotonin in it, as the inflammatory process mediators. Patients' recovery terms were also assessed. The performed clinical studies have proved the comparability of the drug therapy regimens 1 and 2 efficacy and permitted to recommend them for implementation in dental practice.

Key words: generalized periodontitis, closed curettage, gum fluid, histamine, serotonin.

The work is a fragment of the research project "Clinical and laboratory substantiation of the modern medical technologies used in the complex treatment and rehabilitation of major dental diseases" state registration No.0117U006451.

In recent years, the problem of antibiotic resistance, particularly in dental practice, has become increasingly urgent. Widespread availability, non-motivated use of antibiotic group drugs, irrational use in daily medical practice lead to emergence of new pathogenic microorganisms strains resistant to their effects [8, 9]. Therefore, modern dentists, researchers and practitioners are tasked to develop modern regimens of drug therapy for treatment of inflammatory and dystrophic-inflammatory periodontal tissues diseases, which would not involve the local use of antibiotics.

According to studies by Suda K.J., Calip G.S., Zhou J., 2019 [9] recommendations concerning the need for antibiotic prophylaxis before visiting a dentist for a specific category of patients, namely persons with pathological conditions that threaten with the subsequent onset and development of infectious endocarditis, were inappropriate. Estimating the studies results, the authors concluded that over 80% of the antibacterial drugs prescriptions for prevention of infectious complications before dental interventions were unreasonable, since most of the visits were either consultative or aimed at restoration of the teeth crown integrity. Dental procedures requiring the prevention of infectious endocarditis are all procedures including manipulations with gum or periapical tissues.

The list of analogous procedures also included manipulations including injury to the mucous membrane of the cavities and mouth. As a rule, antibiotic prophylaxis is prescribed to middle-aged and elderly people (55-72 years) before such dental manipulations. But despite this, dentists consider it necessary to prescribe antibiotics as a means of preventing secondary bacterial infection, regardless of the patients age [7, 8].

Given that the vast majority of patients with chronic generalized II degree periodontitis have concomitant pathology, mainly diseases of the gastrointestinal tract, cardiovascular, endocrine, kidney diseases, burdened allergic history, and combination of several somatic diseases, the rational antibiotic prevention should be carried out taking into account the side effects of the prescribed drugs (VolosovetsT.M, 2013).

Since widespread antibiotics of penicillin, fluoroquinolone and linkosamide groups have quite a few of side effects, a number of authors consider it advisable to limit the local use of these drugs and only to prescribe them if necessary and after recovery study of the periodontal flora for sensitivity [1].

The purpose of the work was to study the developed regimens efficacy for medical treatment of patients with II degree generalized periodontitis at the stages of surgical treatment (closed curettage) and to perform a comparative efficacy analysis of the scheme, which included local antibiotic application according to the scheme, where non-steroidal anti-inflammatory drugs were used in combination with proteolytic enzymes.

Materials and methods. To perform this task, we examined and treated 69 patients with generalized II degree periodontitis within the age category from 35 to 60 years. The diagnosis was established according to the periodontal tissue diseases classification by M.F. Danilevsky (1994).

Diagnosis was verified based of conventional clinical and paraclinical examination methods with periodontal PI index (Russel, 1956), PMA (Parma, 1960), and gum recession assessment (P.D. Miller, 1985). Oral hygiene was assessed using the GI index (Green - Vermillion, 1964). The diagnosis was confirmed by radiography.

Patients whose periodontal pockets depth did not exceed 3.8 mm were involved in the study. In order to monitor the inflammatory process dynamics, the amount of gum fluid, histamine and serotonin content were performed before, after and during the surgery [1, 4, 5]. Patients were divided into 2 groups, depending on the medication regimens used during the surgery and postoperatively. Group I (main) included 37 patients. Group II (comparison) included 32 individuals. The course of the disease in patients of the both groups I and II was not burdened with excessive exudation and purulent discharge from periodontal pockets. The control group consisted of 20 persons with intact periodontal who consulted a dentist for uncomplicated caries treatment.

For the sake of the comparative analysis correctness in terms of the treatment regimens efficacy, the patients' groups homogeneity assessment was performed before the study and their comparability on demographic and clinical grounds was considered. All patients at phase I of generalized periodontitis treatment received a standard set of local therapies, which included the supra- and sub-gingival calculus removal, correction of butts, and other traumatic factors [2, 6].

Drug treatment included oral irrigation with antiseptic solutions, antibacterial therapy for periodontal pockets, anti-inflammatory and reparative treatment. To consolidate the effect of treatment, patients were offered closed curettage of periodontal pockets. At the time of surgery, patients in both Group I and Group II had an equivalent clinical picture of the disease. In order to prevent the systemic septicemia development and to avoid bacterial endocarditis, patients were prescribed prophylactic oral administration of clindamycin 60 minutes before the assigned surgery in the dose of 600 mg [2]. The operation of closed curettage for both groups was performed in the area of four incisors in the lower jaw according to the conventional method and under local anesthesia with a solution of articaine hydrochloride and irrigation with a warm antiseptic solution (0.05% solution of chlorhexidine bigluconate). Patients of the experimental (I) and the comparison (II) groups received postoperative drug therapy according to our suggested and developed regimens, which included oral administration of the serratiopeptidase drug [3]. Difference between the drug therapy regimens lied in the fact that Regimen 1 included local application of clindamycin phosphate-containing adhesive film, whereas Regimen 2 did not include local antibiotic use.

Regimen No. 1

At the first stage of the surgery:

1. Rinsing the periodontal pocket with a warm solution of antiseptic (0.5% aqueous solution of sodium mefenaminate);
2. Instillation into periodontal pockets in the surgery intervention area (mefenamic acid, vinylin (Mefenate ointment) - 2.0; zinc oxide - 2.0), prepared immediately before use;
3. Application of an adhesive film containing clindamycin phosphate (Diplen-Denta K);
4. Prescription of serratiopeptidase for oral administration at the dose of 10 mg three times a day for 40 minutes before meals for 8 days.

The postoperative treatment of group II (comparison group) patients was performed according to the following scheme:

Regimen No. 2

1. Rinsing the periodontal pocket with a warm solution of antiseptic (0.05% solution of chlorhexidine bigluconate);
2. Instillation into periodontal pockets in the surgery intervention area (mefenamic acid, vinylin (Mefenate ointment) - 2.0; zinc oxide - 2.0), prepared immediately before use;
3. Adhesive bandage (Reso-pac);
4. Prescription of serratiopeptidase for oral administration at the dose of 10 mg three times a day for 40 minutes before meals for 8 days.

The control examination of groups I and II patients was carried out on the second day after the surgery. The term of the second surgery stage depends on the complaints and the clinical picture of the operation area.

At the second stage of surgery, the suggested regimens were supplemented with vitamin preparations (retinol acetate 3.44%, tocopherol acetate 10%) and reparative drugs (dental gel containing deproteinized calf blood hemoderivate). Patients in both groups I and II were given recommendations on oral hygiene. The treatment efficacy was assessed by the dynamics of hygienic and periodontal indices, as well as indices of the gum fluid dynamics and its histamine and serotonin content as biochemical markers of the presence and intensity of inflammatory process in the marginal periodontium and by terms of recovery.

Results of the study and their discussion. To assess the post-operative drug therapy regimens efficacy, clinical observations were made on the second day after the first intervention. Patients' complaints, periodontal dressing condition, presence or absence of exudation were assessed. Given that drug therapy regimens for the both groups included sodium mefenaminate as an analgesic and anti-inflammatory agent and serratiopeptidase, which accelerates the penetration and activity of this drug, the vast majority of patients in both groups did not complain of pain. In addition, the adhesive bandage (Resopac) contains "Mirra" drug, which enhances internal energy metabolism, stimulates cell regeneration and blood microcirculation [6].

3 persons (8.1%) in group I and 2 persons (6.25%) in group II complained of mild pain. Slight edema and exudation were observed in 2 people in group I (5.4%) and in 1 person in group II (3.12%). In the absence of pronounced complaints of pain and a satisfactory clinical picture in the surgery site, the second surgery stage was performed on the third day after the first stage.

After the second stage of closed curettage, patients in the both groups I and II received drug therapy according to the treatment regimens selected for each group, respectively. Biochemical studies of gingival fluid on histamine and serotonin content to assess the intensity of the inflammatory process were performed on the second day (after stage I of the closed curettage) and on day 7 (after stage II). The study results on the dynamics of histamine and serotonin content in the gum fluid in groups I and II patients are presented in tables 1 and 2.

Table 1

Dynamics of histamine content in gum fluid (μg/3 min) in patient groups I and II before treatment, on the third day after the first stage and on the seventh day after the second stage of closed curettage

Group	Intact periodontuim	Indices before treatment	On the 3rd day after stage I	On the 7th day after stage II
Group I (n=37)	_	*0.020±0.0009	* 0.026±0.0009	*0.012±0.0008
Group II (n=32)	_	*0.017±0.0006	*0.024±0.0009	*0.011±0.0007
Control group (n=20)	0.007±0.0005	-	-	-

Note: * - reliability of differences in gum fluid histamine content prior to treatment and at different times after closed curettage ($p \leq 0.05$)

The data on the histamine content dynamics in the gum fluid before treatment, on the third and the seventh day after the surgery indicate an increase in the inflammatory process and exudative phenomena in periodontal tissues in response to traumatization. Moreover, on the second day, the histamine content significantly exceeds the respective indices before and within the shortest terms after the treatment.

The data on the serotonin content dynamics also confirm the increase in the inflammatory process intensity after the first stage of surgery, and the quantitative indices of serotonin content in the gum fluid significantly exceeded the quantitative indices of histamine (table 2), which may indicate the initiation of the inflammatory process in the marginal periodontium.

However, after the medical treatment, at the stage of healing, the severity of the inflammatory process decreased and quantitative indices of physiologically active substances, histamine and serotonin, in groups I and II were closer to those of intact periodontal patients.

Table 2

Dynamics of serotonin content in gum fluid (μg/3 min) in patient groups I and II before treatment, on the third day after the first stage and on the seventh day after the second stage of closed curettage

Group	Intact periodontuim	Indices before treatment	On the 3rd day after stage I	On the 7th day after stage II
Group I (n=37)	-	* 0.024±0.0013	*0.034±0.0012	*0.013±0.0003
Group II (n=32)	-	*0.019±0.0002	*0.031±0.0007	*0.011±0.0004
Control group (n=20)	0.009±0.0006	-	-	-

Note: * - reliability of differences in gum fluid serotonin content prior to treatment and at different times after closed curettage ($p \leq 0.05$)

The respective indices of histamine and serotonin content on the second day after stage I and on the 7th day after stage II in patients of both the main group and the comparison group had no significant difference between them, which may indicate the comparative efficacy of drug treatment regimens No. 1 and 2. After the first stage of closed curettage, which was accompanied by appropriate medical treatment, complications were not detected in either the main group or in the comparison group.

After the second stage of closed curettage, inflammatory exudation and pain in the surgical intervention site disappeared for 2-3 days. As a rule, on the third day the signs of a pronounced inflammatory process disappeared. The recovery terms had no reliable differences in both groups and amounted 4.6±1.16 days in patients of group I and 4.1±1.12 in patients of group II, respectively, as evidenced by the normalization of clinical indices presented in table 3.

Table 3

Dynamics of clinical indices in patient groups I and II before and within the shortest terms after treatment

Indices	Control group (n=20)	Group 1 (n=37)		Group 2 (n=32)	
		Before treatment	After treatment	Before treatment	After treatment
IG	0.32±0.08	2.28±0.05	0.43±0.04*	2.33±0.04	0.36±0.08*
PI	0.1±0.002	2.25±0.15	0.67±0.06*	2.44±0.05	0.54±0.07*
Gingival bleeding index (SBI)	-	2.09±0.56	1.18±0.18*	1.82±0.37	1.01±0.21*
PMA index	6.31±0.61	34.89±1.38	8.10±2.18*	31.19±1.54	7.12±1.64*
Gum fluid amount	0.42±0.02	1.8±0.14*	0.8±0.05*	1.4±0.086	0.6±0.05*

Note: * - reliability of differences in the indices values before and after the performed treatment ($p \leq 0.05$).

In general, results of the above study are consistent with the data obtained by a number of researchers (Petrushanko T.O., Skrypnikov P.M., Litovchenko I.Y.u, Kolomiyets S.V. 2014), who studied the efficacy of the sticking patch containing "Mirra"drug. Studies were performed at the Ukrainian Medical Stomatological Academy According to the researchers, the patch eliminates congestive phenomena, improves microcirculation, provides optimal conditions for periodontal tissues regeneration and prevents possible complications in the postoperative period [6].

Efficacy assessment of the serratiopeptidase drug used in complex treatment regimens for patients with periodontal tissue pathology, especially after invasive intervention, also confirms the data obtained by the researchers (Voloshina L.I., Rybalov O.V., Skikevych M.G., Sokolova N.A. , 2014), who used this drug to treat lesions associated with impaired microcirculation, innervation and metabolism due to traumatic injuries of the oral mucosa in combination with infectious agents [3].

Conclusions

1. Medical treatment regimens proposed and developed by us are quite efficient as evidenced by the positive dynamics of the gum fluid amount in patients in both I (main). and II (comparison) groups. The content of histamine and serotonin in the gum fluid of patients in the both groups also had positive dynamics and on the seventh day after the second stage of surgery was close to the quantitative indices of persons with intact periodontium. There were positive changes in the hygienic condition of the oral cavity, decrease in digital data of gingival bleeding indices, PMA, and the recovery terms reduced.

2. Drug regimens No. 1 and No. 2 are comparable in efficacy, because when applied, quantitative biochemical parameters, periodontal and hygiene indices both in group I (main). and in group II (comparison), showed no significant difference at both the operative and the recovery stages. The recovery terms in patients of groups I and II did not differ significantly.

3. Our study shows that in the absence of expressed patients' complaints and a satisfactory clinical picture of the surgery site, provided that drug therapy is properly selected, local use of antibiotics can be avoided to prevent the formation of pathogenic microflora antibiotic-resistant strains in patients' oral cavities.

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Реферати

УДОСКОНАЛЕННЯ СХЕМ МЕДИКАМЕНТОЗНОЇ ТЕРАПІЇ ПАЦІЄНТІВ ІЗ ГЕНЕРАЛІЗОВАНИМ ПАРОДОНТИТОМ ІІ СТУПЕНЯ НА ЕТАПАХ ПРОВЕДЕННЯ ЗАКРИТОГО КЮРЕТАЖУ ТА ПОРІВНЯННЯ ЇХ ЕФЕКТИВНОСТІ

Волосовець Т.М.. Кравченко А.В.

Невмотивоване використання антибіотиків призводить до виникнення стійких до них штамів пародонтопатогенних мікроорганізмів. Необхідно розробити сучасні схеми медикаментозної терапії для лікування запальних та дистрофічно-запальних захворювань тканин пародонта, які не передбачали б місцевого застосування антибіотиків. Для медикаментозного лікування пацієнтів із генералізованим пародонтитом ІІ ступеня запропоновано два режими медикаментозної терапії, один з яких (№ 1) включав місцеве введення антибіотика та нестероїдного протизапального препарату у поєднанні з пероральним прийомом протеолітичного ферменту (серратіострептидази), а другий режим (№ 2) включав лише нестероїдні протизапальні препарати в поєднанні з пероральним прийомом протеолітичного ферменту. Ефективність режиму оцінювали за динамікою гігієнічних та пародонтальних показників, а також за кількісною динамікою індексу ясенної рідини та наявністю в ній гістаміну та серотоніну як медіаторів запального процесу. Також були оцінені терміни одужання пацієнтів. Проведені клінічні дослідження довели порівнянність ефективності режимів медикаментозної терапії 1 та 2 та дозволили рекомендувати їх для впровадження в стоматологічну практику.

Ключові слова: генералізований періодонтит, закрити1 кюретаж, ясенна рідина, гістамін, серотонін.

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УСОВЕРШЕНСТВОВАНИЕ СХЕМ МЕДИКАМЕНТОЗНОЙ ТЕРАПИИ ПАЦИЕНТОВ С ГЕНЕРАЛИЗОВАННЫМ ПАРОДОНТИТОМ ІІ СТЕПЕНИ НА ЭТАПАХ ПРОВЕДЕНИЯ ЗАКРЫТОГО КЮРЕТАЖА И СРАВНЕНИЯ ИХ ЭФФЕКТИВНОСТИ

Волосовец Т.Н, Кравченко А.В.

Немотивированное использование антибиотиков приводит к возникновению устойчивых к ним штаммов пародонтопатогенных микроорганизмов. Необходимо разработать современные схемы медикаментозной терапии для лечения воспалительных и дистрофически-воспалительных заболеваний тканей пародонта, которые не предусматривали бы местного применения антибиотиков. Для медикаментозного лечения пациентов с генерализованным пародонтитом ІІ степени предложены два режима медикаментозной терапии, один из которых (№ 1) включал местное введение антибиотика и нестероидных противовоспалительных препаратов в сочетании с пероральным приемом протеолитического фермента (серратиострептидазы), а второй режим (№ 2) включал только нестероидные противовоспалительные препараты в сочетании с пероральным приемом протеолитического фермента. Эффективность режима оценивали по динамике гигиенических и пародонтальных показателей, а также по количественной динамике индекса десневой жидкости и наличию в ней гистамина и серотонина как медиаторов воспалительного процесса. Также оценивались сроки выздоровления пациентов. Проведенные клинические исследования доказали сопоставимость эффективности режимов медикаментозной терапии 1 и 2 и позволили рекомендовать их для внедрения в стоматологическую практику.

Ключевые слова: генерализованный пародонтит, закрытый кюретаж, десневая жидкость, гистамин, серотонин.

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METHODOLOGICAL PRINCIPLES OF THE CAUSAL-SYSTEM INJURY PROCESS MODELING

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The method of causal systemic modeling of the natural relations of the traumatic process is developed on the basis of practical examinations of the archive of the Regional Bureau of Forensic Expertise (FE). Constructing the dependence of the trauma process of FE has been developed by combining traditional causal and modern systemic approaches. Causal systemic modeling of temporal pattern linkage (dependence) of the trauma process allowed: differentiate between causal and non-causal relevant factors of the full cause system; diagnose relationships: cause and effect (CER) conditionality relationships (CR), link states (LS); determine the causal roles of the relevant factors. The method of quasi-formal reproduction was developed in the plane of the text of the simulated objects of the traumatic process ensured the documentary recording of information about the relevant properties of the expert objects. Obtained objective system data on the properties of objects depending on the trauma process optimized forensic assessments of the role of objects and trauma events.

Key words: general methodology, common cause-system modeling, relevant forensic system objects, dependency verification, quasi-formal model reproduction.

The work is a fragment of the research project "Early diagnosis of dysplastic, metaplastic and neoplastic changes in the pathology of the gastrointestinal tract, respiratory, urogenital and neuroendocrine system", state registration No. 0117U000001.

Forensic medicine is a multidisciplinary field of science and reflects the realized integration of various scientific knowledge, such as medicine, biology, chemistry, forensics and many other specialties. Forensic examination (FE) of relatively basic science of forensic medicine is the process of scientific and practical knowledge to apply scientific theories and concepts to address issues of law enforcement and the court. Logical and retrospective modeling operations are one of the current topical analytical trends in the

methodology of designing forensic communication in the traumatic process. Diagnosis of "causes of violent and nonviolent death" (see "Specialty Passport 14.01.25 - Forensic Medicine") requires the development of methods of applied general methodology with the use of FE tasks. This is possible taking into account the positions of modern philosophical concepts of causality, the general theory of systems, and the achievements of which must be use in the construction of the methodology of FE. The authors of the fundamental Forensic Forensics O. V. Filipchuk and O. M. Gurov (2013) [3] reasonably define methodology as the doctrine of scientific methods of cognition, the set of research methods applied in a specific science (FE) according to the specifics object under study.

In general, applied logical and philosophical tools of general methodology determine the organization of professional scientific activities and practitioners in specific sciences, including in the FE.

The real methodological work in science takes place in a special cognitive movement between special science and modern philosophy. By this time, the analysis depending injury during medical examiner conducted by orthodox causal analysis. The governing documents of the FE do not contain substantive arguments from the standpoint of scientific systemic knowledge regarding the substantiation of regulatory requirements, which leads to fundamental errors in the results of forensic experts. Thus, according to the current normative “Rules of Forensic Determination of the Severity of Physical Injury”, approved by the order of the Ministry of Health of Ukraine No. 6 of 17.05.1995, experts, by retrospective modeling, verify the cause and cause effect relationship (CCR), but do not determine the causal the role of many causative factors in the dependency chain. For example, they often treat “failure to provide medical care” as a “cause” of a “fatal outcome”. This kind of reasoning, without reservation because of the disclosure of the conditionality of the actual objects, is unjustified from a scientific point of view. Forensic literature and regulatory documents have suggested, for example, contradictory terms such as “accidental causation”, “major causes” and “minor causes”. Examples: The forensic expert concludes that “a fracture of a long tubular bone is the cause of fat embolism” or “damage to the trunk vessels of the limb is the cause of hemorrhagic shock”. These interpretations, with all their accessibility, cannot be scientifically correct, because they do not reveal the essential bases, sources of causation. In modern causal (conditionally-causal) analysis of the constructed system of the full cause above the first example, the base, the source of the cause is the interaction (source of the cause) adipose tissue of the limb (the first causative factor) with the bloodstream of the diaphysis of the bone (the second causative factor) and, as a consequence, the insertion of fat cells into the common circulatory network, fat embolism. In the second example, hypovolemia of the bloodstream (causative factor) and the reaction to this process by the nervous and humoral systems (the second causative factor) in the interaction (source of the cause) form a hemorrhagic shock (consequence).

It is scientifically proven that the use of purely causal analysis does not reveal all aspects of causal assessments of forensic objects in the chain of dependence of trauma – it is necessary to expand logical research toolsof causally consequential relationship (CCR) (Mishalov V. D, Bachinsky V. T, Krivda G. F, Filippchuk O. V, 2015) [3]. V. T. Voronov (2019) [1] substantiates the idea of supplementing the causal analysis of dependence with a *systematic approach* using the method of causal system modeling.

The purpose of the work was to determine the feasibility of the method of joint cause-system modeling of forensic objects in the conditionality of the trauma process.

The methodology of joint cause-system modeling of objects, depending on the trauma process, will provide forensic experts with the logical tools of verification in CCR, both the structure of the full cause and the relevant conditions.

Materials and methods. The material of the study was the archival observations of the Expert Opinion of the Vinnytsya Regional Bureau of Forensics for four years of violent deaths from injuries. Investigated natural relationships in traumatic processes and selectively constructed 10 models of common cause-systemic determinations (deterministic natural relationships, dependencies).

The study CCR regarding FE cause and method of system modeling using causal analysis, which combined with a systematic approach. At the same time, they used textual illustrations of simulated CCR objects using the quasi-formal reproduction method.

Results of the study and their discussion. The complex solution of medical and biological and forensic issues in the study of CCR in the traumatic process necessitated the development of a special methodology for modeling systems of dependencies, based on both the principles of the theory of general human pathology and general scientific philosophy of determinism.

G.V.F. Hegel introduced the philosophical category of conditions in the system of categories he developed in the Science of Logic, and for the first time determined their immanence in real determination, along with the reason for the full reason. This is how the CCR and the conditionality relationship were delineated. Differentiating the role of cause and conditions in the cause of consequence – bodily harm – is

the most important area of work of the expert in the modeling of forensic determinations. The relevant conditions of the full cause system act either as necessary for the action of the cause of the full cause or as necessary for the production of the consequence.

Our study proves that every necessary condition of action of a causal basis in combination with a cause is a necessary condition for producing the consequence and the presence of all the necessary conditions for the action of the cause together with the cause constitute a sufficient condition for producing the effect – bodily injury. Therefore, determinant objects – carriers of conditions form *the system of the full cause* of bodily injury in two causal determinations.

Forensic expert in retrospective study (modeling) of the process of injury with lethal consequences should have complete, accurate and thorough information about the circumstances of the event, compare them with the data of the analysis of the corpse section, differentiate and make correct conclusions in general about the cause and conditions of the traumatic process [4].

External conditions, as revealed in the work, play a special role. Investigated forensic expert consequence – personal injury, pathological condition, traumatic process – is the result of the emergence and development of naturally related material changes in the body. In doing so, the consequence concentrates both the factors behind the cause formation and the various factors, the constituent conditions, which also form the full cause but are external to its foundation.

From the results of our study, it follows that purely causal modeling, by itself, as a study of a particular type of determination, cannot give a complete explanation for the deterministic relationship.

A common variant conditional determination represents the connection states (CR). Unlike causality, previous states do not produce, but consistently change subsequent states. The CR provides for the mapping of the conditions in the logical form of a conditional judgment (sufficient prerequisites) or unspecified (prerequisite conditions).In the temporal chain of phenomena, as confirmed by this study, CR forms a causal evolutionary form of causation (determination) of the traumatic process.

Forensic study of trauma is especially difficult in the presence in the body of such individual physiological or pathological features, which can significantly affect changes in the nature of the clinical and morphological picture of trauma and complications. The following is a causal analysis of the case from expert practice in quasi-formal textual reproduction (model 1).

Story. After extraction of the tooth from patients with hemophilia, bleeding from damaged cell vessels occurred, with the subsequent development of massive blood loss, hypovolemia and hemorrhagic shock. The resolution of questions about the cause of death and the causal evaluation of forensic events (objects) are important for the legal interpretation of the provision of medical care. In this case, the forensic medical examination should diagnose the nature of the addiction and give the status of the reasons or conditions to all relevant objects of the dependency of the traumatic.

*Model 1***,** Evolutionary Multilink Causality: process.

CCR -1 *C1*

[SO→R1← blood vessels] ⊥ {[SO*]+[tooth *]+[damaged blood

hemophilia vessels*]}- →*CR -1*

CR -1 *CCR-2* *C2*

- → [damagedbloodvessels *→R2←blood under pressure]⊥[bleeding]-→

hemophilia →*CR -2*

CR -2

--→ [(a)bleeding]-→[(б) bleeding * continuous]- --→ --→- --→ --→→ *CR -3*

↑hemostasis disorders

↑ hemophilia

CR -3 *CCR -3* *C3*

- → -→[bleeding *→R3←hemostasis disorders] ⊥ [massive blood loss]

↑ hemophilia -→*CR -4*

CCR-4 *C4*

CR -4- →[massive blood loss.→R4←neurohumoral vasc. factors] ⊥ [shock]

↑ hemostasis disorders

↑ hemophilia

SO – solid object CR – state relationship

C – Consequence R – reason

As a result of the causal factors interaction (reason R1) – solid objects (SO) – the dentist's tools, carious tooth – and blood vessels, a certain consequence (C1) is caused in the form of objects summative

formation: {SO * + tooth * + defects of the cell vessels walls *}. The star symbol shows the changes (damage) at the infliction time (SO, tooth, blood vessels). This creates a single-link model that demonstrates the type of interaction when there is a need and sufficiency to change the starting interaction objects as separate consequences. It is important to emphasize that at this stage the individual factor of the organism - hemophilia is a concomitant factor, which is optional and insufficient, neither for the consequence occurrence in causation-1, nor for the system full injury causal basis. The «⊥» marks the causation-1 between cause and effect. It should be noted the transitive nature of the cause between causation -1 and causation-2: in both dependencies, the causes of R1 and R2 are formed by the necessary and sufficient systems of causal factors regarding the corresponding consequences of C1 and C2.

"Damage to the cell wall" and "blood under pressure" are causal factors that formed at the stage of CR-1 state changes and together manifest in interaction the specific R2 cause, which directly causes, revolutionary in causation-2 consequence – "bleeding". In addition to the quasi-formal display (see model), this reason can be formulated verbally as "balancing blood pressure in damaged vessels with the external environment". At this juncture, hemophilia is still an optional condition, both as a consequence of C2 and of causative factors in causation-2.

The cause of R2 also generates the evolutionary qualitative certainty of the bound states "(a) - (b)": CR -2 and CR -3 of the cellular bleeding process, which manifests clinically to a certain stage as normal bleeding in a healthy person, adequate to the degree of vascular damage and intravascular blood pressure.

It is known that in a healthy person the vascular-platelet coagulation mechanism provides prevention and arrest of bleeding from small blood vessels by their primary spasm, swelling and adhesion, adhesion of platelets to the sites of damage to the walls of blood vessels and to the wound surface, as well as further obstruction of bleeding vessels with platelet aggregates, and strengthening (reinforcement) of platelet cortex with fibrin.

On the contrary, when shown in **model 1** variant of the bleeding process development in a patient with hemophilia, the factor of homeostasis disturbance realized, and the bleeding acquires a continuous, gradient nature.

In *model 1*, at the stages of CCR-1, CCR-2 and the onset of CR-3, the abstract factor of homeostasis disturbance in hemophilia is beyond the causal and conditional factors of dependence. In the future, the factor of hemophilia of the first order actualizes the factor of the order – disturbance of hemostasis, from the condition of latent to actual. The further disturbance of hemostasis at the stage of the CR-3 states is already a causal factor in the CCR-3 cause of R3 and the consequence of C3. Further, massive blood loss of the CR-4 state, in conjunction with neurohumoral and vascular factors, forms the cause of R4 in CCR-4, which gives rise to the result – C4 hemorrhagic shock.

It should be note that CR2 at the bleeding stages (a) and (b) does not interrupt, but prolongs during the time of causing in causation-2, forming a fragment of transitive determination. In the course of bleeding, each stage of which is an open system, the specified direction of morphogenesis is support by streams of substance, energy, information, which "flow" from the external systems of organism tissue and organ objects and provide material and information component of the determinative communication systems of bleeding stages. Thus, CR in the development of the system is realized with sufficient grounds: the initial conditions of system formation (causal basis and external conditions) and the material nourishment of development in time of an open system.

Thus, at a certain point in time of the bleeding process manifests the pathogenic factor of the patient with hemophilia body – hemostatic disorder, which is subsequently transformed into a causal factor of the full cause of R3 from a relevant condition. The reason for the R3 model formula can be formulated in natural language verbatim as a "continuous bleeding event".

Some complexity of expert analysis, for example, in cases of evaluating the provision of medical care, is to establish a specific time when the status of a factor changes from the necessary insufficient concomitant hemophilia to the causative factor of cause R3 and the effect of causation-3 - massive C3 blood loss. Such a diagnostic opportunity exists when proving a definite time clinic of continuous bleeding.

Based on the results of the *causal systematic analysis*, the recommendations of the current Forensic Rules (1995) on conditional leveling of an individual peculiarity of an organism – hemophilia from a number of relevant objects in assessing the severity of traumatic tooth extraction, appear to be contradictory. First, from the objective side, the causal analysis shows that the signs of "direct" or "indirect" connections provide grounds not for verifying the cause, but only for determining the commission of systemic action by the conditions, i.e. elucidation of conditionality. Secondly, from a legal point of view, the absence of an expert conclusion of the fact of hemophilia in the text may be incorrect in case of subjective intention to cause injury to a sick person.

Thus, as evidenced by causal systemic modulation (model 1), hemophilia does not cause, but does not accompany indifferently (conditionality), but indirectly, as one of the necessary conditions of trauma adverse effects – massive blood loss, hypovolemia and hemorrhagic shock – models of multi-chain determination systems. Hemophilia, as a permanent individual state of the organism, does not in itself determine the cause of the massive blood loss traumatic process, but identifies at certain stages of bleeding an object factor – a condition of disturbance of hemostasis. Violation of hemostasis and continuous bleeding from damaged blood vessels are the causal factors that, when interacting, manifest the cause of relatively massive blood loss (consequence). Traumatic tooth extraction and damage to the blood vessels are causal factors that manifest with necessity and sufficiency the cause of the bleeding (consequence). However, between traumatic tooth extraction and hemorrhagic shock, causation is absent, and is determined by conditionality. Between hemophilia and hemorrhagic shock, causation and conditionality are absent.

In the systems of structures of the full cause, as the research proves, the interconnection of forensic objects with each other determines different kinds of regular object relations, which in interaction underpin pathological processes in the body, which underlie the mechanisms of trauma formation and complications and, in general, optimize expert and investigative evaluations of objects (events) of reality.

Conclusions

1. The causal modeling of regular communication in the media has been studied very often and has been relevant for many years, but remains relevant to many issues that have not been theoretically and practically resolved. This stagnation is objectively related to the limitation of the use of general methodology methods for the analysis of trauma dependencies. In the guidance of forensic experts, experts are encouraged to use only traditional orthodox causal analysis and to exclude from this analysis some causal factors of dependence.

2. Joint causal system modeling by the expert of the circuit of temporal pattern connection of the traumatic process allows in retrospection: to differentiate between causal and non-causal relevant factors of the system of the full cause, including causal determinants, conditions relevant, conditions necessary and not sufficient, conditions sufficient and insufficient; diagnose regular relationships: cause and effect (causation), conditionality (C), states (S); to determine localization, sequence in time and space of relevant factors chain dependence, their location, causal roles in the traumatic process.

3. Issues that are solved by causal modulation from an objective perspective greatly expand the expertise and investigative capabilities of causal analysis and evaluation of the objects and circumstances of events.

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Реферати

МЕТОДОЛОГІЧНІ ЗАСАДИ ПРИЧИННО-СИСТЕМНОГО МОДЕЛЮВАННЯ ПРОЦЕСУ ТРАВМИ

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Метод спільного причинно-системного моделювання закономірною зв'язку травматичного процесу сконструйований на матеріалі практичних експертиз архіву обласного бюро судово-медичної експертизи (СМЕ). Конструювання закономірною зв'язку (залежності) процесу стосовно СМЕ розроблено шляхом об'єднання традиційного причинного і сучасного системного підходів. Спільне причинно-системне моделювання залежності між об'єктами травматичного процесу дозволило: диференціювати причинні і Непричинні релевантні фактори системи повної причини; діагностувати зв'язку: причинно-наслідкові (ПСС), обумовленості (ОС), станів (СС); визначити роль чинників в процесі травми. Розроблений

МЕТОДОЛОГИЧЕСКИЕ ОСНОВЫ ПРИЧИННО-СИСТЕМНОГО МОДЕЛИРОВАНИЯ ПРОЦЕССА ТРАВМЫ

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Метод совместного причинно-системного моделирования закономерной связи травматического процесса сконструирован на материале практических экспертиз архива областного бюро судебно-медицинской экспертизы (СМЭ). Конструирование закономерной связи (зависимости) процесса применительно СМЭ разработано путем объединения традиционного причинного и современного системного подходов. Совместное причинно-системное моделирование зависимости между объектами травматического процесса позволило: дифференцировать причинные и непричинные релевантные факторы системы полной причины; диагностировать связи: причинно-следственные (ПСС), обусловленности (ОС), состояний (СС); определить роли факторов в процессе травмы.

в площині тексту метод квазіформальной репродукції модельованих об'єктів забезпечив документальне фіксування інформації про релевантних властивості експертних об'єктів. Отримані об'єктивні системні дані про каузальних властивості об'єктів оптимізували експертні оцінки об'єктів і подій.

Ключові слова: загальна методологія, спільне причинно-системне моделювання, релевантні судово-медичні об'єкти системи, верифікація зв'язку, квазіформальная репродукція моделі.

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Разработанный в плоскости текста метод квазиформальной репродукции моделированных объектов обеспечил документальное фиксирование информации о релевантных свойствах экспертных объектов. Полученные объективные системные данные о каузальных свойствах объектов оптимизировали экспертные оценки объектов и событий.

Ключевые слова: общая методология, совместное причинно-системное моделирование, релевантные судебно-медицинские объекты системы, верификация связи, квазиформальная репродукция модели.

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MAIN GOALS OF PSYCHOLOGICAL REHABILITATION OF MILITARY SERVICEMEN IN THE POLTAVA REGION UNDER THE PRESENT CONDITIONS

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The outbreak of the war in the East of Ukraine has created new challenges for the psychological rehabilitation system. The purpose of the work was to analyse the main goals of psychological rehabilitation of military servicemen in the Poltava region in present conditions. The reports of the Rehabilitation Department of the Public Institution "Kremenchug Regional Clinical Hospital for Veterans of War" of the Poltava Regional Council were analysed for the 2014-2018. During 2014 and 2015 medical assistance to servicemen was provided only on an inpatient basis. Since 2016, it has become necessary to consult military personnel on an outpatient basis (2016 – 473 people (51.8%), 2017 – 570 people (48.3%), 2018 – 745 people (47.6%)) The highest percentage of treated military personnel was diagnosed with neurotic, stress-related and somatoform disorders, respectively in 2016 – 58.6%, in 2017 – 59.3%, and in 2018 – 56.7%. The presence among the military personnel of anti-terrorist operation / united forces operation of a constant increase in the number of patients with signs of impaired adaptation requires the earliest possible start of psychological rehabilitation.

Keywords: psychological rehabilitation, military servicemen, adaptation, stress response.

The work is a fragment of the research project "Medical and social justification of optimization of approaches to management and organization of different types of medical care for adults and children in the period of healthcare sector reform", state registration No. 0115U002852.

The outbreak of the war in the East of Ukraine has created new challenges for the system of psychological rehabilitation in our country [3]. The issue of further adaptation of ex-servicemen who returned after the anti-terrorist operation / joint forces operation to the peaceful life has become urgent [5]. Psychological rehabilitation is the most important element in the restoration of mental balance [4, 7]. Its essence is to have various mental influences on the serviceman, taking into account therapy, prevention, hygiene and pedagogy. With the help of psychological influences, it becomes possible to reduce the level of neuropsychological tension, to restore the spent nervous energy faster and, thus, to make a significant impact on the acceleration of the recovery processes in other organs and systems of the body. This differentiates the psychological impact from other means of rehabilitation [4].

The main goals of psychological rehabilitation are:

1. Restoration of combat and labour ability of the participants of the anti-terrorist operation / joint forces operation.

2. Prevention of disability.

3.Social adaptation of military personnel.

Clarification of the goals of psychological rehabilitation allows to determine its tasks, content, structure, forces and resources involved, as well as the responsibilities of government bodies and officials in organizing, implementing and managing the process of restoring the mental balance of military personnel in a peaceful life.

The tasks of psychological rehabilitation:

1. Establishment of the nature and degree of importance of neuropsychological disorders, the determination of the individual and personalized characteristics of the response of military personnel to the received mental trauma and the development of rehabilitation measures.

2. Relieving psycho-emotional tension, irritability and fear through the use of complex effects (psychotherapeutic, medical, biological).

3. Regulation of impaired body functions, correction of the psychophysiological state by methods of psychotherapeutic effects.

4. Formation of an optimal psychological response to the consequences of mental trauma, mobilization of the individual to overcome the conditions that have arisen, development of the necessary volitional qualities in servicemen.

5. Formation of the personnel's clear ideas of risk factors and conscious attitude to measures to eliminate them.

6. Optimal resolution of the psycho-traumatic situation, restoration of social status, adaptation of the person to environmental conditions by stimulating the social activity of the serviceman.

7. Assessment of physical, sensory and mental performance; conducting professional and psychological rehabilitation, focusing on continuing active service activities and performing military service duties.

8. Study of the dynamics of changes in mental states in the process of rehabilitation; diagnostics of the functional state of the physiological systems of the body; assessment of effectiveness and correction (if necessary) of rehabilitation measures.

The purpose of our work was to analyse the main goals of psychological rehabilitation of servicemen in the Poltava region in the current reform conditions on the example of the work of the Rehabilitation Department of the Public Institution "Kremenchug Regional Clinical Hospital for Veterans of War" of the Poltava Regional Council.

Materials and methods. Pursuant to the requirements of the Order of the Director of the Department of Health of the Poltava Regional State Administration dated April 17, 2015 No. 430 "On the organization of treatment and rehabilitation of participants of the anti-terrorist operation in hospitals for disabled war veterans of the region" at the Public Institution "Kremenchug Regional Clinical Hospital for Veterans of War" of the Poltava Regional Council a Rehabilitation Department with 40 beds, which provides psychological rehabilitation, was established. The reports of a psychotherapist, psychiatrist for the 2014-2018 reporting period were analysed.

When examining the participants of the anti-terrorist operation / joint forces operation, in addition to an objective examination, the psychological state of the serviceman, the opportunities for social adaptation, training, retraining, etc. are necessarily taken into account.

All military personnel during their first examination at the department are required to be interviewed according to the hospital Anxiety and Depression Scale (HADS) and Mississippi Post-Traumatic Stress Disorder Scale (PTSD).

The Mississippi Scale (MS) was developed to assess the severity of post-traumatic stress reactions in war veterans [8]. Today, it is one of the widely used tools for measuring the signs of PTSD. The scale contains 35 statements, each rated on a five-point Likert scale. The evaluation of the results is performed by summing the points. The final indicator allows to identify the influence degree of the traumatic experience suffered by the individual. Questionnaire items fall into 4 categories, three of which are related to the DSM criteria: 11 questions are aimed at identifying the intrusion symptoms, 11 – at identifying the avoidance symptoms, and 8 questions are related to the criterion of physiological excitability. Five other questions are aimed at identifying feelings of guilt and suicidality.

Interpretation of test results: 35-96 points – good level of adaptation; 97-111 points – adaptation disorders; 112 points or more – post-traumatic stress disorder.

Results of the study and their discussion. The Rehabilitation Department is a structural unit of the Public Institution "Kremenchug Regional Hospital for Veterans of War" of the Poltava Regional Council, which provides specialized care to patients (on beds with a "general" profile) who, according to indications, require inpatient treatment and rehabilitation, planned medical psychological rehabilitation and social adaptation. In addition, outpatient consultations are being actively conducted not only with military personnel and members of their families in order to assist in establishing constructive relationships in the family and society.

As it can be seen from table 1, during 2014 and 2015 medical assistance to military personnel and displaced persons was provided only in a stationary conditions. Since 2016, it has become necessary to consult military personnel on an outpatient basis (2016 – 473 people (51.8%), 2017 – 570 people (48.3%), 2018 – 745 people (47.6%)), and also to provide rehabilitation assistance to the family members of the killed participants of the anti-terrorist operation / joint forces operation (2016 – 3 people, 2017 – 8 people, 2018 – 13 people). Each year, the number of treated participants of the anti-terrorist operation / joint forces operation increased (from 47 people in 2014 to 1529 people in 2018).

Table 1

Report of the Rehabilitation Department of the Public Institution "Kremenchug Regional Hospital for Veterans of War" of the Poltava Regional Council for 2014-2018

	2014	2015	2016	2017	2018
Total ATO Participants	47	250	896	1151	1529
Inpatient	47(78.4%)	250(92.6%)	423(46.3%)	581(49.2%)	784(50.1%)
Outpatient	-	-	473(51.8%)	570(48.3%)	745(47.6%)
Family members of the killed ATO participants			3(0.4%)	8(0.8%)	13(0.8%)
Displaced Persons	13(21.6%)	20(7.4%)	14(1.5%)	22(1.7%)	23(1.5%)
Total	60	270	913	1181	1565

As it can be seen from table 2, the largest percentage of treated military personnel was diagnosed with F40-49 – "Neurotic, stress-related and somatoform disorders", respectively 58.6% in 2016, 59.3% in 2017, and 56.7% in 2018.

Table 2

The Established Diseases According to the ICD - 10 Based on the Work Results of the Rehabilitation Department of the Public Institution "Kremenchug Regional Hospital for Veterans of War" of the Poltava Regional Council for 2014-2018

ICD -10 Code	Name of the Disease	2016		2017		2018	
		Abs.	**%**	**Abs.**	**%**	**Abs.**	**%**
F00-09	Organic, including symptomatic, mental disorders	0	-	6	6,4	6	2,5
F10-19	Mental and behavioural disorders	7	8	3	2,7	7	2,9
F20-29	Schizophrenia, schizotypal and delusional disorders	1	1,2	0	-	0	-
F30-39	Mood [affective] disorders	19	21,8	21	19,4	38	16
F40-49	Neurotic, stress-related and somatoform disorders	51	58,6	64	59,3	135	56,7
F50-59	Behavioural syndromes associated with physiological disturbances and physical factors	9	10,4	10	9,2	50	21
F60-69	Disorders of adult personality and behaviour	0	-	4	3	2	0,9
F70-79	Mental retardation	0	-	0	-	0	-
Total		87		108		238	

In the second place goes F30-39 – "Mood [affective] Disorders», respectively 21.8% in 2016, 19.4% in 2017, and 16% in 2018. In third place goes F50-59 – "Behavioural Syndromes Associated with Physiological Disturbances and Physical Factors", respectively 10.4% in 2016, 9.2% in 2017, and 21% in 2018. The lowest percentage was recorded for F60-69 – "Disorders of Adult Personality and Behaviour", respectively 0% in 2016, 3% in 2017, and 0.9% in 2018, which was related to the mobilization of young and able-bodied men.

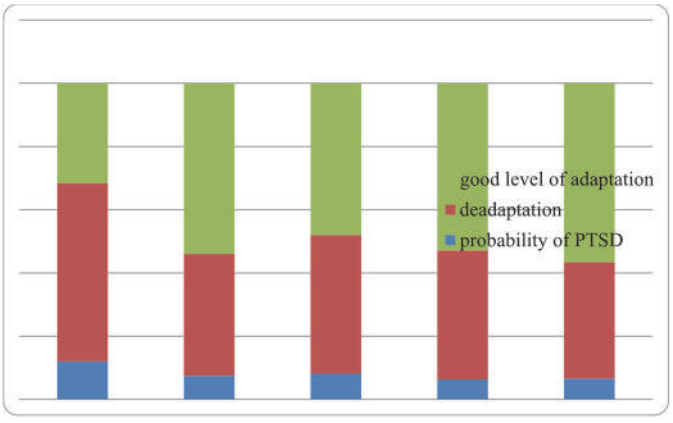

Fig. 1. The Results of a Survey on the Mississippi Scale for Assessing PTSD in the Work of the Rehabilitation Department of the Public Institution "Kremenchug Regional Hospital for Veterans of War" of the Poltava Regional Council for 2014-2018

As it can be seen from fig. 1, the majority of interviewed servicemen had a high percentage of well-defined adaptation level during the period 2014-2018. But if to compare, it becomes clear that in 2014 it is the lowest percentage (35%) and in 2018 it is the highest – 58%, which is related to the gradual development of psychological assistance to soldiers at all levels of medical care. Despite the fact that there is a high level of adaptation impairment among the participants of the anti-terrorist operation / joint forces operation, there is a gradual decrease, respectively in 2014 – 55%, 2015 – 38%, 2016 – 49%, 2017 – 42%, 2018 – 39%.

An analysis of recent research and publications indicates that servicemen after the anti-terrorist operation / joint forces operation are in the category of population requiring a specific approach of complex psychological assistance, special psychocorrection measures, and psychotherapy [1, 6]. This is explained by the fact that after the events in the zone of the anti-terrorist operation / joint forces operation, the servicemen notice significant mental disorders, do not find understanding in society and their families,

encounter difficulties in communication in the workplace and in solving problems in everyday life [2, 3]. The problem of psychological rehabilitation of combatants remains relevant to date [4].

Conclusions

In modern conditions, the rehabilitation of the participants of the anti-terrorist operation / joint forces operation should be carried out as early as it is possible, continuously, consistently, and have an individual approach to rehabilitation treatment. That is, in the acute period, inpatient treatment of military personnel is needed, which is aimed at restoring a person's health and returning him to socially useful activities, preventing disease complications and supporting outpatient therapy.

A high percentage (57.5% on average) of participants in the anti-terrorist operation / joint forces operation with neurotic and somatoform disorders requires psychological support and follow-up, psychotherapy and group work together with an artist and a specialist in labour adaptation.

Therefore, the presence among the participants of the anti-terrorist operation / joint forces operation of a constant upward trend in the number of patients with signs of adaptation impairment who are highly likely to have PTSD, requires the earliest possible start of psychological rehabilitation as long as there is a high rehabilitation potential and a positive prognosis for rehabilitation.

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ГОЛОВНІ ЦІЛІ ПСИХОЛОГІЧНОЇ РЕАБІЛІТАЦІЇ ВІЙСЬКОВОСЛУЖБОВЦІВ У ПОЛТАВСЬКІЙ ОБЛАСТІ В СУЧАСНИХ УМОВАХ

Гавловський О.Д.

Початок війни на Сході України створив нові виклики для системи психологічної реабілітації.

Метою нашої роботи було проаналізувати головні цілі психологічної реабілітації військовослужбовців в Полтавській області в сучасних умовах. Були проаналізовані звіти реабілітаційного відділення КЗ «Кременчуцький обласний клінічний госпіталь для ветеранів війни» за 2014-2018 рр. Впродовж 2014 – 2015 рр. медична допомога військовослужбовцям надавалась в стаціонарних умовах. Починаючи з 2016р. з'явилась необхідність консультувати в амбулаторних умовах (2016р. – 473 особи (51,8%), 2017р. – 570 осіб (48,3%), 2018р. – 745 осіб (47,6%)). Найбільший відсоток пролікованих військовослужбовців був з діагнозами «Невротичні, пов`язані зі стресом та соматоформні розлади», відповідно в 2016р. – 58,6%, 2017р. – 59,3%, 2018р. – 56,7%. Наявність серед учасників АТО/ООС постійної тенденції до зростання кількості хворих з ознаками порушення адаптації, потребує якомога скорішого початку психологічної реабілітації.

Ключові слова: психологічна реабілітація, військовослужбовці, адаптація, стресова реакція.

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ГЛАВНЫЕ ЦЕЛИ ПСИХОЛОГИЧЕСКОЙ РЕАБИЛИТАЦИИ ВОЕННОСЛУЖАЩИХ В ПОЛТАВСКОЙ ОБЛАСТИ В СОВРЕМЕННЫХ УСЛОВИЯХ

Гавловский А.Д.

Начало войны на Востоке Украины создало новые вызовы для системы психологической реабилитации. Целью работы было проанализировать главные цели психологической реабилитации военнослужащих в Полтавской области в современных условиях. Были проанализированы отчеты реабилитационного отделения КУ «Кременчугский областной клинический госпиталь для ветеранов войны» за 2014-2018 гг. В течение 2014 - 2015 гг. медицинская помощь военнослужащим предоставлялась в стационарных условиях. С 2016 появилась необходимость консультировать в амбулаторных условиях (2016. - 473 чел. (51,8%), 2017. - 570 чел. (48,3%), 2018р. - 745 чел. (47,6%)). Наибольший процент пролеченных военнослужащих был с диагнозами «Невротические, связанные со стрессом и соматоформные расстройства», соответственно в 2016 - 58,6%, 2017 - 59,3%, 2018 - 56,7%. Наличие среди участников АТО/ООС постоянной тенденции к росту числа больных с признаками нарушения адаптации, требует скорейшего начала психологической реабилитации.

Ключевые слова: психологическая реабилитация, военнослужащие, адаптация, стрессовая реакция.

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CLINICAL CHARACTERISTICS OF LOWER LIMB WOUNDS IN INJURED PEOPLE IN THE RESULT OF MODERN MILITARY OPERATIONS

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Studying the experience of providing surgical service to the injured people with a mine blast injures in a local armed conflict in the East of Ukraine will allow not only to determine the nature of modern war trauma, but also to make some changes in the formed ideas about the effectiveness of certain measures. The stage of professional medical services was the main one for the injured people with the neuromuscular bundle and the knee joint injuries, which was found in 5.9% and 9.5% respectively and in subsequent stages their number decreased. At the stage of specialized medical services the injured people with lower leg injuries were concentrated. 41.0% were detected at this stage, which is 1.3 times more than at the stage of professional services and almost twice more than at the stage of highly specialized medical services. The stage of highly specialized medical care was the main one for the injured people with injuries of pelvic (4.8%), buttock (7.8%), hips (34.9%), foot (16.5%) traumatic amputation of the lower leg (1.9%) and foot (3.8%).

Keywords: injured people, gunshot wounds, limbs, mine blast injury.

The study is a fragment of the research project "Pathogenetic substantiation of treatment of infectious complications of the traumatic process in injured people in modern military operations", state registration number 0117U003077.

The military medical statistics of local armed conflicts in recent decades confirm the global wars data that the predominant use of conventional firearms, regardless of the military operation scale, causes the prevalence of limb injuries in the structure of combat sanitary losses [1, 4]. Thus, according to the data of Eastridge BJ [6], limbs are affected in 65-70% of all injuries found during counter-terrorism operations in Afghanistan and Iraq. Taking into account the fact that this category of injured people is a huge potential reserve of the opposing armies, it becomes clear how successful and rapid restoration of combat capability will ensure the return to the army of the most experienced and battle-hardened soldiers [8, 9]. According to the Ministry of Defense of Ukraine, at the end of 2016, more than 10 thousand people were killed in the Joint Forces Operation (JFO) area in Eastern Ukraine. For the period 2014-2016, more than 21.000 injured people were reported [2]. In the conditions of hybrid war in the Eastern Ukraine, providing professional medical services to injured military servicemen, their complete treatment and rehabilitation, using the latest technologies, is the highest priority of the state [3]. According to many authors, the organization of providing professional and timely medical services to the wounded, their rapid evacuation, further treatment and rehabilitation provide not only the protection of life, but also the rapid recovery of combat capability in 80% of the injured people in the current armed conflicts [5, 7].

Studying the experience of providing surgical service to the injured people with a mine blast injures in a local armed conflict in the East of Ukraine will allow not only to determine the nature of modern war trauma, but also to make some changes in the formed ideas about the effectiveness of certain measures. This is the purpose of our study.

The purpose of our work was to evaluate the medical characteristics of the lower limbs injures at the stages of medical evacuation in the conditions of JFO and to determine the main directions of optimization of medical services for the injured people.

Materials and methods. In order to fulfill the tasks and purposes of our study, we retrospectively and prospectively analyzed the treatment of 377 injured men with mine blast injuries, which was received during the JFO in 2014-2017. The data were entered into specially designed maps that allowed to analyze the functional and morphological component of mine blast injury, the injuries severity, the injured man condition severity, the surgical interventions nature, the infectious complications type.

For the purpose of qualitative analysis of the actual material of the study, we distributed injured people to the sets according to the place of their treatment at the medical services levels. Set A: the injured people with mine blast injury, who were treated in the Bakhmut (Artemivsk) Central District Hospital, which corresponded to the Level II of medical services. This set included 126 injured people with mine blast injuries, provided medical services corresponded to the Level II and were typical for this level. The injured people's age ranged from 18 to 48 years and averaged 27.7±2.8 years.

122 injured people with mine blast injuries receiving treatment at the I.I. Mechnikov Dnipropetrovsk Regional Clinical Hospital were attributed to the Set B, which corresponded to the Level III of medical evacuation. Medical services to these injured corresponded to the Level III and was typical for this level. The injured people's age ranged from 18 to 50 years and averaged 29.0±3.4 years.

129 injured people with mine blast injuries receiving treatment at the Military Medical Clinical Center of the Central Region, Vinnytsia, were attributed to the Set C, which corresponded to the Level IV of medical evacuation. The injured people's age ranged from 19 to 48 years and averaged 28.4±3.2 years.

Mathematical methods of nonparametric statistics were applied to estimate the statistical probability of materials obtained during the study, due to the considerable variability of wounds in a mine-blast injury. Considering the number of analyzed features and the need to ensure the uniformity of the performance indicators, we used Pearson's polychoric correlation for the correct comparison. The correlation analysis between the mine-blast injury signs of injured in the modern military operations, studied by this method was performed both within the groups and between the groups, which allowed to unify the results of statistical analysis and to ensure correct comparison with the application of formal logic laws.

Results of the study and their discussion. The study revealed 309 injuries of the lower limbs, accounting for 82.0% of the set. Among injured of the Set A, lower limbs injures were detected in 84 cases, which was 66.7% of the Set. In the Set B these injuries were registered in 122 injured, which was 100.0%, and in the Set C – in 103 injured, which was 79.8% of cases. Among the studied injured patients, the following lower limbs injuries were found: pelvic injuries (PI), buttocks injuries (BI), neurovascular bundle injuries (NVBI), hip injuries (HI), knee joint injuries (KJI), lower leg injuries (LLI), foot injuries (FI), traumatic foot amputation (TFA), traumatic lower leg amputation (TLLA). To determine the structure of lower limbs injuries, we performed the analysis, which results are shown in table 1.

Table 1

Distribution analysis of the injured on the lower limbs injuries basis

Anatomical location	Number of injured								
	A			B			C		
	abs.	%	Ri	abs.	%	Ri	abs.	%	Ri
PI	2	2.4	7	4	3.3	7	5	4.8	6
BI	3	3.6	6	5	4.1	6	8	7.8	4
NVBI	5	5.9	5	7	5.7	5	2	1.9	8
HI	24	28.6	2	30	24.6	2	36	34.9	1
KJI	8	9.5	4	8	6.6	4	7	6.8	5
LLI	27	32.1	1	50	41.0	1	22	21.3	2
FI	11	13.1	3	14	11.5	3	17	16.5	3
TLLA	1	1.2	8	1	0.8	9	2	1.9	8
TFA	3	3.6	6	3	2.4	8	4	3.8	7
Total	84	100.0	-	122	100.0	-	103	100.0	-

Analysis of table 1 data indicated that injured with lower leg injuries were most commonly found in the Set A. Such injuries were detected in 32.1% of cases in the Set A. It was these injured who occupied the first place in the Set A. Injured with lower leg injures were found in the Set B in 41.0% of the cases, which is 1.3 times more than in the Set A. As in the Set A, injured with lower leg injures occupied the first place in the Set B. A slightly different situation was observed in the Set C, where such injured were only 21.3% and they occupied the second place (fig. 1). Thus, the analysis indicated that the injured people with lower leg injuries are most concentrated at the specialized medical service stage and that it is the main stage in providing medical services to the injured with these wounds.

The second place in the Set A was occupied by the injured with hip injures. This injury type was registered in 28.6% of the injured. In the Set A, this injury was reported slightly less frequently, in 24.6% of cases, and occupied the second place in the ranking distribution. Hip injuries were most common in the Set C. This injury was found in 34.9% of injured, which is 1.2 times more frequent than in Set A and 1.4 times more frequent than in Set B. At the stage of highly specialized medical services, the basic treatment of hip injuries in injured of modern military operations is organized. Injured with foot injuries occupied the third place in the Set A, where they were identified in 13.1% of cases. The number of injured with foot injuries was slightly less – 11.5%, and in the ranking distribution they also occupied the third place. They also occupied the third place in the Set C. However, it is worth noting that the data of this injured was larger in the Set C compared to both the Set A and B. Based on the analysis data, it was found that the stage of highly specialized medical services is the main stage in the treatment of injured with foot wounds.

Fig. 1 Injured person with a mine blast limb injury at a stage of professional medical service.

Knee joint injuries occupied the fourth place in the Set A. This injury occurred in 9.5% of cases. Similar to the Set A, injured with knee joint injuries also ranked fourth in the Set B, but in the relative value of the indicator they were 1.4% less. The number of injured with knee joint injuries in the Set C was about the same as in the Set B, but in the rank distribution this injury ranked fifth. According to the analysis of the knee joint injuries cases, the main stage of providing medical services to the injured was the stage of professional medical services.

The fifth place in the Set A was occupied by the injured with injuries to the lower limb neurovascular bundle. This wound was found in 5.9% of the injured with lower limbs injuries.

The similar number of injured with the neurovascular bundle injuries were found in the Set B, where they are also on the fifth place. In the Set C, a sharp decrease (3 times) of the injured with these wounds was observed. At the stage of highly specialized medical services, the injured with the neurovascular bundles injuries occupied the last eighth place. As indicated by the analysis data, the main stage in the treatment of injured with the neurovascular bundle injuries was the stage of professional medical services, where the concentration of such injured occurred. 3.6% of the injured in the Set A were diagnosed with buttock injuries. These injured occupied the sixth place in the Set A. Moreover, in 4.1% of cases, this injury was diagnosed in the Set B, where it also occupied the sixth place. In the Set C, there was a significant increase in the number of injured with buttock injuries. Here they were detected in 7.8% of cases, which is more than twice as much as in the Set A. Rank analysis placed them in the fourth place. The data concentration on injured at the stage of highly specialized services indicates that this stage is essential in the treatment of injured with the buttock wounds. Another injury that occupied the sixth place in the Set A was a traumatic foot amputation. This injury was also found in 3.6% of cases. In the Set B, there was some decrease in their level and they occupied the eighth place. In the Set C, these injured were occupied the seventh place, and the relative value of the indicator almost corresponded to the level of the Set A. The main place of treatment for injured with traumatic foot amputation was the stage of highly specialized medical services.

The seventh place in the Set A was occupied by the injured with pelvic wounds. This injury was registered in 2.4% of cases. There were 3.3% of such injured in the Set B, but in the rank distribution they also occupied the seventh place. At the stage of highly specialized medical services, there was an increase in the pelvic injuries level up to 4.8%, which is twice more than in the Set A and 1.5 times more than in the Set B. This statement indicates that the main stage in providing medical care to injured with pelvic injuries is the stage of highly specialized medical services.

The last place in all the Sets was occupied by the traumatic lower leg amputation. This injury was reported in 1.2% of injured of the Set A, in 0.8% of injured of the Set B and in 1.9% of injured of the Set C. The main treatment stage was the stage of highly specialized medical services.

To determine the correlation coefficients and the results reliability, we performed a polychoric analysis, which results are summarized in table 2.

Table 2

Estimated values of the correlation coefficients probability

Coefficient	Value of coefficient	Reliability
Cross-correlation coefficient φ^2	0.11	+
Polychoric correlation coefficient C	0.31	+
Pearson correlation coefficient x^2	33.9	+

Estimated values of polychoric analysis showed that a direct positive expressed binding force was detected between the sign of lower limbs injury and the course of traumatic process in the injured in modern military operations in the stages of medical services, and the indicated positions are within the probability field ($\chi^2 = 33{,}9 \geq \chi^2_{st} = 15{,}5$, $p \leq 0{,}05\%$).

World experience in military medicine, including of the twentieth century wars in Korea (1950-1953), Vietnam (1965-1973), Afghanistan (1979-1989), became the basis of the development of modern principles of organization and tactics in the medical service of the Armed Forces aimed at providing

emergency medical care for the sick and injured at the stages of medical service [2,6]. The experience of international military conflicts in recent years points to the lack or absence of a public health protection concept in many participants. The use of modern weapons of mass destruction, the use of new warfare methods has led to a crisis of outdated methods in therapeutic and diagnostic tactics in the injured, which has certainly led to the search for more optimal measures to protect the population from the most striking factors of military operations [1]. The construction of a modern system of medical and diagnostic measures is carried out with the use of medical military units and formations, mobile and stationary military medical institutions and wide involvement of the existing network of civilian healthcare institutions. Characteristic features of combat injures in the JFO are most of the combined and multiple wounds — 32.1%, which lead to injuries of moderate severity — 37.4% and severe — 14.5%; prevalence of shrapnel wounds — 62,9% and mine injuries — 25,6%, which are caused by the impact of mine blast weapon [3]. In such conditions, the injured treatment tactics have to be determined by the minimal amount of diagnostic manipulations, technical and medical equipment, knowing full well that the treatment effectiveness of severe injury largely depends on the timeliness of the diagnosis and the performed medical measures in the first hours from the moment of injury.

Conclusions

1. The stage of professional medical services was the main one for the injured people with the neuromuscular bundle and the knee joint injuries, which was found in 5.9% and 9.5% respectively and in subsequent stages their number decreased.

2. At the stage of specialized medical services the injured with lower leg injuries were concentrated. 41.0% were detected at this stage, which is 1.3 times more than at the stage of professional services and almost twice more than at the stage of highly specialized medical services.

3. The stage of highly specialized medical care was the main one for the injured people with injuries of pelvic (4.8%), buttock (7.8%), hips (34.9%), foot (16.5%) traumatic amputation of the lower leg (1.9%) and foot (3.8%).

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Реферати

КЛІНІЧНА ХАРАКТЕРИСТИКА ПОШКОДЖЕНЬ ПОЯСУ НИЖНЬОЇ КІНЦІВКИ У ПОСТРАЖДАЛИХ В РЕЗУЛЬТАТІ СУЧАСНИХ БОЙОВИХ ДІЙ

Гур'єв С.О., Танасієнко П.В., Панасенко С.І., Марцинковський І.П., Філь А.Ю.

Вивчення досвіду надання хірургічної допомоги поранених з мінно-вибуховою травмою в локальному збройному конфлікті на Сході України дозволить не тільки визначити характер сучасної бойової травми, а і внести деякі зміни в сформовані уявлення про ефективність тих чи інших заходів. Етап кваліфікованої

КЛИНИЧЕСКАЯ ХАРАКТЕРИСТИКА ПОВРЕЖДЕНИЙ ПОЯСА НИЖНЕЙ КОНЕЧНОСТИ У ПОСТРАДАВШИХ В РЕЗУЛЬТАТЕ СОВРЕМЕННЫХ БОЕВЫХ ДЕЙСТВИЙ

Гурьев С.А., Танасиенко П.В., Панасенко С.И., Марцинковский И.П., Філь А.Ю.

Изучение опыта оказания хирургической помощи раненых с минно-взрывной травмой в локальном вооруженном конфликте на Востоке Украины позволит не только определить характер современной боевой травмы, а и внести некоторые изменения в сложившиеся представления об эффективности тех или иных мероприятий. Этап

медичної допомоги був основним для постраждалих з пошкодженнями нервово-судинного пучка та пораненнями колінного суглобу, що було виявлено у 5,9% та 9,5% відповідно і на подальших етапах їх кількість зменшувалась. На етапі спеціалізованої медичної допомоги концентрувались постраждалі з пораненнями гомілки, яких на цьому етапі було виявлено у 41,0%, що у 1,3 рази більше ніж на етапі кваліфікованої допомоги та майже удвічі більше ніж на етапі високоспеціалізованої медичної допомоги. Етап високоспеціалізованої медичної допомоги був основним для постраждалих з пораненнями тазу (4,8%), сідниці (7,8%), стегна (34,9%), стопи (16,5%) та травматичними відривами гомілки (1,9%) та стопи (3,8%).

Ключові слова: Постраждалі, вогнепальні поранення, кінцівки, мінно-вибухова травма.

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квалифицированной медицинской помощи был основным для пострадавших с повреждениями нервно-сосудистого пучка и ранениями коленного сустава, что было выявлено в 5,9% и 9,5% соответственно и на последующих этапах их количество уменьшалось. На этапе специализированной медицинской помощи концентрировались пострадавшие с ранениями голени, которых на этом этапе было выявлено в 41,0%, что в 1,3 раза больше чем на этапе квалифицированной помощи и вдвое больше чем на этапе высокоспециализированной медицинской помощи. Этап высокоспециализированной медицинской помощи был основным для пострадавших с ранениями таза (4,8%), ягодицы (7,8%), бедра (34,9%), стопы (16,5%) и травматическими отрывами голени (1,9%) и стопы (3,8%).

Ключевые слова: Пострадавшие, огнестрельные ранения, конечности, минно-взрывная травма.

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PERINATAL CONSEQUENCES OF ADAPTATION DISORDER WITH BURDENED OBSTETRIC HISTORY

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Stress experienced against the background of perinatal losses (PL) can adversely affect the course of subsequent pregnancy. The study of the heart rate variability (HRV) of the fetus by cardiointervalography (CIG) of the fetus in women with burdened obstetric history (PL in anamnesis) at 32-34 weeks of pregnancy was performed. The total of 200 pregnant women with PL and 100 pregnant women without PL in the history were examined. Comparison of the cardiotocography and dopplerometry results with fetal CIG data showed that when the adaptation of the fetal regulatory systems was disrupted, distress was diagnosed in 90.0% of women, and when the fetal regulatory systems showed marked stress in 27.3%, i.e. results of the fetus CIG after 32 weeks of pregnancy may be diagnostic markers of its distress. The overwhelming majority (76.1%) of infants from mothers with PL in the history after intrauterine distress are born in a state of asphyxiation, that causes a high incidence of disadaptation syndromes, often including CNS disorders (73.9%) and the cardiovascular system disadaptosis (41, 3%).

Key words: perinatal losses, cadiointervalography, adaptation, distress of the fetus, newborn.

The work is a fragment of the research project "Reducing the incidence of major obstetric syndromes in high-risk pregnancies from a single genesis position by implementing a pathogenetically targeted prevention and treatment complex", state registration No. 0118U001138.

Perinatal losses (PL), such as pre-natal fetal death and stillbirth, account for 2.65 million cases per year worldwide [9]. Unfortunately, the risk of recurrence in subsequent pregnancies grows up to ten times depending on the cause of stillbirth [11].

Complications of obstetric history with perinatal losses are accompanied by depletion of the body's adaptation reserves against the background of prolonged and intense influence of psycho-emotional stress, causing the development of psycho-emotional diseases and disorder of neurovegetative regulation. The stress experienced against the background of PL can negatively affect the course of the next pregnancy [1, 3, 4].

Despite advances in the diagnosis and treatment of many gestational complications, only in 20-30% of newborns timely started treatment of post-hypoxic CNS changes ensure complete recovery, and treatment of fetal distress after diagnosis due to profound pathomorphological changes is ineffective. As a result, the morbidity and mortality of such infants is steadily increasing [2, 10]. Therefore, the prognosis and the possibility of prevention, rather than the diagnosis of the already disturbed fetal state, is a reserve for reducing perinatal morbidity and mortality [5, 6].

Cardiointervalography is an efficient screening method that can be used to assess the fetal status. By studying variability of maternal and fetal heart rhythm in real time, it is possible to obtain information on the state of energy supply, humoral and neurovegetative regulation, their changes in stress and other conditions, the adaptive capability and reserves of the mother-placenta-fetus system [7, 8].

The purpose of the study was to assess the impaired fetal and infant adaptation, to determine the perinatal consequences of a burdened obstetric history.

Materials and methods. The study of fetal heart rate variability (HRV) was performed by cardiointervalography (CIG) of the fetus in women with the burdened obstetric history (PL in the history) at 32-34 weeks of pregnancy by means of "Cardiolab Baby Card" fetal monitor (Kharkiv, Ukraine). The methodology of HRV analysis adopted in the system lies in measuring the HRV parameters and their interpretation. We examined 200 pregnant women with PL (main group) and 100 pregnant women without PL with a history of physiological pregnancy (control group).

The following static characteristics of HRV were under study:

SDNN, ms - mean-square deviation of consecutive RR intervals;

CV - coefficient of variation;

RMSSD, ms - the square root of the consecutive RR intervals mean-square deviation;

pNN50 - the percentage of consecutive cardio intervals pairs that differ more than by 50 ms.

Indices of HRV geometric analysis:

Mo - mode;

AMo - mode amplitude, the percentage of cardio intervals that occur most frequently;

VAR - the variation range, ms - the difference between the duration of the largest and smallest RR interval.

According to the indices of statistical analysis methods, the following indices are calculated: the index of vegetative equilibrium (IVE = AMo/VAR), the vegetative index of rhythm (VIR = 1/AMo* VAR), the stress index (SI = AMo/2Mo x VAR) or the stress index (SI):

The main indices of cardiac rhythm spectrum power were also determined:

TP (total power) - the total power of the spectrum

HF (High Frequency) - the heart rhythm power of high-frequency oscillation.

LF (Low Frequency) - the heart rhythm power of low frequency oscillation.

ELF (Extremely Low Frequency) - an extremely low frequency component of the spectrum.

According to the spectral analysis of cardiac rhythm, the index of centralization: IC = (HF + LF)/ELF and the index of vagosympathetic interaction LF/HF, which reflect the sympathetic-parasympathetic balance of the vegetative nervous system (VNS), were also calculated.

This method of HRV analysis was also used as correlation rhythmography or scatterography, the essence of which is the graphical representation of successive cardio intervals pairs, the totality of points obtained forms an ellipse. Scatterogram indices are calculated: the length of the main (excluding extrasystoles and artefacts) ellipse - L, which corresponds to the variation range, its width - W, and their L/W ratio.

Doppler ultrasound study (US) was performed with Samsung Master 793DF "RADMIR" apparatus. The standard assessment of the fetal functional status was performed by cardiotoctography (CTG) with "Avalon FM20" device.

The numerical data are presented as median (interquartile range) Med (LQ-UQ). Statistic processing of the results was performed using the methods of variational statistics, the Mann-Whitney test and the Fisher test.

Results of the study and their discussion. Analysis of indices obtained by temporal HRV assessment methods, characterizing the general level of the vegetative nervous system (VNS) regulation - the balance of the central and autonomous circuits (table 1), showed a significant decrease in the indices: standard mean-square deviation of consecutive RR intervals SDNN and coefficient of variations CV, indicating the increased activity of the central regulatory circuit.

Table 1

General level of fetal VNS regulation in women with PL in history

Index	Main group		Control group		p
	Med	LQ-UQ	Med	LQ-UQ	
SDNN, ms	33	22-84	56	32-71	p = 0.037
CV, %	13	8-29	39	36-44	p = 0.0091
VAR, ms	156	74-318	258	117-303	p = 0.043
L, ms	337.0	193-334	383.5	119-477	p = 0.114
TP, ms^2	2558	1044-3678	6266	4592-8316	p= 0.015

The use of geometric methods (variational pulse oximetry) showed that the median value of the variance range (VAR) was also significantly reduced in the main group. In addition, the index had a much wider range (74-318 ms vs. 117-303 ms), indicating cases with both an increase in VAR (predominance of the central regulatory circuit), and with its decrease, i.e., a certain imbalance of the system, whereas in most women of the control group, there is a balanced regulation of fetal VNS.

According to our data, the median TP of the fetus (an index of the general regulation characterizing the wave structure of the heart rhythm) was reduced by 2 times, while in the main group the lower quartile was reduced by 4 times, i.e. in the main group the proportion of women with predominance of the fetal VNS central regulatory circuit was much higher.

Analysis of the activity indices in different divisions of the VNS (table 2) revealed an increase in the activity of the fetal sympathetic nervous system (SNS) and a decrease in the parasympathetic nervous system (PSNS). We found that the power of low-frequency oscillations of the fetal heart rate LF in women with PL in the history was reduced more than by 5 times. The amplitude of the mode (AMo) and a decrease in RMSSD and PNN50 also testify in favor of the fetal SNS activating, although it is not reliable due to the range width of the indices.

According to our data (table 2), the median absolute power of the high frequency (HF) spectrum is significantly reduced in the fetuses of the main group women, indicating a decrease in the effect of PSNS, mainly due to humoral effects, since no significant decrease in HFnorm was observed.

Also, in the fetuses of women in the main group, a significant decrease in the width of the scattertogram W ellipse was established, which in its turn confirms the attenuation of the fetal VNS parasympathetic link influence against the background of the tendency towards hypersympaticotonia.

Table 2

Fetal VNS activity in women with PL in history

Index	Main group		Control group		P
SNS activity					
	Med	LQ-UQ	Med	LQ-UQ	
LF, ms ^{2}	261	146-644	1267.5	637-1437	p = 0.002
AMo, %	57	46-62	35	25-50	p = 0.074
PSNS activity					
RMSSD, ms	12	9-59	32	15-49	p = 0.058
pNN50, %	11	0-17	28	3-35	p = 0.061
HF, ms^2	315.5	25-443	1399	818-2155	p = 0.0005
HF norm, %	28	13-41	47.5	36-62	p = 0.089
W, ms	154	117-284	394.5	107-494	p = 0.035

The indices of IC centralization and the index of vagosympathetic LF/HF interaction, which reflects the sympathetic-parasympathetic balance of the VNS, were also calculated by the spectral analysis data of cardiac rhythm (table 3). According to our data, fetal IC in the women of the main group are by 3 times higher than those of the pregnant in the control group, and LF/HF is by 2 times higher, which corresponds to a shift in the balance of the VNS toward sympathetic regulation.

Determination of indices calculated according to the data of statistical analysis methods (VIR and SI) showed the following. The growth of the vegetative equilibrium index is established. Significantly elevated (1.5 times) was the stress index (SI): 754 (262-979) against 505 (356-656), p <0.05. No significant difference in the length and width of the scatterograph ellipse (L/W) was detected.

Table 3

Sympathetic-parasympathetic balance of VNS in women with PL in history

Index	Main group		Control group		p
	Med	LQ-UQ	Med	LQ-UQ	
IC	16.1	5.5-27.5	5.2	2.8-5.8	p=0.001
LF/HF	2.6	1.47-6.41	1.2	0.61-1.81	p=0.032
VIR	373	284-867	222	104-498	p=0.044
SI	754	262-979	505	356-656	p=0.043
L/W	1.5	1-5	1.1	1-2	p=0.062

Thus, the sympatho-parasympathetic balance of the fetus in most women with PL in the history is assessed as sympathicotonia with elevated level of stress.

We identified 4 SI ranges to assess the fetal VNS regulation status:

- a sharp decrease in the total activity of the SNS at SI below 50 relative value units (RVU);
- reduction of activity of SNS at SI from 50 to 150 RVU;
- normotonia at SI from 150 to 500 RVU,
- sympathicotonia at SI from 500 to 900 RVU;
- hypersymaticotonia at SI more than 900 RVU.

Analysis of the total SNS activity in the fetus (fig. 1) showed that the majority of the main group demonstrated sympathico- and hypersympathicotonia, the incidence of these conditions being almost by 2

times higher than the index of the comparison group (58.0% versus 32.0%, respectively, p < 0.05), which indicates a certain stress of the adaptation systems.

In more than half of the women - 58.0% (116/200) - in the comparison group, the total SNS activity of the fetus was assessed as normotonia, among women in the main group this proportion was only 26.0% (26/100, p <0.05). It is important to note that in 4.0% (8/200) of women in the main group there is a sharp decrease in the total SNS activity of the fetus, which is an unfavorable index, indicating a failure of adaptive capacity. In women without a perinatal loss in the history, such conditions were not observed.

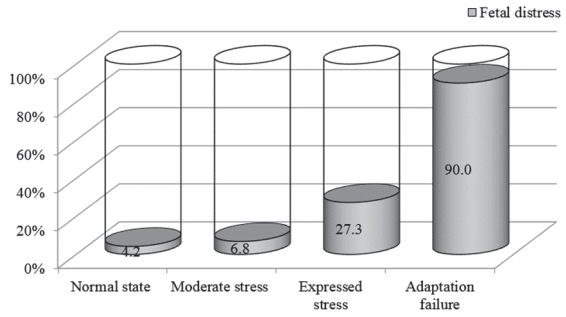

Fig. 1. - Distribution of women in groups by total fetal SNS activity, %

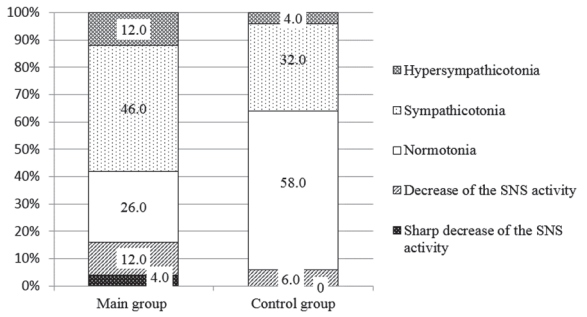

Fig. 2. –Incidence of fetal distress in women with PL in the history depending on the state of fetal regulatory systems, %

Characterizing the condition of the fetus as a whole, according to the cardiointervalography, 3 consecutive stages of its disturbance can be noted in women with a perinatal loss in the history:

- moderate stress of regulatory systems - in 44.0% (88/200) cases;
- expressed stress of regulatory systems - in 22.0% (44/200);
- reduction of regulatory systems activity (failure of adaptation) - by 10.0% (20/200).

In 24.0% (48/200) of women with a history of perinatal loss, fetal distress was diagnosed using a set of instrumental diagnostic methods (cardiotocography, ultrasonography, Doppler ultrasonography).

Comparing these results with the cardiointervalography (CIG) data (fig. 2), it can be noted that in the fetal regulatory systems adaptation failure, distress of the fetus was diagnosed in 90.0% (18/20) of women, with a pronounced stress of the regulatory systems in the fetus - in 27.3% (12/44), at moderate stress - in 6.8% (6/88), at the normal state of regulatory systems - in 4.2% (2/48) of pregnant women with PL in history. Thus, fetal CIG results after 32 weeks of pregnancy may be diagnostic markers of fetal distress.

In women with a perinatal loss in the history, 198 live children were born (one case of antenatal fetal death and one case of stillbirth with fetal distress), and all 100 women of the control group gave birth to live children. Premature preterm birth losses were 6.6% (10/152) of newborns without pre-natal distress and 32.6% (15/46) after distress versus 2.0% (2/100) in the control group (p < 0.05).

Almost all children (91.0%, 91/100) in the control group were assessed by Apgar score of more than 7 points, which corresponds to the normal state of the child (fig. 3). Most children from mothers with PL with status post distress (76.1%, 35/46) were born in asphyxia of varying severity, whereas in mothers with PL there were 37.5% of such infants (57/152). At the same time, severe asphyxia was noted in 23.9% (11/46) of children after intrauterine distress.

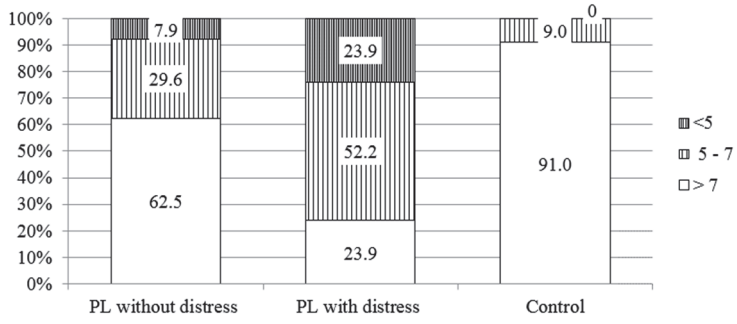

Fig. 3. - Distribution of newborns by their state at birth, %

High incidence of asphyxia at birth caused the incidence and severity of dysadaptation syndromes in infants of the main groups, the most frequent among them being CNS disorders: 73.9% (34/46) from mothers with PL in distress versus 19.1% (29/152) in infants from mothers with PL without distress and 5.0% (5/100) in the control group infants (p <0.05) and cardiovascular dysadaptosis: 41.3% (19/46) versus 15.1% (23 / 152) and 2.0% (2/100) of infants, respectively (p <0.05). In infants after fetal distress, clinical manifestations of hypoxic-ischemic CNS disorders were hyperexcitability syndrome or CNS depression syndrome. Among the clinical manifestations of cardiovascular dysadaptosis due to the status post hypoxia in newborns, the following can be noted: skin pallor with cutis marmorata, periodic

acrocyanosis, extension of the relative cardiac dullness borders, muffling of heart tone I, apical systolic murmur, arrhythmia.

The results obtained indicate a significant impairment of fetal heart rate variability in women with a history of perinatal loss, which is estimated as the tension of fetal adaptation systems in the vast majority (66.0%) of these women. Meanwhile, a group of patients (10.0%) is distinguished, whose hyperstress of the fetal regulatory systems goes into the stage of exhaustion and failure of adaptation, that caused fetal distress in 24.0% of cases and 2 (1.0%) cases of perinatal losses, high frequency of dysadaptation syndromes in newborns, which is consistent with other researchers' data on complications of subsequent pregnancies with previous perinatal losses [1, 4, 9].

It has been shown that in failure of adaptation of fetal regulatory systems (according to SI), its distress is diagnosed in 90.0% of women in the history, i.e. the value of fetal SI according to CIG after 32 weeks of pregnancy can be diagnostic markers of its distress, which is important for simplification and unification of heart rate variability assessment, which importance is emphasized by the authors of the review, where 70 different methods were analyzed [11]. Also, Ushakova G.A. and Petrich L. point out to the potential use of heart rate variability analysis for the assessment of gravid homeostasis [7].

Conclusions

1. The state of fetal VNS regulation in women with PL is characterized by an increase in the activity of the central regulatory circuit, the SNS activation with a tendency to hypersympaticotonia, which can generally be estimated as the stress of the adaptation systems in the fetus in the vast majority (66.0%) of these women (moderate in 44.0% and pronounced stress in 22.0%). The group of patients (10.0%) is distinguished, in which the hyperstress of the fetal regulatory systems goes into the stage of exhaustion and failure of adaptation, which is manifested by a sharp decrease in the activation of the fetal SNS, energy-deficient state. These particular indices are the most prognostically and diagnostically unfavorable in terms of perinatal losses, which is confirmed by the instrumental research data.

2. Comparison of the cardiotocography and dopplerometry results to CIG data showed that in failure of the fetal regulatory systems adaptation, its distress was diagnosed in 90.0% of women, with a pronounced stress of the fetal regulatory systems – in 27.3%, with moderate tension – 6.8%, with the normal state of regulatory systems - in 4.2% of pregnant women with PL in the history, i.e. the results of fetal CIG after 32 weeks of pregnancy can be diagnostic markers of its distress.

3. The overwhelming majority (76.1%) of infants from mothers with the history of perinatal loss after status post intrauterine distress are born in a state of asphyxia, which causes a high incidence of dysadaptation syndromes, the most frequent of which are CNS disorders (73.9%) and dysadaptosis of the cardiovascular system (41.3%).

The prospects of further research lie in development of clear criteria for impaired fetal and neonatal status based on the cardiovascular variability assessment.

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Реферати

ПЕРИНАТАЛЬНІ НАСЛІДКИ ПОРУШЕННЯ АДАПТАЦІЇ ПРИ ОБТЯЖЕНОМУ АКУШЕРСЬКОМУ АНАМНЕЗІ

Жданович О.І., Воробей Л.І., Аношина Т.М., Коломійченко Т.В.

Пережитий стрес на тлі перинатальних втрат (ПВ) може негативно впливати на перебіг наступної вагітності. Проведено дослідження варіабельності серцевого ритму плода шляхом кардіоінтервалографії (КІГ) плода жінок з обтяженим акушерським анамнезом (ПВ в анамнезі) у 32-34 тижні вагітності Обстежено 200 вагітних з ПВ та 100 вагітних без ПВ в анамнезі. Порівняння результатів кардіотокографії та допплерометрії з даними КІГ плода показало, що при зриві адаптації регуляторних систем плода його дистрес діагностовано у 90,0 % жінок, при вираженому напруженні регуляторних систем плода – у 27,3 %, тобто результати КІГ плода після 32 тижнів вагітності можуть бути діагностичними маркерами його дистресу. Переважна більшість (76,1 %) дітей від матерів з ПВ в анамнезі після перенесеного внутрішньоутробно дистресу народжуються у стані асфіксії, що обумовлює високу частоту синдромів дизадаптації, найчастішими з яких порушення ЦНС (73,9 %) та дизадаптоз серцево-судинної системи (41,3 %).

Ключові слова: перинатальні втрати, кадіоінтервалографія, адаптація, дистрес плода, новонароджений

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ПЕРИНАТАЛЬНЫЕ ПОСЛЕДСТВИЯ НАРУШЕНИЯ АДАПТАЦИИ ПРИ ОТЯГОЩЕННОМ АКУШЕРСКОМ АНАМНЕЗЕ

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Пережитый стресс на фоне перинатальных потерь (ПП) может негативно влиять на течение последующих беременностей. Проведено исследование вариабельности сердечного ритма (ВСР) плода путем кардиоинтервалографии (КИГ) плода женщин с отягощенным акушерским анамнезом (ПВ в анамнезе) в 32-34 недели беременности. Обследованы 200 беременных с ПП и 100 беременных без ПП в анамнезе. Сравнение результатов кардиотокографии и допплерометрии с данными КИГ плода показало, что при срыве адаптации регуляторных систем плода его дистресс диагностирован у 90,0% женщин, при выраженном напряжении регуляторных систем плода - у 27,3%, то есть результаты КИГ плода после 32 недель беременности могут быть диагностическими маркерами его дистресса. Подавляющее большинство (76,1%) детей от матерей с ПП в анамнезе после перенесенного внутриутробно дистресс рождаются в состоянии асфиксии, обусловливает высокую частоту синдромов дизадаптации, частыми из которых нарушения ЦНС (73,9%) и дизадаптоз сердечно-сосудистой системы (41,3%).

Ключевые слова: перинатальные потери, кадиоинтервалография, адаптация, дистресс плода, новорожденный

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PREVENTION OF PURULENT-SEPTIC COMPLICATIONS DURING LAPAROSCOPIC SURGERIES ON PELVIC ORGANS WITH THE RISK OF VAGINAL MICROBIOTA CONTAMINATION

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The efficacy analysis of the purulent-septic complications prevention at 115 “clean-contaminated” laparoscopic surgeries on the pelvic organs (laparoscopic hysterectomy, conservative myomectomy with the node resection via colpotomy incision) was performed. In the experimental group of patients (n = 60), 0.02% decamethoxin solution was administered intravaginally. The control group (n = 55) received traditional systemic perioperative antibiotic prevention using cephalosporins. It was shown that the early postoperative period dynamics, as well as indicators of systemic inflammatory response and the number of complications did not show significant differences between the studied groups, and in the experimental group there was an increase in the lactobacilli number and 87.3% decrease in the opportunistic pathogens content, which indicated the feasibility of preventive intraoperative topical decamethoxin application.

Key words: laparoscopy, purulent-septic complications, prevention, decamethoxin.

The study is a fragment of the research project “Improving methods of prevention, diagnosis and treatment of diseases of the reproductive system of women using the latest medical and molecular genetic technologies”, state registration No. 0117U007494.

Endoscopic surgery has a clear place in modern surgical gynecology. Due to the minimal invasiveness, high precision and operative endoscopic technique improvement, the incidence of postoperative purulent-septic complications (PSC) in endoscopic gynecological operations does not exceed 3.5% and depends on the complexity, surgery duration, the presence of risk factors, including vaginal microbiota contamination [1].

Most gynecological surgeries performed by laparoscopic approach are "clean-contaminated", requiring the prophylactic administration of antibacterial drugs in order to counterbalance the benefits of this minimally invasive surgical method [1-3, 5]. The drug choice for the infectious-inflammatory complications prevention should be based on its clinical and pharmacoeconomic efficacy, taking into account the increased opportunistic pathogens virulence and the spread of antibiotic resistance [6, 8, 10]. The emergence of antibiotic-resistant microflora and the widespread of pan-resistant microorganisms significantly reduce the effectiveness of antibacterial prevention and increase the purulent-septic complications incidence [1, 4, 8].

Despite improving knowledge about pathogenesis of early purulent-septic complications and therapeutic technologies development, PSC incidence does not tend to decrease, especially in patients with extragenital and combined gynecological pathology, obesity, impaired neuroendocrine regulation, immune suppression, which often develops against the background of the frequent and uncontrolled application of antibacterial drugs [4, 9].

The results of numerous clinical studies on the application of antibacterial agents in the PSC prevention are quite controversial [7-9]. Difficulties in vaginal microbiome correction are usually attributed to the formation of biofilms by opportunistic pathogens, which matrix prevent the proper penetration of systemic antibacterial drugs and leads to increased resistance of microorganisms to antibiotics [1, 6, 10].

Therefore, it is important to find a rational way to prevent infectious complications in "clean-contaminated" surgeries on the pelvic organs with the risk of vaginal microbiota contamination.

The purpose of the study was to evaluate the effectiveness of topical application of decamethoxin for the purulent-septic complications prevention in “clean-contaminated” laparoscopic operations on the pelvic organs with the risk of the vaginal microbiota contamination.

Materials and methods. The study was performed at the Clinical Trial Centre of the Department of Obstetrics and Gynecology No. 1 at the Multidisciplinary Medical Center of Odesa National Medical University for the period of January 2017 to March 2019. 115 women with low risk of PSC, who underwent “clean-contaminated” laparoscopic surgeries (laparoscopic hysterectomy, myomectomy with wide opening of the posterior vaginal vault) were examined. The exclusion criteria were: intraperitoneal bleeding, presence of urogenital infections, acute or chronic pelvic inflammatory diseases, systemic diseases (diabetes, immunodeficiency, obesity), allergic diseases, the history of laparotomy surgeries.

Depending on the method of antimicrobial prevention of PSC, patients were randomly assigned to two groups by random sampling. Experimental group (Group 1, n = 60) included patients who underwent surgery without systemic perioperative antibiotic prophylaxis (ABP), but with topical use of a disinfectant; the control group (Group 2, n = 55) included patients who underwent systemic perioperative ABP according to the traditional scheme (cephalosporins of II-III generation for 1 g intravenously with the beginning of anesthesia and again 1 g intravenously after 6-12 hours).

30 minutes before surgery, patients of the Group 1 were given intravaginally a swab, irrigated with 40.0-55.0 ml of 0.02% antiseptic solution, the active substance of which is decamethylenedimethylmethoxycarbonylmethylammonium dichloride (decamethoxin). Decamethoxin is a broad-spectrum antiseptic agent with bactericidal, fungicidal, virucidal and sporicidal activity, which has vaginal dysbiosis correction properties, contributes to the destruction of the bacterial biofilm matrix. Removal of this swab was performed during the emptying uterus or myomatous node from the abdominal cavity through the colpotomy incision.

To determine the degree of exo- and endogenous intoxication, a leukocyte index of intoxication (LII), which is an indicator of acute-phase inflammatory reactions according to Ya.Ya. Kalf–Kalif in the modification of B.A. Reys [6] was used.

The study of vaginal biotope before and after surgery included bacterioscopic and bacteriological studies [6, 8, 10]. In bacterioscopic examination, the preparations were stained by the Gram-Syniov, Romanovskyi-Giemsa method, methylene blue, and microscopic at immersion; bacterial forms of microbiota were identified by the Berge method. The analysis of the vaginal bacterial spectrum and the recording of results were carried out in accordance with the Order of the Ministry of Health of Ukraine No. 234 of 2007. The number of bacteria in 1.0 ml of secretions was determined by the number of colonies that grew with the degree of the inoculum dilution. 10^4-10^5 CFU/ml indicators were evaluated as the average degree of microbial genital contamination, at 10^6 or more – as a high degree [4, 10].

Laparoscopic surgery was performed according to the standard procedure under general endotracheal anesthesia, using special sets of equipment and instruments produced by “Karl Storz”.

The study was performed in accordance with the ethical principles of the Helsinki Declaration on Bioethics and obtaining the written consent of patients to participate in the study.

Statistical processing of the results was performed using Microsoft Excel 2019.

Results of the study and their discussion. A study of 115 women aged 20-55 found that patients in both groups had complaints of abdominal or lumbar pain – 86 (74.8%) menstrual disorders – 57 (49.8%), weakness – 43 (37.4%), increased fatigue – 37 (32.2%), sexual disorders – 10 (8.7%). In 33 (28.7%) women, iron deficiency anemia of the first degree of severity was detected. There were no significant differences between the study groups (table 1).

Table 1

Clinical characteristics of patients in the examined groups

Clinical symptoms	In general	Group 1	Group 2	P
Abdominal or lumbar pain	86 (74.8%)	44 (73.3%)	42 (76.4%)	0.375
Menstrual disorders	57 (49.6%)	28 (46.7%)	29 (52.7%)	0.234
Overall weakness	43 (37.4%)	23 (38.3%)	20 (36.4%)	0.453
Increased fatigue	37 (32.2%)	18 (30%)	19 (34.5%)	0.305
Sexual Function Disorders	10 (8.7%)	4 (6.7%)	6 (10.9%)	0.197
Iron deficiency anemia of the first degree of severity	33 (28.7%)	16 (26.7%)	17 (30.9%)	0.316

Prevention of PSC in postoperative patients consisted of pre-operative, intra-and post-operative measures. Preoperative measures included a meticulous clinical and laboratory examination to exclude risk factors for postoperative inflammatory complications (subcompensated extragenital pathology, subclinical inflammatory processes, examination for sexually transmitted infections), and the vagina rehabilitation 3-5 days before surgery. Intraoperative PSC prevention consisted of the surgery technique with scrupulous hemostasis, minimal electrocoagulation, limited suture application, application of synthetic absorbable filaments, antibiotic prophylaxis before the anesthesia administration and again after 6-12 hours, drainage of the pelvic cavity.

Indicators of Complete Blood Count before surgery had no significant differences: hemoglobin level in the Group 1 was equal to 120.2±0.1 g/l, in the Group 2 – 121.1±11.1 g/l, White Blood Cell content was, respectively, in the Group 1 $7.9\pm0.5*10^9$/l, in the Group 2 – $8.10\pm0.4*10^9$/l. Prior to surgery, mild leukocytosis and ESR increasing were noted in 17 (14.8%) cases, and LII before surgery was within the normal range in both study groups.

The study of the bacterial spectrum of the vagina in the examined patients showed that 44 (38.3%) had biotope disorders. Along with lactobacilli that have antimicrobial activity against opportunistic pathogens, associations of opportunistic microorganisms have been found in clinically significant concentrations. Most often, E. coli, Enterococcus faecalis, Candida albicans, Bacillus, Corynebacterium spp., Staphylococcus aureus, Klebsiella were sown.

The vaginal biotope state before surgery had no significant differences: I degree of vagina cleanliness was diagnosed in 61.7% of patients in Group 1 and in 61.8% in Group 2 (p = 1), II degree of vagina cleanliness, respectively, in 38.6 and 37.9% of patients (Fisher's exact test p = 1). Therefore, in examined patients were found endogenous ways of infection: the presence of a significant content of opportunistic bacteria and their associations.

All surgeries were planned and performed by laparoscopic approach: laparoscopic hysterectomy – in 67 (58.3%) patients, conservative myomectomy with posterior colpotomy – in 48 (41.7%) patients.

The duration of surgeries in both groups of patients did not differ (p=0.962): in the experimental group it was 79.5±19.1 minutes, in the control group – 80.5±7.4 minutes. The mean volume of intraoperative blood loss in both groups was not significantly different and amounted to 130.5±40.5 ml.

Post-operative measures consisted of early motor activity of patients, physical therapy, monitoring of heart rate, body temperature, diuresis, as well as the LII monitoring, which characterizes the inflammation severity of cellular and plasma origin and is important for treatment monitoring and prognosis for the PSC development.

The vaginal biotope state before surgery had no significant differences: I degree of vagina cleanliness was diagnosed in 61.7% of patients in Group 1 and in 61.8% in Group 2 (p = 1), II degree of vagina cleanliness, respectively, in 38.6 and 37.9% of patients (Fisher's exact test p = 1).

In the postoperative period, an average hemoglobin content in the patients of both groups also did not differ; in both groups there was mild leukocytosis and ESR increasing; but in patients of Group 1 LII was within the normal range of 1.20±0.02 units, and in the Group 2 it was increased to 1.80±0.04 units (table 2).

In the study of vaginal biotope in the post-surgery period, in the Group 1 was found an increase in lactobacilli number and a decrease of 87.3% in the opportunistic microflora number (Fig. 1). Thus, the pathogenic flora number in the experimental group of patients decreased from 5.1±0.1 lg10 (CFU/ml) to 3.4±0.1 lg10 (CFU/ml), or by 87.3% (p <0.001), while in Group 2, this indicator had no significant changes (table 2).

Table 2

Dynamics of clinical and laboratory parameters in the examined patients

Indices	Group 1 (Experimental, n=60)		Group 2 (Control, n=55)	
	Before treatment	After treatment	Before treatment	After treatment
White blood cells *10^9/l	7.9±0.5	9.2±0.5	8.1±0.4	9.3±0.3
LII, units	1.50±0.05	1.20±0.02*	1.50±0.05	1.80±0.04*
Number of opportunistic bacteria, lg10 (CFU/ml)	5.1±0.1	3.4±0.1*	5.1±0.1	4.9±0.1

Note: * difference between pre- and post-surgery values, p <0.001

In the control group, lactobacilli decreased in 27 (49.1%) patients in the vaginal biotope and in 17 (30.9%) the Candida fungi growth was observed, which indicated dysbiotic disorders.

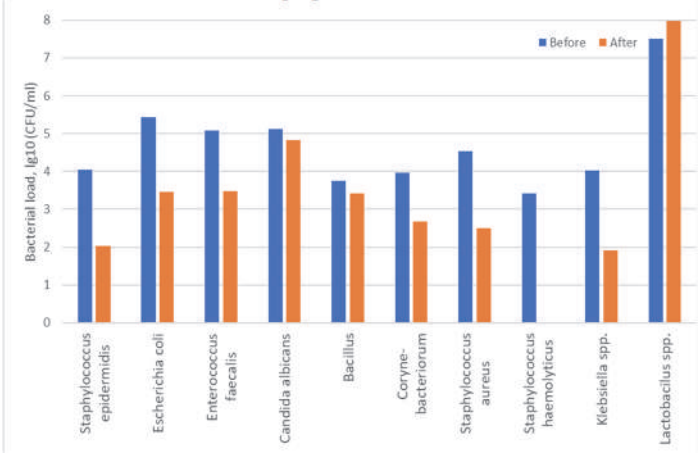

Fig. 1. Changes in vaginal biotope after antiseptic administration in the experimental group.

As a result of antiseptic administration for complex PSC prevention in patients of the experimental group in "clean-contaminated" laparoscopic surgeries in the postoperative period, LII decreased from 1.50±0.05 units to 1.20±0.02 units, and in the vaginal biotope significantly decreased the content of opportunistic microflora (p <0.01); while in the control group the LII indicator had a significant increase from 1.50±0.05 units to 1.80±0.04 units (p <0.01) and there were noted manifestations of dysbiosis (table 2).

The duration of the anesthesia period was 3.4±1.3 days versus 3.5±1.5 days, the period of intestinal function recovery was 3.5±1.5 days versus 2.4±0.9 days and the mean hospital stay of 3.0±0.4 days versus 3.2±0.3 days had no significant differences in the compared groups (table 3).

Table 3

Features of the post-surgery period course

Indices	Group 1	Group 2	p
Duration of anesthesia period, days	3.4±1.3	3.5±1.5	0.960
Intestinal function recovery, days	3.5±1.5	2.4±0.9	0.934
Post-surgery bed day, days	3.0±0.4	3.2±0.3	0.690

In the analysis of early postoperative complications, the PSC incidence was similar in both groups (table 4). There were no severe complications (subphrenic abscess, subhepatic abscess, pelvic cavity abscesses, intestinal abscesses, peritonitis).

In our opinion, the absence of severe forms of infectious-inflammatory complications in the examined groups is associated with careful patients selection without significant risk factors for PSC development (metabolic and endocrine disorders, urogenital infections, immunodeficiency states, allergic reactions, severe anemia, bleeding).

Table 4

Frequency of postoperative complications in studied groups

Indices	Group 1	Group 2	p
Fever >37.5 ˚C for more than 3 days	1 (1.7%)	1 (1.8 %)	0.496
Periculitis, inflammatory infiltrate of a colpotomy wound	1 (1.7%)	1 (1.8 %)	0.496
Signs of intestinal dysbiosis	1 (1.7%)	3 (5.5%)	0.131

The data obtained correlate with the results of studies by Ierano C. et al. (2017), which have shown that topical application of antiseptic agents for high-risk wounds causes a reduction in the infectious complications incidence [9]. Antibiotic prophylaxis should not be used as a temporary measure in the absence of timely application of antiseptics. Proper preoperative preparation and risk assessment are critical to preventing purulent-septic complications in the surgical site [6, 9].

Thus, the effectiveness of topical application of decamethoxin antiseptic solution, as well as the absence of negative factors inherent in systemic antibiotic prophylaxis (increase in the treatment cost, the risk of side effects; the risk of developing polyresistant bacterial strains; difficulty in diagnosis, the clinical picture "vague" of infectious complication), allows to recommend this method for optimization of PSC prevention at “clean-contaminated” laparoscopic surgeries on the pelvic organs with the risk of vaginal microbiota contamination.

Conclusion

The study showed that intravaginal application of decamethoxin in "clean-contaminated" gynecological surgeries contributes to the vaginal microbiome correction, 87.3% reduction in the content of opportunistic flora and the inflammatory processes intensity at the postoperative stage of treatment. The proposed method of treatment is effective and comparable to traditional antibiotic prophylaxis of complications (subject to careful selection of patients, adherence to scrupulous surgical technique and minimization of tissue injury).

Prospects for further research *are to study the long-term results of treatment, as well as the cost-effectiveness of the proposed method of prevention of infectious-inflammatory complications in operations on the pelvic organs.*

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Реферати

ПРОФІЛАКТИКА ГНІЙНО-СЕПТИЧНИХ УСКЛАДНЕНЬ ПРИ ЛАПАРОСКОПІЧНИХ ОПЕРАЦІЯХ НА ОРГАНАХ МАЛОГО ТАЗА З РИЗИКОМ КОНТАМІНАЦІЇ ВАГІНАЛЬНОЇ МІКРОБІОТИ

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Проведений аналіз ефективності профілактики гнійно–септичних ускладнень при 115 “умовно чистих” лапароскопічних операціях на органах малого таза (лапароскопічна гістеректомія, консервативна міомектомія з видаленням вузла через кольпотомний розтин). В основній групі хворих (n = 60) інтравагінально застосували 0,02 % розчин декаметоксину. Контрольна група (n = 55) одержувала традиційну системну періопераційну антибіотікопрофілактику з використанням цефалоспоринів. Показано, що як за динамікою перебігу раннього післяопераційного періоду, так і показниками системної запальної відповіді і кількістю ускладнень достовірних відмінностей між досліджуваними групами не було. В основній групі мало місце збільшення кількості лактобацил і зменшення на 87,3% вмісту умовно-патогенної мікрофлори, що свідчило про доцільність профілактичного інтраопераційного місцевого застосування декаметоксину.

Ключові слова: лапароскопія, гнійно-септичні ускладнення, профілактика, декаметоксин.

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ПРОФИЛАКТИКА ГНОЙНО-СЕПТИЧЕСКИХ ОСЛОЖНЕНИЙ ПРИ ЛАПАРОСКОПИЧЕСКИХ ОПЕРАЦИЯХ НА ОРГАНАХ МАЛОГО ТАЗА С РИСКОМ КОНТАМИНАЦИИ ВАГИНАЛЬНОЙ МИКРОБИОТЫ

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Проведен анализ эффективности профилактики гнойно-септических осложнений при 115 "условно чистых" лапароскопических операциях на органах малого таза (лапароскопическая гистерэктомия, консервативная миомектомия с удалением узла через кольпотомный разрез). В основной группе больных (n = 60) интравагинально применяли 0,02% раствор декаметоксина. Контрольная группа (n = 55) получала традиционную системную периоперационную антибиотикопрофилактику с использованием цефалоспоринов. Показано, что как по динамике течения раннего послеоперационного периода, так и по показателями системного воспалительного ответа и количеством осложнений достоверных различий между исследуемыми группами не было. В основной группе имело место снижение степени эндогенной интоксикации, уменьшение на 87,3% содержания условно-патогенной микрофлоры, нормализация микробиоценоза, что свидетельствовало о целесообразности профилактического интраоперационного местного применения декаметоксина.

Ключевые слова: лапароскопия, гнойно-септические осложнения, профилактика, декаметоксин.

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RELATION OF STRESS-STRAIN STATE IN THE KINEMATIC CHAIN "HIP-AND-KNEE JOINT" WITH THE CERVICAL DIAPHYSEAL ANGLE CHANGING UNDER THE CONDITIONS OF DYSPLASIA

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The article presents the study of biomechanical disorders in the dysplastic process in the hip and knee joints using the finite elements model with different cervical-diaphyseal angles (CDA) of the proximal femoral bone. With the CDA equal to 90°, the femoral neck stress was 42.4 MPa (27.6 in the norm). In the proximal tibia, the level of the stress condition has increased on the medial side up to 17.9 MPa (11.1 normal), and on the lateral side 9.1 MPa (3.5 normal). Thus, on the medial side the stress magnitude is 21.6 MPa (11.2 normal), on the lateral side - 1.7 MPa (2 in the norm). For the CDA equal to 160° the stress in the hip joint reaches 26.5 MPa (27.6 normal). In the proximal tibia on the medial side the tension is 9 MPa (11.1 normal), and on the lateral side it is 3.5 MPa (3.5 normal). Distribution of the stress condition in the knee joint showed that on the medial side the stress magnitude is 13.1 MPa (11.2 normal), and on the lateral side - 3.8 MPa (2 normal). Comparative analysis of the calculations performed for models with different CDA showed that the CDA reduction leads to a significant increase in the stress condition not only in the neck of the femoral bone, but also in the knee joint. Whereas, with increasing CDA the growth of stress-strain state is slight, mainly in the lateral part of the knee joint.

Key words: CDA change, stress-strain state of the hip joint, proximal tibia.

The work is a fragment of the research project "To study biomechanical features of standing and gait of patients with a long course of hip osteoarthritis", state registration No. 0118U006950.

The past decade is characterized by an increase in syndromic pathology, which is based on connective tissue dysplasia. Scientific advances in this field have permitted to consider the problem of dysplastic diseases in a different way. It is believed that these diseases formation causes a hereditary susceptibility factor that adversely affects the connective tissue development, including that in the musculoskeletal system, which further leads to anatomic and functional unconformity of the joint's surfaces (discongruence), and further to biomechanical imbalance and arthrosis [4].

A sufficiently detailed review of modern biomechanical studies in the hip joint was made in B. Vafaeian's et al. study [13]. The stress state of the femur for different CDA values was analyzed in the studies of I.B. Zelenetsky [1], Diplesh Gautam [8]. The researchers [2, 3, 7, 11] studied the stress condition of the knee joint both normal and with dysplastic changes.

Since the dysplastic process relates to all systems of the human body, it is natural that changes in the biomechanical parameters of the joints, to varying degrees, will mutually affect each other [5]. Together, multiple pathological, especially biomechanical, changes form a multilevel spatial system of the musculoskeletal system with impaired function.

However, mutual compensatory processes (concordance) that mask anomalies of joint development are possible, often temporarily.

Insufficient supply of the necessary equipment (CT, MRI) in domestic medicine complicates the construction of the entire human musculo-skeletal system (MSS) model. Geometric constructions of pathological abnormalities in the joints were applied in the individual approach for the purpose of diagnosis, treatment and prevention. Therefore the preferred local approach to the joints, complicates early diagnosis and treatment.

Increased load on particular areas of the articular surfaces leads to an increase of the stress-strain state (SSS). Chronic stress of their cartilaginous tissue creates conditions for the development of arthrosis, the start for which in the prenatal period is dysplasia [4, 13].

In this regard, numerous tasks stand out clarifying the impact of each dysplastic component in the overall disease process.

In the process of studying this problem by means of the finite elements method (FEM), isolated models of the hip and knee joints were built to solve various problems. However, in order to bring the model closer to real conditions, as well as to establish the correlation and mutual influence of the lower extremity joints, it is necessary to build a model adapted to the set tasks.

When studying the stresses in the hip and knee joints (both in normal and with different pathology) by FEM, data were obtained on their uneven distribution, localization in particular areas of the joint

elements. However, the main factor of the joint load was considered insufficiently due to disorganized location of the limb's mechanical axis.

Taking into consideration the significant priority of biomechanical disturbances in this process, it is of interest to study their interaction in the "hip-knee joint" system. It is known that change of the limb's anatomical-mechanical axis and, accordingly, the angles of muscles insertion affects their muscle strength and muscle imbalance [1]. In their turn, different conditions arise for the local loading on the articular surfaces. It can be assumed that the axial parameters disturbance also affects the stress-strain state (SSS) in all elements of the joints. However, to date, we believe that for the sake of the study completeness, it is more appropriate to consider joints not isolated, but within the kinematic chain of the musculoskeletal system, which brings them closer to the real object.

Since dysplasia in the lower extremity is frequently a combination of anatomical and parametric abnormalities, it can be considered that their total impact will increase the negative effect on the joints function. We have not found any similar studies in the available literature.

The purpose of the work was to study the correlation of stress-strain state of the "hip-knee joint" system in the norm and with the increased cervical-diaphyseal angle (CDA) in dysplasia.

Materials and methods. In this work, we studied the "hip-knee joint" system SSS with the changed cervical-diaphyseal angle of the femur and the normal knee joint. The studies were performed on a volumetric model of the lower extremity, developed in the Biomechanics Laboratory of State Institution «Sytenko Institute of Spine and Joint Pathology NAMS of Ukraine». Three models have been constructed with the CDA 127°, 90° and 160°.

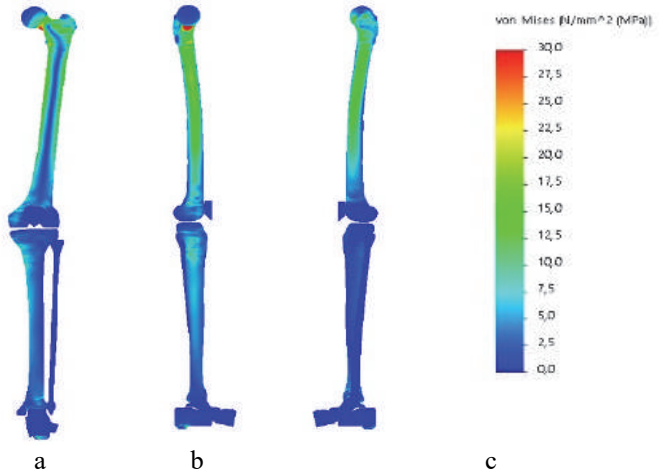
The model has restrictions on movement, the heel bone and the foot bones are fixed. The single-support standing was considered. The main load is the body weight: the mean value for an adult is 700 N, excluding of the weight of the support foot from the load: 700-126 = 574 N. The musculoskeletal apparatus action was replaced by the equivalent load action (1580 N), which is added to the trochanter major. Angles, applications and load values were taken according to the studies [6, 14]. The finite element model consists of 902647 10-node tetraidal finite elements with quadratic approximation [9, 15]. The calculations were performed in the Solid Works software [10].

The calculations took into account different types of biological tissues: cortical and spongy bone, cartilage tissue, the material was considered homogeneous and isotropic. The data that are most commonly found in the literature are used in the work [12].

Results of the study and their discussion. The model's calculations with the CDA of 127° (fig. 1) showed that in the hip joint, the femoral neck is the most stressed, where the stress level reaches 27.6 MPa.

The stress values by Mises in the central part of the femur both on the medial and on the lateral sides reach values of 15-18 MPa. In the proximal tibia on the medial side, the stress magnitude by Mises is 11.1 MPa, and on the lateral side - 3.5 MPa.

The stress distribution in the knee joint according to Mises is equal to 11.2 MPa on the medial side, and to 2 MPa on the lateral side.



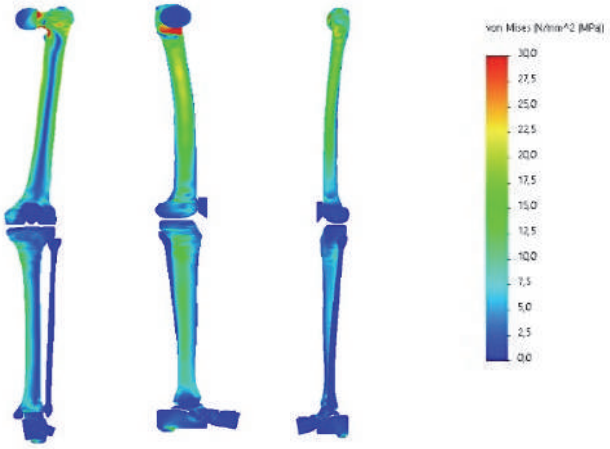
a b c

Fig. 1. The stress distribution according to Mises in the proximal tibia at CDA 127°: a) frontal view; b) medial view; c) lateral view.

Comparison of the study results with the work of the author [8] showed that the maximum stress value according to Mises in the work [8] is 21.3 MPa (27.6 MPa in our study). The difference in values is explained by the difference in the load on the femur head 627 N (574 N in our study), as well as by the action of muscles - 1580 N, applied to the large femoral head, which is not taken into account in the work [8]. The difference in the materials properties should also be noted; for example, the modulus of the tubular bone elasticity in the work of the author [8] is 15500 MPa (18350 MPa in our study).

Comparative analysis of the stress condition in the knee joint to the work of the authors [10] shows that the nature of the stress state distribution coincides, the medial side of the knee joint is more stressed, and the lateral side is less stressed.

The model calculations at CDA 90° (fig. 2) show that in the area of the hip joint, as in the previous calculation, the most stressed is the femoral neck, but the level of the stress state is much higher - 42.4 MPa (27, 6 MPa for the model is normal).



a b c

Fig. 2. Stress distribution by Mises in the design model at CDA 90°: a) frontal view; b) medial view; c) lateral view.

The stress values by Mises in the central part of the femur on both the medial and lateral sides reach values of 18-21 MPa (15-18 MPa for the model is normal). In the proximal tibia, the level of stress also increased and was 17.9 MPa on the medial side (11.1 MPa for the normal model) and 9.1 MPa on the lateral side (3.5 MPa for the normal model).

Also, in the tibia as a whole, there was the SSS increase in the knee joint. Thus, on the medial side, the stress magnitude according to Mises is 21.6 MPa (11.2 MPa for the model is normal), on the lateral side - 1.7 MPa (2 MPa for the model is normal).

Comparison of the study results with the work of the author [8] shows that the maximum stress value by Mises in the work [8] is 66.3 MPa (42.4 MPa in our study).

The difference in values is explained by both the factors mentioned above and the difference in the CDA value. In the work [8], the angle of 106º (90º in our research) was studied.

The model calculations at the CDA equal to 160° (fig. 3), show that in the area of the hip joint, as well as in the previous calculations, the most stressed is the femoral neck, where the level of the stress state reaches the value of 26.5 MPa (27.6 MPa for the model is normal).

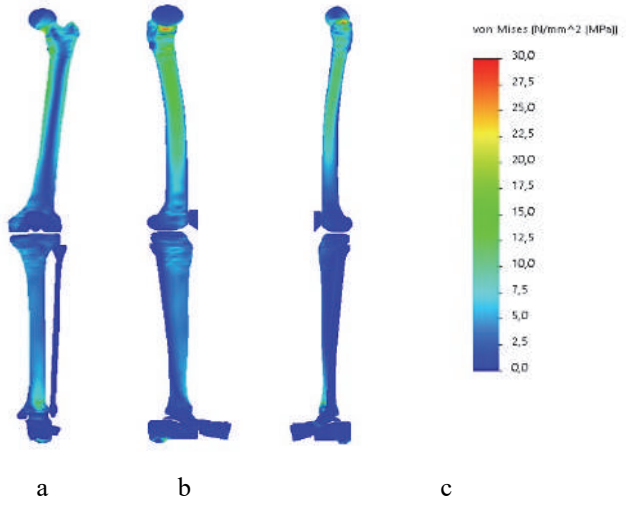


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Fig. 3. Mises stress distribution in the design model at CDA of 160°: a) frontal view; b) medial view; c) lateral view.

The stress values by Mises in the central part of the femur from on the medial and the lateral sides reach values of 12-23 MPa (15-18 MPa for the model is normal). In the proximal tibia on the medial side, the stress value by Mises is 9 MPa (11.1 MPa for the model is normal), and on the lateral side - 3.5 MPa (3.5 MPa for the model is normal). The stress distribution in the knee joint shows that on the medial side, the stress values by Mises is 13.1 MPa (11.2 MPa for the model is normal), and on the lateral side - 3.8 MPa (2 MPa for the model is normal).

Stress distribution in the knee joint according to Mises is equal: on the medial side, the stress value is 13.1 MPa (11.2 MPa for the model is normal), and on the lateral side - 3.8 MPa (2 MPa for the model is normal).

Comparison of the study results with the work of the author [8] shows that the maximum stress value by Mises in the work [8] is 73.2 MPa (26.5 MPa in our study). In contrast to the previous calculations, the difference in the stress state is sufficient and it is not explained by the factors mentioned above. The difficulty of comparison is caused by the lack of modern works to study the CDA effect on the stress state of the femur. In the work of the authors [10], who carried out studies by another method (analytical estimates of the stress state with the changed CDA), the CDA ratio with the maximum stress value is close to that in our studies. The minimal stress values at CDA are 138º and 1500 º [10] (in our study - 1270 and 1600 respectively).

The comparative analysis of the calculations performed for models with different CDA is presented in table 1.

Thus, the study showed that the CDA reduction leads to a significant increase in the stress state not only in the neck of the femur, but also in the knee joint, with an increase in CDA, the growth of SSS occurs slightly, mainly in the lateral part of the knee joint.

In the available literature, we have practically failed to find works in this formulation of tasks. Somewhat close to our study are the works by R.O. Solodilov and S.I. Loginov [5] in the clinical field confirming our calculations and hypotheses [2].

Table 1

Comparison of the stress values by Mises at different CDA in the femur and the knee joint

Segment	Normal	CDA 90°	CDA 160°
Neck of the femur	27.6	42.4	26.5
Medial side of the femur	18.9	22.7	22.6
Lateral side of the femur	15.3	18.3	12
Medial side of the knee joint	11.2	21.6	13.1
Lateral side of the knee joint	2	1.7	3.8
Medial side of the tibia	11.1	17.9	9
Lateral side of the tibia	3.5	9.1	3.5

We believe that expanding medical knowledge about the correlation and mutual influence of pathological changes in the dysplastic joints will help to change the tactics of conservative and surgical treatment, especially at the early stages, which significantly inhibits development of arthrosis.

Because the technologies for radical elimination of dysplasia at the cellular level are at their initial stages, such a complex and multidisciplinary problem requires further study, which will influence the inhibition of dystrophic processes.

Conclusions

1. The CDA change leads to an increase in SSS in the “hip and knee joint” design models.

2. CDA reduction leads to an increase in SSS both in the femur and the tibia, to a greater extent on the medial side. At CDA equal to 90°, stress in the neck of the femur and in the knee joint grows practically twice.

3. At CDA of 160°, the stress state in the bones varies within 20%. In the knee joint from the lateral side there is stress increase by 47%.

4. A direct correlation between the stresses in the model of the lower extremity with CDA changing is established.

5. An increase in the SSS in the model of a normal knee at 160° CDA may be a “risk zone” especially for its lateral surface under the dysplasia conditions.

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Реферати

ВЗАЄМОЗВ'ЯЗОК НАПРУЖЕНО-ДЕФОРМОВАНОГО СТАНУ В КІНЕМАТИЧНОМУ ЛАНЦЮЗІ «КУЛЬШОВО-КОЛІННОГО СУГЛОБУ» ПРИ ЗМІНІ ШИЙКОВО-ДІАФІЗАРНОГО КУТА В УМОВАХ ДИСПЛАЗІЇ

Зеленецький І.Б., Мітелева З.М., Снісаренко П.І., Яресько А.В.

Статтю присвячено дослідженню біомеханічних порушень при диспластичному процесі у кульшовому та колінному суглобах з використанням моделі кінцевих елементів при різних шийково-діафізарних кутах (ШДК) проксимального відділу стегнової кістки. При ШДК рівним 90°, напруження шийки стегнової кістки склала - 42,4 МПа (27,6 в нормі). У проксимальному відділі великогомілкової кістки рівень напруженого стану зріс на медіальній стороні до 17,9 МПа (11,1 в нормі), а на латеральній стороні 9,1 МПа (3,5 в нормі). Так на медіальній стороні величина напружень дорівнює 21,6 МПа (11,2 в нормі), на латеральній стороні - 1,7 МПа (2 в нормі). Для ШДК рівного 160° напруження в області кульшового суглоба досягає 26,5 МПа (27,6 в нормі). У проксимальному відділі великогомілкової кістки на медіальній стороні напруження становить 9 МПа (11,1 в нормі), а на латеральній стороні 3,5 МПа (3,5 в нормі). Розподіл напруженого стану в колінному суглобі показав, що на медіальній стороні величина напружень дорівнює 13,1 МПа (11,2 в нормі), а на латеральній стороні - 3,8 МПа (2 в нормі). Порівняльний аналіз проведених розрахунків для моделей з різним ШДК показав, що зменшення ШДК призводить до значного збільшення напруженого стану не тільки в шийці стегнової кістки, але і в колінному суглобі. При збільшенні ШДК зростання напружено-деформованого стану відбувається незначно, в основному, в латеральній частині колінного суглобу.

Ключові слова: зміна ШДК, напружено-деформований стан стегнової кістки, проксимального відділу великогомілкової кістки.

Стаття надійшла 15.09.2019

ВЗАИМОСВЯЗЬ НАПРЯЖЕННО-ДЕФОРМИРОВАННОГО СОСТОЯНИЯ В КИНЕМАТИЧЕСКОЙ ЦЕПИ «ТАЗОБЕДРЕННЫЙ-КОЛЕННЫЙ СУСТАВ» ПРИ ИЗМЕНЕНИИ ШЕЕЧНО-ДИАФИЗАРНОГО УГЛА В УСЛОВИЯХ ДИСПЛАЗИИ

Зеленецкий И.Б., Мителева З.М. , Снисаренко П.И., Яресько А.В.

Статья посвящена исследованию биомеханических нарушений при диспластическом процессе в тазобедренном и коленном суставах с использованием модели конечных элементов при различных шеечно – диафизарных углах (ШДУ) проксимального отдела бедренной кости. При ШДУ равным 90°, напряжение шейки бедренной кости составила - 42,4 МПа (27,6 в норме). В проксимальном отделе большеберцовой кости уровень напряженного состояния вырос на медиальной стороне до 17,9 МПа (11,1 в норме), а на латеральной стороне 9,1 МПа (3,5 в норме). Так на медиальной стороне величина напряжений равна 21,6 МПа (11,2 в норме), на латеральной стороне - 1,7 МПа (2 в норме). Для ШДУ равного 160° напряжение в области тазобедренного сустава достигает 26,5 МПа (27,6 в норме). В проксимальном отделе большеберцовой кости на медиальной стороне напряжение составляет 9 МПа (11,1 в норме), а на латеральной стороне 3,5 МПа (3,5 в норме). Распределение напряженного состояния в коленном суставе показало, что на медиальной стороне величина напряжений равна 13,1 МПа (11,2 в норме), а на латеральной стороне - 3,8 МПа (2 в норме). Сравнительный анализ проведенных расчетов для моделей с различным ШДУ показал, что уменьшение ШДУ приводит к значительному увеличению напряженного состояния не только в шейке бедренной кости, но и в коленном суставе. При увеличении ШДУ рост напряженно-деформированного состояния происходит незначительно, в основном, в латеральной части коленного сустава.

Ключевые слова: изменение ШДУ, напряженно-деформированное состояние бедренной кости, проксимального отдела большеберцовой кости.

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ANALYSIS OF DENTURE BASE IMPACT ON THE DENTURE FOUNDATION AREA TISSUES

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The article presents the results of the study of the dental base impact on the denture foundation area tissues. The study was conducted in 149 patients aged 41 to 74 years. Removable partial laminar dentures for the upper and lower jaws were made of plastics "Ftorax" and "Etacryl-02" by three technologies: in a "water bath", in a dry polymerizer under the pressure and in an advanced injection molding machine. The results obtained allow us to recommend the technology of manufacturing removable partial laminar dentures in the advanced injection molding machine for using in dental orthopedics clinic.

Key words: removable partial laminar dentures, polymerization technologies, base plastics, denture foundation area.

The study is a fragment of the research project "New approaches to the diagnosis and treatment of secondary adentia, periodontal and TMJ tissue lesions in adults", state registration No. 0117U000302.

Modern orthopedic dentistry offers a large number of structures that are used in the restoration of partial defects of the dental arches [6].

Rehabilitation of patients with partial teeth loss is a difficult problem in the manufacturing dentures, which must be high-grade as to functional, aesthetic and psycho-emotional. Despite the emergence of new base materials, acrylic plastics are usually essential for the manufacturing removable partial laminar dentures [2].

The experience of using acrylic plastics for the manufacturing removable partial laminar dentures testifies to their relative chemical resistance, satisfactory strength, good aesthetic properties and functionality. At the same time, long-term clinical observations point to some of their disadvantages [4].

One of the ways to eliminate the disadvantages of base acrylic plastics is to improve their physical, mechanical and chemical characteristics. It is possible to increase various physical, mechanical and chemical properties of these plastics by using different technologies of manufacturing bases of removable partial laminar dentures [1, 3].

Manufacturing of removable partial laminar dentures using different technologies of acrylic plastics polymerization will solve the problem of the negative impact of bases of removable partial laminar dentures on the denture foundation area tissues [5].

Thus, the problem of the direct impact of materials used for the manufacturing removable partial laminar dentures is one of the main and relevant in the dental orthopedics clinic.

The purpose of the work was to analyze the dental base impact, made by various technologies, on the denture foundation area tissues.

Materials and methods. The study of the dental base impact on the denture foundation area tissues was performed by observation of 149 patients aged 41 to 74 years, for which were made of plastics "Ftorax" and "Etacryl-02" 188 removable partial laminar dentures on the upper and lower jaws. The base plastics polymerization was carried out in a "water bath", in a dry polymerizer under the pressure and in an advanced injection molding machine.

Group I (control group) included patients who had removable partial laminar dentures made of base acrylic plastic "Ftorax". Polymerization of base acrylic plastic "Ftorax" was carried out in a "water bath".

Patients of Group II were made removable partial laminar dentures of base acrylic plastic "Ftorax". Polymerization of base acrylic plastic "Ftorax" was carried out in a dry polymerizer under the pressure.

Patients of Group III were made removable partial laminar dentures of base acrylic plastic "Ftorax", the polymerization of which was carried out in an advanced injection molding machine.

Group IV (control group) included patients for whom were made removable partial laminar dentures of base acrylic plastic "Etacryl-02" in a "water bath".

Group V included patients with removable partial laminar dentures of base acrylic plastic "Etacryl-02" in a dry polymerizer under the pressure.

Patients of Group VI were made removable partial laminar dentures of base acrylic plastic "Etacryl-02" by injection molding technique.

The patients have been under our observation for three years.

The dental prosthetic rehabilitation effectiveness and the use period of removable partial laminar dentures depends on the completeness of clinical examinations, the denture foundation area state, and the dentures manufacturing technology. In order to establish the validity of this conclusion, we performed comparative clinical and laboratory studies of the extent of the dental base impact on the denture foundation area tissues, as well as the study of the chewing effectiveness with removable laminar dentures, which were made in various polymerization methods.

Results of the study and their discussion. Clinical assessment of removable partial laminar dentures quality, which bases were made by various methods, was carried out using subjective data (complaints, disease and life history) and basic objective data (examination, palpation).

When using partial removable partial laminar dentures, some patients complained of pain under the denture base, the impossibility of prolonged use of the denture. Physical examination revealed limited inflammation sites in certain denture foundation areas: hyperemia, edema, abrasion, erosion up to 1 cm^2, which is due to the mechanical pressure of individual sections of the denture bases.

Other patients complained of mucous membrane burning under the denture base, its dryness. The mucous membrane of the denture foundation area, especially on the upper jaw, is diffusely hyperemic, swollen, painful on palpation, which depends rather on the toxic effect of the denture bases residual monomer. This significantly leads to an increase in the adaptation time to removable laminar dentures, unnecessarily more relines, accelerated development of atrophic changes of the mucous membrane and bone tissue of the denture foundation area.

Schiller-Pisarev solution was used for objective comparative evaluation of removable partial laminar dentures, determination of inflammation of the denture foundation area mucosa as a result of mechanical over stressing and the base plastics toxicity. Mucous staining was performed not only to asset the damage area in the toxic effect and over stressing, but also to improve the accuracy of the denture bases areas reline during mechanical action.

Clinical assessment of the state of the denture bases areas tissues and the quality of dentures was performed at different times of using removable partial laminar dentures (24 hours, 7 days, 1 month).

One of the quality indicators of manufacturing removable partial laminar dentures is the need for their reline at various stages of their use.

Table 1 shows data on the frequency and number of relines of removable partial laminar dentures made using different polymerization methods for base plastics.

Table 1

Number of removable partial laminar dentures relines in experimental groups of patients

Number of relines	Group I		Group II		Group III		Group IV		Group V		Group VI	
	abs.	%	abs.	%	abs.	%	abs.	%	abs.	%	abs.	%
	33	100	32	100	33	100	28	100	35	100	27	100
1 reline	27	81.8	25	78.1	24	72.7	24	85.7	24	68.5	16	59.3
2 relines	20	60.6	12	37.5	10	30.3	14	50.0	10	28.6	8	29.6
3 relines	8	24.2	2	6.3	2	6.1	5	17.9	2	5.7	2	7.4

In Groups I and IV (control groups), 27 and 24 relines were performed 24 hours after the removable partial laminar denture delivery, which is 81.8±0.012% and 85.7±0.019%, respectively, according to the manufactured dentures. The repeated denture relines of patients in these groups were respectively 60.6±0.015% and 50.0±0.26%. The third reline of dentures made by the conventional polymerization technology ("water bath") were, respectively, 24.2±0.029% and 17.9±0.032%.

In the patients of Groups II and V, studies have shown that 25 and 24 removable partial laminar dentures needed reline in 24 hours after the delivery to the oral cavity, which is 78.1±0.015% and 68.5±0.017%, respectively. 12 and 10 dentures of these groups were subject to repeated reline, which was respectively 37.5±0.019% and 28.6±0.026%. Two dentures were subject to reline for the third time and this was 6.3±0.1% and 5.7±0.1%, respectively.

Dentures of patients of Groups III and VI were also subject to reline, but their number was much fewer in comparison with the Groups I and IV. Thus, 24 dentures of the Group III and 16 prostheses of the Group VI were subject to the first reline, which was 72.7±0.018% and 59.3±0.018% respectively. But only 30.3±0.023% and 29.6±0.029% of dentures in these groups needed a second reline. The third reline was subject to 6.1±0.1% and 7.4±0.1% dentures of patients of Groups III and VI.

Table 2 shows the data of Schiller-Pisarev test in the examined patients, which revealed limited inflammation sites (the result of traumatic action) and diffuse inflammatory processes of the denture foundation area (toxic effect).

Table 2

Indicators of the Schiller-Pisarev test in the experimental groups of patients

Group of patients	Number of patients	Indices of Schiller-Pisarev test								
		after 24 hours			after 7 days			after 1 month		
		+	++	+++	+	++	+++	+	++	+++
I	абс.	3	2	1	6	3	1	9	3	1
	%	11.1	7.4	3.7	22.2	11.1	3.7	33.3	11.1	3.7
II	абс.	1	1	-	2	2	-	5	1	-
	%	4.2	4.2	-	8.4	8.4	-	20.8	4.2	-
III	абс.	2	1	-	3	-	-	-	-	-
	%	8.0	4.0	-	12.0	-	-	-	-	-
IV	абс.	3	2	-	5	3	-	10	4	1
	%	11.5	7.7	-	19.2	11.5	-	38.5	15.4	3.8
V	абс.	4	3	1	3	1	-	2	-	-
	%	17.4	13.1	4.3	13.1	4.3	-	8.7	-	-
VI	абс.	3	2	-	3	-	-	1	-	-
	%	12.5	8.4	-	12.5	-	-	4.2	-	-

As it is shown in table 2, after 24 hours traumatic lesions in patients of Groups I and IV were 18.5±0.037% and 20.0±0.32%, respectively.

After 7 days, local inflammation associated with the traumatic effect of removable laminar dentures in Groups I and IV was noted in 33.3±0.05% and 32.0±0.33%, respectively.

After 1 month of observation, traumatic injuries in these groups were within 44.4±0.023% (Group I) and 56.0±0.021% (Group IV).

In 24 hours after the denture delivery local inflammation in Groups II and V was 8.3±0.1% and 30.4±0.02%, respectively. After 7 days, local lesions in Group II were diagnosed in 16.7±0.082%, and in

Group V in 17.4±0.04%. After 1 month of observation, they were detected in 25.0±0.037% of patients of Group II and in 8.7±0.1% of patients of Group V.

In 24 hours after using dentures, local inflammation In patients of Groups III and VI was 12.5±0.033% and 20.8±0.037%, respectively. After 7 days, these indicators in both Groups III and VI were equal to 12.5±0.06%. After 1 month of observation, local inflammation of the mucous membrane was detected in 1 patient of Group VI, which is 4.2%.

From the data in Table 2, it is seen that the toxic lesions frequency of mucous membrane of the denture foundation area at all observation periods in patients of Group I is 3.7%, in Group IV toxic lesion of the mucous membrane was detected in 1 patient, which is 4.0%.

After 24 hours of denture use, there was also a toxic lesion in 1 patient (4.3%) in Group V.

However, in Groups III and VI, a toxic lesion of mucous membrane of the denture foundation area was not visible.

One of the quality criteria for the manufacturing removable partial laminar dentures is the frequency of repairs.

Table 3 shows the frequency of removable laminar dentures breakdowns manufactured by various polymerization technologies. The observation period was 3 years.

Table 3

The frequency of removable partial laminar dentures repairs

Patient groups and number of manufactured dentures	Number of removable partial laminar dentures, which were subject to repair		
	n	M±m (%)	Significance test
Group I (33)	9	27.3±0.03	$p < 0.05$
Group II (32)	2	6.25±0.05	$p < 0.001$
Group III (33)	1	3.0	$p < 0.05$
Group IV (28)	7	25.0±0.03	$p < 0.05$
Group V (35)	3	8.6±0.03	$p < 0.05$
Group VI (27)	-	-	$p > 0.05$

Data in table 3 indicate that removable partial laminar dentures manufactured in a "water bath" were more often subject to repair than removable partial laminar dentures made in an advanced injection molding machine ($p < 0.05$).

With regard to this indicator in the Groups II and III, V and VI, we can only say that there is a tendency to improve the removable partial laminar dentures quality manufactured in an advanced injection molding machine compared to removable partial laminar dentures manufactured in the dry polymerizer under the pressure.

The analysis of the literature data confirmed the relevance of further study of the polymerization efficiency of acrylic plastics by "water bath" polymerization and dry polymerizer under the pressure in a comparative aspect.

Differences in the obtained results, in our opinion, is explained not only by the manufacturability of the polymerization technologies, but also by the differences in the ratio of the acrylic plastics components (monomer-polymer), which, in turn, affects the quality of the manufactured structure [1].

Thus, the obtained data analysis with respect to the reline's number made it possible to obtain a statistically significant reliability of differences ($p > 0.05$), which testifies to the influence of polymerization technologies on the frequency and the number of removable partial laminar dentures relines.

The data obtained regarding the frequency of traumatic mucosal lesions that cause removable partial laminar dentures manufactured by various polymerization technologies is statistically significantly different ($p < 0.05$). The toxic effect of removable partial laminar dentures from base acrylic plastics "Ftorax" and "Etacryl-02" made by the polymerization technology in a "water bath" is significantly different from the action of removable partial laminar dentures from the same base plastics made in a dry polymerizer under the pressure and in an advanced injection molding machine ($p < 0.05$).

The data obtained coincide with the results of other authors [6], which indicate the potential risk of injury to the denture foundation area mucosa and the toxic effect of residual monomer as the most common complications when using acrylic base plastics.

Due to the fact that all dentures were made by the same Dental Technician in accordance with technological methods, we can express an opinion on the polymerization technologies influence on the quality of manufactured removable partial laminar dentures. This opinion is validly confirmed by the frequency of repair of the dentures bases manufactured using various technologies.

Conclusions

1. The development and duration of inflammatory processes in the mucous membrane of denture foundation area depend on the action of removable partial laminar dentures manufactured by various polymerization technologies.

2. The duration of the inflammatory processes of the mucous membrane under dentures, polymerized under pressure in a dry environment and in an advanced injection molding machine of base plastics, is much shorter.

3. Removable partial laminar dentures manufactured in an advanced injection molding machine have no toxic effect on the mucous membrane of the denture foundation area.

Prospects for further research *will concern a detailed study in the comparative aspect of restoring chewing efficiency using partial removable plate prostheses manufactured by the above technologies.*

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Реферати

АНАЛІЗ ВПЛИВУ ПРОТЕЗНОГО БАЗИСА НА ТКАНИНИ ПРОТЕЗНОГО ЛОЖА

Калашніков Д.В., Кіндій Д.Д., Король Д.М., Кіндій В.Д.

У статті наведено результати дослідження впливу протезного базису на тканини протезного ложа. Дослідження проведено на 149 хворих віком від 41 до 74 років. Часткові знімні пластинкові протези на верхню та нижню щелепи з пластмас «Фторакс» і «Етакрил-02» виготовлялися трьома методами: на «водяній бані», в апараті для сухої полімеризації під тиском та в удосконаленому апараті для литтьового пресування. Отримані результати дозволяють рекомендувати до використання в клініці ортопедичної стоматології методику виготовлення часткових знімних пластинкових протезів в удосконаленому апараті для литтьового пресування.

Ключові слова: частковий знімний пластинковий протез, методи полімеризації, базисні пластмаси, протезне ложе.

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АНАЛИЗ ВЛИЯНИЯ ПРОТЕЗНОГО БАЗИСА НА ТКАНИ ПРОТЕЗНОГО ЛОЖА

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В статье приведены результаты исследования влияния протезного базиса на ткани протезного ложа. Исследование проведено на 149 больных в возрасте от 41 до 74 лет. Частичные съёмные пластиночные протезы на верхнюю и нижнюю челюсти из пластмасс «Фторакс» и «Этакрил-02» изготавливались тремя методами: на «водяной бане», в аппарате для сухой полимеризации под давлением и в усовершенствованном аппарате для литьевого прессования. Полученные результаты позволяют рекомендовать к использованию в клинике ортопедической стоматологии методику изготовления частичных съёмных пластиночных протезов в усовершенствованном аппарате для литьевого прессования.

Ключевые слова: частичный съёмный пластиночный протез, методы полимеризации, базисные пластмассы, протезное ложе.

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RADIOGRAPHIC CHANGES IN THE BONE GRAFTS DURING GUIDED BONE REGENERATION WITH THE USE OF TITANIUM MESH ON CLASSICAL AND AUTHORS' OWN METHODS FOR THE MUCOSAL FLAPS DETACHMENT

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One of the major problems in rehabilitation of bone volume loss in preparing patients for dental implantation is the bone graft exposure and its infection in the result of ischemic processes in the mucousal flap that covers it. We performed 27 surgical interventions for guided bone regeneration using titanium mesh according to the classical method of detachment of trapezoidal mucousal flap and 30 surgical interventions on authors' own method of detachment and mobilization of the mucousal flap. The augmentation was performed in the mandibular distal segments. Our studies have shown that the optimization of the limits of detachment and mobilization of mucousal and mucoperiosteal flaps, compared with the classical method of trapezoidal flaps, leads to a decrease in bone graft volume loss by 1.9%. The data indicate the possibility of improving the flap surgery efficiency during bone augmentation in patients with acquired edentulism.

Keywords: dental augmentation, CBCT, mucosal flaps

The work is a fragment of the research project "Diagnostics, surgical and drug treatment of patients with injuries, defects and deformities of tissues, inflammatory processes of the maxillofacial area", state registration No.: 0119U102862.

The method of dental implantation is increasingly used in the dental practice for the treatment of congenital and acquired edentulism, which in many clinical cases allows to achieve a stable and long-term treatment outcome [1, 9].

Partial or complete edentulism is always accompanied by the signs of jawbone atrophy. Therefore, in 30% of clinical cases, there are indications for the correction of alveolar bone loss before dental implant placement. In such situations, either a previous bone rehabilitation or a simultaneous (with implant placement) grafting of the alveolar process by auto-, allo-, or xenograft material (bone augmentation) is required [6]. Bone graft is the volume of bone mass for artificial enlargement, gaining the organ size, in this case – the mandible. However, often due to the technical complexity of the bone augmentation surgery and the high incidence of ischemia-related complications after mucosal flaps tension, these interventions are not practiced. In this case, as a rule, small dental implants are used, which are installed with their incorrect positioning, or patients are refused treatment [10]. This is due to the absence of conventional surgical protocols for bone rehabilitation at different degrees and forms of atrophy. The part of specialists whose professional level allows performing the reconstruction of bone tissue of the alveolar process by various methods, is characterized by unnecessary subjectivity, based on the use of them only separate, proven methods of the bone reconstruction, which is dissonant with the choice of the most effective treatment tactics. The result of such treatment is often poor clinical outcomes regarding short-term prognosis and/or poor aesthetics [4, 6].

The purpose of the study was to increase the effectiveness of flap surgery during bone augmentation in patients with acquired edentulism and reduce the risk of postoperative ischemia-related complications after mucosal flaps tension, by optimizing the boundaries of detachment and mobilization of the mucousal and mucoperiosteal flaps.

Materials and methods. The study involved patients with acquired edentulism of the mandibular distal segments of both sexes aged 38 to 57 years with vertical atrophy of no more than 4 mm. The augmentation dimension did not exceed 25 mm. We performed 27 surgical interventions for guided bone regeneration using titanium mesh according to the classical method of detachment of trapezoidal mucousal flap (control group) and 30 surgical interventions on authors' own method of detachment and mobilization of the mucousal flap (experimental group). The radiographic examination was performed using "Veraviewepocs 3De" (J. Morita Manufacturing Corporation, Japan) Cone-Beam Computed Tomography (CPCT) before surgery, on the 1st day after surgery, 60 days and 180 days after surgery. The height (X), width and thickness of bone graft (Y) were measured using the software provided with the study results (One Volume Viewer Program). The area (Z) of bone graft was also determined using One Volume Viewer. The area was calculated automatically in mm^2. Bone density was measured in the augmentation area and intact areas and determined by CBCT using the One Volume Viewer software provided with the study results. The unit of measurement was the Hunsfield (HU) ionizing radiation attenuation.

The obtained data were processed by the method of variation statistics. To achieve the above, the variational series were calculated taking into account arithmetic mean (M), standard deviation, mean square error (m).

Results of the study and their discussion. Radiographic results of the control group.

We analyzed the CBCT of patients before and after the mandibular bone augmentation. The augmentation height from the native bone, the jaw segment area in the cross section, the parameters of the bone graft volume reduction in a result of osteogenesis, density of the newly formed bone, the osteogenesis rate were taken into account.

For further comparison after the surgery, the bone graft volume obtained on cone-beam computer tomographic images was recorded immediately after guided bone regeneration using the classical method of mucousal flap detachment.

The bone graft was a homogeneous area without cavities and condensation with the same radiographic pattern, to which a sharply contrasting flat perforated titanium mesh with locking screws around the periphery fits. The jaw bone and the bone graft are clearly separated. The greatest thickness of the inserted bone material is marked in the middle zone of the mesh and gradually becomes thinner in the direction of the mesh edges. On average, the cross-sectional area of the sagittal section, that is, the bone graft proportion, was increased by 21.24% (Table 1). Density indicators in the bone graft center averaged 389 HU. In comparison, cortical layer of the jaw bone was 1400-1900 HU, the cancellous layer ranged from 240 to 700 HU. Low graft density may indicate the onset of rehabilitation, vascular invasion, osteoclast activation, and macrophage inflammation phase.

At the sixth month of observations, the bone graft was a homogeneous area without cavities and condensation with the same radiographic pattern. There is a decrease in the bone graft volume. There was a clear boundary zone of non-contrasting space between the titanium mesh and the graft. The radiographic contrast of the graft increased. The transition zone of jaw bone and graft is not determined. The locking screws on the periphery did not change their location. Density indicators in the bone graft center averaged 913 HU (Table 2). The above may indicate the completion of artificial bone remodeling, condensation of the bone graft, its integration into the patient's own jaw bone, osteoblast proliferation, and osteon formation.

As a result of the CBCT analysis, it was found that in 2 patients of the control group the bone graft volume at the moment of the titanium mesh removal (after 6 months) was decreased by 24%, in 2 patients – by 18% in the rest the bone graft volume at the moment of the titanium mesh removal was decreased from 12 to 15%.

At the twelfth month, the graft borders at the CBCT are not marked, the formation of cortical and cancellous layers is observed in the augmentation area. The radiographic contrast of the graft has increased compared to the previous observation, which indicates the continuation of bone compaction in this area. Density indicators in the augmentation center averaged 1350-1450 HU. The bone tissue around the installed implants was no different from that in the peripheral areas.

On average, the cross-sectional area of sagittal section during this period, i.e., the graft proportion, decreased by another 6.9% (Table 1), relative to the previous observation period.

Therefore, analyzing the data on changes in the of bone graft volume and increasing in its radiographic density, we can make an assumption about the osteogenesis rate. After guided bone regeneration using the classical method of the mucousal flap detachment, we have found that the bone mass after surgery and for up to six months loses in the volume but increases in density. So, we can assume the phase of blood flow organization in the bone graft and the osteoclasts activation, the bone matrix construction and the phase of bone remodeling. But later, as a result of osteogenesis, density gradually approaches the indices in the adjacent intact zones, but does not reach them.

The bone graft density on the Hounsfield scale in 94% of cases ranged from 381 to 401 HU right after surgery. And for the newly formed bone, in different periods it was equal to the following indicators: after 6 months – increased by 232.3% and averaged 904 HU, after 12 months – increased by 156% from the previous period, and amounted to 1411 HU (Table 2). Volume indicators showed the opposite dynamics: on average, after 6 months of observations, the bone graft volume decreased by 14,83%, and in the period from 6 to 12 months it decreased by another 6,9%.

Clinical results of the experimental group.

We analyzed the CBCT of patients before and after the mandibular bone augmentation. For further comparison, the volume of bone graft obtained at the CBCT was recorded immediately after guided bone regeneration using the author's own method of the mucousal flap detachment. The bone graft was a homogeneous area without cavities and condensation with the same radiographic pattern, to which a sharply contrasting flat perforated titanium mesh with locking screws around the periphery fits. The jaw bone and the bone graft are clearly separated. The greatest thickness of the inserted bone material is marked in the middle zone of the mesh and gradually becomes thinner in the direction of the mesh edges. On average, the cross-sectional area of the sagittal section, that is, the bone graft proportion was increased by 19,17% (Table 3).

Density indicators in the bone graft center averaged 392 HU. In comparison, cortical layer of the jaw bone was 1400-1900 HU, the cancellous layer ranged from 240 to 700 HU. Low graft density may indicate the onset of rehabilitation, vascular invasion, osteoclast activation, and macrophage inflammation phase.

Table 1

Changes in bone graft volume during twelve months of observation

	Before surgery	After surgery, mm^2	After 6 months, mm^2	After 12 months, mm^2
Patient No. 1	236.21	279.78	273.98	271.41
Patient No. 2	255.95	317.66	308.85	306.34
Patient No. 3	245.22	299.41	290.8	288.73
Patient No. 4	236.96	286.74	277.54	276.77
Patient No. 5	206.05	249.36	246.46	245.63
Patient No. 6	262.09	310.86	303.74	301.46
Patient No. 7	243.44	292.35	285.44	281.44
Patient No. 8	234.99	281.28	274.94	272.47
Patient No. 9	219.77	261.22	254.38	251.93
Patient No.10	258.57	309.51	302.53	301.01
Patient No. 11	201.2	239.64	233.64	230.42
Patient No. 12	227.86	273.64	268.08	265.17
Patient No. 13	200.3	237.58	231.61	229.39
Patient No. 14	181.18	218.35	211.72	209.17
Patient No. 15	270.14	325.09	319.69	317.36
Patient No. 16	198.95	240.83	236.65	234.25
Patient No. 17	205.96	249.29	241.12	235.9
Patient No. 18	184.46	242.85	218.23	215.87
Patient No. 19	201.57	243.94	241.1	240.29
Patient No. 20	213.33	251.36	249.6	247.17
Patient No. 21	195.05	241.35	234.56	223.35
Patient No. 22	236.93	286.8	281.83	280.35
Patient No. 23	173.67	220.93	216.58	214.23
Patient No. 24	242.04	289.54	281.96	279.18
Patient No. 25	234.45	283.73	279.47	276.4
Patient No. 26	231.94	286.32	276.42	275.5
Patient No. 27	217.72	266.95	259.58	256.15
On average, %	-	18.92	16.75	16.73

Table 2

Changes in bone graft density on the Hounsfield scale over twelve months of observations

	After surgery, HU	After 6 months, HU	After 12 months, HU
Patient No. 1	388	900.1	1404.2
Patient No. 2	390	904.8	1411.4
Patient No. 3	395	916.4	1429.5
Patient No. 4	398	923.3	1440.4
Patient No. 5	379	879.2	1371.6
Patient No. 6	392	909.4	1418.7
Patient No. 7	381	883.9	1378.9
Patient No. 8	386	895.5	1397
Patient No. 9	384	890.8	1389.7
Patient No. 10	378	876.9	1368
Patient No. 11	387	897.8	1400.6
Patient No. 12	380	881.6	1375.2
Patient No. 13	401	930.3	1451.2
Patient No. 14	377	874.6	1364.4
Patient No. 15	382	886.2	1382.5
Patient No. 16	390	904.8	1411.4
Patient No. 17	383	888.5	1386.1
Patient No. 18	396	918.7	1433.2
Patient No. 19	389	902.4	1407.8
Patient No. 20	393	911.7	1422.3
Patient No. 21	399	925.6	1444.0
Patient No. 22	397	921	1436.8
Patient No. 23	389	902.4	1407.8
Patient No. 24	391	907.1	1415.1
Patient No. 25	394	914	1425.9
Patient No. 26	400	928	1447.6
Patient No. 27	385	893.2	1393.3

At the sixth month of observations, the bone graft was a homogeneous area without cavities and condensation with the same radiographic pattern. There is a decrease in the bone graft volume. There was a clear boundary zone of non-contrasting space between the titanium mesh and the graft. The radiographic contrast of the graft increased. The transition zone of jaw bone and graft is not determined. The locking screws on the periphery did not change their location. Density indicators in the bone graft center averaged 910.6 HU (Table 4). The above may indicate the completion of artificial bone remodeling, condensation of the bone graft, its integration into the patient's jaw bone, osteoblast proliferation, and osteon formation.

As a result of the CBCT analysis, it was found that the bone graft volume at the time of titanium mesh removal (after 6 months) was decreased by 21% in 1 patient of the experimental group (Table 3), in the rest of patients the bone graft volume decreased by 11.78%.

At the twelfth month, the graft borders at the CBCT are not marked, the formation of cortical and cancellous layers is observed in the augmentation area. The radiographic contrast of the graft has increased compared to the previous observation, which indicates the continuation of bone compaction in this area. Density indicators in the augmentation center averaged 1350-1500 HU. The bone tissue around the installed implants was no different from that in the peripheral areas. On average, the cross-sectional area of sagittal section during this period, i.e., the graft proportion, decreased by another 5.67% (Table 3), relative to the previous observation period.

Table 3

Changes in bone graft volume during twelve months of observation

	Before surgery	After surgery, mm^2	After 6 months, mm^2	After 12 months, mm^2
Patient No. 1	234,56	280,46	275,18	273,14
Patient No. 2	230,71	271,15	266,5	264,46
Patient No. 3	236,93	284,34	278,89	277,85
Patient No. 4	240,95	283,72	278,8	276,76
Patient No. 5	173,87	204,92	201,35	200,32
Patient No. 6	237,29	279,98	275,07	274,03
Patient No. 7	237,77	286,61	280,99	278,95
Patient No. 8	207,7	249,95	245,09	241,05
Patient No. 9	201,85	238,85	233,71	230,67
Patient No. 10	184,68	218,73	214,81	214,78
Patient No. 11	206,24	244,5	240,1	238,06
Patient No. 12	198,43	235,46	231,2	230,17
Patient No. 13	270,22	320,94	315,11	311,06
Patient No. 14	181,39	215,64	211,7	210,67
Patient No. 15	200,3	238,38	234	231,96
Patient No. 16	227,42	270,9	265,9	261,86
Patient No. 17	201,12	239,8	235,35	234,31
Patient No. 18	234,79	276,21	271,45	268,41
Patient No. 19	224,14	267,76	262,74	260,7
Patient No. 20	213,62	252,52	248,05	245,01
Patient No. 21	244,04	293,07	286,55	287,51
Patient No. 22	253,73	303,94	296,4	294,34
Patient No. 23	212,57	254,87	253,55	251,54
Patient No. 24	217,56	255,46	251,1	250,07
Patient No. 25	244,18	291,4	285,97	282,93
Patient No. 26	263,59	316,91	310,78	310,73
Patient No. 27	194,54	229,75	225,7	221,67
Patient No. 28	235,58	282,91	273,76	267,69
Patient No. 29	247,77	299,85	292,5	290,51
Patient No. 30	229,08	282,28	277	274,09
On average, %	-	19,17	16,91	15,95

The bone graft density on the Hounsfield scale in 94% of cases ranged from 240 to 700 HU. And for the newly formed bone, in different periods it was equal to the following indicators: after 6 months – increased by 197% and averaged 910.6 HU (Table 4), after 12 months – increased by 155% from the previous period, and amounted to 1420.8 HU.

The bone graft density on the Hounsfield scale in 95% of cases ranged from 383 to 400 HU right after surgery. And for the newly formed bone, in different periods it was equal to the following

indicators: after 6 months – increased by 231.2% and averaged 912 HU, after 12 months – increased by 157% from the previous period, and amounted to 1441 HU (Table 4). Volume indicators showed the opposite dynamics: on average, after 6 months of observations, the bone graft volume decreased by 11.78%, and in the period from 6 to 12 months it decreased by another 5.67%.

Table 4

Changes in bone graft density on the Hounsfield scale over twelve months of observations

	After surgery, HU	After 6 months, HU	After 12 months, HU
Patient No. 1	402.7	934.3	1457.6
Patient No. 2	396.6	920.2	1435.4
Patient No. 3	388.3	900.8	1405.2
Patient No. 4	404.8	939	1464.9
Patient No. 5	385.4	894.1	1394.9
Patient No. 6	398.7	924.9	1442.8
Patient No. 7	405.8	941.3	1468.5
Patient No. 8	383.4	889.4	1387.4
Patient No. 9	390.5	905.9	1413.3
Patient No. 10	384.4	891.8	1391.3
Patient No. 11	393.6	913.1	1424.4
Patient No. 12	373.5	866.6	1351.8
Patient No. 13	407.8	946.1	1475.9
Patient No. 14	383.4	889.5	1387.6
Patient No. 15	388.5	901.3	1406
Patient No. 16	396.6	920.2	1435.4
Patient No. 17	376.5	873.4	1362.5
Patient No. 18	392.6	910.7	1420.7
Patient No. 19	395.6	917.7	1431.7
Patient No. 20	399.7	927.2	1446.5
Patient No. 21	394.6	915.4	1428.1
Patient No. 22	403.7	936.7	1461.2
Patient No. 23	388.3	889.4	1392.3
Patient No. 24	397.6	922.5	1439.2
Patient No. 25	400.7	929.5	1450.1
Patient No. 26	393.2	912.2	1423
Patient No. 27	391.5	908.4	1417
Patient No. 28	387.5	898.9	1402.3
Patient No. 29	382.4	887.1	1383.9
Patient No. 30	393.2	912.2	1423

Therefore, based on the data obtained on changes in the bone graft volume and increasing its radiological density, we can make an assumption about the osteogenesis rate, which correlates with similar indicators of other authors [7, 8]. The results of clinical and radiographic studies of other authors have shown that the adverse marginal bone resorption around the installed dental implants during alveolar ridge splitting is most pronounced when cutting full-thickness flaps [9], which is fully confirmed by our study. After guided bone regeneration using the author's own method of the mucousal flap detachment, we have found that the bone mass after surgery and for up to six months loses in the volume but increases in density. So, it is possible to assume a phase of the blood flow organization in the bone graft and osteoclasts activation, bone matrix formation and bone remodeling phase, but subsequently, as a result of osteogenesis, the density gradually approaches the indices of the intact zones,but does not reach them, which coincides with the data obtained by other scientists [7,8]. Clinical and radiographic results [3] confirm the possibility of using this method in dentistry to repair defects of the jawbone alveolar ridge.

Conclusion

Our studies have shown that the optimization of the limits of detachment and mobilization of mucousal and mucoperiosteal flaps, compared with the classical method of trapezoidal flaps, leads to a decrease in bone graft volume loss by 1.23%. The data indicate the possibility of improving the flap surgery efficiency during bone augmentation in patients with acquired edentulism with greater efficiency. The results obtained are useful for practicing dental surgeons when planning a bone augmentation surgery on the mandible.

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Реферати

РЕНТГЕНОЛОГІЧНІ ЗМІНИ У КІСТКОВИХ АУГМЕНТАТАХ ПРИ ПРОВЕДЕННІ НАПРАВЛЕНОЇ КІСТКОВОЇ РЕГЕНЕРАЦІЇ З ВИКОРИСТАННЯМ ТИТАНОВОЇ СІТКИ ЗА КЛАСИЧНОЮ ТА АВТОРСЬКОЮ МЕТОДИКАМИ ВІДШАРУВАННЯ СЛИЗОВИХ КЛАПТІВ

Каплун Д.В., Аветіков Д.С., Іваницька О.С., Бойко І.В., Гаврильєв В.М.

Однією з основних проблем відновлення втраченого об'єму кісткової маси під час підготовки пацієнтів до дентальної імплантації, є оголення кісткового аугментату і його інфікування в результаті ішемічних процесів в слизовому клапті, що його прикриває. Нами було проведено 27 хірургічних втручань направленої кісткової регенерації з використанням титанової сітки за класичною методикою відшарування трапецієподібного слизового клаптя та 30 хірургічних втручань за авторською методикою відшарування та мобілізації слизового клаптя. Аугментація проводилась у дистальних відділах нижньої щелепи. Проведені нами дослідження показали, що оптимізація меж відшарування та мобілізації слизових та слизово-окістних клаптів в порівнянні з класичною методикою трапецієподібних клаптів, веде до зменшення втрати об'єму кісткового аугментату на 1.9%. Дані свідчать про можливості підвищення ефективності проведення клаптевих операцій під час кісткової аугментації у хворих на вторинну адентію.

Ключові слова: дентальна аугментація, КПКТ, слизові клапті

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РЕНТГЕНОЛОГИЧЕСКИЕ ИЗМЕНЕНИЯ В КОСТНЫХ АУГМЕНТАТАХ ПРИ ПРОВЕДЕНИИ НАПРАВЛЕННОЙ КОСТНОЙ РЕГЕНЕРАЦИИ С ИСПОЛЬЗОВАНИЕМ ТИТАНОВОЙ СЕТКИ ПО КЛАССИЧЕСКОЙ И АВТОРСКОЙ МЕТОДИКАМ ОТСЛОЕНИЯ СЛИЗИСТЫХ ЛОСКУТОВ

Каплун Д.В., Аветиков Д.С., Иваницькая О.С., Бойко І.В., Гаврильев В.М.

Одной из основных проблем восстановления утраченного объема костной массы при подготовке пациентов к дентальной имплантации, является обнажение костного аугментата и его инфицирование в результате ишемических процессов в слизистом лоскуте, который его прикрывает. Нами было проведено 27 хирургических вмешательств направленной костной регенерации с использованием титановой сетки по классической методике отслойки трапециевидного слизистого лоскута и 30 хирургических вмешательств по авторской методике отслойки и мобилизации слизистого лоскута. Аугментация проводилась в дистальных отделах нижней челюсти. Проведенные нами исследования показали, что оптимизация границ отслоения и мобилизации слизистых и слизисто-надкостничных лоскутов по сравнению с классической методикой трапециевидных лоскутов, ведет к уменьшению потери объема костного аугментата на 1.9%. Данные свидетельствуют о возможности повышения эффективности проведения лоскутных операций при костной аугментации у больных вторичной адентией.

Ключевые слова: дентальная аугментация, КЛКТ, слизистый лоскут.

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EFFICIENCY OF DRAINAGE OF ASCIT-PERITONITIS IN DIFFERENT DIFFICULTY OF ACUTE PANCREATITIS

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The global incidence of acute pancreatitis ranges from 5 to 30 cases per 100,000 people per year and continues to grow in recent years. A fifth of patients are diagnosed with a severe form of acute pancreatitis with a mortality rate of up to 30%. Publications and randomized clinical trials show conflicting data on the effectiveness of abdominal drainage in acute pancreatitis complicated by ascites-peritonitis. The aim of the study was to analyze the effectiveness of drainage interventions in acute pancreatitis complicated by ascites-peritonitis depending on the initial severity of the patient's condition. We analyzed the results of a comprehensive examination and treatment of 166 patients with acute pancreatitis complicated by enzymatic ascites peritonitis. In the subgroups with the severity of the condition at the time of hospitalization, defined on the APACHE II scale of 5 or more points, a statistically significantly lower number of unsatisfactory results ($p < 0.05$) was observed 72 hours after the start of treatment in drained patients compared with patients whose treatment included only complex conservative therapy. In the subgroups with the severity of the condition at the time of hospitalization, the APACHE II score of less than 5 points, active surgical tactics did not have a statistically significant effect on the incidence of unsatisfactory treatment results and there was no significant difference between the condition of the drained and non-drained patients. These results confirm the absence of the influence of routine abdominal drainage for all patients with acute necrotic pancreatitis. However, patients with an APACHE II score of 5 and above are the category of patients who will be most justified in early drainage of ascites-peritonitis.

Key words: ascites-peritonitis, acute pancreatitis, abdominal drainage, severity of condition.

The work is a fragment of the research project "Differentiated surgical tactics for parapancreatic infectious-septic complications of destructive pancreatitis", state registration No. 0116U005439.

The global incidence of acute pancreatitis ranges from 5 to 30 cases per 100,000 people per year and continues to grow in recent years [5]. A fifth of patients are diagnosed with a severe form of acute pancreatitis with a mortality rate of up to 30% [1, 3]. Pancreatic ascites occurs in the early period of acute pancreatitis. Components of pancreatic ascites protease, lipase, unsaturated fatty acids and cytokines are highly toxic and contribute to the early development of systemic inflammatory reactions, multiple organ failure, and worsening disease prognosis [4].Publications and randomized clinical trials show conflicting data on the effectiveness of abdominal drainage in acute pancreatitis complicated by ascites-peritonitis [2].Moreover, the elimination of toxic ascites results in reduction of severity and duration of organ and multiple organ failure and avoids probable death in the early period of illness in patients with severe and extremely severe acute pancreatitis. [2].

The purpose of the study was to analyze the effectiveness of drainage interventions in acute pancreatitis complicated by ascites-peritonitis depending on the initial severity of the patient's condition.

Materials and methods. We analyzed the results of a comprehensive examination and treatment of 166 patients with acute pancreatitis complicated by enzymatic ascites-peritonitis, including 44 patients treated at the surgical department of municipal enterprise “Poltava Regional Clinical Hospital named after M.V. Sklifosovsky of Poltava Regional Council”, and 122 patients treated at in-patient surgical department No. 2 of Kyiv City Clinical Hospital of Emergency Medical Services for the period 2013-2017.Patients were divided into two groups: 1st croup included patients to whom only complex conservative therapy was applied according to the protocols of treatment of acute pancreatitis, and 2nd group included patients, to whom surgical interventions for enzymatic ascites-peritonitis was applied in addition to conservative treatment. Patients of each group were divided by severity of the condition at the time of hospitalization as determined by the APACHE II scale. There were no significant differences in age and sex in the study groups.

To remove the enzymatic exudate from the abdominal cavity, patients of the second group were subject to the following surgical interventions: 98 patients were subject to laparocentesis and drainage of the abdominal cavity, 24 patients were subject to transcutaneous drainage of the abdominal cavity under ultrasound control, 13 patients were subject to laparocentesis laparotomy and abdominal drainage and 8 patients were subject to surgical operations using median laparotomy of intraoperative rehabilitation and drainage of the abdominal cavity.

Statistical analysis of the study materials was performed using the program STATISTICA 10.0 (StatSoft, Inc., USA) using descriptive statistics methods calculated in the study groups of qualitative indicators in the form of frequencies and their percentages.

Spearman's non-parametric correlation criterion (R correlation coefficient) was calculated to analyze the relationship of qualitative indicators. The correlation coefficient was considered probable when error probability p <0.05.

The statistical significance of the differences was determined by the nonparametric method between the indexes of the independent groups using Fisher's exact test. Differences at p <0.05 were considered statistically significant for all types of analysis.

Results of study and their discussion. Patients, depending on the severity of the condition at hospitalization evaluated using the scale of Acute Physiology And Chronic Health Evaluation II (APACHE II) and selected treatment policy were distributed as shown in table 1.

Table 1

Distribution of patients according to the APACHE II scale severity at the time of hospitalization and chosen treatment policy

APACE II scale at the time of hospitalization (points)	Drainage operation was not performed		Drainage operation was performed	
	Abs. units	%	Abs. units.	%
0	1	4.35	41	28.67
1	1	4.35	12	8.39
2	2	8.7	8	5.6
3	3	13.04	5	3.5
4	2	8.7	7	4.9
5	2	8.7	12	8.39
6	4	17.39	14	9.79
7	3	13.05	9	6.29
8	2	8.7	10	6.99
9	1	4.35	20	13.99
10	2	8.7	5	3.5
Total	23	100	143	100

To ensure objective evaluation of the efficacy of drainage interventions in patients with acute pancreatitis complicated by ascites-peritonitis, a statistical analysis of differences was performed using the Fisher exact test between the initial severity of the condition, estimated using the APACHE II scale and surgical policy and t efficiency criterion. Pain, the recovery of independent enteral nutrition and the presence of organ failure according to the Marshal scale were evaluated after 72 hours from the beginning of treatment as criteria for the effectiveness of more active surgical policy. Correlation relationship between these indexers was determined by Spearman's rank correlation method as shown in Table 2.

Table 2

The correlation between the indexes is determined by the Spearman's rank correlation method

	Drainage interventions were not performed			Drainage interventions were performed		
	Enteral nutrition recovery after 72 hours.	The presence of organ dysfunction on the Marshal scale after 72 hours.	Intense pain syndrome after 72 hours.	Enteral nutrition recovery after 72 hours.	The presence of organ dysfunction on the Marshal scale after 72 hours.	Intense pain syndrome after 72 hours.
The severity of the condition by Apache II scale at the time of hospitalization	R=-0.61 p=0.02	R=0.47 p=0.02	R=-0.16 p=0.46	R=0.37 p=0.0001	R=0.047 p=0.57	R=-0.14 p=0.09

Probable relationship of negative mean strength between the severity of the condition at the time of hospitalization on the Apache II scale, the recovery of enteral feeding after 72 hours for patients who did not undergo drainage interventions for ascites-peritonitis and a likely positive low-strength relationship between the severity of the condition at the time of hospitalization on the APACHE II scale, the recovery of enteral feeding after 72 hours for patients who underwent drainage interventions for ascites-peritonitis shows positive effect of drainage interventions on the recovery of enteral nutrition after 72 hours from the moment of hospitalization.

Possible positive mean strength is the relationship between the severity of the condition at the time of hospitalization on the APACHE II scale, the presence of organ dysfunction after 72 hours determined under Marshal scale in patients who did not undergo ascites-peritonitis drainage interventions and the unlikely positive low-strength relationship between APACHE II hospitalization and organ dysfunction after 72 hours determined by Marshal scale in patients who underwent drainage interventions for ascites-peritonitis show a positive effect of drainage interventions on the regression of organ dysfunction after 72 hours from the moment of hospitalization.

A statistical analysis of the differences in pain, the presence of organ failure according to the Marshal scale and the restoration of enteral nutrition after 72 hours was also performed from the beginning of treatment of patients with acute pancreatitis, depending on the drainage operation and the severity of the condition of patients at the time of hospitalization by means of Fisher's exact test. The following results were obtained. In the subgroups with the severity of the condition at the time of hospitalization, determined by APACHE II scale was 5 or more points, a statistically significantly lower number of unsatisfactory results ($p < 0.05$) was observed after 72 hours after initiation of treatment in drained patients compared to patients who were subject to only comprehensive conservative treatment In the subgroups with the severity of less than 5 points at the time of hospitalization defined on the APACHE II scale, active surgical policy had no statistically significant effect on the incidence of unsatisfactory treatment results and no significant difference between the condition of drained and untrained patients.

Thus, we can agree with the opinion of L. Zhu, J. Lu, J. Yang et al. [7] that early stage drainage can reduce local and systemic toxicity to an acceptable level, and this may subsequently delay the rate of disease progression, while active surgical policy did not have a statistically significant effect on the rate of poor results of treatment in patients with severity of less than 5 points according to APACHE II scale.

Conclusion

These results confirm the absence of the influence of routine drainage of the abdominal cavity for all patients with acute necrotic pancreatitis [6]. However, patients with an APACHE II of 5 and more points are the category of patients for whom early drainage of ascites-peritonitis was the most justified.

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Реферати

ЕФЕКТИВНІСТЬ ДРЕНАЖУВАННЯ АСЦИТУ-ПЕРИТОНІТУ ЗА РІЗНОЇ СКЛАДНОСТІ ГОСТРОГО ПАНКРЕАТИТУ

Кас'ян В.В., Черкун О.Ю., Ткаченко О.А., Шейко В.Д.

Світова захворюваність на гострий панкреатит становить від 5 до 30 випадків на 100 000 людей на рік і продовжує зростати в останні роки. У п'ятої частини пацієнтів діагностують важку форму гострого панкреатиту зі смертністю до 30%. Публікації та рандомізовані клінічні дослідження показують суперечливі дані про ефективність черевного дренажу при гострому панкреатиті, ускладненому асцитом-перитонітом. Метою дослідження був аналіз ефективності дренажних втручань при гострому панкреатиті, ускладненому асцитом-перитонітом залежно від початкового ступеня тяжкості стану пацієнта. Ми проаналізували результати комплексного обстеження та лікування 166 пацієнтів з гострим панкреатитом, ускладненим ферментативним асцитом-перитонітом. У підгрупах із ступенем тяжкості стану на момент госпіталізації, визначеним за шкалою APACHE II у 5 і більше балів, за 72 години після початку лікування спостерігали статистично достовірно меншу кількість незадовільних результатів ($p < 0,05$) у дренованих пацієнтів порівняно з пацієнтами, лікування яких включало лише комплексну консервативну терапію. У підгрупах із ступенем тяжкості стану та

ЭФФЕКТИВНОСТЬ ДРЕНАЖИРОВАНИЯ АСЦИТ-ПЕРИТОНИТА ПРИ РАЗНОЙ СЛОЖНОСТИ ОСТРОГО ПАНКРЕАТИТА

Касьян В.В., Черкун А.Ю., Ткаченко А.А. 1, Шейко В.Д.

Мировая заболеваемость острым панкреатитом составляет от 5 до 30 случаев на 100 000 человек в год и продолжает расти в последние годы. У пятой части пациентов диагностируют тяжелую форму острого панкреатита со смертностью до 30%. Публикации и рандомизированные клинические исследования показывают противоречивые данные об эффективности брюшного дренажа при остром панкреатите, осложненном асцитом-перитонитом. Целью исследования был анализ эффективности дренажных вмешательств при остром панкреатите, осложненном асцитом-перитонитом в зависимости от начальной степени тяжести состояния пациента. Мы проанализировали результаты комплексного обследования и лечения 166 пациентов с острым панкреатитом, осложненным ферментативным асцитом-перитонитом. В подгруппах со степенью тяжести состояния на момент госпитализации, определенным по шкале APACHE II в 5 и более баллов, за 72 часа после начала лечения наблюдали статистически достоверно меньшее количество неудовлетворительных результатов ($p < 0,05$) у дренированных пациентов по сравнению с пациентами, лечение которых включало только комплексную консервативную терапию. В подгруппах со степенью тяжести состояния и с показателем APACHE II

показником APACHE II менше 5 балів на момент госпіталізації, активна хірургічна тактика не мала статистично значущого впливу на частоту незадовільних результатів лікування, і не було суттєвої різниці між станом дренованих та не дренованих пацієнтів. Ці результати підтверджують відсутність впливу рутинного абдомінального дренажу на всіх пацієнтів з гострим некротичним панкреатитом. Однак пацієнти з оцінкою APACHE II 5 і вище є категорією пацієнтів, у яких найбільш виправданий ранній дренаж асциту-перитоніту.

Ключові слова: асцит-перитоніт, гострий панкреатит, черевний дренаж, тяжкість стану.

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менее 5 баллов на момент госпитализации, активная хирургическая тактика не имела статистически значимого влияния на частоту неудовлетворительных результатов лечения, и не было существенной разницы между состоянием дренированных и не дренированных пациентов. Эти результаты подтверждают отсутствие влияния рутинного абдоминального дренажа на всех пациентов с острым некротическим панкреатитом. Однако, пациенты с оценкой APACHE II 5 и выше являются категорией пациентов, у которых наиболее оправдан ранней дренаж асцита-перитонита.

Ключевые слова: асцит-перитонит, острый панкреатит, брюшной дренаж, тяжесть состояния.

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DAILY BLOOD PRESSURE PATTERN DISORDERS IN PATIENTS WITH STAGE II ESSENTIAL HYPERTENSION AND FREQUENT PREMATURE BEATS

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156 patients (65 men and 91 women) with stage II hypertension (stage II EH) were examined. The main group consisted of 124 of them, which according to the daily monitoring of the electrocardiogram had frequent supraventricular (SVPB) (74 persons) or ventricular PB (VPB) (50 persons). The comparison group included 32 patients with stage II EH without arrhythmia. It was established that patients with stage II EH and PB had significantly higher values of systolic (SBP) and diastolic blood pressure (DBP) during the day according to the data of daily blood pressure monitoring (DBPM). In patients with stage II EH, regardless of the presence of arrhythmia, there was a decrease in patients with dipper type and an increase in the number of pathological types of diurnal profile by SBP level, without a significant difference between the groups. In patients with stage II EH with PBs, the daily profile of non-dipper according to the DBP level was more frequent ($p = 0.03$). The presence of frequent VPB was associated with a predominance of the non-dipper profile in terms of DBT (76.0%, $p = 0.0003$) compared with patients with SVPB. The data obtained indicate a certain associative link between the disturbance of the diurnal BP profile, mainly DBT and the presence of PBs, namely in patients with stage II EH.

Key words: hypertension, supraventricular PB, ventricular PB, daily blood pressure monitoring, daily blood pressure profile.

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Patients with arterial hypertension (AH) may have a variety of cardiac arrhythmias that contribute to cardiovascular complications. At present, atrial fibrillation is the most studied rhythm disorder. Despite that, the factors and mechanisms of the occurrence of supraventricular (SVPB) and ventricular (VPB) premature beats in hypertension have not been investigated sufficiently [1, 4, 8, 11].

There is evidence of a higher level of systolic blood pressure during the day (DSBP) and night (NSBP) in patients with arrhythmias. Episodes of SVPB have been registered on the background of high systemic blood pressure (BP) irrespective of the presence of left ventricular hypertrophy (LVH), which denies the leading role of myocardium structural remodeling in the occurrence of premature beats (PB) [8, 10]. According to other researchers, more frequent or more threatening VPB were associated not only with increased SBP but also with increasing LV myocardial mass [5]. Also, the influence of BP circadian variability on ventricular and atrial arrhythmias has been demonstrated [6]. It is determined that the continuous prolonged increase in blood pressure at night (non-dipper pattern) is an independent predictor of frequent and severe ventricular arrhythmias. The electrical instability of the myocardium on the background of changes in the circadian BP pattern could be explained by the direct relationship between BP changes and QT interval duration as well as the magnitude of its dispersion. The severity of structural changes of the atria and ventricles also can lead to the electrical instability of the atria and ventricles and to the occurrence of SVPB and VPB in such patients [6].

The state of the autonomic nervous system plays an important role in the BP regulation and the occurrence of hypertension [10]. According to the Framingham study, individuals with high blood pressure

had a decrease in heart rate variability. Also, low heart rate variability in individuals with normal BP indicated a high risk of hypertension. Other scientists have drawn attention to the pathogenetic relationship between the severity of hypertension and low heart rate variability. These disorders were circadian in nature and were more pronounced in patients with insufficient nocturnal BP decrease (non-dippers) [4].

Today, the role of cardiac arrhythmias as predictors of the development of acute circulatory disorders is well known. The combination of high BP and arrhythmia increases the likelihood of stroke dramatically even without taking into account other adverse factors [8, 9]. According to large-scale epidemiological studies, the presence of PBs in hypertension increases the risk of cardiac death, even in the absence of concomitant coronary heart disease [8, 9]. However, the role of daily BP pattern disorders in the incidence of various cardiac arrhythmias in patients with hypertension is not fully clarified despite the abovementioned information and requires additional study.

The purpose of the study was to evaluate the changes in daily blood pressure pattern in patients with stage II hypertension and frequent PBs.

Materials and methods. The study was preceded by a screening and thorough collection of complaints and medical history. The signing of informed consent to participate in the study was done in accordance with the ethical rules of the Helsinki Declaration.

The study included 124 patients with stage II essential hypertension (EH) and frequent symptomatic PBs aged from 27 to 75 (mean age 58.2 ± 0.9) years, who formed the main clinical group. The comparison group consisted of 32 patients aged within 32 and 72 (mean age 55.9 ± 1.7) years with stage II EH without any cardiac arrhythmias. In the main group, 50 (40.3%) patients were male and 74 (59.6%) were female. The comparison group consisted of 15 (46.9%) men and 17 (53.1%) women. There were no statistically significant differences between the main and the comparison groups by age and sex ($p > 0.05$), which indicated to the age and gender homogeneity of the participants.

Among 124 patients with EH and concomitant frequent PBs there were 74 (59.7%) cases of supraventricular (SVPB) and 50 (40.3%) of ventricular (VPB). Arrhythmic history ranged from 1 to 27 years and averaged 8.06 ± 0.42 years. 30 (24.2%) patients of the main group have felt a variety of symptoms during the last year. The most common was the feeling of failed heartbeat or pauses in cardiac rhythm. Instead, the vast majority (94 (75.8%) patients) experienced episodic arrhythmias in the form of intermittent episodes. In 32 (25.8%) patients arrhythmia occurred in the active part of the day (from 06:00 to 21:00) and was associated with exposure of physical or psycho-emotional stress, and in 14 (11.3%) persons – during the passive period of the day (from 21:00 to 06:00) at rest during asleep (according to the HM data). It is noteworthy that 48 (38.7%) patients had no clear association of their arrhythmia with the period of the day and the arrhythmia was observed regardless of their activity at any time of day. All patients were examined and treated in the cardiology department of the Vinnytsia Pirogov Memorial Regional Clinical Hospital, in the clinical and diagnostic department or the department of heart rhythm disorders of communal non-commercial enterprise “Vinnytsia Regional Clinical Treatment Center of Cardiovascular Pathology” during 2016-2019.

All patients were examined at the inclusion stage by complete clinical, laboratory and instrumental methods in order to verify the main diagnosis and concomitant conditions. General clinical and anthropometric examination, office BP measurement, 12-lead ECG, daily BP and ECG monitoring, cardiac and carotid ultrasound were performed in all patients who agreed to participate in the study.

The identification of indications and contraindications, the establishment of the diagnosis and concomitant pathology, the evaluation of medical history were obligate in all participants. They followed by the formation of clinical study groups. The anthropometric examination included measurement of height and weight with the calculation of the body mass index (BMI) by the Kettle formula. It was calculated as the ratio of body weight in kilograms to height in meters, elevated to the square (kg / m^2), waist circumference (WC) and hip circumference (HC) [2]. BP was measured according to the recommendations of the Ukrainian Society of Cardiologists (2013) using a sphygmomanometer “Microlife”. Electrocardiography was performed according to the standard procedure in 12 leads on the electrocardiograph "UKARD" (Hungary).

Daily BP monitoring (DBPM) and HM were performed using the hardware and software “DiaCard” (JSC “Solvaig”, Ukraine) according to the standard protocol. The following generally accepted parameters were estimated based on DBPM data: daily average systolic BP, daytime systolic BP, and nighttime systolic BP (SBP, DSBP, and NSBP, respectively), diastolic BP (DBP, DDBP, and NDBP, respectively) and pulse BP (PBP, DPBP, and NPBP, respectively, mm Hg). The following indexes were also calculated: hypertensive time index for SBP and DBP per day, in % (HI SBP, HI DBP respectively); diurnal index of SBP and DBP (DI SBP and DI DBP respectively) in %; the variability of daytime and

nighttime SBP (Var SBPd and Var SBPn respectively) and DBP (Var DBPd and VarDBPn respectively) in mm Hg. Art. The analysis of the SBP and DBP daily pattern was performed using standard criteria for the DI for SBP and DBP separately: dipper – DI from 10 to 20%, non-dipper – DI from 0 to 10%, night-peaker – DI <0% and over-dipper – DI> 20% [3, 7].

The indicators that characterized the structure of the daily heart rate were evaluated based on the HM data: daily average, day and night heart rate (HR, DHR, and NHR respectively) and circadian index (CI), which was calculated by the formula CI = DHR / NHR. The following parameters were evaluated to assess the arrhythmias: the number of SVPB and VPB per 24 hours of ECG monitoring; the number of SVPBs and VPBs registered per 1 hour ($SVPB_1$ and VPB_1 respectively); the number of paired and group VPB (VPBp) and the number of patients with such arrhythmias [3, 7].

Statistical processing was performed using the software "Statistica" v.12.0 (StatSoft). The results are presented as the mean (M) and the mean error (m) for the quantitative values, as the median and the limit of the interquartile interval with the indication of 25 and 75 percentiles, and as percentages (%) for the relative values. A comparison of relative values (%) was performed using the χ^2 criterion. A comparison of quantitative values of independent samples was performed by the Mann-Whitney U test [7].

Results of the study and discussion. The results of DBPM showed that significantly lower levels of blood pressure such as SBP, DSBP, NSBP, DBP, DDBP, NDBP, NPBP, and HI SBP were recorded in patients with EH without arrhythmias rather than in patients with frequent PBs (p<0,02) (table 1).

Table 1

DBPM parameters in the main and comparison groups

DBPM parameters	Comparison Group (n=32)	Main Group (n=124)	P
SBP, mm Hg	148 (137; 158)	161 (147; 170)	**0.0004**
DBP, mm Hg	86 (78; 92)	91 (85; 98)	**0.009**
DSBP, mm Hg	150 (139; 163)	166 (148; 177)	**0.001**
DDBP, mm Hg	88 (80; 97)	96 (89; 100)	**0.01**
NSBP, mm Hg	140 (127; 155)	160 (140; 166)	**0.0002**
NDBP, mm Hg	78 (71; 86)	85 (73; 90)	**0.02**
DPBP, mm Hg	59 (55; 68)	67 (54; 78)	0.10
DPBP, mm Hg	59 (55; 71)	68 (55; 78)	0.07
NPBP, mm Hg	60 (54; 66)	67 (58; 74)	**0.01**
DI SBP, %	9 (5; 12)	9 (8; 12)	0.42
DI DBP, %	11 (4; 15)	9 (6; 11)	0.35
HI SBP, %	85 (57; 97)	99 (73; 120)	**0.003**
HI DBP, %	82 (56; 96)	87 (80; 97)	0.07
Var DSBP, mm Hg	18 (15; 22)	18 (14; 21)	0.43
Var NSBP, mm Hg	15 (12; 19)	15 (11; 19)	0.67
Var DDBP, mm Hg	13 (9; 18)	15 (10; 18)	0.29
Var NDBP, mm Hg	9 (7; 14)	11 (9; 16)	0.09

Notes (hereinafter): DBPM - daily blood pressure monitoring, SBP, DSBP and NSBP - daily, daytime and nighttime systolic blood pressure, respectively; DBP, DDBP and NDBP - daily, daytime and nighttime diastolic blood pressure, respectively; PBP, DPBP and NPBP - daily, daytime and nighttime pulse blood pressure, respectively; HI - hypertensive index, DI - diurnal index, Var – variability. Here and in the following tables, the quantitative values are presented as the median and the boundary of the interquartile interval with 25 and 75 percentiles; P - between-group significance calculated on the Mann-Whitney U Test.

The obtained results about higher blood pressure levels in patients with hypertension and heart rhythm disorders compared with patients without arrhythmias are in the agreement with other researchers [1, 5, 6, 8, 10].

The results of the analysis of the DBPM levels in clinical groups, depending on the topical version of PB are presented in the table. 2. It was established that in patients with EH and frequent VPB, unlike patients with SVPB, significantly higher levels of DSBP and NSBP, DI SBP, Var DDBP, Var NDBP (p<0.04) were registered, which also to some extent coincides with results of some scientists [5, 8].

Therefore, there were significantly higher blood pressure levels during the day: daily, daytime and nighttime SBP and DBP between patients with II stage EH with PBs compared with patients without arrhythmias. The presence of VPB in patients with II stage EH was accompanied by significantly higher values of day and night SBP, DI SBP and variability of day and night DBP relative to the corresponding levels in patients with stage II EH and SVPB. The obtained data demonstrate a certain association of the

presence of frequent PBs with a number of indicators that characterize circadian regulation of BP during the day in patients with II stage EH.

Table 2

Indicators of DBPM in patients of the main group with different variants of PB

Indicators of DBPM	SVPB (n=74)	VPB (n=50)	P
SBP, mm Hg	145 (136; 158)	150 (139; 159)	0.51
DBP, mm Hg	86 (78; 92)	87 (78; 97)	0.67
DSBP, mm Hg	148 (138; 158)	155 (142; 168)	**0.03**
DDBP, mm Hg	87 (80; 95)	89 (80; 100)	0.72
NSBP, mm Hg	136 (130; 145)	147 (137; 154)	**0.04**
NDBP, mm Hg	78 (72; 86)	77 (70; 89)	0.63
DPBP, mm Hg	59 (54; 68)	61 (55; 70)	0.42
DPBP, mm Hg	58 (54; 68)	60 (55; 71)	0.80
NPBP, mm Hg	60 (54; 66)	60 (54; 66)	0.88
DI SBP, %	7 (3; 10)	10 (6; 14)	**0.02**
DI DBP, %	10 (3; 15)	12 (9; 16)	0.08
HI SBP, %	79 (50; 96)	90 (63; 97)	0.22
HI DBP, %	84 (54; 97)	81 (56; 96)	0.87
Var DSBP, mm Hg	17 (14; 21)	18 (16; 25)	0.12
Var NSBP, mm Hg	15 (11; 19)	15 (12; 21)	0.59
Var DDBP, mm Hg	10 (7; 17)	14 (9; 19)	**0.04**
Var NDBP, mm Hg	8 (6; 15)	12 (8; 17)	**0.03**

Notes: SVPB is supraventricular and VPB is ventricular PB; DBPM - daily blood pressure monitoring, SBP , DSBP and NSBP - daily, daytime and nighttime systolic blood pressure, respectively; DBP, DDBP and NDBP - daily, daytime and nighttime diastolic blood pressure, respectively; PBP, DPBP and NPBP - daily, daytime and nighttime pulse blood pressure, respectively; HI - hypertensive index, DI - diurinary index, Var - variability; P - between-group significance calculated on the Mann-Whitney U Test.

Analysis of the nature of the diurnal profile of BP in patients with stage II EH without arrhythmias compared with the main clinical array (patients with stage II EH and PBs) revealed the presence of disorders of the daily profile on circadian level of SBP with an increase in the percentage of pathological types (non-dipper, night-peaker, over-dipper) and reducing the number of patients with dipper type which to some extent coincides with the results of other researchers [5, 6, 8]. It should be noted that no significant differences were found between the two groups for different types of daily profile on the level of SBP (table 3). However, at the DBP level, the non-dipper daily profile was significantly more frequently reported in the group of patients with PBs (56.5% vs. 34.4%, p = 0.03) (table 3). The daily night-peaker profile (by DBP level) was not registered in the main clinical group in any case, so it was significantly different from the comparison group, where there were 3 cases, which was 9.4% (p = 0.0006).

Table 3

Daily BP patternin the main clinical group and comparison group

Daily BP profile	Comparison group (n=32)	Main group (n=124)	P
Daily profile by SBP level			
Dipper	12 (37.5%)	50 (40.3%)	0.77
Non-dipper	15 (46.9%)	58 (46.8%)	0.99
Night-peaker	4 (12.5%)	12 (9.7%)	0.63
Over-dipper	1 (3.1%)	4 (3.2%)	0.97
Daily profile by DBP level			
Dipper	14 (43.8%)	39 (31.5%)	0.19
Non-dipper	11 (34.4%)	70 (56.5%)	**0.03**
Night-peaker	3 (9.4%)	0 (0)	**0.0006**
Over-dipper	4 (12.5%)	15 (12.1%)	0.95

Notes: BP - blood pressure; P - significance of the difference of results between groups is calculated by the criterion χ^2

Analysis of changes in the diurnal BP pattern between groups of patients with different PB variants showed that there were significant differences between the groups in terms of both SBP and DBP profiles (table 4).

Table 4

Daily profile of BP in patients of the main group with different variants of PB

Daily profile of BP	SVPB (n=74)	VPB (n=50)	P
Daily profile by SBP level			
Dipper	35 (47.3%)	15 (30.0%)	**0.048**
Non-dipper	33 (44.6%)	25 (50.0%)	0.55
Night-peaker	4 (5.4%)	8 (16.0%)	**0.047**
Over-dipper	2 (2.7%)	2 (4.0%)	0.69
Daily profile by DBP level			
Dipper	30 (40.5%)	9 (18.0%)	**0.008**
Non-dipper	32 (43.2%)	38 (76.0%)	**0.0003**
Night-peaker	0 (0)	0 (0)	-
Over-dipper	12 (16.2%)	3 (6.0%)	0.09

Notes: BP - blood pressure; SVPB is supraventricular PB, VPB is ventricular PB; P - significance of the difference of results between groups is calculated by the criterion χ^2

Thus, VPB in patients with SBP levels were less likely to have a dipper profile compared to patients with SVPB (30.0% versus 47.3%, p = 0.048), whereas the night-peaker daily enrollment rate was significantly higher (16.0% versus 5.4 %, p = 0.047). According to the daily DBP profile, more significant disorders were also identified in the group of patients with VPB: non-dipper type (p = 0.0003) was registered in the vast majority of patients (76.0%), while dipper type was only in 18.0% of patients (p = 0.008). The revealed changes indicate more significant abnormalities of the diurnal BP patternin patients with stage II EH compared with patients with SVPB in both SBP and DBP profile, which to some extent coincides with the results of other researchers [5, 6, 8]. However, it should be noted that the violation of the daily profile of DBP according to our data was associated with the presence of frequent PBs in patients with stage II EH, and was more unfavorable in the prognostic plan of ventricular rhythm disorders. The obtained data indicate the need for separate analyzes of circadian disorders of the daily profile of blood pressure at the levels of both SBP and DBP in patients with EH. The presence of a certain association between extrasystolic arrhythmia, including VPB, with disorders of the DBP daily profile requires further investigation and analysis.

Thus, our study suggests that patients with II stage EH and frequent PB have higher values of both SBP and DBP during the day, which was accompanied by a violation of the daily profile of BP, mainly by non-dipper type of DBP. In patients with stage II EH and VPB, these changes were more pronounced compared with patients with CVPB. Based on these data, it cannot be excluded that the pathogenetic mechanisms involved in the regulation of the daily profile of blood pressure are responsible for the development of electrical instability of the myocardium in patients with EH.

Conclusions

1. In patients with EH and PB (regardless of its topical variant), compared to patients with EH without cardiac arrhythmias, significantly higher levels of blood pressure were registered, namely SBP, DSBP, NSBP, DBP, DDBP, NDBP, NPBP and HI SBP p <0.02). Significantly higher values of daytime and nighttime SBP (p <0.05) and increased variability of nighttime and daytime DBP (p <0.05) were found in the group of patients with stage II EH and VPB (p <0.05) relative to the corresponding parameters in patients with SVPB.

2. In patients with stage II EH, irrespective of the presence of arrhythmia, there was a violation of the daily profile of BP by the level of SBP, with an increase in the number of pathological types and a decrease in the dipper type, but without a significant difference between the groups. However, in the group of patients with stage II EH with PBs, the pathological profile of non-dipper was significantly more frequently reported by the level of DBP (56.5% vs. 34.4%, p = 0.03).

3. The presence of VPB in patients with stage II EH was accompanied by a significant (p <0.05) decrease in dipper diurnal profile and an increase in the night-peaker profile by SBP and a non-dipper type predominance by DBP in 76.0% of patients (p = 0.0003).

4. The data obtained indicate a certain associative relationship between the violation of the diurnal BP profile, mainly DBP, and the presence of PBs, namely, in patients with stage II EH. Therefore, we can assume that the pathogenetic mechanisms involved in the regulation of the daily profile of blood pressure are responsible for the development of electrical instability of the myocardium in patients with EH.

Further studies in this area *will improve the diagnosis and optimize the treatment of patients with heart disease, decrease the vascular risk and improve the prognosis of this rather severe category of patients with the aim of establishing*

associative links between circulatory disorders and the emergence of arrhythmias, pathogenetic mechanisms of blood pressure regulation disorders and the appearance of electrical instability of the myocardium.

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Реферати

ХАРАКТЕР ПОРУШЕНЬ ДОБОВОГО ПРОФІЛЮ АРТЕРІАЛЬНОГО ТИСКУ У ХВОРИХ НА ГІПЕРТОНІЧНУ ХВОРОБУ ІІ СТАДІЇ ТА ЧАСТОЮ ЕКСТРАСИСТОЛІЄЮ

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Обстежено 156 хворих (65 чоловіків та 91 жінка) на гіпертонічну хворобу ІІ стадії (ГХ ІІ). Основну групу склали 124 з них, які за даними добового моніторування електрокардіограми мали часту суправентрикулярну (СВЕ) (74 особи) або шлуночкову екстрасистолію (ШЕ) (50 осіб). В групу порівняння увійшли 32 хворих на ГХ ІІ ст. без аритмії. Встановлено, що у хворих на ГХ ІІ та екстрасистолією спостерігались достовірно вищі величини систолічного (САТ) та діастолічного артеріального тиску (ДАТ) протягом доби за даними добового моніторування артеріального тиску (АТ). У хворих на ГХ ІІ незалежно від наявності аритмії спостерігалось зменшення пацієнтів з типом dipper та зростанням кількості патологічних типів добового профілю за рівнем САТ без суттєвої різниці між групами. У хворих на ГХ ІІ із екстрасистоліями достовірно (p=0,03) частіше реєстрували добовий профіль non-dipper за рівнем ДАТ. Наявність частої ШЕ асоціювалась з переважанням профілю non-dipper за рівнем ДАТ (у 76.0 %, p=0,0003) порівняно із хворими із СВЕ. Отримані дані свідчать про певний асоціативний зв'язок між порушенням добового профілю АТ, переважно ДАТ та наявністю екстрасистолій, а саме ШЕ у хворих на ГХ ІІ стадії.

Ключові слова: гіпертонічна хвороба, суправентрикулярна екстрасистолія, шлуночкова екстрасистолія, добове моніторування артеріального тиску, добовий профіль артеріального тиску.

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ХАРАКТЕР НАРУШЕНИЙ СУТОЧНОГО ПРОФИЛЯ АРТЕРИАЛЬНОГО ДАВЛЕНИЯ У БОЛЬНЫХ ГИПЕРТОНИЧЕСКОЙ БОЛЕЗНЬЮ ІІ СТАДИИ И ЧАСТОЙ ЭКСТРАСИСТОЛИЕЙ

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Обследовано 156 больных (65 мужчин и 91 женщина) гипертонической болезнью ІІ стадии (ГБ ІІ). Основную группу составили 124 из них, которые по данным суточного мониторинга электрокардиограммы имели частую суправентрикулярную (СВЭ) (74 человека) или желудочковую экстрасистолии (ЖЭ) (50 лиц). В группу сравнения вошли 32 пациента с ГБ ІІ ст. без аритмии. Установлено, что у больных ГБ ІІ и экстрасистолией наблюдались достоверно более высокие величины систолического (САД) и диастолического артериального давления (ДАД) в течение суток по данным суточного мониторирования артериального давления (АД). У больных ГБ ІІ независимо от наличия аритмии наблюдалось уменьшение пациентов с типом dipper и увеличение количества патологических типов суточного профиля по уровню САД без существенной разницы между группами. У больных ГБ ІІ с экстрасистолиями достоверно (p=0,03) чаще регистрировали суточный профиль non-dipper по уровню ДАД. Наличие частой ЖЭ ассоциировалось с превалированием профиля non-dipper по уровню ДАД (у 76.0 %, p=0,0003) по сравнению с больными с СВЭ. Полученные данные свидетельствуют об определенной ассоциативной связи между нарушением суточного профиля АД, преимущественно ДАД и наличием экстрасистолий, а именно ЖЭ у больных ГБ ІІ стадии.

Ключевые слова: гипертоническая болезнь, суправентрикулярная экстрасистолия, желудочковая экстрасистолия, суточное мониторирование артериального давления, суточный профиль артериального давления

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ASSESSMENT OF IMMUNOLOGICAL DISORDERS IN THE GENESIS OF BRONCHIAL ASTHMA IN CHILDREN WITH DIFFERENT DEGREES OF THE DISEASE CONTROLLABILITY

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It is established that children with bronchial asthma may have pronounced changes in their immunological status, concerning both its cell and humoral components, and to a significant extent they are determined by the disease severity. In the examined patients with bronchial asthma, a limited reserve of phagocytic cells and their phagocytic activity have been established. The maximum inhibition of phagocytosis was observed in patients with uncontrolled bronchial asthma ($p < 0.05$). At the same time, in patients with uncontrolled and partially controlled bronchial asthma, a reduction of their regulatory index was registered, which was caused by the reduction of CD4+ portion and the increase of CD8+ content ($p < 0.05$). Manifestation of a positive highest degree correlation ($r=0.79$, $p<0.05$) between the blood serum IL-6 content and the BA course severity in children.

Key words: bronchial asthma, children, immunity.

The work is a fragment of the research project "Development of methods for prediction, treatment and rehabilitation of widespread somatic and surgical pathology in children in modern environmental conditions", state registration No. 0114U005518).

Allergic diseases are among the public health indicators that are regulated by the WHO Regional Office for Europe under the Health for All strategy. The increase in the prevalence of bronchial asthma (BA), which is one of the most frequent and severe allergic diseases in the population, including children, indicates the need for further fundamental studies on the mechanisms of pathogenesis, and on this basis the development of new treatment and prevention programs for the disease control.

Today, as defined by GINA (2016), asthma is considered as a chronic inflammatory disease of the respiratory tract, in the pathogenesis of which a large number of cells and cellular elements is involved. The latter include, first of all, factors of nonspecific (innate) immunity: mononuclear phagocytes (monocytes, tissue macrophages) and granulocytes (neutrophils, eosinophils, basophils of peripheral blood and tissue) [1, 2].

Nevertheless, it is established that in BA there are changes in different components of the immune system (T and B lymphocytes, phagocytic cells, natural killers), activation of specific and enzymatic processes is noted, reactions to pathologically altered lung tissue develop. At the same time, there is an increase in the content of circulating immune complexes (CIC), the level of both general and specific Ig E increases, the level of sIg A decreases, which is caused by pathological changes of the respiratory tract mucous membrane and by alteration of the epithelium [3, 4].

Development of asthma is associated with various disorders of the quantitative and functional status of the immune system [5, 6]. Thus, it has been shown that the morpho-functional changes that are associated with chronic inflammatory process in the tracheobronchial tree in BA are due to the disruption of complex regulatory responses between bronchial cells and the immune system with cytokine involvement at the local and systemic levels.

The intensity of these changes in the immune system, their directivity and the possibility of combinations in children BA are extremely variable and depend on the influence of various factors, namely: the severity of intoxication and antigenemia, the level of biologically active substances, blocking complexes, C-reactive protein, stress etc. [7, 8].

The purpose of the study was to determine the immunological features in BA children with varying degrees of the disease controllability.

Materials and methods. The total of 87 children aged 10 to 18 years with bronchial asthma who were treated in the allergic department at the CSTO of Ivano-Frankivsk were examined. The diagnosis was verified in compliance with the Protocol for the diagnosis and treatment of asthma in children (No. 868 of 08.10.2013). According to the results of the asthma test for the level of the disease controllability, the children were distributed as follows: 27 (31.0%) - controlled (CBA), 38 (44.0%) - partially controlled (PCBA), and 22 (25.0%) - with uncontrolled bronchial asthma (UCBA). The control group consisted of 20 healthy children of the same age.

State of the nonspecific body resistance was studied by determining the indices of phagocytosis (in compliance with the method of I.V. Petrov et al., 1984): phagocytic index (PI), phagocytic number (PN) in neutrophilic granulocytes.

Oxygen-dependent metabolic activity of neutrophils was determined by the reduction of nitroblue tetrazolium (NBT test) (by B. Park method in the modification of M.E. Vicksman, M.M. Maysky, 1982). A spontaneous and zamozine-stimulated test was performed with the calculation of NBT-positive neutrophils (N, %) and neutrophil activation index (IA, units).

A comprehensive immunological examination included the study of mature T-lymphocytes (CD3+) and their subpopulations (CD4+, CD8+, CD16+), as well as B-lymphocytes (CD22+) by conventional methods using the erythrocyte rosette formation test, using kits of erythrocyte diagnostics (produced by TOV NVL "Granul", Kharkiv).

To assess the B-component of the immune system the content of Ig class G, M, A (Manchini et al., 1965) was studied. The IgE content was determined by means of enzyme immunoassay.

The CIC concentration in the blood serum was studied by the precipitation method with subsequent photometry.

Serum cytokine content (IL-6, IL-4) was determined by enzyme-linked immunosorbent assay with a "STAT-Fax 303 Plus" apparatus (USA) using test systems manufactured by "Diaclone" (France) in compliance with the manufacturer's instructions.

The obtained study results were processed using the "MedStat" software (Ukraine) using descriptive statistics and correlation analysis methods.

Results of the study and their discussion. In the course of the study it was found that the development and course of asthma in children is accompanied by changes in their immunological status. The nature of the immunological changes and their severity were largely determined by the degree of the disease controllability.

In particular, patients with UCBA experienced significant changes in the neutrophils phagocytic activity, manifested by the lowest possible number of cells capable of phagocytosis and by a decrease in their phagocytic capacity. At the same time, the PI and PN indices in the UCBA patients surveyed, accounting for (28.1±1.1)% and (3.5±0.9) relative units (RU), respectively, were reliably lower than those in healthy children (pH <0.05), but similar in children with higher controllable disease (p <0.05) (table 1).

Table 1

Indices of phagocytosis status in healthy persons and patients with bronchial asthma of varying controllability (M±m)

Indices	UCBA(n=22)	PCBA (n=38)	CBA (n=27)	Healthy (n=10)
PI, %	28.1±1.1*◊^	47.1±0.9*^ Δ	78.3±1.2◊ Δ	64.8±1.8
PN, ум. од.	3.5±0.9*◊	4.2±0.08* Δ	6.8±0.09*◊ Δ	7.5±0.06
NBT spontaneous:				
- IA, RU	0.09±0.01*◊	0.10±0.01	0.12±0.01*◊	0.15±0.02
- N, %	8.0±0.01*^	9.0±0.01*^	11.1±0.01*	12.0±0.07
NBT stimulated:				
- IA, RU	0.7±0.01*^◊	1.2±0.01^	2.0±0.03*◊	1.2±0.02
- N, %	41.3±0.01*^◊	52.4±0.06*^	97.2±0.08*◊	76.3±0.5

Notes: 1. * - difference reliability compared to healthy (p<0.05); 2. ^ - difference reliability between indices in patients with UCBA and PCBA (p<0.05); 3. ◊ - difference reliability between indices in patients with із UCBA та CBA (p<0.05); 4. Δ - difference reliability between indices in patients with PCBA та CBA (p<0.05).

The opposite is the situation with regard to the factors of nonspecific protection in children with CBA. Thus, the increase of PI (%) in children with CBA was almost indistinguishable from that in the control group; the PN was lower than that in healthy subjects (p_N <0.05), but reliably higher than the similar index in children with UCBA and PCBA (p <0.05).

In children with PCBA, the vector of phagocytosis disorders tendency was shifted toward deficiency. The percentage of phagocytic cells was significantly reduced compared to the healthy group (P_N<0.05), although the PN was greater than that of children with UCBA, but significantly lower than that of the healthy (P_N<0.05) and patients with CBA (p <0.05).

Indices of spontaneous NBT test revealed insufficient degree of the phagocytic cells irritation and their low killing ability in patients with UCBA (P_N<0.05). In the other groups surveyed, the changes were less significant.

The stimulated NBT test showed low potential activity of phagocytic cells and the completion of phagocytosis in children with UCBA compared to those in healthy (p <0.05) and children with CBA (p <0.05) groups. In children with PCBA, the IA (RU) and N (%) rates were higher than those of the UCBA (p <0.05), but significantly lower than in children with PCBA (p <0.05) and healthy ones (P_N <0.05). Oxygen-dependent neutrophil microbicidal activity was found to be maximally increased in children with

CBA (p <0.05), which suggests that there is a correlation between neutrophil granulocytes activation and the manifestation of chronic inflammatory process in the respiratory tract inherent of BA.

Thus, in patients with BA, there are pronounced changes in the nonspecific body resistance, which are manifested, first of all, by the limitation of the phagocytic cells reserve and their phagocytic activity. The most pronounced inhibition of phagocytosis was observed in patients with UCBA, while in patients with CBA the phagocytic activity tended to increase. Therefore, it can be argued that at the beginning of the chronic inflammatory process development in the bronchi the phagocytic activity grows and decreases sharply as the chronicity of inflammatory changes in the bronchial tree increases and the severity of the asthma course grows. That is, in the case of severe uncontrolled course of asthma there is a more pronounced manifestation of the inflammatory process, which correlates with a number of studies.

Верифіковано дисбаланс клітинної ланки імунітету у пацієнтів із усіма варіантами БА у гострому періоді захворювання (табл.2).

The imbalance of the immunity cellular component in patients with all BA variants in the acute period of the disease was verified (table 2).

Table 2

Indices of cellular and humoral immunity in healthy children and those with bronchial asthma depending on its controllability (M±m)

Indices	UCBA(n=22)	PCBA (n=38)	CBA (n=27)	Healthy (n=10)
CD3+,%	41.1±0.44*^◊	44.1±0.37*^	60.3±0.46*◊ Δ	63.8±0.63
CD4+,%	29.4±0.72*^◊	38.1±0.54*^	41.8±0.61*◊	45.5±0.73
CD8+,%	43.2±0.68*^◊	39.5 ±0.45^ Δ	25.6 ±0.69◊ Δ	28.7±1.09
IPI (CD4+/ CD8+)	0.87±0.05*◊	0.97±0.02*	1.96±0.03◊ Δ	1.98±0.12
CD16+,%	19.7±0.22*^◊	22.4±0.31*^ Δ	26.9±0.44◊ Δ	27.7±0.61
CD22+,%	52.8±2.7*^◊	43.9 ±3.6*^ Δ	39.8 ±3.1*◊ Δ	21.7±2.90
Ig G, g/l	14.1±0.22*^◊	12.6±0.15*^	10.9±0.3◊	9.71±0.27
Ig A, g/l	0.87±0.05*	0.9±0.02*	0.9±0.03*	1.3±0.10
Ig M, g/l	2.8±0.12*◊	2.6±0.07*	1.9±0.13◊	1.7±0.09
Ig E, IU/ml	389.7±3.13*^◊	246.7±1.46*^ Δ	198.0±1.24*◊ Δ	29.3±1.40
CIC, RU	62.9±0.69*◊	53.1±0.91* Δ	44.6±0.83*◊ Δ	40.1±1.04

Notes: 1. * - difference reliability compared to healthy (p<0.05); 2. ^ - difference reliability between indices in patients with UCBA and PCBA (p<0.05); 3. ◊ - difference reliability between indices in patients with із UCBA та CBA (p<0.05); 4. Δ - difference reliability between indices in patients with PCBA та CBA (p<0.05).

Thus, in patients with CBA, changes in the cellular immunity component were manifested by a slight decrease in the content of total T lymphocytes (CD3+), which was mainly due to a decrease in the number of T cells with CD8+ phenotype and the tendency to increasing absolute and relative content of CD22+ cells in the blood. Obviously, the absence of changes in the CD4+ fraction in patients with CBA is explained by the redistribution of Th toward the pool of Th 2 cells, which determines the immune response in BA.

In patients with PCBA and UCBA the total T-lymphocyte (CD3+) content did not differ significantly between them, but it was reliably higher than in patients with CBA (p <0.05). At the same time, patients with UCBA showed a significant decrease in CD4+ lymphocytes compared to those with higher controllability of the disease (p <0.05), and their level of cytotoxic suppressors was by 1.4 times higher than CD8 + in patients with PCBA and by 1.8. – than in those with CBA (p <0.05). At the same time, in patients with UCBA and PCBA a significant decrease in the regulatory index was registered due to a decrease in the CD4+ fraction and an increase in the CD8+ content (p <0.05). The decreased content of T lymphocytes in the blood in BA may be due to the accumulation of these cells in the respiratory tract and is a predictor of inflammation in the bronchi.

When analyzing the level of lymphocytes with the CD16+ phenotype, the major part of which is represented by natural killer cells, in children with UCBA this index was reliably lower compared to that in the control group (P_N <0.05). In children with PCBA and CBA the CD16+ content was lower compared to that in the control group, but the difference was not reliable in children with CBA.

Despite the heterogeneity of the groups in terms of the BA severity, the nature of the humoral immune system's response had common tendencies, and differences were only observed in the intensity of the reaction processes. Thus, in children with UCBA the number of lymphocytes with the CD22+ phenotype was high and amounted to 52.8%, in patients with PCBA - 43.9% and in children with CBA - 39.8%. At the same time, the increase of CD22+ cells (p <0.05) in patients with UCBA and PCBA was characterized by a decrease of CD3+ content by 1.5 and 1.2 times, respectively, and the decrease in CD8+

exceeded the decrease in CD4+ cells with the formation of a relative suppressor variant. secondary immune response, which is a common phenomenon in chronic respiratory diseases.

With regard to the total CIC content, its highest values are verified in patients with UCBA, slightly lower in PCBA. Thus, they exceeded the reference value by 2.1 and 1.7 times, respectively (P_N <0.05). In patients with CBA, the CIC content did not virtually differ from that in healthy persons. The data obtained may indicate a significant role of the immunocomplex component in the pathogenesis of BA with a low degree of controllability.

Quantitative disorders of the regulatory part of the humoral link have been largely reflected in the synthesis of different classes immunoglobulins. An inadequate, probably compensatory, statistically significant difference in providing children with Ig E was revealed, which consists in its overproduction in comparison with healthy ones. At the same time, its concentration exceeded the normal values in children with all variants of BA and was maximal in children with UCBA (P_N <0.05).

Analysis of the major immunoglobulins classes showed that patients with BA were characterized by an increase in the level of total Ig G and Ig M (P_N <0.05), with a simultaneous decrease in Ig A level (P_N <0.05). The most pronounced deviations from the normal values of these indices were in patients with UCBA, but they were not reliably different from the respective values in patients with higher levels of the disease controllability.

An increase in the IgE and IgG content in patients with BA indicates the functional tension of B lymphocytes. This reaction of the immune system reflects the severity of the systemic immune response to the inflammatory response in the body of patients and progresses with increasing severity of the disease. Increasing IgG levels, in turn, can contribute to the formation of excessive CIC.

The study found that all patients with BA have an imbalance in the cytokine status, which is largely determined by the degree of the disease controllability (table 3).

Table 3

The content of cytokines in the blood serum of healthy and children with different levels of BA controllability (M±m)

Index. pg/ml	UCBA[1] (n= 22)	PCBA [2] (n=38)	CBA [3] (n=27)	P^{1-2}	P^{1-3}	P^{2-3}	Healthy (n=10)
IL-6	25.49±1.54	13.72±0.34	5.30±0.23	* ^	* ^	*	3.59±0.11
IL-4	21.21±0.55	18.45±0.28	11.46±0.39		* ^	*	11.15±0.84

Notes: 1. * - difference reliability compared to healthy children (p<0.05); 2. ^ - difference reliability between indices in patients with different levels of БА controllability(p<0.05)

Thus, a significant (P_N <0.05) IL-6 content increase in the blood serum was observed in patients with CBA with the IL-4 level preserved.

A significant increase in IL-6 levels was observed in patients suffering from PCBA compared to the healthy group (P_N <0.05) and patients with CDA (p <0.05), with the simultaneous significant decrease in the blood serum IL-4 level (P_N <0.05).

In patients with UCBA, the IL-6 content was elevated compared to the normal (P_N <0.05), but slightly different from those of PCBA patients, which, in our opinion, is due to the administration of higher doses of inhaled glucocorticosteroid drugs, as well as to the depletion of immune inflammation mechanisms in this category of patients. At the same time, the level of IL-4 in children with UCBA, being (21.05±0.27) pg/ml, probably exceeded not only the similar index in healthy (P_N <0.05), but also that in children with CBA (p <0.05). Such changes indicate a high intensity of the inflammatory process, with simultaneous pronounced sensitization of the body and the intensity of nonspecific protection factors in children with UCBA.

High degree positive correlation (r = 0.79, p <0.05) was found between the blood serum IL-6 content with BA severity in children.

Thus, the increased content of proinflammatory while maintaining the level of anti-inflammatory cytokines in the blood serum of patients with CBA reflects the initial inflammatory changes in the bronchial tree, when the mucous membrane has not completely lost its protective properties, there is no permanent persistence of bacterial infection.

In children with PCBA, activation of proinflammatory cytokines may be associated with a predominantly prolonged persistence of bacterial infection and relatively more frequent exacerbations of viral-bacterial etiology, it can also testify to depletion of the cytokine-producing capacity of the producing cells. At the same time, the decrease of IL-4 content in children with PCBA may indicate a depletion of the compensatory anti-inflammatory mechanisms of the immune system and insufficient anti-inflammatory response.

The maximum blood serum IL-4 level that occurs in UCBA is a manifestation of a pronounced allergic component in the pathogenesis of the disease in this category of patients and indicates a Th2 mechanism of the allergic reaction and inflammation that redirect the synthesis of IgG and IgM in B-lymphocytes to the IgE synthesis, and thus significantly affects the BA severity. At the same time, a probable increase in the level of proinflammatory cytokine (IL-6) in children with UCBA leads to the induction of other proinflammatory cytokines synthesis, including TNF-α, and determines the degree and severity of the inflammatory process, namely the development of its proliferative stage, and processes of the bronchi remodeling. Thus, the most pronounced changes in the cytokine status of patients with UCBA are determined by the multifactorial genesis of this clinical form and determine the severity of clinical symptoms and the degree of resistance to therapy in such patients.

Thus, the variant and severity of immunological shifts in patients with BA are strictly determined by the degree of disease controllability. Thus, in children with UCBA, a decrease in the functional capacity of natural killers, hyperproduction of IgE and IgG with simultaneous imbalance of the phagocytic link is observed against the background of reduction in the total number of T lymphocytes (mainly CD3+ and CD4+). In children with PCBA, a decrease in most components of the T-cell subpopulation (excluding CD8+) is determined against the background of pronounced hyperimmunoglobulinemia and limitation of the phagocytic function. Hyperimmunoglobulinemia was predominant in CBA patients with relatively normal indices of the phagocytic system's components.

The heterogeneity of fluctuations in indices within a single component of the immune system in children with varying degrees of BA controllability may be due to adaptive functional abilities that form individual adaptive responses and permanent functional readiness for different antigen load.

Conclusions

1. In BA, the following changes in the immune status are typical of the child: a decrease in the number and functional status of T-lymphocytes, dysfunction of B-lymphocytes (increase in the number of B-cells, decrease in their functional activity), disimmunoglobulinemia (increase in the IgG, IgE content with simultaneous reduction of IgA), increasing content of CIC, reduction of natural and increase of the specific antibodies level, reduced number of NBT-positive neutrophils and their functional activity.

2. The level of immunological changes in children with BA can serve as a marker of systemic cellular metabolism disturbance and is strictly determined by the nosology severity.

Prospects for further research *are to study the possibility of drug correction for immunological shifts in children with bronchial asthma.*

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Реферати

ОЦІНКА ІМУНОЛОГІЧНИХ ПОРУШЕНЬ У ГЕНЕЗІ БРОНХІАЛЬНОЇ АСТМИ РІЗНОГО СТУПЕНЯ КОНТРОЛЬОВАНОСТІ У ДІТЕЙ

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Встановлено, що у дітей із бронхіальною астмою мають місце виражені зміни в імунологічному статусі, що торкаються як клітинної, так і гуморальної його ланок та в значній мірі визначаються ступенем тяжкості захворювання. У обстежених із бронхіальною астмою встановлено обмеження резерву фагоцитуючих клітин та їх фагоцитарної активності. Максимально виражене пригнічення фагоцитозу відмічалося у обстежених із

ОЦЕНКА ИММУНОЛОГИЧЕСКИХ НАРУШЕНИЙ В ГЕНЕЗЕ БРОНХИАЛЬНОЙ АСТМЫ РАЗНОЙ СТЕПЕНИ КОНТРОЛИРОВАННОСТИ У ДЕТЕЙ

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Установлено, что у детей с бронхиальной астмой имеют место выраженные изменения в иммунологическом статусе, что касается как клеточного, так и гуморального звеньев и в значительной мере выражаются степенью тяжести заболевания. У обследованных с бронхиальной астмой установлено ограничения резерва фагоцитирующих клеток и их фагоцитарной активности. Максимально выраженное угнетение фагоцитоза наблюдалось у обследованных с

неконтрольованою бронхіальною астмою (p<0,05). Одночасно у пацієнтів із неконтрольованою та частково контрольованою бронхіальною астмою реєструвалось вірогідне зниження регуляторного індекса, зумовленого зменшенням частки CD4+ та зростанням вмісту CD8+ (p<0,05). Встановлено наявність позитиваного кореляційного зв'язку високого ступеня (r=0,79, p<0,05) між вмістом в сироватці крові IL-6 із тяжкістю перебігу БА у дітей.

Ключові слова: бронхіальна астма, діти, імунітет.

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неконтролированной бронхиальной астмой (p<0,05). Одновременно у пациентов с неконтролированной и частично контролированной бронхиальной астмой регистрировалось достоверное снижение регуляторного индекса, выражавшегося уменьшением процента CD4+ и увеличением CD8+ (p<0,05). Установлено наличие положительной корреляционной связи высокой степени (r=0,79, p<0,05) между содержанием в сыворотке крови IL-6 и тяжестью течения бронхиальной астмы у детей.

Ключевые слова: бронхиальная астма, дети, иммунитет.

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PECULIARITIES OF TLR9 EXPRESSION ON IMMUNE COMPETENT CELLS IN REACTIVE ARTHRITIS PATIENTS WITH CHRONIC EPSTEIN-BARR VIRUS INFECTION

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The work presents the study findings on the TLR9 expression in immune competent cells in reactive arthritis patients with chronic Epstein-Barr virus infection, and considers the possibility of the reactive arthritis transformation into rheumatoid arthritis. It was established that expression of TLR9+CD123+ on monocytes was reliably higher in the blood of reactive arthritis patients as compared to healthy individuals, while in patients in active phase of EBV-infection the expression of this receptor was reliably higher as compared to similar indices of patients at the latent phase. At that, the number of TLR9+CD123+-monocytes in patients with reactive and rheumatoid arthritis was not reliably different. The number of TLR9+CD123+-lymphocytes as compared to indices of healthy individuals was reliably higher in patients with rheumatoid arthritis at both phases of chronic EBV-infection, while in patients with reactive arthritis it was only characteristic at the active phase of the infection. Expression of this receptor on lymphocytes turned out to be reliably higher in patients with rheumatoid arthritis as compared to patients with reactive arthritis, particularly at the active phase of chronic EBV infection.

Key words: reactive arthritis , rheumatoid arthritis, chronic Epstein-Barr Virus Infection, TLR9.

The work is a fragment of the research project "Prediction of development of allergic diseases virus-induced phenotypes with personification of their diagnosis and treatment", state registration No. 0118U000110.

Over the last years, there has been a wide spread of reactive arthritis cases (ReA), especially among young people. The relevance of the problem of ReA is attributed to its high incidence and difficult differential diagnostics [14]. It is very often the case when clinically similar joint problems could be initial signs of systemic diseases. Currently, ReA is treated as a multifactor joint disease which belongs to the group of seronegative spondilo-arthropathies HLA-B27-associated that develop due to immune disorders after having the urogenital, intestinal, respiratory, and tonsilogenic infections. Today, dependency of the incidence of contraction of the ReA on the type of the pathogen has been well studied, however, there is no clear answer to the question why different micro-organisms can cause ReA, or cause it with different incidence. Currently, special focus in the development of ReA is allocated to the role of viruses, including also the chronic Epstein-Barr virus (EBV) [4]. EBV infection is one of the most widespread infections in the world. In the recent years, during primary introduction of infection, the virus has often caused blurred atypical forms of disease with rapid chronization. EBV persists lifelong in the human body due to its ability to suppress effector mechanisms of immune competent cells [3]. One of the theories on complications in ReA development is about its transformation into rheumatoid arthritis (RA). RA is an autoimmune disease characterized with chronic inflammation of joints that will gradually result in damage of cartilages and bones; it is characterized with synovial hyperplasia with massive infiltration of inflamed cells. Immune cells play a key role in RA progression due to production of pro-inflammatory cytokines [1]. One of the causing factors for the transformation could be Herpesviruses.

A conducting system providing for recognition of infections, and viruses in particular, is a system of Toll-like receptors (TLRs), and more specifically TLR9 [12]**.** The TLR9 is an important intracellular receptor expressed on immune competent cells; it mostly binds the DNA that is present in viruses; it launches signal cascades that lead to pro-inflammatory response of cytokines [4]. It has been found a different interaction of EBV with TLRs expressed on different cells [9].

The research proved that TLRs are actively engaged in the development of autoimmune diseases via direct and indirect activation of T-cells, activation of autoreactive B-cells [15]. Activation of TLRs has several functions in aggravation and progression of joint damage related to the increase of the polymorphism number in TLRs [6]. Some studies indicate the contrary, the lack of expression of TLR9 that contributes to aggravation and progression of autoimmune diseases [2].

For this reason, we set an objective to explore the immunepathogenetic mechanisms of ReA development engaging TLR9, and its possible impact on the transformation of ReA into RA.

The purpose of the work was to assess the extent of TLR9 expression on mononuclear cells of peripheral blood in reactive arthritis patients with chronic EBV infection, and values of TLR9 at the risk of transformation of reactive arthritis into rheumatoid arthritis.

Materials and methods. We had 64 patients under observation (33 ReA patients and 31 RA patients) who were staying on in-patient care in the rheumatology unit of Lviv Regional Clinical Hospital, and in out-patient care at the Regional Center for Clinical Immunology and Allergology. Among the 33 ReA patients, 19 were men (57.6%), and 14 women (42.4%), aged 18-35 (average age 26.5±7.4). The patients were divided into two sub-groups: 1) 21 active ReA patients of chronic EBV-infection – ReA EBV (+); 2) 12 patients with signs of ReA in latent phase of chronic EBV-infection – RA EBV (-).

Among the 31 RA patients, there were 12 men (38.7%) and 19 women (61.3%), aged 18-54 (average age 38.2±6.9). The group of patients was also divided into two sub-groups: 1) 10 RA patients with active chronic EBV-infection – RA EBV (+); 2) 21 RA patients with latent chronic EBV-infection – RA EBV (-).

Verification of ReA and RA was conducted on the basis of clinical data on joint damage, laboratory and instrumental tests. ReA patients met the diagnostics criteria pursuant to the protocol of the Ministry of Health Care of Ukraine dated 12.10.2016. RA patients complied with the diagnostic criteria of American and European collegium of rheumatologists ACR/EULAR (2010).

The phase of chronic EBV-infection (active or latent) was verified on the basis of the clinical laboratory tests, serologic (identification of specific IgM, IgG to different EBV antigens), and molecular-genetic (detecting the virus DNA) tests. Detection of specific antibodies was done with the method of immunoferment test using the Euroimmun test-systems (Germany). EBV DNA in blood serum, saliva, and mucous scraping of posterior pharyngeal wall was identified with the method of polymerase chain reaction (PCR) with the use of Ampli Sens diagnosticum (Russia) on Rotor Geen 6000 (Corbett Recearch, Australia). All patients with identified antibodies of class IgG EBNA of IgG VCA on the background of absent EBV DNA in three media were referred to the group of patients in latent phase of chronic EBV-infection. Patients with identified antibodies of class IgG (EBNA) and/or capsid antibodies of class IgM/IgG (VCA) and DNA virus were classified as patients in active phase of chronic EBV-infection. All patients underwent bacteriological testing to identify a possible infection with bacterial agents. In addition, they were also tested for markers of Chlamydia infection. Tests of TLR9 were made on the basis of the identified $CD123^+$ on mononuclear cells of peripheral blood with the method of ductal cytofluorometry with the use of flow cytofluorometer and Bekton Dickenson test system (USA).

The control group included 24 apparently healthy individuals of the corresponding age and gender.

Statistical processing of findings was carried out with the help of the Statistika software for Windows 6.0, using the Student criterion.

Results of the study and their discussion. Clinically, all 33 ReA patients showed arthritic syndrome. The pathological process affected shoulder, knee, ankle, and small joints of the feet. Among the 21 ReA EBV (+) patients, arthritis of one joint was recorded in one person (4.8%), two joints – in 8 individuals (38.1%), three and more – in 12 patients (57%). Among 12 ReA EBV (-) patients, arthritis of one joint was recorded in three (25%), two joints – in seven (58.3%), three and more – in two (16.7%) patients. Moreover, 11 (53.4 %) patients with ReA EBV (+) showed prolonged subfebrile condition, 17 (80.9%) patients showed a chronic fatigue syndrome, seven patients (33.3%) – had respiratory immunodeficit disorder, six persons (28.6%) had lymphadenopathy of mostly cervical and mandibular lymph nodes.

All RA patients showed signs of arthritic syndrome, while mostly small joints of hands and feet were affected. Activity of RA was identified with the help of visual analogue scale and activity index DAS28, when patients with EBV (+) had it with 5.94±1.31 and it was probably different from DAS28 in patients with EBV (-) - 4.11±1.09 ($P<0.05$). In addition, eight (25.8%) patients complained about temperature rise up to 38.5.

RA patients with EBV (+) had the average number of leukocytes of 6.80±2.14 g/l, ESR – 23.01±4.15 mm/h, CRP – 18.92±2.18 nmol/L. In 10 (47.6%) patients an absolute or relative lymphocytosis

was identified; in 7 (33.3%) - absolute lymphopenia, mild cases. In ReA patients with EBV (-), the number of leukocytes was 8.83±2.14 g/L, ESR average value - 19±3.15 mm/h, CRP – 9.92±2.18 nmol/L. All patients had a negative RF and antibodies to cyclic citrulline peptide; high levels of IgG EBNA and increased level of VCA-EBV (6 times higher and above norm). Of them, 4 patients from this group (19.1%) had a raised level of IgM-VCA EBV. With 3 (14.3%) persons, it was identified DNA of EBV (+) simultaneously in blood, saliva, and in mucous scraping of posterior pharyngeal wall, 6 (28.6%) patients had it at the same time in saliva and mucous scraping of posterior pharyngeal wall, 10 (47.6%) patients had in mucous scraping of posterior pharyngeal wall, and two persons (9.5%) –in saliva only.

Laboratory tests of RA patients with EBV (+) revealed the following: mean values of leukocytes – 7.14±1.10 g/L, ESR – 28.91±6.80 mm/h, CRP – 225.24±84.52 nmol/L. RA patients with EBV (-) had the mean values of leukocytes of 8.27±2.33 g/L, ESR – 23.60±4.46 mm/h, CRP – 169.24±65.25 nmol/L. Positive RF was identified in 26 (83.9%) patients; autoantibodies to cyclic citrulline peptide found in 27 (87.1%) patients. Mollecular genetic test of RA patients with EBV (+) showed DNA of EBV at the same time in blood, saliva, and mucous scraping of posterior pharyngeal wall – in one (10.0%) patient, in saliva and in the mucous scraping of posterior pharyngeal wall – in three (30.0%) persons, in mucous scraping of posterior pharyngeal wall – in four (40.0%), in saliva only – in two (20.0%) patients. In addition, three patients (30.0%) from this group showed a raised level of IgM-VCA EBV. 21 RA patient with EBV (-) showed only nuclear antibodies of class IgG (EBNA) and IgG (VCA), which levels were 6 times above norm on the background of no DNA of EBV in three media. The patients were referred to the sub-group of rheumatoid arthritis with EBV (-).

Bacterial swab test from the throat of all patients showed an opportunistic pathogenic microflora in physiological and slightly raised amount, which did not exclude engagement of bacteria in the development of ReA. All patients had negative markers of Chlamydia infection.

Table 1 shows data on expression of TLR9 on lymphocytes and monocytes of peripheral blood in reactive arthritis patients and rheumatoid arthritis patients with active and latent phase of EBV-infection.

Table 1

Activity of expression of TLR9$^+$ CD123$^+$ on monocytes and lymphocytes in patients with reactive arthritis and rheumatoid arthritis at the background of active and latent phases of chronic EBV-infection (M±m)

	Healthy individuals	ReA EBV(-)	ReA EBV(+)	RA EBV(-)	RA EBV(+)
TLR 9$^+$ CD 123$^+$ monoc., %	0.03±0.01	0.06±0.01*	0.09±0.01*^{o}	0.09±0.02*	0.12±0.03*
TLR 9$^+$ CD123$^+$ limphoc., %	0.80±0.12	1.22±0.34	1.62±0.15 *	1.50±0.12*	2.11±0.11*^{o}^

Notes:*P <0,05 – validity of difference between the indicators of healthy individuals and ReA and RA patients with EBV (+) and EBV (-); ^{o}P <0.05 – validity of difference between the indicators of ReA patients with EBV (+) and EBV (-) and RA EBV (+) and EBV (-); ^P<0.05 – validity of difference between the indicators of ReA patients with EBV (-) and RA EBV (-) and ReA patients (+) and RA EBV (+)

As the data from Table 1 shows, expression of TLR 9$^+$CD123$^+$ on monocytes in both ReA and RA patients, both in active, and latent phases of chronic EBV infection was validly higher as compared with indicators of healthy individuals (P <0.05). Compared to indicators of healthy individuals, expression of TLR 9$^+$CD123$^+$ on lymphocytes was also validly higher in RA patients in latent and active phases of chronic EBV-infection, while in ReA patients – it was only in active phase of the infection.

ReA patients in latent phase of infectious process had expression of TLR9 on monocytes (0.06±0.01%) validly 33.3% lower than in active patients of EBV-infection (0.09±0.01%, P<0.05). Expression of TLR9 on lymphocytes of these patients was validly not different in the active phase (1.62±0.15%) as compared to patients in latent phase with EBV-infection (1.22±0.34, P>0.05).

Patients with rheumatoid arthritis had expression of TLR9$^+$CD123$^+$ on monocytes validly not different in active phase (0.12±0.03%), as compared to patients in latent phase of EBV-infection (0.09±0.02%, P>0.05). Expression of TLR9 on lymphocytes in RA patients in latent phase of the infection (1.50±0.12%) showed as probably 28.9% lower as compared to patients in active phase of EBV-infection (2.11±0.11%, P<0.05).

Patients with rheumatoid arthritis had expression of TLR9 on monocytes which actually did not differ as compared to ReA patients both in active (0.09±0.01% and 0.12±0.03%, P>0.05, respectively), and in latent phase (0.06±0.01% and 0.09±0.02%, P>0.05, respectively) of chronic EBV-infection. The number of TLR9$^+$CD123$^+$-lymphocytes turned out higher by 23.2 % in RA patients (2.11±0.11%), as compared to ReA patients (1.62±0.15, P<0.05). However, it was only shown in active phase of the infection.

ReA patients has expression of TLR9$^+$CD123$^+$ on mononuclear cells (both in active and in latent phases of chronic EBV infection) validly higher compared to healthy individuals (P<0.05). The obtained

results can be explained by the fact that EBV infection activates a signal pathway of TLR9, which leads to production of Tumor necrosis factor alpha (TNF-α), Interleukin 6 (IL-6), and to the development of inflammatory response. TLR9 on monocytes recognizes motives of CpG EBV DNA and enhances immune response caused by EBV infection [13]. After stimulation, EBV cells can release chemokine MCP-1 that has strong anti-inflammatory properties [8]. Number of TLR9+CD123+-monocytes in ReA and RA patients was validly not different in active and in latent phases of chronic EBV-infection. As we know, monocytes/macrophages cause inflammation in tissues where they are concentrated. The cells can recognize different ligands through TLR. In the process, production of anti-inflammatory cytokines is taking place. Thereupon, it has been described that synovia of RA patients might show enhanced expression of TLR2 and TLR9 [2]. Activation of TLR9 by EBV genome can facilitate inflammation in joints inducing production of a wide spectre of chemokynes and cytokines [2]. High level of expression of TLR9 on monocytes indicates to the possible contribution of this receptor into the development of autoimmune process [11]. Thus, increased number of TLR9+CD123+-monocytes in ReA patients with chronic EBV-infection and lack of valid difference from RA patients may indicate further progression of inflammatory process with transition into autoimmune process, through exhaustion of monocyte macrophage link of immune system.

However, the study of TLR9 in experimental models showed its anti-inflammatory effect [8]. Therefore, the function of TLR9 on monocytes can be interpreted twofold: as such that can activate or suppress inflammation, including also autoimmune one [7]. With EBV-infection, additional mechanisms may develop related to polymorphism of TLR9, which can cause in some patients transformations of reactive arthritis into rheumatoid arthritis.

As we know, RA patients have dominant autoimmune processes involving a humoral link into pathological process, with activation of autoreactive B-lymphocytes and T-cell link of immune system. Increased number of $TLR9^{+}CD123^{+}$-lymphocytes in RA patients in active phase of EBV-infection in our study can be explained by presence of direct and indirect activation of T-lymphocytes under the impact of TLR9, and activation of B-lymphocytes engaging them in the process of auto-aggression. The research conducted with RA patients points out the role of TLR9 in the phase of initiation of autoimmune processes engaging T-lymphocytes into pathological process [5]. B-lymphocytes can function as antigen-presenting cells, and enhanced expression of TLR9 on them, with active EBV-infection, can support switching of antibodies classes, expanded synthesis of auto-antibodies, intensification of inflammation and increase in activated $CD4^{+}$T-cells. One should mention the role of apoptosis in RA, and its relation to TLR9. It was demonstrated that DNA released due to cell damage can induce TLR9-dependent production of cytokines, thus intensifying the inflammatory process. As we know, during RA there is initiation of apoptosis with production of molecular patterns associated with tissue damage, with their further interaction with TLR, which is referred to key mechanisms of initiation of inflammation in the process of tissue damage with the development of auto aggression.

Chronic active EBV-infection facilitates broad infecting of immunocompetent cells (primarily, monocytes/macrophages, lymphocytes, neutrophils), which eventually leads to auto-aggression. No difference in expression of $TLR9^{+}CD123^{+}$ on monocytes in ReA and RA patients with chronic EBV-infection, and enhanced expression on lymphocytes in RA patients as compared to active ReA patients can be the precondition for transformation of reactive arthritis in rheumatoid arthritis. That is why the use of antiviral medications can fully prevent or slow down the development of auto immune process [8]. Instead, the use of steroid and disease modulatory medication will facilitate favorable conditions for the development of immune disorders and replication and generalization of viral infection. It has been confirmed by other researchers who claim that even in patients with periodic activation of viral infections, including EBV, who do have good disposition for disease modulatory medications, have serious interrupted fluctuations in clinical activity of the disease [12]. Application of antiviral medication that control active replication of the virus can restrain the enhancement of inflammatory process, including also the one of autoimmune origin.

Conclusions

Average age of reactive arthritis patients with chronic EBV-infection turned out to be lower, and was 26.5±7.4 years, with a higher share of men (56.6%), than the average age of rheumatoid arthritis patients – 38.2±6.9 years, with a higher share of women (76.2%).

The number of affected joints was higher in reactive arthritis patients in active phase of EBV infection than in latent phase; strength of inflammatory process of DAS28 was likely higher in rheumatoid arthritis patients with active EBV infection, rather than with latent.

Expression of TLR9+CD123+ on monocytes turned out to be validly (P<0.05) higher in the blood of ReA and RA patients, both in latent and in active phases of EBV infection, as compared to healthy individuals. In ReA patients in active phase of EBV-infection, expression of TLR9+CD123+ on monocytes was higher by 33.3% as compared with similar indicators of patients in latent phase of infection, while the number of TLR9+CD123+-monocytes in patients with ReA and RA in both phases of chronic EBV infection was validly not different.

The number of TLR9+CD123+-lymphocytes compared to the indicators of healthy individuals was validly higher in RA patients in both phases of chronic EBV-infection, while in ReA patients it was only in active phase of the infection. Expression of TLR9 on lymphocytes in RA patients in active phase was by 28.9% higher than in patients in active phase of EBV-infection. Expression of this receptor on lymphocytes turned out to be higher by 23.2% in RA patients as compared with ReA patients in active phase of chronic EBV infection.

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Реферати

ОСОБЛИВОСТІ ЕКСПРЕСІЇ TLR9 НА ІМУНОКОМПЕТЕНТНИХ КЛІТИНАХ У ХВОРИХ НА РЕАКТИВНИЙ АРТРИТ З ХРОНІЧНОЮ ЕПШТЕЙНА-БАРР ВІРУСНОЮ ІНФЕКЦІЄЮ

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У даній статті авторами представлені результати дослідження експресії TLR9 на імунокомпетентних клітинах у хворих на реактивний артрит з хронічною Епштейна-Барр вірусною інфекцією та розглянуто можливість трансформації реактивного артриту в ревматоїдний артрит. Встановлено, що експресія TLR9+CD123+ на моноцитах виявилась достовірно вищою у крові хворих на реактивний артрит порівняно зі здоровими особами, при цьому в хворих в активній фазі ЕБВ-інфекції експресія цього рецептора була достовірно вищою порівняно з аналогічними показниками хворих в латентній фазі, а число TLR9+CD123+-моноцитів - у хворих на реактивний та ревматоїдний артрит достовірно не відрізнялось. Кількість TLR9+CD123+-лімфоцитів порівняно із

ОСОБЕННОСТИ ЭКСПРЕССИИ TLR9 НА ИММУНОКОМПЕТЕНТНЫХ КЛЕТКАХ У БОЛЬНЫХ РЕАКТИВНЫМ АРТРИТОМ С ХРОНИЧЕСКОЙ ЭПШТЕЙНА-БАРР ВИРУСНОЙ ИНФЕКЦИЕЙ

Ломиковская М.П., Гайдучок И.Г., Потемкина Г.О., Зубченко С.О., Криль И.Й., Ищейкин К.Е., Чопяк В.В.

В данной статье авторами представлены результаты исследования экспрессии TLR9 на иммунокомпетентных клетках у больных реактивным артритом с хронической Эпштейна-Барр вирусной инфекцией и рассмотрена возможность трансформации реактивного артрита в ревматоидный артрит. Установлено, что экспрессия TLR9+CD123+ на моноцитах оказалась достоверно выше в крови больных реактивным артритом по сравнению со здоровыми лицами, при этом у больных в активной фазе ЭБВ-инфекции экспрессия этого рецептора была достоверно выше по сравнению с аналогичными показателями больных в латентной фазе, а число TLR9+CD123+ моноцитив - у больных реактивным и ревматоидным артритом достоверно не отличалось. Количество TLR9+CD123+лимфоцитов по сравнению с

показниками здорових осіб була достовірно вищою у хворих на ревматоїдний артрит в обох фазах хронічної ЕБВ-інфекції, а в пацієнтів з реактивний артритом - тільки в активній фазі цієї інфекції. Експресія цього рецептору на лімфоцитах виявилась достовірно вищою у хворих на ревматоїдний артрит порівняно із хворими на реактивний артрит саме в активній фазі хронічної ЕБВ інфекції.

Ключові слова: реактивний артрит, ревматоїдний артрит, хронічна Епштейна-Барр вірусна інфекція, TLR9.

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показателями здоровых лиц была достоверно выше у больных ревматоидным артритом в обеих фазах хронической ЭБВ-инфекции, а у пациентов с реактивным артритом - только в активной фазе этой инфекции. Экспрессия этого рецептора на лимфоцитах оказалась достоверно выше у больных ревматоидным артритом по сравнению с больными реактивным артритом именно в активной фазе хронической ЭБВ инфекции.

Ключевые слова: реактивный артрит, ревматоидный артрит, хроническая Эпштейна-Барр вирусная инфекция, TLR9.

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MEASLES PNEUMONIA IN CHILDREN: CLINICAL AND MORPHOLOGICAL FEATURES OF THE COURSE

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The article presents the results of a retrospective analysis of 96 patients' histories with measles established, with a detailed course study and the anamnestic data analysis. The measles infection course was accompanied with signs of the intoxication syndrome, the classic catarrhal triad manifestation (coughing, rhinorrhea and conjunctivitis), and the exanthema syndrome. Most of the diseased children are not vaccinated against measles. The patients had a complicated disease course with manifested symptoms of measles pneumonia, as the most common complication in this pathology. Morphological and histological changes of the lungs in children with severe mesles course were characterized by abundant infiltration of both the interalveolar septa and alveolar lumens by polymorphocellular infiltrate, consisting of neutrophilic leukocytes, eosinophils, lympho-histiocytes with numerous parietal hyaline masses (hyaline membranes). There was a giant-cell metaplasia of the alveolar epithelium.

Key words: measles in children, pneumonia, pathomorphological changes, histological examination.

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At the present stage, measles remains an extremely important problem of today. Both in the world and in Ukraine, every five to six years an increase in the measles incidence is observed. According to the European Regional Bureau of the World Health Organization (WHO), since 2017, over 22,300 measles cases have been reported in different countries of Europe. In 8 countries of the European Region, 57 people died from measles during the first half of 2018 [2].

At the same time, Ukraine occupies a leading position among the countries of the said region. In the period from 1 January to 31 August 2018, 29 465 measles cases were reported in Ukraine, with fatal cases (13 deaths) [2].

Measles is a very threatening and contagious infection. It is known that the risk of this infection lies in the development of serious complications, such as pneumonia, otitis, encephalitis, renal toxicity, polyneuritis, etc. [4, 5]. They are caused directly by the action of the virus itself [6]. Since the measles virus causes cells dystrophy in all mucous membranes, particularly in the respiratory tract, and due to its effect on monocytes, there is an increased production of interleukins, tumor necrosis factor, histocompatibility molecules, and the presentation of antigens to T-lymphocytes is inhibited, these factors cause immunosupression, reduce cellular immunity [7]. T-cell immunodeficiency is particularly pronounced, persisting for 25-30 days after the disease (post-measles anergy) [4]. Against this background, all conditions are created for the development of secondary bacterial complications [7].

In the Vinnytsya region, for the period from January 2018 to February 2019, 4805 persons were diagnosed with measles, including 2210 children. It should be noted that children with the most severe measles course were treated at the Vinnytsya Regional Children's Clinical Infectious Diseases Hospital (VOCDIL).

Within the period from January 2018 to April 2019, 781 patients with measles were treated in hospital. Among all cases of the complicated measles course, measles pneumonia was most commonly reported. In one of the complicated measles cases, the disease had fatal outcome. The death was due to the development of pneumonia against the background of congenital lung pathology.

The purpose of the study was to find out clinical and morphological features of the pneumonia course in children with measles.

Materials and methods. According to the purpose of the study, 96 children between the ages of 1 month and 17 years (mean age 8.6±1.2 years) who were hospitalized in VOCDIL with measles diagnosed during 2018-2019 were monitored. Among 96 patients, boys - 50 children (52%) - were more likely to suffer from measles, the number of girls was 46 (48%) respectively. The patients were divided into two subgroups: 1) 77 children diagnosed with measles without pneumonia (mean age 7.79±4.83); 2) 19 patients with signs of measles pneumonia (mean age - 5.75±3.79).

Determining the severity of the disease was performed by analyzing clinical and medical records and laboratory parameters. At the same time, epidemiological, general clinical, instrumental (ultrasound examination of the abdominal organs, radiological examination of the thoracic organs) research methods were applied. To verify the measles infection, an enzyme immunoassay method was used to detect M. antimeasles immunoglobulins in the patients' blood serum. The severity of pneumonia was assessed by the pneumonia severity scale in children, based on the pneumonia severity index in children (Pneumonia Severity Index).

The disease clinical manifestations' severity was determined, such as age, presence of concomitant diseases, impaired consciousness, labored breathing, cyanosis, chest pain, toxic encephalopathy, body temperature <36°C, tachycardia; and laboratory-functional parameters such as: leukocytosis, leukopenia, anemia, pH <7.35, residual nitrogen> 11 mmol/l, hematocrit <30%, SaO2 <90%, cardiovascular disorders, radiographic multilobar infiltration, infectious-toxic shock, pleural exudate, destruction.

In this case, a score was developed for each identified symptom. According to the definition of some of the above symptoms, it is possible to establish the severity of pneumonia, namely: if less than 50 are registered when calculating points, this condition indicates the first severity degree of the disease, with the risk of mortality being 0.1%; in the case when the sum of points ranges from 51 to 70 points, the second severity degree is established when the risk of lethality makes 0,6%. With the third severity degree (71 - 90 points) mortality risk makes 2,8%, data on 91 to 130 points testify to the fourth severity degree when mortality risk makes 8,2%. The worst course of the disease is the fifth severity degree (> 130 points), which indicates a high risk of mortality - 29,2% [3]. Given that the main complication in children with measles was pneumonia, the performed scientific research demonstrates the study of this particular contingent of patients.

Statistical processing of the results was performed using STATISTICA 10.0 software for Windows 10 using descriptive statistics methods. Data calculation was performed by processing absolute values taking into account intensive and extensive indices using standard statistic research methods. The results are presented as mean (M) and mean error (m) for quantitative values. Assessment of the difference reliability between the parametric values obtained in the process of scientific research was carried out according to the Student's t-test. The Relative Risk, confidence interval (CI), and its reliability were calculated using the Fisher method in the "2×2" conjugate tables.

Results of the study and their discussion. In the course of our work, it was found that in 59 children (62%) the measles diagnosis was confirmed by laboratory methods, and in 37 patients (38%) it was based on clinical data.

All patients had a typical form of measles. In 92 (96%) children, the disease course was of moderate severity, whereas the severe form of the disease was only diagnosed in 4 patients. Among all the patients, 44 children (46%) had a burdened premorbid background. Complications of the perinatal period were identified in 33 (34%) patients. During the collection of epidemiological histories, it was found that 58 (56%) children had previous contact with measles patients. The overwhelming number of patients –78 patients (81%) - were unvaccinated. In 70 patients (73%) measles progressed without complications. Among the 26 patients (27%) who had a complicated measles course - in 19 (20%) patients, pneumonia was diagnosed as the most common complication. Among 19 children diagnosed with pneumonia, 11 children (58%) were aged 3 - 17 years, 6 (31%) patients were aged 6 months. - 3 years and 2 (10%) infants were less than 6 months old. Burdened premorbid background was significantly more common in children of group 2 than among patients in group 1 ($p < 0.001$) (table 1).

In addition, it was determined that patients with burdened premorbid background were by 37.44 times more likely to develop pneumonia against the background of measles infection (SI - 4.73; 296.53; $p < 0.00001$). The features of measles pneumonia clinical symptoms revealed by us are in agreement with the data of literature sources [8, 11], namely: intoxication syndrome was characterized by severe fever in all patients, with the hectic type of temperature curve (39.1 - 40.2°C), it was reliably more frequently encountered among patients in group 2 ($p < 0.001$), whereas pyretic fever was reliably more frequently reported in patients of group 1 ($p < 0.01$). The average duration of fever in measles diseased children with development of pneumonia was significantly longer than in children without pneumonia ($p < 0.05$) (table 1). The catarrhal period was characterized by clear clinical symptoms and included the presence of a typical

symptoms triad: cough, rhinorrhea, conjunctivitis, which was noted in the vast majority of patients in both groups 1 and 2, with catarrhal symptoms more common in patients of both groups 1 and 2, with catarrhal symptoms being some more frequently reported in patients of group 2 (table 1).The presence of pathognomic measles signs, such as measles enanthema, was more frequently observed in patients of group 2 ($p < 0.01$) than in patients of group 1; as well as the presence of Koplik spots on the mucous membrane of the oral cavity, which was diagnosed more frequently ($p < 0.01$) in patients with measles pneumonia than in those with uncomplicated pneumonia (table 1). The mean duration of catarrhal period in patients of group 1 was significantly less than in patients of group 2 ($p < 0.05$) (table 1). Therefore, it can be concluded that the oral mucosa injuries were more intense in children with measles pneumonia. The data obtained by us coincide with the data of foreign literature [12].

The rash period was characterized by the onset of typical spotty-papular exanthema in children, with a tendency to fuse mainly on the face skin and the upper chest, as evidenced by the literature data [4, 9].

Table 1

Distribution of patients by severity and duration of clinical symptoms

Symptom	Nosological entity			
	Measles without pneumonia n–77		Measles with pneumonia n–19	
	abs.	%	abs.	%
burdened premorbid background	25	32	18	95***
Fever				
subfebrile	6	8	0	0
febrile	64	83	4	21**
hectic	7	9	15	79***
mean temperature in patients, ºC	38.02±0.62		39.6±0.48*	
mean duration of fever, days	4.88±0.92		7.32±0.72*	
measles enanthema	11	14	13	71***
Koplik symptom	6	8	12	61**
cough	63	82	19	100
rhinorrhea	60	79	15	81
conjunctivitis	54	71	14	77
mean duration of catarrhal period, days	3.36±1.13		6.78±1.2*	
mean duration of rash period, days	4.2±0.56		5.52±0.32*	
mean duration of hospital stay, days	5.54±1.28		8.58±0.82*	

Notes: *** statistically reliable data difference between groups at $p<0.001$ (by Student's t-test); ** statistically reliable data difference between groups at $p<0.01$ (by Student's t-test); * statistically reliable data difference between groups at $p<0.05$ (by Student's t-test).

The mean duration of the rash period in patients of group 2 was reliably longer than in patients of group 1 ($p < 0.05$) (table 1).

Given that changes in the lower respiratory tract were mainly determined in children with measles pneumonia, it was found that the development of lung damage in all patients of group 2 was accompanied by frequent painful low-productivity heavy cough, signs of respiratory failure of varying degrees, namely: degree I respiratory failure (RF) was diagnosed in 17 (90%) patients, while degree II RF, as well as degree III RF was diagnosed in 1 case each (5%), respectively. Almost every third child – namely 7 (37%) patients - had sluggishness and retardment of movements, while severe impairment of consciousness was registered in 2 patients (10%): in one child - due to the development of measles encephalitis; in the other - due to swelling of the brain. Cyanotic changes in the skin and in visible mucous membranes as a result of respiratory failure were observed in 3 (16%) patients of group 2. Given the above, it was found that the mean duration of hospital stay for children with measles pneumonia (group 2) was significantly longer than for patients in group 1 ($p < 0.05$) (table 1). Therefore, the presence of such a complication as pneumonia affects the length of the patient's stay in hospital. Physical data in the examination of patients in group 2 were typical of interstitial pneumonia: laboured breathing, which was recorded in all patients in the study group; as well as suppressed breath sounds in a limited site, unstable dry rales, percussion - tympanic sound. Tachycardia was more frequently reported in children of group 2 - 13 (68%) patients than in group 1 patients - in 18% (14 patients) ($p < 0.01$).

In laboratory studies, it was found that in patients of group 2 - 14 (74%) children were reliably more frequently diagnosed with leukopenia (mean leukocyte $2.8 \pm 1.35 * 10^9$/l) than in patients of group 1 - 7 (9%) patients ($p < 0.001$). Noteworthy is the fact that in all patients of group 2 in the general blood test, the main deviation from the norm in the leukocyte formula study was a large number of stab neutrophiles

(16-25%) with a reduced number of leukocytes, which can be considered as a manifestation of measles anergy. According to foreign researchers, in studying the measles infection, in the presence of the leukocyte formula left shift, leukopenia was rarely reported [1]. Pulse oximetry (SaO_2) was used in the treatment of group 2 patients. The critical level of SaO_2 <90% was determined in 3 (16%) patients, the SaO_2 level in the range of 92-95% was registered in 4 (21%) patients, but in more than half of the patients - 12 (63%) children, the level of arterial blood oxygen saturation remained within the normal range, namely 95-98%.

All patients with pneumonia without exception were subjected to radiography of the thoracic organs. The radiographs showed characteristic signs - the cord-like or reticulated deformation of the lung pattern, as well as a symptom of "ground-glass opacity" [10]. Multilobar infiltration of the lungs was diagnosed in one patient (5%) in the radiograph, severe cardiovascular disorders were detected in the same patient. Assessing the severity of pneumonia by the pneumonia severity scale in children [3], it was determined that the majority of patients in group 2 - 16 (85%) had the III degree of severity with the risk of lethality - 2.8%. The IV degree of severity and lethality risk of 8.2% were observed in 2 (10%) children of group 2, and only in 1 child (5%) of group 2 was diagnosed with the V severity degree of pneumonia, with mortality risk increasing to 29.2% (table 2). Children with the IV and V severity degree were treated in the intensive care unit (ICU).

Table 2

Pneumonia severity in children

Severity degree	Number of points	Lethality risk, %
III (n – 16)	77.5±2.5	2.8
IV (n – 2)	115±5	8.2
V (n – 1)	180	29.2

All patients received pathogenetic, detoxification, desensitizing and symptomatic therapy according to treatment protocols. Antibiotic therapy was prescribed in case of a secondary bacterial infection taking into account the empirical sensitivity of the pathogen.

Clinical case of measles infection with a fatal outcome. Patient M., aged 8 months, was hospitalized in the Vinnytsia OCDIL. The final diagnosis is: measles, typical form, rash period, severe course. Bilateral polysegmental overwhelming interstitial pneumonia. Respiratory failure of the 3rd degree. Respiratory distress syndrome of adults. Multiorgan failure (hepatitis, nephritis, carditis). Disseminated intravascular coagulation syndrome (DIC-syndrome) in the hypocoagulation phase. Edema and swelling of the brain. Acute cardiovascular failure, carditis.

It is known that the infant had a burdened premorbid background and had not been vaccinated according to the vaccination schedule. Having analyzed the clinical course of the disease and the data of the pathoanatomical incision, it became clear that the fatal case occurred because the child had congenital lung pathology, namely, connective tissue dysplasia. Therefore, we were interested in the results of pathomorphological and pathohistological changes in lung tissue against a background of measles infection.

During the study, it was found that the airways mucosa was swollen, white and cyanotic. The lungs do not fill the pleural cavities, occupying about 2/3 of them, with numerous vesicles, mostly subpleural, having the diameter of 0.5 to 2.0 cm, with thin transparent walls (fig. 1). The perihilar divisions are cord-like, with the compacted walls of the bronchi projecting above the incision level in the form of "goose feathers". The lungs consistency is nonuniform, indurated, doughy, fleshy.

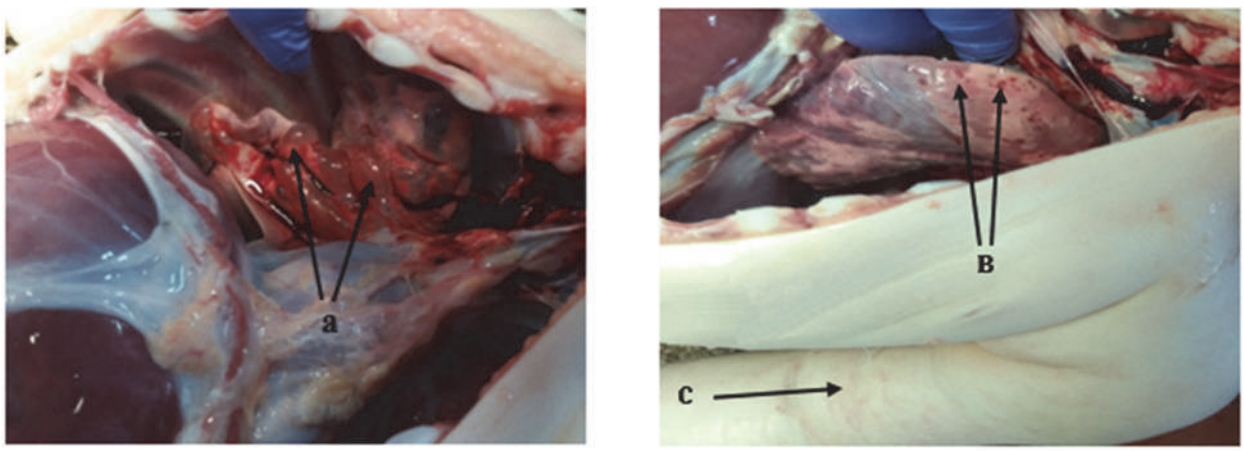

Fig. 1. Blebs located subpleurally in the lungs (a), numerous hemorrhages (b) skin rash (c).

Histological examination of the internal organs showed that the measles virus has particular tropism to respiratory organs' cells. A typical response of the respiratory tract tissues in measles patients was epithelial metaplasia into stratified squamous epithelium with keratinization and spreading from the larynx to terminal bronchioles. The structure of the lungs is impaired due to numerous multifarious cavities, mostly subpleural ones, which are almost unconnected to the bronchial tree and covered both with flattened alveolar and atypical giant cell epithelium; bronchi are polymorphous – their epithelium is metaplastic stratified squamous, vessels are irregularly full-blooded with widespread extravasates, abundant infiltration of both the interalveolar septum and the alveoli lumens with polymorphocellular infiltrate, consisting of neutrophilic leukocytes, eosinophils, lympho-histiocytes, with numerous parietal hyaline masses (hyaline membranes).

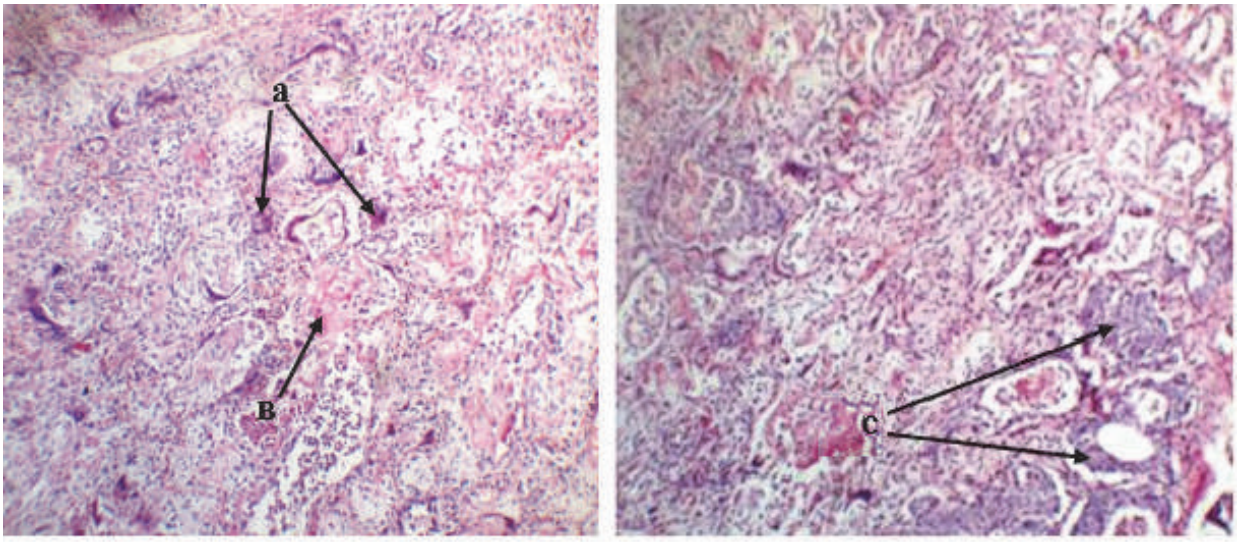

Fig. 2. Interstitial infiltrate of mononuclear and multinucleated cells (a), swelling of the interveolar septa interstitium (b), squamous cell metaplasia (c). Microslide (magnification x100, stain - hematoxylin - eosin).

There is a giant cell metaplasia of the alveolar epithelium (2nd order alveolocytes) (fig. 2). Peribronchial lymphoid tissue is "depleted", mainly represented by immature lymphocytes, without light centers in the lymphoid follicles.

During the analysis of the disease lethal case, certain risk factors for the unfavorable course development were identified, namely, early age of the child, burdened epidemiological history, unsatisfactory vaccinal status, burdened premorbid background, and most important being congenital lung pathology –connective tissue dysplasia.

Thus, having studied clinical and laboratory features of the measles infection course in children, it is established that children of school age are more likely to be diseased (mean age - 8.6±1.2 years). A significant impact on the disease development is produced by unsatisfactory planned immunization. The infection most frequently occurs in a typical form, which has been demonstrated among other foreign researchers [8, 10]; with acute onset and predominance of moderate severity course. The complexity of the comparison is due to the lack of modern work to study the features of the course of measles pneumonia in children. Somewhat close to our study are the scientific works of V. Gnatyuk and T. Pokrovskaya [1] in the clinical field, confirming some of our findings. Most frequently, the complicated course of infection is characterized by damaged lower respiratory tract, i.e. by the development of interstitial measles pneumonia. This complication was more common among children aged 3 to 17 years (mean age - 5.75±3.79), almost all patients with pneumonia having a burdened premorbid background ($p < 0.001$) in contrast to children in group 1. Development of measles pneumonia was accompanied by prolongation of the disease periods, more pronounced manifestations of intoxication syndrome ($p<0,05$), catarrhal manifestations ($p<0,05$), compared to patients with measles in group 1 (without the pneumonia development); signs of respiratory failure, decreased levels of SaO_2, against the background of measles anergy development, which was manifested by pronounced leukopenia, at the same time, comparing with the literature, it should be noted that the number of leukocytes in patients with measles in other studies remained within the normal range [1]. Pathohistological examination revealed signs of interstitial pneumonia with giant cell metaplasia of the alveolar epithelium, which is typical for the lesion of the measles virus [10].

Conclusions

1. During the 2018-2019 epidemic season there was a high incidence of measles in Ukraine and Vinnitsa region in particular.

2. Children from 6 to 17 years of age were more likely to suffer from measles, 81% of them were not vaccinated against measles. Among the complications, pneumonia was most commonly diagnosed (20%).

3. Interstitial measles pneumonia is by 37.44 times more likely to occur in measles patients with a burdened premorbid background (CI – 4.73; 296.53; p <0.00001). The mean age of patients with pneumonia is 5.75±3.79. The development of pneumonia is accompanied by a longer period of catarrhal manifestations (p <0.05), intoxication syndrome (p <0.05), with more frequent hectic fever (p <0.001); and the rash period is prolonged (p <0.05). In the vast majority of children (90%) the I degree respiratory failure occurs. In 37% of children a decrease in the SaO_2 level below 95% is reported. In the analysis of hemograms in patients with pneumonia, leukopenia is determined much more frequently (p <0.001), with a left shift diagnozed in the leukocyte formula.

4. A case of V degree measles pneumonia (mortality risk 29.2%), had a fatal outcome in the study, with the morphological and histological changes revealed in the respiratory tract of children with complicated disease course, which are characterized by the epithelium metaplasia into multilayer flat; giant cell metaplasia of the alveolar epithelium; abundant infiltration of the inter-alveolar septum with polymorphocellular infiltrate, with numerous parietal hyaline masses (hyaline membranes).

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Реферати

КОРОВА ПНЕВМОНІЯ У ДІТЕЙ: КЛІНІКО-МОРФОЛОГІЧНІ ОСОБЛИВОСТІ ПЕРЕБІГУ

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В статті наведені результати ретроспективного аналізу історій хвороб 96 хворих з діагнозом кір, з детальним вивченням перебігу захворювання і аналізом клініко-анамнестичних даних. Перебіг корової інфекції супроводжувався ознаками інтоксикаційного синдрому, наявністю класичної катаральної тріади (кашель, нежить та кон'юнктивіт), та синдромом екзантеми. Більшість дітей, що захворіли, не вакциновані проти кору. У хворих на кір мав місце ускладнений перебіг з проявами корової пневмонії, як найбільш частого ускладнення при даній патології. Морфологічні та гістологічні зміни легень у дітей з важким перебігом кору характеризувались рясною інфільтрацією як міжальвеолярних перетинок, так і просвітів альвеол поліморфноклітинним інфільтратом, який складався з нейтрофільних лейкоцитів, еозінофілів, лімфо-гістіоцитів, з чисельними пристінковими гіаліновими масами (гіалінові мембрани). Мала місце гігантоклітинна метаплазія альвеолярного епітелію.

Ключові слова: кір у дітей, пневмонія, патоморфологічні зміни, гістологічні дослідження.

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КОРЕВАЯ ПНЕВМОНИЯ У ДЕТЕЙ: КЛИНИКО-МОРФОЛОГИЧЕСКИЕ ОСОБЕННОСТИ ТЕЧЕНИЯ

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В статье приведены результаты ретроспективного анализа историй болезней 96 больных с диагнозом корь, с детальным изучением течения заболевания и анализом клинико-анамнестических данных. Течение коревой инфекции сопровождалось признаками интоксикационного синдрома, наличием классической катаральной триады (кашель, насморк и конъюнктивит) и синдромом экзантемы. Большинство заболевших детей не 93акцинированы против кори. У больных корью имело место осложненное течение, с проявлениями коревой пневмонии, как наиболее частого осложнения при данной патологии. Морфологические и гистологические изменения легких у детей с тяжелым течением кори характеризовались обильной инфильтрацией как межальвеолярных перегородок, так и просветов альвеол полиморфноклеточным инфильтратом, который состоял из нейтрофильных лейкоцитов, эозинофилов, лимфо-гистиоцитов, с многочисленными пристеночными гиалиновыми массами (гиалиновые мембраны). Имела место гигантоклеточная метаплазия альвеолярного эпителия.

Ключевые слова: корь у детей, пневмония, патоморфологические изменения, гистологические исследования.

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ANXIETY AND ITS SIGNIFICANCE IN THE STRUCTURE OF SOMATOFORM DISORDERS IN CHILDREN AND THE ROLE OF SEROTONINE AND TRIPTOPHAN IN THEIR NASCENCE

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The work was aimed to study the confidence and significance of anxiety in the occurrence of somatoform disorders (SD) in children, to establish the role of serotonin and tryptophan in its development. 111 children were diagnosed with SD. In 109 (98,2%) children were diagnosed with excessive anxiety. Serotonin levels in children with personality and reactive anxiety were 1,16 ± 0,33 μmol/l and 1,17 ± 0,33 μmol/l, respectively and were lower compared to the control group, where its level reached 1,35 ± 0,34 μmol/l ($p<0,004$ and $p<0,008$, respectively). The level of serotonin in patients with anxiety in combination with depression was lower compared with patients with anxiety without depression ($p<0,0001$). It is possible to suspect the existence of several subtypes of SD, where one can occur as a variant of depression with somatic manifestations and secondary anxiety in which serotonin metabolism may play a key role, whereas the second variant of SD can arise as a variant of anxiety disorder with somatic manifestations and somatic manifestations and secondary disorders as a personality response to a disease in which serotonin metabolism does not play a key role in the development of pathology.

Key words: somatoform disorder, anxiety, serotonin, tryptophan, children.

The paper is a fragment of the research project "Physiological and hygienic assessment of the features of adaptation of children, adolescents and young people to the conditions of study in modern educational institutions and scientific bases of university hygiene: vocational aspects, problems of introduction of health-saving technologies and creation of preventive educational environment", state registration No. 0116U000038.

A study of mental health disorders in primary care by the World Health Organization has found widespread anxiety among pediatric outpatients [2].

It is difficult for children to express emotions and feelings through language, so psychological stress and anxiety can be expressed as somatic symptoms [10].

Somatization can be characterized as a tendency to express psychological dysphoria with bodily symptoms. Somatic symptoms are known to be associated with many psychiatric disorders, but are usually accompanied by anxiety and depression [11].

Somatization of emotional disorders in ICD-10 is considered in the heading F45.3 as "Somatoform dysfunction of the autonomic nervous system" or "Somatoform disorder" (SD) [1].

Somatoform disorder brings together a group of psychogenic diseases characterized by pathological symptoms reminiscent of somatic disease, but in which, according to the survey results, there aren't detected morphological manifestations, although there are often nonspecific functional disorders [1, 4]. These symptoms lead to numerous medical consultations, additional unnecessary research and manipulation and in children cause family and social maladaptation, impaired educational functioning [8].

With the release of DSM-5, the SD was renamed "Somatic Symptoms Disorder" [9].

It is known that serotonin deficiency in the brain and the impact of psychosocial stress play an important role in the development of depression and anxiety disorders [14].

Serotonin is an amine that is synthesized in the gut (95%) by enterochromaffin-like cells and it is stored in platelets and it is only minimally contained in the brain (5%) as a neurotransmitter [12, 13].

Dysfunction of the serotonergic system is involved in the etiology of many psychiatric (depression, schizophrenia, alcoholism) and neurological (migraine, epilepsy, Alzheimer's disease) pathologies, including the development of anxiety disorders [12].

Unfortunately, data on the mechanisms and factors of development of SD and anxiety, especially the role of serotonin in their onset and other pathogenesis chains in children are rather limited and need further investigation.

The purpose of the work was to study the presence, severity and significance of anxiety in the occurrence of somatoform disorders in children, to establish the role of serotonin and tryptophan in its development.

Materials and methods. The studies were performed on the clinical basis of the Department of Pediatrics, Obstetrics and Gynecology Faculty of Postgraduate Education, Vinnytsia National Pyrogov Memorial Medical University in the gastroenterological, cardiological, nephrological and neurological departments of Khmelnytskyi regional children's hospital in Khmelnitskyi.

Following the informed consent of parents and children, 111 patients diagnosed with SD were included in the study. The average age of children was 13.6±2.3 years (M±σ), of which boys were 37.8%

(n = 42) and girls were 62.2% (n = 69). In the gastroenterology department 39 children with SD were examined, in the cardiology - 26 children, in the nephrological - 16 children and in the neurological - 30 children. Also 33 children with average age of 13.2±2.0 years (M±σ) were treated in somatic wards and did not have emotional disorders, who were in the control group were examined.

The selection of children and the diagnosis of SD were performed after a general clinical examination and according to the criteria of SD ICD-10. For identifying the presence of depression and its clinical symptoms in a selected group of children with somatoform disorders, the Children's Depression Inventory (M. Kovacs) was used to assess the affective and cognitive symptoms of depression.

For investigation of the anxiety we used the Spielberger (STPI - State Trait Personal Inventory) questionnaire modified by A. D. Andreeva.

In all 111 children diagnosed with SD blood samples were taken to determine serum concentrations of serotonin and tryptophan, which were determined in the certified laboratory of "Diagnostics Plus", Kharkiv.

Serotonin was investigated by a biochemical method. The tryptophan was examined by liquid chromatography using the Milchrom-6 microcolonial liquid chromatography.

Statistical analysis was performed using Statistica 8.0.360, MedCalc.7.4.4.1. Quantitative features are given as M±σ (arithmetic mean ± mean deviation). The likelihood of differences was assessed using a two-tailed Student's t-test and plotting a 95% confidence interval (CI) for the mean difference. Values at $p<0.05$ were considered significant.

Results of the study and their discussion. In our study of SD by the gastrointestinal tract in children was predominantly manifested as functional dyspepsia (FD) - in 30 (27.0%) children, irritable bowel syndrome - in 8 (7.2%), SD by other organs and systems manifested with various pain syndromes (headache, fibromyalgia, arthralgia, dorsalgia) - in 10 (9.0%), violation of thermoregulation - 7 (6.3%), SD by the cardiovascular system cardiac and hyperventilation syndromes - 39 (35.1%), extrasystolic arrhythmia - in 1 (0.9%) case, SD by the urinary systems neurogenic dysuric disorders - in 16 children (14.5%).

Anxiety is an individual psychological trait that involves an increased tendency to feel anxious in a wide variety of situations. There are two types of anxiety - situational, or reactive, and personal. Reactive anxiety is an indicator of the intensity of experiences that occur in relation to typical events. Reactive or situational anxiety is characterized by tension, anxiety, nervousness. Personal anxiety - the readiness of a person to experience fear and anxiety about a wide range of subjectively significant phenomena [3].

According to the questionnaire, among 111 children in 2 (1.9%) cases there were no personal anxiety disorders, 39 (35.1%) children had moderate personal anxiety, and 70 (63.0%) children had severe personal anxiety (fig. 1). Also, 5 (4.0%) children reported no reactive anxiety, moderate reactive anxiety was detected in 70 (63.6%) children, severe reactive anxiety in 36 (32.4%) children (fig. 2).

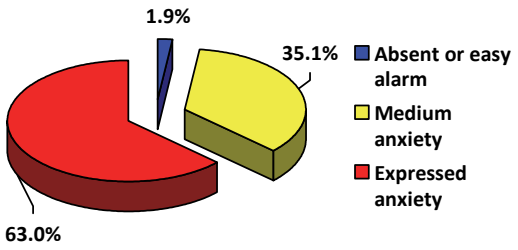

Fig. 1. General structure of personal anxiety in children with SD according to the questionnaire STPI.

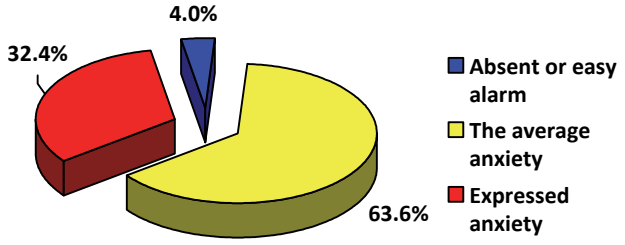

Fig. 2. General structure of reactive anxiety in children with SD according to the questionnaire STPI.

Thus, it should be noted that in all patients with SD significant anxiety disorders, both personal and reactive nature, which can be a factor in the propensity to develop SD and a key cause of their occurrence.

The average personal anxiety score for all children with anxiety disorders according to the questionnaire was 25.2±3.3 points, and reactive anxiety 23.8±4.3 points indicating the average severity of anxiety disorders in children with SD. In the general structure of adolescents signs of marked personal and reactive anxiety were found in 18 (16.2%) persons whose data significantly exceeded the average and reached submaximal figures (maximum 40), which is quite significant and needs appropriate attention, since they are the largest risk of development in the future of SD and other pathologies of the anxiety spectrum.

The mean age of children with anxiety symptoms was 13.6±2.3 years and was not significantly different from the mean age of children in the control group, who was 13.2±2.0 years.

Among patients with anxiety disorders a significant prevalence of girls was noted - 68 (61.8%). over boys - 42 (39.2%), their ratio was 1.6:1. The prevalence of female sex over male (75% vs. 25%) in SD in children was also noted in the study by Bujoreanu S. et al. (2014), with the mean age of 14.4 years [6].

Our findings also indicate that women are more likely to develop anxiety disorders and accordingly to develop of SD.

The highest incidence of severe personal anxiety disorders was observed in patients with SD by the cardiovascular system (73.1%), slightly lower in patients with gastrointestinal tract and SD by other organs and systems (66.6%, respectively) and the lowest was in the SD from the urinary system (56.3%).The available data also correlate with the incidence of SD which is also more commonly occurring on the part of the cardiovascular system and gastrointestinal tract, which may indicate the decisive value of personality disorders of the anxiety spectrum in the occurrence of SD.

The highest incidence of severe reactive anxiety disorders was observed in patients with SD by the urinary system (37.5%), slightly lower with SD by other other organs and systems (33.3%) and even lower with SD by the cardiovascular system (26. 9%) and gastrointestinal tract (20.5%).

Reactive anxiety is an indicator of the intensity of experiences that occur in relation to typical events [3]. Probably dysuric disorders have the greatest stressful effect on the child with complex formation, limitations and constant experiences and expectations, which forms the most pronounced reactive anxiety in response to the manifestation of the disease.

It is known that a decrease in serotonergic activity can lead to the development of anxiety disorders and depression, while the use of antidepressants lead to modulation of the serotonergic system and decrease the symptoms of anxiety and depression which indicates the important role of serotonin in their development [5].

In view of this we aimed to determine the role of serotonin and its precursor tryptophan in the development of anxiety disorders in patients with SD and its importance in the development of SD.

Serum serotonin levels in patients with children with excessive personal anxiety were 1.16±0.33 μmol/l and were significantly lower compared to children in the control group without SD and anxiety, whose level was 1.35±0.34 μmol/l (95% CI, 0.06 – 0.32 μmol/l, p<0.004) (fig. 3).

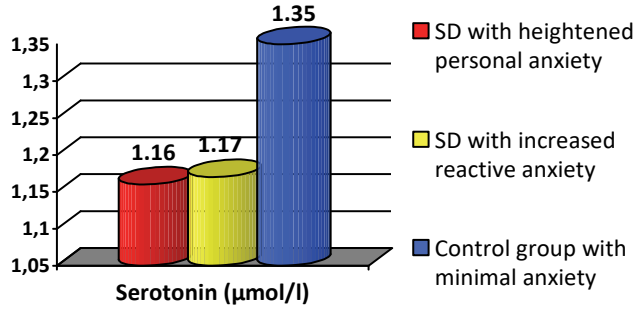

Fig. 3. The average serotonin levels in the serum of children with SD and high anxiety and minimal anxiety.

Also serum serotonin levels in patients with overactive reactive anxiety were 1.17±0.33 μmol/l and were also significantly lower compared with control children (95% CI, 0.05 – 0.31 μmol/l, p<0.008).

In contrast to serotonin serum tryptophan levels in patients with SD with excessive personality and reactive anxiety were 0.029±0.024 and 0.031±0.028 mmol/l, respectively and practically did not differ from the control group, whose level was 0.030±0.028 mmol/l (p>0.05).

Analyzing the levels of serotonin and tryptophan in patients with excessive anxiety depending on the manifestation of SD from the side of systems and organs, we can note certain features that are shown in table. 1.

Table 1

Levels of serotonin and tryptophan depending on the manifestations of SD from the side of organs and systems and excessive anxiety compared with the control group

	Serotonin (μmol/l)			Tryptophan (mmol/l)		
	n	M±σ	p	n	M±σ	p
SD by the gastrointestinal tract	39	1.18±0.25	<0.01	39	0.026±0.024	>0.05
Control	33	1.35±0.34		27	0.029±0.024	
SD by the cardiovascular system	26	1.21±0.31	>0.05	28	0.040±0.036	>0.05
Control	33	1.35±0.34		27	0.029±0.024	
SD by other organs and systems	30	1.31±0.33	>0.05	28	0.032±0.028	>0.05
Control	33	1.35±0.34		27	0.029±0.024	
SD by the urinary systems	16	0.87±0.46	<0.001	9	0.027±0.021	>0.05
Control	33	1.35±0.34		27	0.029±0.024	

The lowest levels of serotonin were observed in children with SD by the urinary systems and gastrointestinal systems which were significantly lower compared to the control group. Children with SD on the part of the cardiovascular system and SD on the part of other organs and systems also showed a

decrease in serotonin levels but the difference with the indicators of children in the control group is not statistically significant. No significant deviation in tryptophan concentration compared to the control group was found in any of the subgroups of children with SD.

The level of serotonin in children with SD by the urinary systems and excessive anxiety was significantly lower compared to patients with SD by other organs and systems and excessive anxiety (95% CI, 0.20 – 0.67 μmol/l. $p<0.0005$), compared with SD on the part of the cardiovascular system (95% CI, 0.10 – 0.58 μmol/l. $p<0.006$), and compared with SD by the gastrointestinal tract (95% CI, 0.11 – 0.50 μmol/l. $p<0.002$).

Serotonin levels in girls with SD and anxiety were slightly lower compared to boys – 1.15±0.34 μmol/l and 1.19±0.31 μmol/l, respectively, while at the same time tryptophan levels in boys compared to boys girls were higher – 0.032±0.031 and 0.029±0.028 mmol/l, respectively but these differences were not statistically significant. At the same time, in comparison with the control group the level of serotonin was significantly lower both in girls (95% CI, 0.057 – 0.343 μmol/l, $p<0.006$) and in boys (95% CI, 0.01 – 0.31 μmol/l, $p<0.03$). There were no significant deviations from tryptophan compared to the control group.

It is known that serotonin can play a significant role in the development of not only anxiety but also depression. Quite often anxiety and depression are comorbid to one another. Depression can be a factor of anxiety, while depression itself can be a reaction to the long-existing anxiety itself including during SD.

Somatic symptoms in SD are consistently associated with anxiety-depressive disorders in childhood. The likelihood of associated anxiety and depression increases with the number of somatic symptoms present [7].

In our study, 48 (43.2%) children with SD with excessive anxiety on the CDI scale were found to varying degrees of depressive disorders. Subsequently it was found that serotonin in patients with anxiety in combination with depression had the lowest rates in this study and was 1.03±0.37 μmol/l and was significantly lower than patients with excessive anxiety without depression, where the level was 1.30±0.27 μmol/l (95% CI, 0.15 – 0.39 μmol/l, $p<0.0001$) and compared to the control group where its level was 1.35±0.34 μmol/l (95% CI, 0.16 – 0.48 μmol/l, $p<0.0002$). At the same time patients with excessive anxiety without depression compared with the control group, serotonin levels were also lower but not significant. Tryptophan levels were slightly higher in patients with excessive anxiety and depression (0.035±0.031 mmol/l) compared with patients with excessive anxiety and without depression (0.026±0.026 mmol/l) but were not statistically different and compared with the control group, where the tryptophan level was 0.029±0.024 mmol/l.

Thus depression of both primary and secondary origin in relation to anxiety can significantly impair the course of SD. Considering the data obtained from the serotonin study, it can be noted that there are several subtypes of SD, where one variant of SD can occur as a variant of a depressive episode with somatic manifestations and secondary anxiety as a symptom of depression in which serotonin metabolism can play a key role and can occur as a variant of anxiety disorder with somatic manifestations and secondary depression, as a personality response to a disease in which serotonin metabolism may not be disturbed or play a key role a role in the development of disease. It is possible that in the second embodiment, other neurotransmitters (norepinephrine, dopamine, GABA and others) may play a key role in the development of SD. However, it is almost impossible to determine clinically a possible version of SD based on clinical symptoms alone. It is difficult to establish the basis on which SD occurs (primarily based on depression or anxiety disorder), but the detection of low levels of serotonin may be a predictor of a good response to the treatment of such conditions with serotonin-selective serotonin and serotonin inhibitors that occur on the basis of a depressive episode.

It should be noted that studies by Shidhaye R. et al. (2013), also indicate a strong association between SD and depression/anxiety (odds ratio 2.5 – 3.5). The authors also observed patients with SD without depression/anxiety. It is likely that these disorders may include common etiological factors can be variants of the same mental disorder and that one disorder may be a factor in the occurrence of another disorder [15].

We have not received conclusive data on the involvement of tryptophan and the involvement of the tryptophan-serotonin chain in the development of anxiety disorders in children with SD.

Although in our study the presence of anxiety and depression was associated with a decrease in serotonin concentration in the blood but their severity hadn't dependence on serotonin concentration including tryptophan concentration. The severity of depression and its various clinical manifestations can also depend on other brain mediators (norepinephrine, dopamine), the activity of enzyme systems and receptors and other factors that need further investigation.

Thus the high prevalence of excessive anxiety among children with SD (99.1%) indicates its importance in the course and development of the disease, its clinical manifestations and possibly prognosis. The question of the relationship between depression and SD, anxiety and SD, and depression and anxiety remains important. Probably SD can be a multifactorial pathology for the existence of different pathogenetic subtypes, however, with similar somatic symptoms, the detection of which will improve and improve treatment.

Conclusion

Excessive anxiety was evident in 98.2% of children with SD of whom severe personal anxiety was identified in 63.0% and severe reactive anxiety in 32,4% of children, indicating its widespread prevalence and significant role in the occurrence of SD. The prevalence of girls (61.8%) over boys (39.2%) was noted among patients with SD and excessive anxiety, which amounted to 1.6:1, indicating a greater tendency of women to develop anxiety disorders and, accordingly to SD development.

The highest frequent severe personal anxiety was observed in patients with SD by the cardiovascular system (73.1%) and the lowest in patients with SD by the urinary system (56.3%), which correlates with the highest number of patients with cardiac and hyperventilation manifestations syndromes (35.1%), where personal anxiety can be the basis for their development.

Serum serotonin levels in patients with SD with excess personality and reactive anxiety were lower compared to controls (95% CI, 0.06 – 0.32 μmol/l, $p<0.004$) and (95% CI, 0.05 – 0.31 μmol/l, $p<0.008$), respectively, indicating its importance in the development of anxiety disorders in SD. Low serotonin was also associated with excessive anxiety and SD from the urinary system (95% CI, 0.24 - 0.77 μmol/l, $p<0.0002$) and from the gastrointestinal tract (95% CI, 0.031 – 0.309 μmol/l, $p<0.01$), which confirms its special relationship and physiological function in the operation of these systems.

Given that the level of serotonin in patients with excessive anxiety in combination with depression was lower compared with patients with excessive anxiety without depression (95% CI, 0.15 – 0.39 μmol/l, $p<0.0001$), it is possible to suspect the existence of several subtypes of SD, where one subtype of SD may occur as a variant of a depressive episode with somatic manifestations and secondary anxiety as a symptom of depression, in which impaired serotonin metabolism may play a key role, while a second variant of SD may occur as a variant of anxiety disorder with somatic manifestations and layers of sec other depression, as a personality response to a disease in which serotonin metabolism may not be impaired.

We did not find conclusive evidence of involvement in the mechanisms of SD development with disturbing disorders of the serotonin precursor tryptophan and the tryptophan-serotonin chain.

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Реферати

ТРИВОГА ТА ЇЇ ЗНАЧЕННЯ В СТРУКТУРІ СОМАТОФОРМНИХ РОЗЛАДІВ У ДІТЕЙ, А ТАКОЖ РОЛЬ СЕРОТОНІНУ І ТРИПТОФАНУ В ЇХ ВИНИКНЕННІ

Пипа Л.В., Лисиця Ю.М., Свістільнік Р.В., Булат Л.М.

Метою роботи було дослідити наявність, вираженість та значення тривоги у виникненні соматоформних розладів (СР) у дітей, встановити роль серотоніну і триптофану в її розвитку. Обстежено 111 дітей, в яких було діагностовано СР. У 109 (98,2%) дітей діагностовано надмірну тривогу. Рівень серотоніну у дітей з особистісною і реактивною тривогою складав 1,16±0,33 мкмоль/л та 1,17±0,33 мкмоль/л, відповідно, і був нижчим, порівняно з контрольною групою, де його рівень сягав 1,35±0,34 мкмоль/л, ($p<0,004$ і $p<0,008$, відповідно). Рівень серотоніну у хворих на тривогу в поєднанні з депресією був нижчим у порівнянні з хворими на тривогу без депресії ($p<0,0001$). Можна запідозрити існування декількох підтипів СР, де один може виникати як варіант депресії з соматичними проявами і вторинною тривогою, в якому порушення обміну серотоніну може відігравати ключову роль, тоді як другий варіант СР може виникати як варіант тривожного розладу з соматичними проявами і вторинною депресією, як реакція особистості на захворювання, в якому обмін серотоніну не відіграє ключову роль в розвитку патології.

Ключові слова: соматоформний розлад, тривога, серотонін, триптофан, діти

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ТРЕВОГА И ЕЕ ЗНАЧЕНИЕ В СТРУКТУРЕ СОМАТОФОРМНЫХ РАССТРОЙСТВ У ДЕТЕЙ, А ТАКЖЕ РОЛЬ СЕРОТОНИНА И ТРИПТОФАНА В ИХ ВОЗНИКНОВЕНИИ

Пыпа Л.В., Лисица Ю.Н., Свистильник Р.В., Булат Л.М.

Целью работы было исследовать наличие, выраженность и значение тревоги в возникновении соматоформных расстройств (СР) у детей, определить роль серотонина и триптофана в ее развитии. Обследовано 111 детей, в которых было диагностировано СР. В 109 (98,2%) детей диагностирована высокий уровень тревоги. Уровень серотонина у детей с личностной и реактивной тревогой составлял 1,16 ± 0,33 мкмоль/л и 1,17 ± 0,33 мкмоль/л, соответственно, и был ниже по сравнению с контрольной группой, где его уровень достигал 1,35 ± 0,34 мкмоль/л, ($p<0,004$ и $p<0,008$, соответственно). Уровень серотонина у больных с наличием тревоги в сочетании с депрессией был ниже по сравнению с больными с тревогой но без депрессии ($p<0,0001$). Можно подозревать существование нескольких подтипов СР, где один может возникать как вариант депрессии с соматическими проявлениями и вторичной тревогой, в котором нарушение обмена серотонина может играть ключевую роль, тогда как второй вариант СР может возникать как вариант тревожного расстройства с соматическими проявлениями и вторичной депрессией, как реакция личности на заболевание, в котором обмен серотонина не играет ключевой роли в развитии патологии.

Ключевые слова: соматоформное расстройство, тревога, серотонин, триптофан, дети

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EVALUATION OF HEALTHY LIFESTYLING LEVEL IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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In order to develop a personalized approach in patients with COPD - an individual and effective strategy to implement the recommendations, observance of the principles of healthy lifestyle in the first stage, the study of the main risk factors for the disease, on the basis of which developed for each patient an effective personalized strategy for observing the health of the elderly complex with the implementation of patients with curative respiratory gymnastics by Buteyko and hardening of the body - pouring cold water. The authors of the article prove that the observance by the patients with COPD of recommendations for the regulation of lifestyle, nutrition, systematic performance of therapeutic gymnastics by Buteyko and quenching of the body contribute to the achievement of long remission, improvement of quality of life.

Key words: healthy lifestyle (HLS), chronic obstructive pulmonary disease (COPD).

The work is a fragment of the research project "Development of algorithms and technology for the introduction of a healthy lifestyle in patients with non-communicable diseases on the basis of studying the psycho-emotional status", state registration No. 0116U007798.

Chronic Obstructive Pulmonary Disease (COPD) is one of the most important medical and social problems in Ukraine and in the world, according to the WHO, 0.8% of the world's population is affected today [3]. Due to the long-term effects of risk factors and the aging population around the world, an accelerated increase in COPD is observed [6]. Often severe exacerbations are associated with higher mortality. [3]. According to forecasts, by 2020, COPD will rank third among the leading causes of death

[5]. It is known that exacerbation of COPD negatively affects the quality of life of patients [9]. That 's why, one of the main goals of treating patients with COPD is to prevent severe aggravation [10]. Prevention of exacerbations becomes of special urgency. At present, most countries in the world, including Ukraine, have joined the Global Plan of Action to Prevent Non-Communicable Diseases [1]. The strategic key points of the GOLD-2017 document is a personalized; prognostic; prophylactic approach, which involves patient's active participation in treatment [10]. Therefore, pulmonary rehabilitation is considered as one of the main stages of treatment for patients with COPD, which allows to achieve those positive changes, which is impossible only with medication therapy [5,11]. Current international recommendations for pulmonary rehabilitation of patients with COPD include aerobic physical exercises to improve tolerance to physical activity and quality of life of patients [11]. The study of the main risk factors in patients with COPD, providing recommendations for lifestyle management, nutrition, compliance with work and rest regimen, therapeutic exercises, hardening of the body contribute to the achievement of a long remission of the disease.

The use of natural factors in the system of hardening is affordable, effective, and helps to increase the body's resistance to disease. Temperament is considered as an adaptation, which is achieved by multiple training effects of a hardening factor. The systematic application of hardening processes produces a complex of conditioned reactions (reflexes) that help the body adequately respond to changes in temperature [2]. All this leads to a decrease in the number of colds. The effect of hardening is not only that the body's resistance to colds increases, but also that in the course of quenching, the internal system of the organism improves. As a result, the overall endurance and performance of the organism increase [12]. Flooding starts at a temperature of 34-35 ° C. Every 3-4 days, the temperature is reduced to 1-2 ° C, bringing it to room temperature.

It is known that classes by different types of breathing gymnastics contribute to the adaptation of the body of the patient, his cardiovascular system and respiratory organs to physical activity, increase his immunological reactivity with regard to viral and bacterial infection. With the purpose of rational restoration of the breathing act, the method of arbitrary breathing control for Buteyko is widely used - a method of volitional reduction of respiration (VLGD). The patient is explained that each breath consists of breathing, exhalation and respiratory pause; it is necessary to breathe only through a nose both at rest and at physical loading; Inspiration is slow, 2-3 seconds, as it is possible more superficial (0.3 – 0.5 l), followed by calm passive full exhalation 3-4 seconds, then pause 3-4 seconds, breath again, etc. The respiration rate should be 6-8 breaths per minute. Training should be carried out constantly, at least 3 hours per day in rest (at the beginning), then in the movement, the efforts of the will of the patient reduces the speed and depth of breath, and also breaks down after a complete, exhausting, trying to gradually bring the breath to normal [4]. In the end, the use of respiratory exercises leads to a more coherent work of the rib-diaphragm breathing mechanism with a great ventilation effect and with less energy for breathing. Improving the coordination of the work of the respiratory muscles increases the rate of inhalation and exhalation, which facilitates respiration with narrowed bronchial apertures, and promotes increased drainage function of the bronchi [4].

The purpose of the study is developing a personalized approach to COPD patients - an individual and effective strategy on the implementation of the necessary guidelines for the observance of healthy lifestyles.

Material and methods. The study included 50 patients with COPD gr.B in the stage of unsuccessful remission, and 35 practically healthy persons. The average age was 45.7±2.5 p. Groups were matched by age and gender. The diagnosis of COPD was formulated in accordance with the Ministry of Health Order of 27.06.2013. N555 [7]. The parameters of the external respiration function (ERF) were analyzed. A determination and assessment of the level of formation of the principles of a healthy lifestyle (HLS) was individually determined for each patient with COPD, using the questionnaire Nosova A.G "The formation of components of a healthy lifestyle" [8]. Bioimpedance assessment of the body composition with the determination of parameters: weight, body mass index (BMI), percentage of fat, internal fat, percentage of skeletal and muscle tissue, metabolism in complete rest was carried out on the monitor (model HBF-500-E, Omron, Japan) and screening testing, which allows detecting deviations from the ambiguities of the HLS [13]. For each patient, effective recommendations were developed, which included compliance with the HLS, the implementation of patients with curative respiratory gymnastics by Buteyko, hardening of the body - infusion with cold water. Water procedures started gradually, from wiping the body with a wet towel, hands, shoulders, neck, trunk, after morning exercise. Then they switched to watering with cold water (first the lower extremities: feet, legs, thighs, then the entire body, water temperature - 28-30 degrees, in each of the next two or three days, gradually decreased by one degree (up to 18 degrees), depending on from the individual characteristics of the body. The temperature in the room is 18-20 degrees.

At the second stage, after 6 months of follow-up, a re-examination of patients was conducted to evaluate, compare the results, and identify the most effective measures needed to select the most effective and economically most beneficial COPD relapse prevention strategy.

The probability of the obtained results was determined using the student's t-reliability criterion. Differences were believed to be plausible in the medical biology studies of the probability of error $p<0.05$. For semi-quantitative and qualitative indicators, the frequency tables were constructed and the non-parametric U Mann-Whitney criterion was calculated as a nonparametric analogue of the Student's t-criterion.

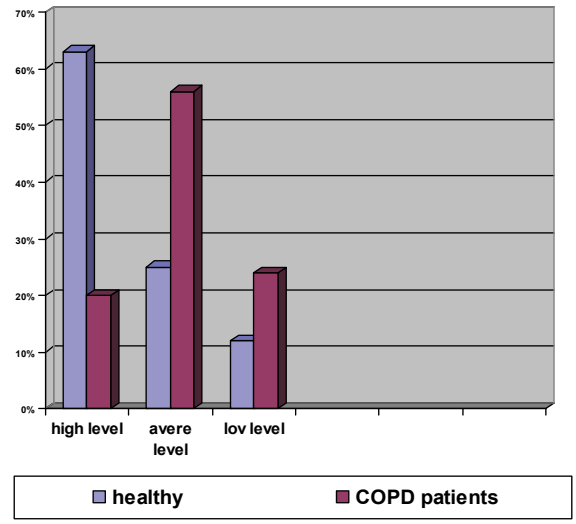

Fig. 1. Level of a healthy lifestyle formation from respondents of the main and the control group.

Results of the study and their discussion. In the primary examination of patients with COPD and practically healthy persons, with the help of a questionnaire Nosova AG, the level of the development of the HLS was determined. In COPD patients included in the study, the object-passive (low level - less than 50%) in all three components was found in 24% (12/50) persons, while in the group of practically healthy low levels were noted in 12% (4/35) ($p<0,05$); objective-active (average) level - in 56% (28/50) patients and 25% (9/35) of practically healthy ($p<0,05$); high (subjective) - in 20% (10/50) patients, compared with 63% (22/35) healthy ($p<0,05$). The received data is presented in fig. 1.

Thus, in the overwhelming majority of practically healthy persons - 63%, a high level of HLS was noted, which indicates the importance of observing the principles of HLS in the prevention of diseases.

When studying the level of shortness of breath in patients with COPD on the scale of mMDR, the mean level was 0.92±0.48 points, indicating an unstable remission at the time of the survey. According to the results of the ERF study in patients with COPD, the average FEV_1 values were 73.2±0.89%, OFV1/FVC - 71.4±1.19%. Results of ERF study in patients with COPD, depending on the distribution of the level of formation of the principles of healthy lifestyle, are given in table 1.

Table 1

Indices of external respiration function in patients with COPD

Index of dimension	Patients with COPD at the levels of healthy lifestyle formation		
	object-passive level (group I) 21%	object-active (average) level (group II) 55%	high level subjective (group III) 24%
VC, %	72.9±1.22	72.5 ±1.5	73.72±1.6
FEV_1,%	72.1±1.1	72.05±1.4	74.9±0.8*
FEF 25,%	57.9±1.8	56.4±1.43	58.4±1.61
FEF 50,%	50.6±1.1	51.3±1.9	50.9±1.32
FEF 75,%	55.2±1.3	54.8±1.42	56.4±1.2
FEV_1/FVC,%	69.2±0.9	70.5±0.84	74.3±1.1*
Genci test	28.3±1.48	28.5 ±1.39	28.9±1.32

Notes: * - significant differences between patients I and III ($p<0.05$),

From the data obtained, it is shown that in patients with high levels of healthy lifestyle components, FEV_1, FEV_1/FVC values were significantly higher compared to the group of patients with the object-passive level of lifestyle. In the study of bioimpedance analysis of the body in patients with COPD, when compared with the group of virtually healthy, significant differences were noted for the following indicators: BMI in patients with COPD was 27.03±0.89 kg /m^2, whereas in patients of the control group 29.8±0.96 kg /m^2 ($p<0.05$); % of muscles – 25.03±0.76 in patients with COPD and 28.1±0.93% in patients in the control group ($p<0.05$). These results indicate a significant reduction in BMI and% of muscle in COPD patients, compared to a group of practically healthy individuals, suggest that metabolic disorders (body mass deficiency, peripheral myopathy) are often the background in which COPD manifests itself coincides with the views of the authors [4].

When evaluating the results of stage "B" - screening testing for detecting deviations from the basics of HLS, the presence of risk factors and objective evidence of HLS, significant differences were noted ($p<0.05$); between the respondents of the main and the control group on the following scales: 4 .- Do you do the morning charge ?; 9 - Are you a cook?; 10.- Do you take more than 6 g of salt? The obtained results

allow to confirm the significant influence of the revealed factors - smoking, excessive salt intake and morning exercise on the development and course of COPD compared with a group of practically healthy respondents.

Based on the revealed violations in the behavior of patients with COPD, in relation to compliance with HLS, determination of dependence of indicators of FEV1 from lifestyle, an individualized approach was developed, an algorithm of actions and personal behavior for each patient was determined. The algorithm of behavior involves eliminating the identified risk factors - smoking, excessive salt intake. In addition, each patient was given recommendations on the implementation of a complex of exercises of breathing gymnastics on Buteyko - 2 times a day, and hardening (watering) 1 time a day, in the morning.

The second stage of the study was conducted after 6 months of observation, after the implementation of patients with personified recommendations, for compliance with the HLS, the performance of the therapeutic exercises on Buteyko and the body hardening (daily fluidization at a temperature of 18-20°) and included a reexamination of patients, with the definition of HLS, the study of the biompendance composition body, ERF indicators.

According to the results of a re-examination of patients with COPD, after 6 months, using the questionnaire Nosova AG Significant discrepancies were found between the levels of HLS in comparison with the results obtained during the primary examination. Thus, the object-passive (low level - less than 50%) was detected in 16% (8/50) patients, compared to 24% (12/50) in the primary examination ($p>0,05$); the object-active (average) level was noted in 36% (18/50) versus 56% (28/50) ($p<0,05$); high level of subjects - in 48% (24/50) versus 20% (10/50) patients ($p<0,05$). The obtained results indicate that most patients are aware of the importance of HLS.

After 6 months of observation of COPD patients, we have identified groups: the main group - patients who followed the developed recommendations (n=21) and the control group - patients who did not follow the recommendations (n=29). At studying the level of shortness of breath in patients with COPD on the scale of MMDR in 6 months, the average level of shortness of breath in patients in the main group was 0 points, which indicates a stable remission at the time of the survey, while in patients in the control group - 0.4±0.12 points. The analysis of ERF results after 6 months indicates a significant improvement in the indicators in the group of patients who performed personalized recommendations compared to a group of patients in the control group. The results obtained are presented in Table 2.

Table 2

Indices of external respiration function in patients with COPD after 6 months

Index of dimension	Patients with COPD			
	Main group (n=21)		Control group (n=29)	
	Initial examination	Repeated examination	Initial examination	Repeated examination
VC, %	72.3±1.11	77.12±1.05	72.9±1.22	72.2±1.19**
FEV_1,%	72.4±1.28	80.5±1.16*	73.2±1.21	72.9±1.34**
FEF 25,%	57.3±1.52	58.4±1.61	56.1±1.19	56.7±1.22
FEF 50,%	50.8±1.18	51.2±1.32	50.2±1.28	50.1±1.08
FEF 75,%	54.9±1.26	56.8±1.12	53.5±1.14	53.2±1.27
FEV_1/FVC,%	71.6±1.15	75.9±1.33*	70.9±1.16	70.1±1.28**
Genci test	28.4±1.3	36.2±1.18*	28.6±1.5	28.1±1.39

Notes: * - discrepancies are reliable in patients with the main group during a re-examination; ** - there are significant differences between patients in the primary and control groups with a re-examination.

In patients of the main group, after 6 months, significant positive results of the FEV_1 indicators were obtained at 10.1%, VC - 6.3%, FEV_1/FVC by 5.7%, Genichi tests by 21.6%, indicating the effectiveness of the recommendations developed and coinciding with the results of researchers who used as a rehabilitation measure for patients with COPD a set of elements of respiratory gymnastics with volitional elimination of deep breathing by Buteyko [6]. According to the data of FEV_1, one can judge the rate of tiredness of the respiratory muscles. In clinical practice, this indicator is used both to determine the severity of the disease and to assess the adequacy of treatment. Thus, adequate treatment is considered with the increase of the indicator by 10-12% of the initial [6]. The increase in VC by 6.0% also gives grounds for judging positive dynamics. The dynamics of the breath hold test has significantly increased in patients in the main group and amounted to 36.2% in the Genci test. Improvement of the Genichi test in patients with the main group indicates that the breathing has become more productive. Then, in patients in the control group, after 6 months, reduction in FEV_1-0.0.4%, VC by 0.96%, positive results of the FEV_1/FVC by 1.13%.

A comparative analysis of the evaluation of bioimpedance analysis of the body in COPD patients by groups, after 6 months, indicates a significant increase in% muscle. Thus, in the main group of patients

adhering to the developed recommendations,% of muscles was 27.05±0.43 versus 24.9±0.51 group of patients who did not follow the recommendations ($p<0.05$). Significant changes in BMI in patients in the main and control group after 6 months were not noted 26.12 ± 0.62 kg /m ^{2} and 25.58 ± 0.48 kg /m ^{2} ($p>0.05$). In addition, in the group of patients with COPD who followed the developed recommendations for relapse of the disease for 6 months was not noted, while in patients with control group, there were 7 relapses (24%). These results suggest that the formation and strict observance of the components of CVL, respiratory gymnastics by Buteyko and hardening significantly improve the clinical and functional parameters in COPD patients, increase the duration of remission.

Conclusion

Thus, the results of the conducted research allow to recommend inclusion in the comprehensive examination of patients with COPD testing using the Nosov questionnaire, assessment of bioimpedance analysis of the body, which will allow to develop personalized recommendations for each patient. Compliance with COPD patients with recommendations for lifestyle management, nutrition, the systematic implementation of medical gymnastics by Buteyko and the quenching of the body contribute to the achievement of long remission, quality of life.

Prospects for further research *include further introduction of HLS in patients with COPD, analysis of indicators of biompendasometry, ERF in more distant observation time - after 12 months.*

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Реферати

ОЦІНКА РІВНЯ ЗДОРОВОГО СПОСОБУ ЖИТТЯ У ХВОРИХ НА ХРОНІЧНЕ ОБСТРУКТИВНЕ ЗАХВОРЮВАННЯ ЛЕГЕНЬ

Потяженко М.М., Іщейкін К.Є., Настрога Т.В., Соколюк Н.Л., Кітура О.Є.

З метою розробки персоніфікованого підходу у пацієнтів з ХОЗЛ - індивідуальної та дієвої стратегії, щодо виконання дієвих рекомендацій дотримання засад здорового способу життя (ЗСЖ) на першому етапі проводилось вивчення основних факторів ризику захворювання, на підставі чого розроблялась для кожного пацієнта дієва персоніфікована стратегія щодо дотримання ЗСЖ в комплексі з виконанням хворими лікувальної дихальної гімнастики по Бутейко

ОЦЕНКА УРОВНЯ ЗДОРОВОГО ОБРАЗА ЖИЗНИ У БОЛЬНЫХ ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БОЛЕЗНЬЮ ЛЕГКИХ

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С целью разработки персонифицированного подхода у пациентов с ХОБЛ - индивидуальной и действенной стратегии по выполнению действующих рекомендаций соблюдения принципов здорового образа жизни (ЗОЖ) на первом этапе проводилось изучение основных факторов риска заболевания, на основании чего разрабатывалась для каждого пациента действенная персонифицированная стратегия по соблюдению ЗОЖ в комплексе с выполнением больными лечебной дыхательной

і загартовування організму – обливання холодною водою. Авторами статті доведено, що дотримування хворими на ХОЗЛ рекомендацій щодо врегулювання способу життя, харчування, систематичне виконання лікувальної гімнастики по Бутейко та загартування організму сприяють досягненню тривалої ремісії, підвищенню якості життя.

Ключові слова: здоровий спосіб життя (ЗСЖ), хронічне обструктивне захворювання легень (ХОЗЛ)

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гимнастики по Бутейко и закаливание организма - обливание холодной водой. Авторами статьи доказано, что соблюдение больными ХОБЛ рекомендаций по урегулированию образа жизни, питания, систематическое выполнение лечебной гимнастики по Бутейко и закаливание организма способствуют достижению длительной ремиссии, повышению качества жизни.

Ключевые слова: здоровый образ жизни (ЗОЖ), хроническая обструктивная болезнь легких (ХОБЛ).

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CLINICAL CHARACTERISTIC OF AFFECTIVE VIOLATIONS IN DISORDERS OF ADAPTATION FROM COMBATANTS

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A comprehensive clinicopsychopathological and pathopsychological study of 186 combatants with diagnosed stress reactions and adaptation disorders, who underwent inpatient treatment in the clinical departments of the Vinnitsa Regional Clinical Hospital of War Veterans was performed. The study included socio-demographic (questionnaire), clinical-anamnestic, clinical-psychopathological (clinical interview), psychodiagnostic (pathopsychological) and statistical methods. In the course of this study, the severity of affective disorders in the study group was established, data variability was determined, and a statistical-mathematical analysis of the survey results was carried out. The results of the proposed algorithm of psychodiagnostic research reflect the structure of changes in the affective sphere and certain personal predispositions in patients with affective variants of adaptation disorders. It was revealed that a cognitive defect can be formed later through the consolidation and progression of organic changes, and the transition of an adaptation disorder to a behavioral level will be associated with personality traits and characteristics of respondents' social rehabilitation. Determination of clinical and psychopathological features of prevailing variants of adaptation disorders in combatants is the basis for the development of new diagnostic algorithms and integrated approaches to the treatment of this contingent.

Key words: affective violations, combatants, disorders of adaptation, psychotic and non-psychotic mental disorders, response to stress.

The work is a fragment of the research project "Scientific substantiation of diagnostic and therapeutic rehabilitation measures for endogenous and exogenously-organic psychotic and non-psychotic mental disorders", state registration № 0116U000856.

Mental health protection is one of the most pressing problems of any state. Mental health is one of the parameters that determine the quality of life of the population. This is due to the fact that it is the mental health of its citizens that determines the national security of the country. The peculiarities and nature of psychiatric care in any country is determined by historical, economic, geographical, cultural, political and other factors. Thus, mental health - is a certain reserve of human strength that can overcome stress or difficulties that arise in exceptional circumstances [14].

The armed conflict between the illegal armed groups (for direct support and active participation of the Russian Army) and the Armed Forces of Ukraine in Donetsk and Luhansk regions resulted in getting into a war zone both military personnel and large numbers of civilians who suffer injuries of varying severity and killed [1, 4, 13]. According to the United Nations (UN), the war has somehow affected 5 million people [2]. At the same time, a large part of the military personnel entered the combat zone without knowing the basic rules and lacking the skills of providing first aid [2]. According to official United Nations (UN) statistics, 5486 soldiers were killed and 12,972 injured in the conflict in Ukraine. Among the most common injuries limb injuries (62.6%) and the head (37.4%) [2]. In addition to physical injuries, the soldiers also receive psychological injuries. About 80% of soldiers and civilians in the war zone have psychological and mental disorders - from combat fatigue to acute mental [1].

The experience of fighting in Vietnam, Afghanistan, the Persian Gulf and elsewhere in the world suggests that pharmacological agents can be used to enhance the activity of personnel actions in terms of danger and chronic fatigue (stimulants), removal of excessive mental tension (relaxers), accelerating the process of adaptation to extreme conditions of military life, increase performance efficiency of individual mental functions etc. [9, 10]. Psychological rehabilitation is part of the medical and psychological rehabilitation and carried out with military personnel undergoing treatment due to injuries, concussion, burns, radiation, mental disorders. In some cases, psychological and psychological rehabilitation is

supplemented by vocational rehabilitation and social rehabilitation [15]. WHO estimates that traumatic events may lead to the development of conditions such as: depressive disorder, psychosis, behavioral disorders, alcohol or drug use, self-harm / suicide and other significant emotional or medically unclear complaints, prolonged grief response, or post-traumatic stress disorder (PTSD) [15]. Statistical data also show that for every soldier who died in the war accounted for one case of suicide in the aftermath of veterans of military service [8]. So, by 1990, more than 50,000 (according to other figures, about 100,000) Vietnam war veterans had committed suicide since the return of troops (with the total number of U.S. soldiers killed in Vietnam at about 58,000) [6].

This makes determining the relevance of the clinical features of mental and behavioral disorders in the combatants, which will allow to develop the most effective diagnostic and treatment algorithm for this contingent.

The purpose of the work was to study clinical and psychopathological features and pathopsychological characteristics of patients (combatants) with diagnosed stress reactions and adaptation disorders.

Materials and methods. A total of 186 respondents were surveyed. All patients underwent inpatient treatment after combat injuries in clinical departments (therapeutic, neurological, surgical) of Vinnitsa Regional Clinical Hospital of War Veterans during 2016-2019. All surveyed men between 20 and 57 years of age. Clinical diagnoses of patients were consistent with the nature of the lesions and were established according to the criteria of the current International Classification of Diseases X Review. All patients provided written informed consent to participate in the study. The specifics of our study led to the most optimal type of organization - voluntary participation in the experiment. Patient information were collected directly from patients during a complete clinical and psychopathological and clinical psychodiagnostics examination and contained the following items: date of examination; medical history number; department; surname, first name, patronymic of the patient; age; mobilization; profession, education; home address; complaints. The data were supplemented with information on premorbid personality traits (in the presence). The examination included thematically important anamnestic information, test results and the mental status of patients which were recorded in a specially designed survey results card. Important was the information about the course of the illness, which the reflection of the disease receives in the subjective world of the patient, as reflected on his behavior, throughout the system of personal relationships, or paid particular attention to previous stressful situations and changes in life, features that are inherent in the respondent (the ability to overcome difficulties and resist psycho-traumatic factors), the state of social environment and moral support, not only from relatives but also other outsiders. In the presence of psychopathological symptoms, its nature, time and circumstances of their occurrence, dynamics, duration, and factors that accelerate the appearance of these signs were clearly defined. For the pathopsychological examination, a number of techniques appropriate to the purpose of the work were selected. Inclusion in the methodical study specific apparatus tests and corresponding experimental parameters was carried out on the following criteria: conceptual validity of methods, high validity, psychometric reliability and the possibility of comparing the results. The respondents researched anxiety (situational - as a variant of reaction, personal - as a rice, and general mental - as a condition), presence of manifestations of depression, functional state (state of health, activity and mood as its constituents). Primary research has included assessment of cognitive functions. But in the final analysis of the results of clinical psychodiagnostics studies from the assessment of cognitive functions (memory, retention mechanisms; stability of attention, ability to concentrate, distribute, switch), we refused, because at this stage in most of the cognitive defect has not been formed and the data of these methods were not demonstrative. Therefore, presented study included only methods of evaluating affective sphere and behavior.

Results of the study and their discussion. In this study it was found severity of affective disorders in the study group, defined variability data and performed statistical and mathematical analysis resultative examination. In the patients of the complaints are not concerned underlying disease came to the fore headaches, weakness, lethargy, increased fatigue, decreased performance, poor memory and attention, irritability, nervousness, depressed mood, loss of appetite, insomnia, interrupted sleep with nightmares, a pessimistic assessment of the future and lack of prospects which to some extent coincides with the results of other researchers [3, 7, 8]. More than 75% of the surveyed complained of impaired social functioning, first and foremost the inability to work at the same job (more than 67%) as to participation in hostilities, increased conflict in the family, feelings of frustration, inability to find themselves, their place, inability to adapt in a peaceful life; more than 40.5% of them showed a tendency to use psychoactive substances for the first time or have significantly increased. Information on the presence of organic brain damage in this group of patients has not been documented. An analysis of this factor revealed that the most common were indications for infectious diseases (childhood viral infections), concussion, and traumatic brain lesions with

and without loss of consciousness. When examining the family genealogy background, it was found that none of the patients had an inherited burden of mental illness. The socio-demographic characteristics of the group are presented in table 1 and some extent coincides with results of some scientists [3, 8].

Table 1

Socio-demographic characteristics of the group

Characteristic	Specialty			
	%	%	%	%
age	20-29 years	30-39 years	40-49 years	over 50 years
	23.66%	37.63%	31.18%	7.53%
educational level	secondary education	average special	incomplete higher education	higher education
	13.98%	57.53%	9.14%	19.35%
place of residence	city	urban village	village	Vinnitsa region
	28.49%	36.02%	35.49%	77,42%

All respondents were male, aged 20 to 57 years. Of these, 23.66% (44) were aged 20-29 years, 37.63% (70) - 30-39 years, 31.18% (58) - 40-49 years, 7.53% (14) - older than 50 years. The educational level of the group was presented as follows: 13.98% (26) had general secondary education, 57.53% (107) had secondary specialized education, 9.14% (17) had incomplete higher education, 19.35% (36) - completed higher education. Regarding the place of residence, 77.42% (144) of the respondents were from Vinnitsa region and Vinnitsa; 28.49% (53) were city residents, 36.02% (67) lived in urban settlements, 35.49% (66) lived in villages.

According to the results of pathopsychological research, the average arithmetic indicator of situational anxiety in the respondents was 30.98 ± 1.34, which indicates a moderate level of it, the indicator of personal anxiety 46.21 ± 1.23 indicated its high level. According to the analysis of individual data (Table 2), the indicator of situational anxiety was high at 7.53% of the studied, moderate - at 44.62%, low - at 47.85%. The indicator of personal anxiety was low at 7.3% of respondents, moderate - at 32.9%, high - at 59.8%.

The arithmetic mean of general mental anxiety is 21.42 ± 1.13, which indicates the average level of overall mental anxiety with a tendency to high. Thus, 2.69% of respondents has a low level of anxiety-state, 30.65% - a medium level with a tendency to a low level, 26.88% - a medium level with a tendency to a high level, 35.3% - a high level, 4.9% had a very high level of general mental anxiety (table 2).

Table 2

Results of the study of situational, personal and general mental anxiety

parameter| level		situational anxiety		personal anxiety		general mental anxiety	
		number of patient (n)	%	number of patient (n)	%	number of patient (n)	%
low		89	47.85%	14	7.53%	5	2,69%
moderate/ medium	with a tendency to low	83	44.62%	62	33,33%	57	30,65%
	with a tendency to high					50	26,88%
high		14	7.53%	110	59.14%	66	35,48%
very high		-	-	-	-	8	4,3%
average, points		30.98±1.34		46.21±1.23		21.42±1.13	

A significant correlation was found between indicators of situational, personality, and general mental anxiety by Pearson and Spearman correlation coefficients (P <0.01). The obtained results about anxiety levels in patients with adaptation disorders are in the agreement with other researchers [3, 5, 7, 8]. The positive point of the examination was the absence of a true depressive state in the study group. So, the arithmetic mean was 38.23 ± 1.08. But 12.37% of the respondents showed mild depressive state of situational or neurotic genesis and 1.61% sub depressive state or masked depression (table 3), which also to some extent coincides with results of some scientists [3, 7, 8].

Found a reliable correlation between indicators of situational, personal, general mental anxiety and depression by Pearson and Spearman correlation coefficients (P <0.01).

Table 3

Results of the study severity of depressive states

parameter	respondents by severity of depressive states	
	number of patients (n)	%
no depressive state	160	86.02%
slight depression of situational or neurotic genesis	23	12.37%
sub depressive state or masked depression	3	1.61%
average, points	38.23±1.08	

In the analysis of the survey results is noteworthy that a significant majority of respondents rated their complex functional condition as satisfactory and good (59.68 and 29.03%, respectively), and only 11.29% as poor (table 4). The arithmetic mean of the functional state is 4.63 ± 1.32 points, which indicates a satisfactory state of health, interest, emotional tone and mental activity with a tendency to good. The analysis of the average results of the calculations showed that the respondents had a satisfactory level of mental activity (4.48 ± 1.29) and well-being (4.49 ± 1.37) and good mood (4.86 ± 1.55).

Table 4

Results of the study of the functional state and its components: "Well-being - activity - mood"

options / categories	average	distribution of respondents of the functional state					
		bad		satisfactory		good	
		(n)	%	(n)	%	(n)	%
well-being	4.49±1.37	28	15.05%	101	54.3%	57	30.65%
activity	4.48±1.29	24	12.9%	122	65.59%	40	21.51%
mood	4.86±1.55	33	17.74%	78	41.94%	75	40.32%
functional state	4.63±1.,32	21	11.29%	111	59.68%	54	29.03%

A significant correlation was found between indicators of situational, personality, general mental anxiety and depression with indicators of mental activity, well-being, mood and functional state according to Pearson and Spearman correlation coefficients ($P < 0.01$).

The analysis of the structure and prevalence of stress-related mental disorders among servicemen, combatants, their clinical typology and the peculiarities of these states were presented in the professional literature [3, 5, 7, 8, 11, 12]. This information indicates high specificity of this category of disorders and coincides with the trends presented by us. Analysis of anamnestic data and complaints indicates that social drift is an important complication of adaptation disorders. The most significant manifestation of social drift among combatants is the change of place of employment or unemployment through loss of place of work; increased conflict in the family; the use of surfactants. No correlation was found between age, educational level and place of residence. There are also no correlations with the features of clinical complaints and the results of clinical and psychopathological examination. In most patient's situational anxiety was low. Increasing its level coincided with an increase in patient irritability. But a significant increase in anxiety-traits could be explained as a permanent internal stress in individuals who were in a combat situation. Dependencies of anxiety on socio-demographic characteristics such as age, educational attainment and place of residence were not detected. Draws attention the fact, that respondents living in urban areas have better rates than residents of small towns and villages. We believe that this may be due to greater social security, the higher the probability to get a job after treatment of the inhabitants of large towns. Thus, on the forefront in cohort of the combatants at this stage get out violations of the affective sphere. A cognitive defect can be formed later due to the fixation and progression of organic changes which to some extent coincides with the results of other researchers [12]. And the transition of the disorder of adaptation to the behavioral level will be connected with the personal traits and peculiarities of the social readaptation of the respondents.

Conclusions

1. In the clinic there are two main options for disorders of adaptation: affective and behavioral. The special relevance of the study of adaptation disorders associated not only with their widespread - 5-20% of outpatients, but with susceptibility to chronic process and fixing symptoms as persistent personality changes.

2. The results of our proposed algorithm of psychodiagnostics research reflect the structure of changes in the emotion sphere in patients with affective variants of disorders of adaptation.

3. Determination of clinical and psychopathological features of prevailing variants of adaptation disorders in ATO victims is the basis for development of new diagnostic algorithms and complex approaches to treatment of this contingent.

4. Given the still insufficient level of psychological rehabilitation for this contingent, further inactivity in the future may lead to the phenomenon of social drift, increased levels of deviance, addiction, torts and suicides. The presence of adaptation disorders is an indication of the psychological rehabilitation of servicemen, so it is important to detect its signs early and provide timely rehabilitation that meets such principles as early onset, continuity, complexity, individuality, the need for rehabilitation in the team, return to active work.

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Реферати

КЛІНІЧНА ХАРАКТЕРИСТИКА АФЕКТИВНИХ ПОРУШЕНЬ ПРИ РОЗЛАДАХ АДАПТАЦІЇ У КОМБАТАНТІВ

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Проведено комплексне клінікопсихопатологічне та патопсихологічне дослідження 186 комбатантів, з діагностованими стресовими реакціями та порушеннями адаптації, які проходили стаціонарне лікування у клінічних відділеннях Вінницького обласного клінічного госпіталю ветеранів війни. Дослідження включало соціально-демографічний (анкетування), клініко-анамнестичний, клініко-психопатологічний (клінічне інтерв'ю), психодіагностичний (патопсихологічні методики) та статистичний методи. В ході даного дослідження було встановлено ступінь вираженості афективних порушень у групі дослідження, визначено варіабельність даних та проведено статистично-математичний аналіз результатів обстеження. Результати запропонованого алгоритму психодіагностичного дослідження відбивають структуру змін афективної сфери та певні особистісні предиспозиції у хворих з афективними варіантами розладів адаптації. Виявлено, що когнітивний дефект може бути сформований пізніше через закріплення та прогресування органічних змін, а перехід розладу адаптації на поведінковий рівень буде пов'язаний з особистісними рисами та особливостями соціальної реадаптації респондентів. Визначення клінічних та психопатологічних особливостей переважаючих варіантів порушень адаптації у комбатантів є основою для розробки нових діагностичних алгоритмів та комплексних підходів до лікування цього контингенту.

Ключові слова: афективні порушення, що воюють, розлад адаптації, психотичні і непсихотические психічні розлади, реакція на стрес.

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КЛИНИЧЕСКАЯ ХАРАКТЕРИСТИКА АФФЕКТИВНЫХ НАРУШЕНИЙ ПРИ РАССТРОЙСТВАХ АДАПТАЦИИ У КОМБАТАНТОВ

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Проведено комплексное клиникопсихопатологическое и патопсихологическое исследования 186 комбатантов, с диагностированными стрессовыми реакциями и нарушениями адаптации, которые проходили стационарное лечение в клинических отделениях Винницкого областного клинического госпиталя ветеранов войны. Исследование включало социально-демографический (анкетирование), клинико-анамнестический, клинико-психопатологический (клиническое интервью), психодиагностические (патопсихологические методики) и статистический методы. В ходе данного исследования была установлена степень выраженности аффективных нарушений в группе исследования, определена вариабельность данных и проведен статистически-математический анализ результатов обследования. Результаты предложенного алгоритма психодиагностического исследования отражают структуру изменений аффективной сферы и определенные личностные предиспозиции у больных с аффективными вариантами расстройств адаптации. Выявлено, что когнитивный дефект может быть сформирован позже через закрепление и прогрессирования органических изменений, а переход расстройства адаптации на поведенческий уровень будет связан с личностными чертами и особенностями социальной реадаптации респондентов. Определение клинических и психопатологических особенностей преимущественных вариантов нарушений адаптации у комбатантов является основой для разработки новых диагностических алгоритмов и комплексных подходов к лечению этого контингента.

Ключевые слова: аффективные нарушения, комбатанты, расстройства адаптации, психотические и непсихотические психические расстройства, реакция на стресс.

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PATHOGENETIC JUSTIFICATION OF DIFFERENTIAL THERAPY IN MENTAL DISORDERS WITH SOMATIC SYMPTOMS (PSS-BY DSM-5)

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The problem of prevalence and chronicity of psychogenic diseases becomes one of the most important in modern medicine in view of the economic losses associated with the compensation for this pathology treatment and its consequences. The purpose of the study was to formulate approaches for differential diagnosis and demonstrative use of medicines and psychotherapy for treatment of psychiatric disorders with somatic symptoms, taking into account pathogenic factors and their pathomorphosis. Conclusion was made that the evidence-based use in treatment of psychiatric disorders with somatic symptoms, taking into account pathogenic factors and their pathomorphosis, involves the predominant use of pregabalin as a universal neuromediator balance stabilizer in therapy of both anxiety disorders and other psychogenic disorders.

Key words: psychogenic disorders, anxiety disorders, neurotransmitters, pregabalin, somatic component, differential therapy.

The work is a fragment of the research project "Scientific substantiation of diagnostic and treatment-rehabilitation measures for endogenous and exogenous-organic psychotic and non-psychotic mental disorders", state registration No. 0116U000856.

Chronic stress can lead both to behavioral reactions and structural changes in many areas of the brain, as a consequence of cerebral hypoxia, due to nitric oxide increase, its cytotoxic effect on neuroglial elements, both in the cerebral cortex and in the hippocampus. [9].

Duration and intensity of stress effects on functionally overloaded cells depletes adaptation reserves and leads to their destruction by apoptosis / necrosis.

Under the influence of chronic stress, structural and functional changes occur, both in the neuro- and in satellite oligodendroglia, which are responsible for the information reception and transmission, and for the formation of pathological relationship ("closed circle") in the sensory-motor area and in the hippocampus, as an adaptive reaction to their ultrastructures impairment.

Given that, vegetative dysfunction, which develops as a result of supra-segmental vegetative structures dysregulation, manifests itself both as vegetative and emotional-cognitive disorders.

The development of psychosomatic disorders (PSD) is associated with many etiologic and predisposing factors.

In addition, a shift in the balance toward ergotropically tuned amines (catecholaminergic and serotoninergic) leads to impairment of neurohumoral regulation between glutamate - aspartate and the GABA-ergic system.

Shifting the balance towards the excitatory amines leads to the growing level of anxiety, agitation, insomnia. A shift towards GABA-ergic results in sedation, drowsiness, decreased mental activity, impaired attention and memory [9].

Serotonin and histamine are included into the humoral system of physiological processes regulators and modulators, which, under pathology or stress, turn into a disease releasing factor.

As a neurohormone, serotonin regulates noradrenaline release from synaptic nerve endings, and regulates vascular tone due to binding to specific receptors on vascular walls' endothelial cells [8].

Hereditary-constitutional predisposition plays an important role. Usually the inherited type of vegetative response, which depends on a certain ratio of MLA antigens, the activity of α- and β-adrenergic receptors, the ANS suprasegmentary centers sensitivity, metabolism features. (Multifactorial and autosomal dominant type of inheritance. The type of autonomic response determines the adaptability of the body or the stress-limiting activity.)

Thus, it can stated that simultaneously with the psychopathological response to the psycho-traumatic effects (stress) of any somatic disease, the symptoms of autonomic dysfunction are necessarily formed, and only at a later stage they are transformed into a somatic disorder, somatoform or affective disorder of a particular organic system.

The purpose of the work is to carry out differential diagnosis and evidence-based use of medicines for treatment of psychiatric disorders with somatic symptoms.

Materials and methods. In order to study clinical features of psychosomatic disorders in adolescence, we examined 329 adolescents.

The criteria for inclusion into the study were: signing of the informed consent by both parents, individuals of both genders aged 10 to 18 years and an expert-proved diagnosis of a psychosomatic disorder according to International Classification of Diseases ICD-10 or PSD according to DSM-V.

The average age of the patients under study was 14.0±2.0 years, male - 49.54%, female - 50.46%.

The patients were divided into groups according to the main functional syndrome affecting this or that particular system.

In order to exclude organic pathology, the patients were subjected to clinical and instrumental studies.

Diagnosis of mental disorders was carried out using: clinical-psychological questionnaire by Maria Rovacs (1992), Spielberger's method (STPI-State Trait Personal Inventori), clinical-psychopathological (clinical) interview, follow-up methods "Questionnaire of the adolescent health status", filled in by parents.

Statistic processing was performed using Statistica v.12.0 (StatSoft) software package. Nonparametric correlation analysis was performed using the Spearman method (correlation coefficient, r). The results were considered significant at $p < 0.05$.

Results of the study and their discussion. Studies of the somatic complaints incidence depending on adolescents' age are presented in table 1 with the reliability determined ($p < 0.05$).

Complaints of the cardiovascular system were dominated by heart pains, palpitations, rapid or slow pulse. On the part of the digestive system, complaints of epigastric pain, heartburn and constipation were prevalent. Shortness of breath, coughing, labored breathing, timed inspiratory capacity, expiratory hold exhalation, dominated among the complaints of the respiratory system. Pain and frequent urination were the main complaints of the excretory system.

Adolescents associated the onset of symptoms, i.e., the onset of the disease, with stress factors, such as family and school conflicts, parents' divorce, death or serious illness of their near and dear ones, moving with change of school.

Table 1

Somatic complaints incidence, depending on adolescents' age

Symptoms	adolescents aged 10-14 n=179		adolescents aged 15-16 n=96		adolescents aged 17-18 n=54	
	Young males n=94	Girls n=85	Young males n=46	Girls n=50	Young males n=21	Girls n=33
Cardio-vascular system	8 8.51 %	4 4.71 %	3 6.52 %	3 6.0 %	1 4.76 %	1 3.03 %
Respiratory system	5 5.32 %	5 5.88 %	4 8.69 %	8 16.0 %	1 4.76 %	2 6.06 %
Digestive system	4 4.26 %	4 4.71 %	7 15.22 %	5 10.0 %	6 28.57 %	4 12.12 %
Presence of Several syndroms	10 10.64 %	9 10.59 %	13 28.26 %	16 32.0 %	6 28.57 %	9 27.27 %

It is known that in the formation of psychosomatic diseases an important role is played by a personal factor, which determines the appropriate response of the individual to stressful impacts [12]. Various psychosomatic disorders are united by a common feature - the combination of mental and somatic disorders, which emphasizes the close correlation between the individual's personality development and the biological factors acting on him [13]. This fact prompted the analysis of the two traits correlation without taking into account the nature of their distribution among adolescents of different age groups and social status by means of nonparametric Spearman correlation analysis (correlation coefficient, r). The results were considered reliable at $p < 0.05$.

We have established reliable correlations between somatic complaints and mental disorders manifestations. Thus, there is a correlation between the stress factor's impact and the intensity of central nervous system complaints ($r = 0.63$, $p < 0.05$); those of the cardiovascular system ($r = 0.71$, $p < 0.05$), in particular in girls ($r = 0.79$, $p < 0.05$); of the digestive system ($r = 0.84$, $p < 0.05$), in particular in young males ($r = 0.87$, $p < 0.05$). In addition, impaired digestive function under the stress impact correlated with neuropsychic disorders ($r = 0.76$, $p < 0.05$). The identified reliable correlations between the effects of stressors and the internal organs disorders in adolescents indicate the leading role of the stress factor.

The following syndromes have been verified in the clinic of somatic psychopathological disorders: hysteroconversive, anxiety-phobic, depressive, autonomic dysfunction.

The results of studying the incidence of psychopathological disorders depending on the adolescents' age are presented in table 2.

Table 2

Psychopathological disorders depending on adolescents' age

Syndroms	Adolescents aged 10-14: n=179		Adolescents aged 15-16: n=96		Adolescents aged 17-18: n=54	
	Young males n=94	Girls n=85	Young males n=46	Girls n=50	Young males n=21	Girls n=33
hysteroconversive	3 3.19 %	3 3.53 %	2 4.35 %	2 4.0 %	2 9.53 %	2 6.06 %
anxiety-phobic	10 10.64 %	6 7.06 %	18 39.13 %	14 28.0 %	6 28.57 %	11 33.33 5
depressive	4 4.26 %	5 5.88 %	8 17.39 %	9 18.0 %	4 19.05 %	8 24.24 %
autonomic dysfunction	13 13.83 5	10 11.76 %	17 36.96 %	14 28.0 %	7 33.33 5	9 27.27 %

Hystero-conversive disorders in the form of globus pharyngis in swallowing, chilly sensation, palpitations and irregular heart rhythm, were reliably ($p < 0.05$) frequently observed in adolescents aged 17-18 years (7.41%).

Anxiety-phobic syndromes dominated with panic attacks and sleep disorders ("pavor posturnus") in 33.3% of adolescents aged 15-16, 31.48% of persons aged 17-18.

Depressive syndrome with anhedonia, hypotension, circadian oscillation of affection is more commonly diagnosed in adolescents aged 15-16 (17.7%), 17-18 years (22.2%).

The syndrome of autonomic dysfunction in the form of vascular dystonia, impaired secretory and motor function of the gastrointestinal tract, long-term subfebrility was found in adolescents aged 15-16 (32.3%), 17-18 years (29.63%).

Thus, the performed analysis of the somatized psychopathological disorders incidence depending on age has determined the dominance of these symptoms in adolescents of 15-16 and 17-18 years.

Spearman's rank correlation method revealed a relationship between causative factors and psychosomatic disorders.

The existence of reliable correlation between the stress factor impact and the complaints severity of the digestive system ($r = 0.83$, $p < 0.05$), cardiovascular system ($r = 0.74$, $p < 0.05$) and of the central nervous system ($r = 0.61$, $p < 0.05$) was established. In addition, impaired digestive function under the stress factor impact was correlated with neuropsychic disorders ($r = 0.79$, $p < 0.05$). Thus, the reliable correlations revealed between the stressor's impact and digestive, cardiovascular and neuropsychic functional disorders in adolescents testify to the significant effect of stress factor in the pathogenesis of pathological manifestations.

В результаті нашого дослідження встановлено високу частоту (81,5 %) психосоматичних розладів серед тих підлітків, які потребували медичної допомоги.

Psychosomatic disorders (PSD) treatment requires a step-by-step multidisciplinary client-centered approach (family psychiatrist-psychotherapist) for treatment of somatic, anxiety, and depressive symptoms. The results obtained are confirmed by the survey data. It has been proved that psycho-traumatic events contribute to the development of psychosomatic disorders [13].

Pharmacotherapy of patients with psychosomatic disorders is directed to the main groups of target symptoms: affective and somatic vegetative.

Among the syndromes in the clinical structure of psychosomatic disorders are anxiety, asthenic and depressive disorders.

Features of the depressive syndrome clinical picture in children include atypical symptomatology, polymorphic structure of the syndrome, asthenic coloration of depressive disorders, neurotic level of their manifestations, rudimentary affective component, requiring the use of specific pharmacotherapy. At the initial stages of the anxiety syndrome development, in autonomic disorders, the main pathogenetically justified treatment method is prescription of anxiolytics. [2].

The considered pathogenetic mechanisms of somatic symptoms formation require a comprehensive approach, both to the use of diagnostic instruments and to the provision of care taking into account socially determined factors, atypical course of pathological symptoms, features of medical care stages with selection of the most appropriate pharmacotherapy drug, within the treatment protocols.

Currently, one of the most important problems, both in clinical pharmacology and in practical medicine, is selection of the most appropriate pharmacotherapy drug for a particular patient, based on the pathogenetic principles of his symptoms formation within the treatment protocols.

The best efficacy of a particular drug's action is determined not only by its "nerve-point" effect on one of the neurally mediated systems or chains of neuronal metabolism, but by its universal regulatory influence at the level of the CNS as a whole, which will ensure its maximum safety and "multiple" selectivity.

Table 3

Algorithm for PSD treatment

Without concomitant anxiety or depressive syndrome		With concomitant anxiety or depressive syndrome	
Line I	Eclectic psychotherapy	Line I	Eclectic psychotherapy
Plus	Psychiatrist's consultation	Plus	Psychiatrist's consultation
Additionally	Physical activity	Plus	Antidepressant drugs
Additionally	Relaxation technique	Additionally	Physical activity
		Additionally	Relaxation technique
Line II	Antidepressant drugs	Line II	Other types of psychotherapy
		Plus	Antidepressant drugs
Line III	Other types of psychotherapy	Line III	Atypical antipsychotics

Such a natural universal inhibitory neurotransmitter is GABA, which has most of the receptors in the CNS, which are located in the vast majority of structures (cerebral cortex, olfactory bulb, hypothalamus, amygdaloid body, cerebellum, dorsal horn of the gray matter). GABA is synthesized from glutamic acid due to glutamate dehydrocarboxylase only in the CNS.

The structural analogue of GABA is pregabalin, whose mechanism of action is to bind to the α2-σ-protein substance of the CNS potential-dependent calcium channels, which reduces the release of excitatory neurotransmitters, in particular glutamate, norepinephrine (noradrenaline) and P-substance, which participate in forming anxiety disorders. This process only occurs under the conditions of increased (pathological) depolarization of the neuron, which determines the singularity of pregabalin action mechanism. That is, Ca^{2+} ions cannot enter the middle of the excited neuron (key in the lock), thus inhibiting the release of the excitatory neurotransmitters into the synaptic cleft.

In physiological depolarization, the "lock is open", resulting in maintaining neurotransmitter balance between excitatory and inhibitory neurotransmitters. In this case pregabalin does not bind to any of the known mediator receptors in the CNS, both pre- and postsynaptic, which confirms its maximum "multiple" selectivity, especially in treatment of anxiety disorders in which, as it was noted, a "closed circle" is formed due to the imbalance between activating and inhibitory neurotransmitters, namely the activation of noradrenaline, P-substance, glutamate, and attenuation of anti-anxiogenic GABA systems, adenosine.

The result of medical treatment in adolescents was the positive dynamics of psychopathological symptoms.

Thus, after 18 days of therapy, there was a tendency for the indices improvement, and after 60 days changes were pronounced, especially in the reactive and personal anxiety indices.

Given the above data, it was of scientific interest to determine the impact of drug therapy on the dynamics of psychopathological syndromes. Thus, in the case of somatized conversion-dissociative syndrome, a high level of personal anxiety was diagnosed in 57.14% of patients before treatment, 50.00% - after 18 days of treatment and 42.86% of patients after 60 days of treatment. Low level of personal cognitive activity was found in 35.71% of adolescents before treatment. After 18 days of treatment, the level of personal cognitive activity increased and was diagnosed low in 28.57% of patients and after 60 days of treatment - in 14.29%.

High values of personal negative emotional experiences occurred in 21.43% of persons before treatment, 35.71% - after 18 days and in 42.86% of students after 60 days of treatment. High values of situational anxiety were found in 78.57% of persons before treatment, in 64.29% and 57.14% of persons - 18 days and 60 days after treatment, respectively. Low levels of situational cognitive activity were found in 14.29% of adolescents before treatment and 7.14% after treatment. High values of situational negative emotional experiences occurred in 57.14% of persons before treatment and in 64.29% of schoolchildren after 18 days and 60 days of treatment, respectively (table 4).

In the case of somatized depressive syndrome, a high level of personal anxiety was diagnosed in 33.33% of patients before treatment and in 25.0% of patients after 18 days and 60 days of treatment. A low level of personal cognitive activity was found in 33.33% of adolescents before treatment, in 50.0% after 18 days and in 41.67% after 60 days of treatment, respectively. High values of personal negative emotional experiences occurred in 25.0% of persons before treatment and these values did not change against the background of treatment. High rates of situational anxiety were found in 50.0% of patients before treatment,

in 41.67% of patients after 18 days of treatment and in 33.33% of patients after 60 days of treatment. Low levels of situational cognitive activity were found in 8.33% of adolescents before treatment and in 16.67% after treatment. High values of situational negative emotional experiences occurred in 58.33% of patients before treatment and in 50.0% and 41.67% of schoolchildren after treatment.

In somatic phobic syndrome, a high level of personal anxiety was diagnosed in 25.0% of patients before treatment and in 45.45% of patients after treatment. Low levels of personal cognitive activity were detected in 72.73% of adolescents before treatment in 50.0% and in 45.45% after 18 days and 60 days of treatment, respectively.

High values of personal negative emotional experiences were not determined before treatment and occurred in 22.72% of schoolchildren after treatment. High indices of situational anxiety were found in 45.45% of patients before treatment. After treatment, high values remained in 22.73% after 18 days and in 18.18% of patients after 60 days. A low level of situational cognitive activity was detected in 22.73% of adolescents before treatment and this index did not change after treatment. High values of situational negative emotional experiences occurred in 72.73% of persons before treatment. After 18 days and 60 days of treatment, these values remained high in 50.0% and in 40.91% of schoolchildren, respectively (table 4).

Analysis of the school anxiety dynamics by the Phillips test, against the background of drug therapy, revealed a tendency to increase the body's adaptive capacity in stressful situations. The expediency of analyzing each anxiety factor and their changes dynamics according to the Phillips method within the biopsychosocial approach to helping clarify the role of psychopedagogical work (psychoeducation) with family, teachers and peers and was carried out in all the study groups.

Table 4

Indices of Spielberger anxiety scale (modified by A.D. Andreeva) against the background of drug treatment (M ± σ)

Groups	anxiety	cognitive activity	negative emotional experiences	anxiety	cognitive activity	negative emotional experiences
	Personal			Situational		
Conversion-dissociative syndrome, n=23						
Before treatment	24.09 ± 0.24	23.72 ± 0.27	22.36 ± 0.45	26.54 ± 0.23	22.18 ± 0.20	22.36 ± 0.40
18 days after treatment	23.92 ± 0.27	26.14 ± 0.22	23.85 ± 0.42	24.96 ± 0.25	24.71 ± 0.16	24.21 ± 0.43
60 days after treatment	23.80 ± 0.31	24.80 ± 0.26	24.10 ± 0.55 *	24.40 ± 0.32	24.40 ± 0.19 *	24.70 ± 0.53 *
Depressive syndrome, n=24						
Before treatment	24.07 ± 0.25	24.21 ± 0.20	22.42 ± 0.22	23.07 ± 0.21	25.57 ± 0.22	19.92 ± 0.20
18 days after treatment	22.58 ± 0.27	24.50 ± 0.21	23.08 ± 0.23	23.08 ± 0.17	25.25 ± 0.19	19.75 ± 0.30
60 days after treatment	22.06 ± 0.26 *	25.46 ± 0.21	23.06 ± 0.25	23.40 ± 0.17	25.26 ± 0.18	20.73 ± 0.33 *
Phobic syndrome, n=10						
Before treatment	23.80 ± 0.23	23.60 ± 0.37	21.40 ± 0.44	25.40 ± 0.10	22.80 ± 0.24	19.40 ± 0.23
18 days after treatment	24.00 ± 0.66	25.00 ± 0.70	22.75 ± 0.88	25.00 ± 0.38	23.75 ± 0.62	20.75 ± 0.89
60 days after treatment	23.80 ± 0.51	26.00 ± 0.57 *	23.80 ± 0.68 *	24.20 ± 0.29 *	25.00 ± 0.48 *	22.60 ± 0.75 *

Note. "*" a reliable difference ($p < 0.05$) when compared to pre- and post-treatment data.

The main feature and advantage of this test is that it permits to identify the level of anxiety in different school situations, to determine what spheres of intraschool relationships anxiety is localized in and what specific forms it takes.

The performed analysis of school anxiety before treatment revealed an increased level of general anxiety in 29.63% of adolescents in group 1 and 30.00% - in group 2.

In general, our results are consistent with those reported by medical researchers from around the world [1, 2, 3, 4, 5, 8, 10]. Thus, the feasibility is emphasized [1] of using anticonvulsants in the PSD treatment, the complexity of drug selection in the disease manifestations diversity [2], the PSD formation in adolescence with differentiation of certain somatic manifestations prevalence [9], a sharp increase in stress effects on school-age children with simultaneous reduction of their adaptive capacity, with formation of anxiety and depressive disorders [3, 12].

Features of the depressive syndrome clinical picture in children include: atypical symptomatology, polymorphic structure of the syndrome, asthenic coloration of depressive disorders, neurotic level of their manifestations, rudimentary affective component, that require the use of specific pharmacotherapy. At the initial stages of the anxiety syndrome development, with autonomic disorders, the main pathogenetically justified method of treatment is prescription of anxiolytics (Lytvyn LB, 2016).

Conclusion

Evidence-based use of medicines and psychotherapy for treatment of psychiatric disorders with somatic symptoms, taking into account pathogenic factors and their pathomorphosis, involves the preferential use of pregabalin as a universal stabilizer of neuromediator balance in therapy of anxiety and other disorders, which is sufficiently effective. The results of numerous randomized placebo-controlled trials allow us to draw the following conclusions:

-anxiolytic effect of pregabalin is not inferior to the action of benzodiazepines;

- it has an impact on both the mental and somatic PSD components;

-it has ability to influence concomitant comorbid symptoms (dysomnia, cephalgia);

- the drug provides rapid therapeutic effect (1 week of therapy);

- pregabalin has high profile of safety (even in old age);

- it does not cause addiction and dependence;

- the drug has a high degree of compliance;

- there are no side effects of GABA hyperactivation (CNS suppression, addiction) or serotonergic effects (dyspepsia, sexual disorders), cholinolytic effects, excitomotor crises at the beginning of treatment with selective serotonin reuptake inhibitors (SSRIs).

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Реферати

ПАТОГЕНЕТИЧНЕ ОБГРУНТУВАННЯ ДИФЕРЕНЦІЙОВАНОЇ ТЕРАПІЇ ПСИХІЧНИХ РОЗЛАДІВ ІЗ СОМАТИЧНИМИ СИМПТОМАМИ (РСС ЗА DSM-V).

Римша С.В., Лук'янович І.Л., Римша О.В.

Проблема поширеності та хронічності психогенних захворювань стає однією з найважливіших у сучасній медицині з огляду на економічні втрати, пов’язані з компенсацією лікування цієї патології та її наслідками. Метою дослідження було сформулювати підходи до диференціальної діагностики та демонстративного використання медикаментів та психотерапії для лікування психічних розладів із

ПАТОГЕНЕТИЧЕСКОЕ ОБОСНОВАНИЕ ДИФФЕРЕНЦИРОВАННОЙ ТЕРАПИИ ПСИХИЧЕСКИХ РАССТРОЙСТВ С СОМАТИЧЕСКИМИ СИМПТОМАМИ

Рымша С.В., Лукьянович И.Л., Рымша Е.В.

Проблема распространенности и хроничности психогенных заболеваний становится одной из важнейших в современной медицине ввиду экономических потерь, связанных с компенсацией за лечение этой патологии, и ее последствий. Целью исследования было сформулировать подходы к дифференциальной диагностике и демонстративному использованию лекарственных средств и психотерапии для лечения психических расстройств с

соматичною симптоматикою з урахуванням патогенних факторів та їх патоморфозу. Зроблено висновок, що доказове використання при лікуванні психічних розладів із соматичними симптомами з урахуванням патогенних факторів та їх патоморфозу передбачає переважне застосування прегабаліну як універсального стабілізатора балансу нейромедіатора в терапії як тривожних, так і інших психогенних розладів.

Ключевые слова: психогенные расстройства, тревожные расстройства, нейромедиаторы, прегабалин, соматический компонент, дифференциальная терапия

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соматическими симптомами с учетом патогенных факторов и их патоморфозов. Был сделан вывод о том, что доказательное использование в лечении психических расстройств с соматическими симптомами с учетом патогенных факторов и их патоморфозов предполагает преимущественное использование прегабалина в качестве универсального стабилизатора нейромедиаторного баланса в терапии как тревожных, так и других психогенных расстройств.

Ключевые слова: психогенные расстройства, тревожные расстройства, нейромедиаторы, прегабалин, соматический компонент, дифференциальная терапия.

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DYNAMIC CHANGES IN THE CELLULAR COMPOSITION IN THE UROPSAMMUS OF ARTIFACTUAL BLADDER

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The purpose of the work was to evaluate the dynamic changes in the cellular composition of the artifactal bladder uropsammus. The dynamics of structural changes in the urine sediment after surgery was revealed, which indicates that, in the presence of positive clinical results after the operation, the processes of restructuring the epithelial lining of the intestinal fragment transplanted instead of the bladder, aimed at performing other functions, are being completed. Based on the data obtained, it is possible to use a cytological study in the clinic to establish the dynamics of the process after surgical treatment, to determine the degree of epithelium exfoliation in the transplanted intestine, as well as to correct individual links of the adaptation process under the new conditions of the transplanted intestinal fragment functioning, which are fundamentally different.

Key words: artifactual bladder, cell composition, adaptation.

The work is a fragment of the research project "Phenomenology, pathogenesis, features of clinical course, topical diagnosing and treatment of dysfunctional pelvic pain syndromes and neurogenic disorders of urination", state registration No. O115U006656.

The gold standard of treating the muscular invasive cancer of the bladder is the radical cystectomy with the orthotopic bladder formation [4, 6]. Many studies have been carried out on the safety and efficacy of using a fragment of the colon and small intestine, stomach, but the best transplant is considered to be a site of the terminal ileum: due to the smallest electrolyte disturbances and the ability of adaptive restructuring it is considered the optimal transplant [3].

Initially, the ileum mucosa contains many cells: Paneth cells, goblet, absorbent, enteroendocrine, stem, undifferentiated, and M-cells with known diverse functions [5]. The enterocyte microvilli are covered with a glycocalyx membrane, which contains various protective proteases, lysozyme, etc. [10]. The physical barrier is formed by the mucosal epithelial absorbent goblet cells and mucus secreted by the latter [1].

Functioning of the ileum site under new conditions, the influence of urinary components on the artifactual bladder's mucous membrane, the possibility of adaptation and transformation of the neocyst epitheliocytes, early detection of atypical cells have determined our interest to the study of the urine sediment cytological features in dynamics. The data of the researchers are quite diverse: some scientists report the hypersecretion of sulfomycin, sialomycin, progressive microvilli atrophy, adenomatous hyperplasia and dysplasia of mucous cells in the artifactual bladder [13, 14]. Cytological control of atypical cells is defined by many authors as a non-invasive way of early detecting the recurrence of urothelial carcinoma [7].

In the routine practice, study of urine sediment is an integral and important part of the general urine analysis. The main elements of organized urinary sediment are erythrocytes, leukocytes, epithelium, and cylinders; unorganized sediment includes crystalline and amorphous salts. Normally in the field of view of the microscope, single cells of the squamous (urethra) and transitional epithelium (bowl, ureter, bladder) are detected. The renal epithelium is normally absent.

The purpose of the work was to assess dynamic changes in the cellular composition of the artifactual bladder's urine sediment (uropsammus).

Materials and methods. The study of the urinary sediment cellular composition was performed in 26 patients after radical cystectomy with orthotopic ileocystoplasty for muscular invasive bladder cancer

within the periods of 1; 3; 6; 12 months and 2 years. The urine sampled from the artifactual bladder was centrifuged, the sediment was fixed on a slide.

Specimens, obtained as a result of the urine precipitation after fixation with 10% neutral formalin and dehydration in alcohols, were stained with hematoxylin and eosin. Light optical microscopy and photographing were performed using JNAMED2 microscope.

Results of the study and their discussion. One month after the surgery, the microscope's field of view is almost completely covered with large layers of quite differentiated epithelial tissue with inclusion of swollen goblet cells. Layers of epithelial tissue have a concentric structure of cell aggregates, resembling microvilli of the intestinal mucosa. The epithelial cells' cytoplasm is slightly eosinophilic, the cells are located close to each other, which indicates that intercellular contacts are preserved. Attention is drawn to the presence of slight cellular polymorphism, changes in the ratio of the cytoplasm and the nucleus sizes. This is manifested by the presence of different sizes cells with unevenly colored cytoplasm, oval or grumose hyperchromic nuclei. In some groups of epithelial cells there is an increase in the cytoplasm area with the cell boundaries vanishing.

In this case, it becomes less eosinophilic, reflecting the phenomenon of vacuolar degeneration, which is manifested by the emergence of numerous different sizes vacuoles, which sometimes completely fill the cytoplasm (fig. 1). Between the layers of cells throughout the slides, small granularity intensely stained with hematoxylin can be detected, immersed in a slightly eosinophilic or basophilic structureless material. Sometimes fine-granulated slightly basophilic material is found, which is apparently coagulated protein. Due to the peculiarities of obtaining the material and its processing, it is difficult to conclude on the type of epithelial cells, but they apparently belong to the intestinal epithelium, it is almost impossible to detect atypical cells due to the large amount of mucus. A feature of the studied cytograms is the absence of any inflammatory reaction signs. Lymphocytes, segmental leukocytes and macrophages were not detected throughout the slides.

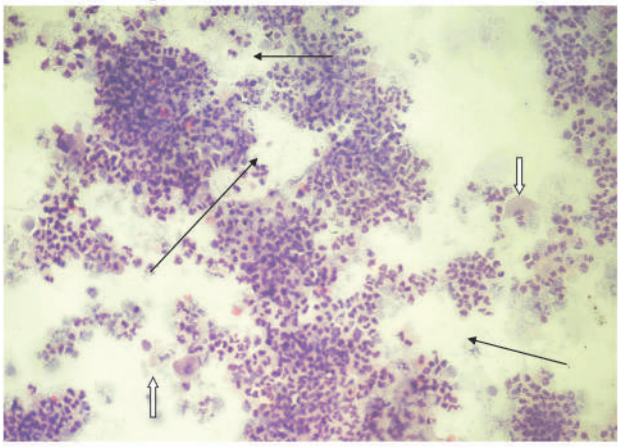

Fig. 1. Urine sediment cytogram features of patient K. one month after the surgery. Areas of epithelial cells with concentric cell aggregates between which there are large cells with light cytoplasm and small nucleus in the state of vacuolar degeneration (goblet cells) (arrows). Squamous epithelial cells (fancy arrows) (hematoxylin-eosin; x 120)

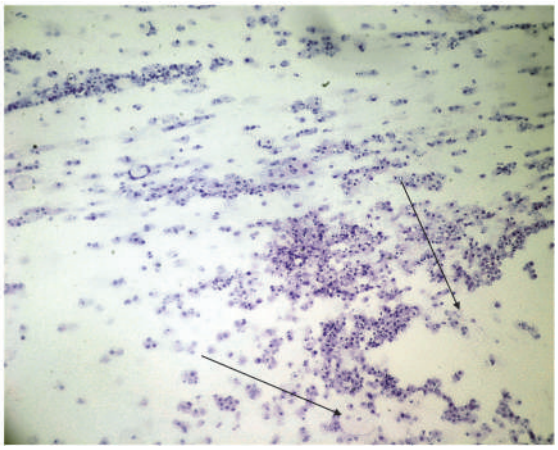

Fig. 2. Features of a urine sediment cytogram of patient L. 3 months after the surgery. Single epithelial cell complexes of different shapes and single cells diffusely distributed. Part of cells have oval and oblong shape. Groups of large cells, probably goblet (arrows) (hematoxylin-eosin; x 120)

One month after the surgery, single or small goblet cells complexes, different from epithelial cells by their much larger size, wide rim of slightly eosinophilic cytoplasm and light oval nucleus, can be detected in the slides. Noteworthy is the presence of the peculiar for these cells distinct border between goblet cells in the form of a distinct thin black stripe. Between the layers of epithelial cells against the background of homogeneous structurally weakly basophilic mass, isolated oval cells lying separately, which were apparently separated from the layers, are observed. The nuclei of such cells are small in size, deformed. The cytoplasm is basophilic.

Three months after the surgery, the urine sediment cytogram looks different. Instead of the large size epithelial cells layers occupying almost the entire field of view, even with a small magnification of the microscope, the cytogram looks reticular. Microscopically, it looks like an aggregate of small bundles or groups of differently sized epithelial cells with irregular shape. In this case, the groups and bundles of epitheliocytes interact. Cell-free space is left between the cells, filled either by unstructured mass, or by fine-granulated material, or by separate cells isolated from epithelial complexes, subjected to degeneration or necrosis (fig. 2). Part of the cells has a round, oval or spindle shape.

In the epithelial layers, some of the epitheliocytes have swollen cytoplasm (or in a state of vacuolar degeneration). In vacuolar degeneration, in the cell cytoplasm numerous, approximately the same size,

vacuoles are determined. It should be noted that the cytoplasm of epitheliocytes in some layers remains eosinophilic, in others - basophilic. The cells have intensely blue-colored cytoplasm of large size and irregular shape. In their cytoplasm large vacuoles are detected. Basophilia of the cytoplasm is most likely associated with mucoid aggregation.

Noteworthy is the presence of a cell aggregate similar to the tubular structures to which the bundles of loose connective tissue are attached. Apparently, these structures are preserved fragments of the intestinal villi.

A feature of urine sediment cytograms 3 months after the surgery is the presence of cell groups or single cells surrounded by a weakly basophilic material (mucin). Some observations show “shadows” of large cells. The latter are much larger than epitheliocytes, located in the form of single cells or small groups. Their cytoplasm is light and subjected to vacuolar degeneration. The nuclei are small, grumose. A distinct border of the cell in the form of a dark strip is observed. Apparently, such cells belong to the goblet ones. With a larger magnification of the microscope, it turns out that such “shadows” of cells are nothing else but goblet cells, which were subjected not only to vacuolar degeneration, but also to necrosis. This process is manifested by induration and basophilia of the deformed cell, karyolysis, and cytoplasm swelling.

This time period after the surgery is characterized by the fact that in some areas of the slide it is possible to detect signs of an acute inflammatory process. This is manifested in the cytogram by aggregates of lymphocytes, segmental leukocytes and eosinophilic leukocytes diffusely distributed among epitheliocytes in a small number. It is noted that near the leukocyte aggregations the most pronounced degeneration of epithelial cells is observed. Atypical urothelial carcinoma cells were detected in 1 patient, accounting for 3.8% ($p \leq 0.01$), which was due to upper urinary tract cancer not diagnosed before the radical cystectomy.

Six months after the surgery, significant microscopic differences in the urine sediment cytograms are determined. First of all, it should be noted that the number of structural elements in the prints is small and difficult to determine, even scanning the entire area of the slide. In cases where the material is found, it is an aggregate of epithelial cells with a pronounced degree of degenerative changes, destruction and disintegration of the epithelial layer. In this case, small groups or single cells are found in a state of marked degeneration or necrosis. The preserved cells are rounded, spindle-like or oval in shape. In this case, the cytoplasm area is significantly increased in them, and they are flattened, pale. The nuclei of such cells are deformed and undergo pycnotic changes (fig. 3). Microscopically, phenomena of pycnosis are manifested by the reduced size of the nucleus, its hyperchromia, and its disintegration into different numbers of irregularly shaped basophilic fragments.

Some epitheliocytes resemble squamous epithelial cells. As with less durable observation after the surgery, in some places of the slide it is possible to find fragments in the form of a “tubular” structure, which is nothing else but a fragment of the villi.

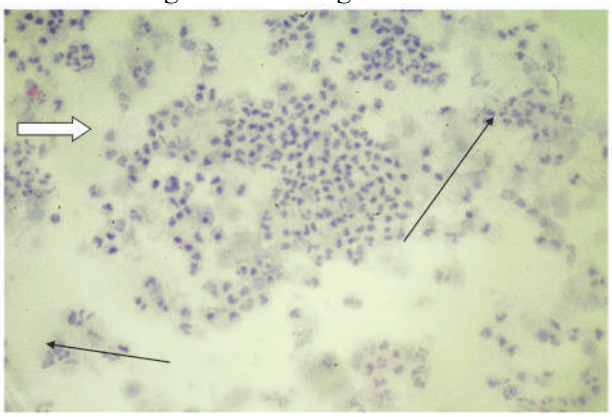

Fig. 3. Urine sediment cytogram features of patient L. 6 months after the surgery. Inflammatory response is preserved in the form of a small number of segmental leukocytes. Small fragments of epithelial flattened cells with preserved intercellular contacts (arrows) are identified. Between the epitheliocyte complexes there are structures resembling villi (arrow) (hematoxylin-eosin; x 120)

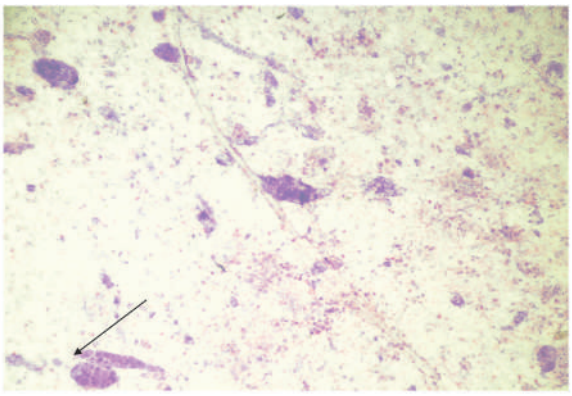

Fig. 4. Features of a urine sediment cytogram of patient L. one year after the surgery. In the heterogeneous fine-granulated slightly eosinophilic material, several necrotic-altered epithelial cell complexes with different shapes and basophilia degrees are detected. A preserved epithelial cell complex (arrow) is also determined (hematoxylin-eosin; x 120)

In some observations, fields of completely necrotic small cell aggregates or isolated cells are identified in the slides. They are intensely basophilic and have a fine-granulated structure. Diffusely distributed numerous erythrocytes can also be detected in the slide.

It should be noted that after 6 months in some places of the slide there are signs of inflammatory reaction, as evidenced by the detection of epithelial cells diffusely distributed between the layers or in the form of a small group of segmented leukocytes aggregation.

After 6 months, the inflammatory reaction intensity is significantly lower than that observed 3 months after ileocystoplasty. Eosinophilic leukocytes are virtually undetectable. There are no signs of inflammation at all in some places. Atypical urothelial cancer cells were detected in two patients, accounting for 7.69% ($p \leq 0.05$), and it was due to the underlying disease recurrence and progressive growth into the neobladder.

Twelve months after the surgery, urine sediment cytograms are characterized by a small amount of structural elements found in cytological slides. Single unevenly distributed small epithelial cell aggregates are observed in the slides (fig. 4). Some of the cells forming the complexes are characterized by a small rim of slightly eosinophilic cytoplasm, and some of them are in a state of vacuolar degeneration or necrosis. Cells subjected to vacuolar degeneration have a wide rim of slightly eosinophilic cytoplasm, in which different size vacuoles are found. There are no cell borders.

Cells subjected to necrosis are intensely blue-colored structures seen as tubules of irregular shape and different size. They are surrounded by a fine-granulated heterogeneous mass, sometimes of a reticular structure. The reticular component often has a fibrous structure and consists of various lengths and thicknesses fibers intensely stained with hematoxylin in blue, which form aggregates of oblong shape and small size. It can be assumed that such formations are proteins that have undergone coagulation.

It should be noted that some isolated or small groups of cells resemble squamous epithelial cells, as they have a wide rim of cytoplasm, which have sufficiently intense eosin staining. In some observations, single diffusely distributed eosinophilic leukocytes can be detected in the slides, indicating that there is an allergic reaction. However, it is unknown which of the underlying urinary tract parts it takes place in. Atypical cells in the study group were not observed within a year, possibly due to the early control of the cellular elements in the urine sediment.

Cytograms of urine sediment 24 and 12 months after the surgery cytologically practically do not differ in features of their structure. In such cases, it is seldom possible to find single aggregates of epithelial cells located at a considerable distance from each other. Complexes of epithelial cells are immersed in heterogeneous, unstructured material of pink color, in which particles of irregular shape and different size intensely colored with hematoxylin are observed. Some of them have a narrow rim of weakly eosinophilic cytoplasm and resemble lymphocytes. Fragments of slightly fibrous basophilic material of unknown origin are sometimes identified. The fibers are oriented in parallel to each other, between them slit-like structureless space is defined.

The quantitative assessment in the field of view of the main cellular elements in the urine sediment of patients with artifactual bladder showed a certain pattern in the cytological composition and is presented in table 1.

Table 1

Dynamics of the neobladder urine cytological profile

Cell elements	1 month	3 months	6 months	12 months
Epitheliocytes	83.3±12.2%	29.4±6.13%	28.7±5.14%	11.9±1.4%
Goblet cells	7.6±2.12%	24.5±8.11%	18.5±4.21%	5.5±1.7%
Leukocytes	6.53±3.1%	53.7±14.7%	34.9±7.12	78.3±16.4%
Erythrocytes	2.57±2.6%	16.9±3.1%	17.9±18.5%	4.3±1.2%

It should be noted that over time, the number of cellular elements in the urine decreases progressively, with the tendency to the epithelial cells reduction. Epitheliocytes in the first month - 83.3±12.2% - cover the entire field of view, being the dominant cellular component, exfoliating as a result of the urine toxic effect on the ileum wall. Three months later, the percentage ratio changed significantly with a smaller proportion of epithelial cells by 53.9% to 29.4±6.13% ($p \leq 0.01$), with a progressive reduction to 11.9±1.4% in the 12th month of the study. In its turn, the highest level of goblet cells in the urine sediment is observed three months after the ileocystoplasty and is 24.5±8.11%, with a progressive tendency to decrease in dynamics. Leukocytes in their highest proportion are observed in the 3rd and 12th months and are 53.7±14.7% and 78.3±16.4%, respectively, characterizing the inflammation processes at these stages of the study. Erythrocytes in the highest percentage were observed in the 3rd and 6th months and made 16.9±3.1% and 17.9±18.5% respectively.

As a result, the study revealed a certain pattern of changes in the cellular composition of urine sediment after the surgery, depending on the time duration after the surgery. First of all, it should be noted that the structural features of cytograms to some extent reflect the dynamics of the processes that occur in the postoperative period.

Shortly after the surgery (1 month) in almost all slides and throughout the specimen under study large layers of epithelial cells belonging to the intestinal mucosa can be detected, as evidenced by the

histoarchitectonics of epithelial cell complexes (concentric location of cells in the small amount of stromal elements). Quantitative assessment of cytological data also revealed prevalence of epitheliocytes - 83.3±12.2%, which is consistent with the opinion of the researchers regarding the atrophy of the epithelial layer and the desquamation of the epithelium [2]. Meanwhile, the revealed structural changes reflect the process of the mucosal surface layers desquamation, mucin accumulation in the form of large basophilic homogeneous formations, degeneration of goblet cells, which preserve the cytoplasmic membrane, but lose intracytoplasmic inclusions. It is important to emphasize that in this period of time there are no microscopic signs of inflammatory reaction, which is manifested in the absence of lymphocytes, segmental neutrophils and eosinophilic leukocytes, plasma cells and macrophages in the slides. Quite pronounced inflammatory reaction is detected only 3 months after the surgery, its intensity is decreasing up to 6 months. Moreover, there is an acute reaction manifested by the presence of a large number of segmented neutrophil leukocytes and eosinophilic leukocytes. The presence of eosinophilic leukocytes indicates the presence of an allergic reaction that develops in this time period after the surgery. At the same time, the phenomena of vacuolar degeneration of epithelial cells, reduction in the number of cellular complexes, goblet cells and mucins, which is consistent with other researchers' studies [12]. In some observations, sediment shows deposits of calcium salts (calcificates) at the sites of degeneration and epithelial cells necrosis, reflecting, to some extent, the severety of degenerative changes in epithelial cells of the intestinal mucosa.

A few years after the surgery, the cytograms show: exceptionally small numbers of cells of unknown origin, coagulated proteins and crystals (possibly uric acid), and complete absence of an inflammatory reaction signs. Similar data were obtained by Pirola G.M. in their study of the ileum morphological changes [9].

The possibility of dynamic control of atypical urine cells permits the early detection of the underlying disease recurrence or the detection of urothelial carcinoma of another localization [8, 11]. Dynamic changes in the cytological composition of urine sediment reflect the processes of adaptation and rearrangement of the ileum mucous membrane to new conditions of existence and are manifestations of its contact with a new aggressive environment - urine.

Conclusions

1. The revealed dynamics of structural changes in urine sediment after the surgery indicates that, in the presence of positive clinical results of the surgery, the processes of restructuring the epithelial lining in the intestinal fragment transplanted instead of the bladder, aimed at performing other functions, are completed.

2. The presence of single epithelial cells in the cytograms does not indicate the presence of the intestinal mucosa squamous metaplasia phenomena, predicted by some authors, as such cells may emerge as a result of the mucous membranes exfoliation in the urinal tract.

3. Based on the data obtained, we can assume the possibility of using the cytological study in the clinic to determine the dynamics of the process after surgical treatment, to determine the degree of the transplanted epithelium exfoliation, as well as to correct individual links in the process of the transplanted intestinal fragment's adaptation to the fundamentally new conditions of functioning.

4. Atypical cells in the urinary sediment were detected in 11.54% of patients, indicating this method of control as simple, non-invasive and specific for early diagnosis of local recurrence or primary upper urinary tract cancer.

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Реферати

ДИНАМІЧНІ ЗМІНИ КЛІТИННОГО СКЛАДУ ОСАДУ СЕЧІ АРТИФІЦІЙНОГО СЕЧОВОГО МІХУРА

Савчук Р.В., Костєв Ф.І., Віт В.В.

Метою роботи було оцінити динамічні зміни клітинного складу осаду артифіційного сечового міхура. Виявлена динаміка структурних змін осаду сечі після оперативного втручання свідчить про те, що, при наявності позитивних клінічних результатів операції, завершуються процеси перебудови епітеліального вистилання пересадженого замість сечового міхура фрагмента кишечника, спрямовані на виконання інших функцій. На підставі отриманих даних можна припустити можливість використання в клініці цитологічного дослідження для встановлення динаміки процесу після оперативного лікування, виявлення ступеня ексфоліації епітелію пересадженого кишечника, а також корекції окремих ланок процесу адаптації в нових умовах функціонування пересадженого фрагмента кишечника, які принципово відрізняються.

Ключові слова: артифіційний сечовий міхур, клітинний склад, адаптація.

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ДИНАМИЧЕСКИЕ ИЗМЕНЕНИЯ КЛЕТОЧНОГО СОСТАВА ОСАДКА МОЧИ АРТИФИЦИАЛЬНОГО МОЧЕВОГО ПУЗЫРЯ

Савчук Р.В., Костев Ф. И., Вит В.В.

Целью работы было оценить динамические изменения клеточного состава осадка артифициального мочевого пузыря. Выявленная динамика структурных изменения осадка мочи после оперативного вмешательства свидетельствует о том, что, при наличии положительных клинических результатов операции, завершаются процессы перестройки эпителиальной выстилки пересаженного вместо мочевого пузыря фрагмента кишечника, направленные на выполнение других функций. На основании полученных данных можно предположить возможность использования в клинике цитологического исследования для установления динамики процесса после оперативного лечения, выявления степени эксфолиации эпителия пересаженного кишечника, а также коррекции отдельных звеньев процесса адаптации в новых условиях функционирования пересаженного фрагмента кишечника, которые принципиально отличаются.

Ключевые слова: артифициальный мочевой пузырь, клеточный состав, адаптация.

Рецензент Старченко І.І.

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RISK OF ADENOCARCINOMA IN BARRETT'S ESOPHAGUS

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The total of 7396 videoesophagogastroscopy cases were analyzed. The presence of metaplastic columnar epithelium of esophagus was found in 2910 patients (39.4%) at pathohistological examination. The gastric metaplasia was evaluated in 876 cases (11.9%), the specialized intestinal metaplasia without dysplasia - in 1970 (26.6%), the low-grade dysplasia - in 48 (0.65%), the high-grade dysplasia - in 16 (0.22%). Esophageal adenocarcinoma was evaluated in four patients (0.05%, CI 0.01 - 0.12%). Low probability of esophageal adenocarcinoma formation in all types of metaplasia was demonstrated. Only the presence of dysplasia of metaplastic epithelium should cause increased alertness for the occurrence of esophageal adenocarcinoma. Exaggerated value of Barrett's esophagus may result in additional traumatization of mucosa, increase the risk of bleeding and stenosis.

Key words: Barrett's esophagus, metaplasia, dysplasia, esophageal adenocarcinoma.

The work is a fragment of the research project "Differential – diagnostic criteria for tumors and pre – tumor changes and their value in a prognosis", state registration No. 0120U1006.

Barrett's esophagus (BE) is the condition in which metaplastic columnar epithelium replaces the stratified squamous epithelium that normally lines the distal esophagus. BE predisposes to cancer development. In addition to Barrett's mucosa, a source of esophageal adenocarcinoma (EAC) may be cardiac or submucosal glands. Estimates of the prevalence of BE in the general population have varied widely from 0.4 to more than 20 percent, although the large majority of cases go unrecognized [12, 13].

EAC is a type of cancer that has been increasing in incidence in many Western societies over recent decades [14]. There is some evidence to suggest that EAC arise from BE, however the details of pathogenesis of it remain unknown. In surveillance programs of BE only a minority of patients develop EAC raising the question of what factors are implicated in the development of EAC from BE [2, 15].

In the National Cancer Registry № 20 "Cancer in Ukraine 2017-2018" incidences of esophageal adenocarcinoma are not separated from other forms of malignant neoplasms of the esophagus and its level is unknown.

It is estimated that the risk of cancer progression for patients with nondysplastic BE is ~ 0.2-0.5% per year, for patients with low-grade dysplasia the annual risk of BE progression to cancer is ~ 0.7% per year, for patients with high-grade dysplasia the annual risk of neoplastic progression is ~ 7% per yeaer [8, 10].

In spite of this at Clinical Guideline of American College of Gastroenterology (ACG) is reported that the majority (>90%) of patients diagnosed with BE die of causes other than EAC [14].

The purpose of the study was to estimate the number of patients who developed EAC among patients with the different types of BE in unselected cohort of subjects.

Materials and methods. We analyzed 7396 cases of videoesophagogastroscopies for the period from January 2010 to December 2018 in the Medical Centre “Oberih” clinic, Kyiv, Ukraine. Among them 2910 patients had histologically proven BE and were 10 to 79 years old. Patients' endoscopic findings (endoscopically suspected esophageal metaplasia), and pathological findings (the type of metaplasia, degree of dysplasia) were collected for further analysis.

Esophagogastroscopies were made by gastroscopes Olympus Q160-Z, Olympus EVIS EXERA II, with using NBI and 115 magnification according to the sampling protocol. Target biopsies were performed from all areas of suspected metaplasia, as well as from 4 quadrants of esophageal wall and every 2 cm along the metaplastic segment.

Diagnosis of BE was set endoscopically by visualization of a columnar lined epithelium at least 1 cm above the gastroesophageal junction. BE was divided into short- and long-segment BE. Short-segment BE had a maximal length less than 3 cm, whereas long-segment had a length more than 3 cm. In previous studies it was shown that long-segment BE had a higher risk for development of EAC. The length of the BE segment is known to be associated with risk of progression to neoplasia.

Statistical analysis was performed with using MedStat programme. To estimate the prevalence of changes in the esophagus a 95% confidence interval was calculated with using the Fisher angular transformation method. The data was analyzed with using the Student’s *t*-test for continuous variables, and Chi-square test for categorical variables. The difference between the mean values was considered significant at $p < 0.05$.

Results of the study and their discussion. In order to detect the BE we used endoscopic studies with biopsy and morphological verification. We analyzed 7396 cases of videoesophagogastroscopies in the period from 2010 to 2018. The study was conducted at the Medical Centre “Oberih” clinic in Kyiv, Ukraine.

There was an equal number of male and female patients included in the study (3684 men and 3708 women).

The age of the patients was from 10 to 79. In the statistical evaluation of the results revealed low peaks of gastric metaplasia at the age of 20 - 29 and high frequency of intestinal metaplasia at the age of 60 - 69. For gastric metaplasia, the rate was 2 times lower in this age category. For intestinal metaplasia - 1.25 times higher in the category of 60 - 69 years old.

The presence of columnar lined metaplasia with forming the columnar-lined esophagus was demonstrated in 2910 patients (39.4% of 7396, CI 38.3 - 40.5%). Long-segment BE was present in 54 patients (1.8%, CI 1.4 - 2.3%) in other 2856 cases the short-segment BE was present (98.2%, CI 97.7 - 98.6%).

Among all the cases (7396) the gastric metaplasia was evaluated in 876 cases (11.9%, CI 11.1 - 12.6%), in 1970 cases the specialized intestinal metaplasia without dysplasia was found (26.6%, CI 25.6 - 27.6%). From all the cases (7396) in 48 cases the low-grade dysplasia of the specialized intestinal metaplasia (Fig. 1) was detected (0.65%, CI 0.48 - 0.85%), in 16 cases the high-grade dysplasia of the specialized intestinal metaplasia (0.22%, CI 0.12 - 0.34%) was found. Esophageal adenocarcinoma was evaluated in four patients (0.05%, CI 0.01 - 0.12%) (fig. 1).

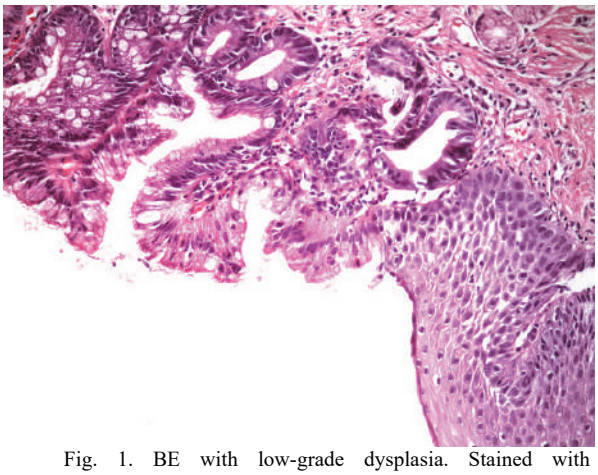

Fig. 1. BE with low-grade dysplasia. Stained with hematoxylin and eosin. ×100 magnification.

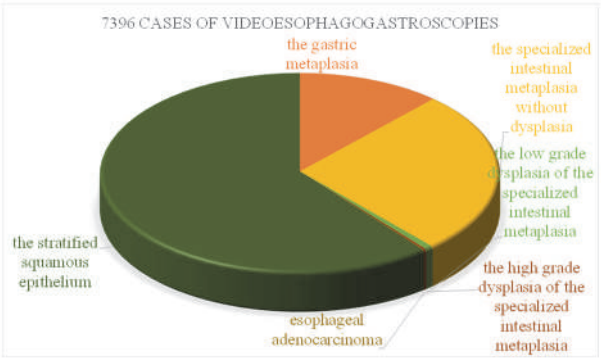

Fig. 2. The results of videoesophagogastroscopies of esophageal mucosa.

It the study the frequency of EAC detection was 0.05%. All those four cases of EAC were primarily diagnosed (fig. 3). There was no data of the previous changes in esophageal epithelium for the further analysis. It can be expected that there might be a couple of possible sources for EAC. Among them there are cells from the area of epithelium metaplasia, esophageal cardiac glands and their ducts, esophageal stem cells.

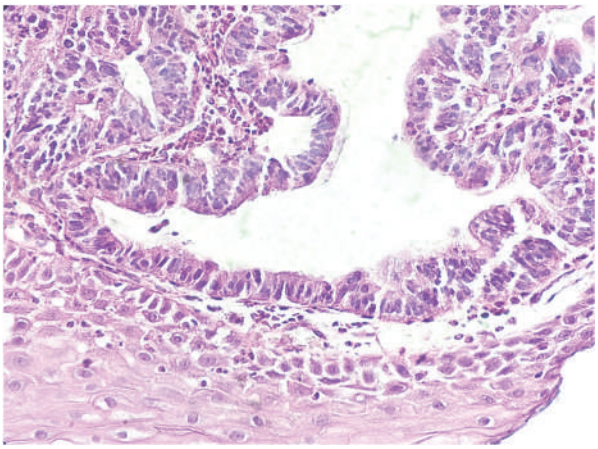

Fig. 3. EAC in the setting of BE. Stained with hematoxylin-eosin. ×200 magnification.

The probability of cancer progression for patients with nondysplastic BE with gastric type of metaplasia is 0.5% per year, for patients with nondysplastic BE with intestinal type of metaplasia is 0.2% per year. For patients with low-grade dysplasia the probability of progression of BE to cancer is 8.33% per year, for patients with high-grade dysplasia the probability of neoplastic progression is 25% per year and for patients without metaplasia – 0.09% per year. Noteworthy is the high probability of transformation of metaplasic epithelium with dysplasia into adenocarcinoma.

BE is the condition in which a metaplastic columnar epithelium replaces the stratified squamous epithelium that normally lines the distal esophagus.The metaplastic epithelium is acquired as a consequence of chronic gastroesophageal refluxe disease, and is a predisposing factor for the development of EAC.

Frequency of detection of Barrett's esophagus depends on the frequency of biopsy taking and the level of informative videoesophagogastroscopy. Incidence rates of esophageal adenocarcinoma among patients with the different types of BE are variable.

Recent studies have indicated a lower incidence rate of EAC in individuals with BE than earlier studies.

Holmberg D. et al. found that among 7932 participants with BE and 18,415 person-years of follow-up, the overall incidence of EAC was 1.47 (95% CI 0.91–2.02) per 1000 person-years [5].

Liu S. et al. presented large-scale longitudinal clinical and histological data on 5401 esophageal cancers patients diagnosed during the 10-year period. All 217 EAC patients from these 5401 esophageal cancers patients were examined for better understanding of the relationship between BE and EAC. They found that EAC was relatively rare and accounted for approximately 5% of all esophageal cancers each year during 2002–2011. Only 10 out of 217 (4.6%) EAC cases had any evidence of BE [9].

In western countries BE is generally considered to be the premalignant condition for EAC. The risk of malignant progression has been examined in over 8,500 patients with BE with using the Northern Ireland BE Register and followed-up for a mean of 7 years [1]. Patients with specialized intestinal metaplasia had the combined incidence 0.38% per year.

In a nationwide population-based cohort study that included all patients with BE collected in Denmark in the period from 1992 to 2009 the relative risk of EAC among patients with BE, compared with the risk in the general population, was 11.3 and the annual risk of esophageal EAC was 0.125 [6]. Some large population-based studies indicated that BE remained a strong risk factor for EAC, but the absolute

annual risk was remarkably lower than the previously assumed risk of 0.5%, and suggested that current surveillance guidelines should be revised [7].

Our data provide the evidence of the rare occurrence of EAC.

Mortality in the overwhelming majority of BE patients is not related to EAC but is rather due to non-esophageal malignancies and cardiovascular disorders [3, 11].

Conclusion

According to the data we have received, the range of EAC was 0.5%. Low probability of esophageal adenocarcinoma formation in all types of metaplasia was demonstrated. Therefore, only the presence of dysplasia of metaplastic epithelium should cause increased alertness for the occurrence of esophageal adenocarcinoma.

Consequently, the Barrett's esophagus without dysplasia should not be qualified as a pre-malignant condition. The wrong evaluation of this condition leads to misguided patients' management with additional biopsies, mini-endoscopic surgeries. Those procedures may result in additional traumatization of mucosa, increase the risk of bleeding and stenosis, lead to financial expenses and have psycho-emotional load for patients.

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Реферати

РИЗИК ВИНИКНЕННЯ АДЕНОКАРЦИНОМИ ПРИ СТРАВОХОДІ БАРРЕТТА

Серга Т.В., Курик О.Г., Яковенко В.О., Ткаченко Р.П.

Проаналізовано дані 7396 відеоезофагогастроскопій. При патогістологічному дослідженні підтверджено наявність метаплазії епітелію стравоходу у 2910 обстежених (39,4%). Шлункова метаплазія була виявлена у 876 пацієнтів (11,9%), у 1970 випадках виявлена спеціалізована кишкова метаплазія епітелію стравоходу без дисплазії (26,6%), у 48 випадках виявлена дисплазія низького ступеня (0,65%), у 16

РИСК ВОЗНИКНОВЕНИЯ АДЕНОКАРЦИНОМЫ ПРИ ПИЩЕВОДЕ БАРРЕТТА

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Проанализированы данные 7396 видеоэзофагогастроскопий. При патогистологическом исследовании подтверждено наличие метаплазии эпителия пищевода у 2910 обследованных (39,4%). Желудочная метаплазия была выявлена у 876 пациентов (11,9%), в 1970 случаях определена специализированная кишечная метаплазия эпителия пищевода без дисплазии (26,6%), в 48 случаях определена дисплазия низкой степени (0,65%), в 16

випадках – дисплазія високого ступеня (0,22%). Аденокарциному стравоходу встановлено у 4 пацієнтів (0,05%, ДІ 0,01-0,12%). Продемонстровано низьку ймовірність виникнення аденокарциноми при всіх типах метаплазії епітелію стравоходу. Лише наявність дисплазії метаплазованого епітелію повинна викликати підвищену настороженість щодо виникнення аденокарциноми. Стравохід Барретта без дисплазії не повинен розцінюватися як передраковий стан. Перебільшення його значення призводить до додаткової травматизації слизової, підвищення ризику кровотеч та стенозів.

Ключові слова: стравохід Барретта, метаплазія, дисплазія, аденокарцинома стравоходу.

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случаях - дисплазия высокой степени (0,22%). Аденокарциному пищевода диагностировано у 4 пациентов (0,05%, ДИ 0,01-0,12%). Была продемонстрирована низкая вероятность возникновения аденокарциномы при всех типах метаплазии. Только наличие дисплазии метаплазированного эпителия должно вызывать повышенную настороженность в отношении возникновения аденокарциномы. Пищевод Барретта без дисплазии не должен оцениваться как предраковое состояние. Преувеличение его значения приводит к дополнительной травматизации слизистой, повышению риска кровотечений и стенозов.

Ключевые слова: пищевод Барретта, метаплазия, дисплазия, аденокарцинома пищевода.

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EFFECT OF NATURAL MINERAL BISCHOFITE CONTAINING PREPARATION ON THE ORAL MICROFLORA

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The oral cavity can be considered as an ecological system complex in which external factors (biological, individual, social) interact with internal ones (periodontium, bacterial community, local immune system, oral epithelium). If the favorable conditions arise, one or another disease of the oral mucosa may be developed and must be adequately treated. The arsenal of drugs is large and requires the doctor's knowledge, skills in using of the most optimal means and providing the appropriate recommendations to the patient. We studied the efficacy of the oral care product Antiqua Mare MAX, containing natural mineral Poltava's Bischofite, on the representatives of the oral microflora. To achieve this goal, museum strains of E. coli ATCC 25922, S. aureus ATCC 25923, S. epidermidis ATCC 14990, E. faecalis ATCC 29212, M. lysodeicticus ATCC 4698 and C. albicans ATCC1023 were used. As a control, a well-known antimicrobial agent 0.02% aqueous solution of chlorhexidine bigluconate was used. The ability of the Antiqua Mare MAX drug to inhibit the growth of museum cultures of the yeast-like fungi, colon bacilli, enterococci, micrococci, epidermal and golden staphylococci in the liquid medium was shown to coincide completely in three repeated determinations during the study of the effect of Bischofite containing oral care product. The fungiostatic activity of the studied preparation Antiqua Mare MAX exceeded the effect of 0.02% solution of chlorhexidine bigluconate by 4 times ($p<0,001$), but the fungicidal effect did not differ.

Keywords: OCMM microflora, chlorhexidine bigluconate, Antiqua Mare MAX.

The work is a fragment of the research project "Dental health restoration in patients with underlying diseases and their rehabilitation", state registration No. 0116U004191.

Oral mucosa diseases are common lesions of the human body among dental diseases. They reflect changes in organs and tissues of the body. Notwithstanding the diversity of causes, mechanisms of development and clinical course of the disease, the majority of these diseases are characterized by some common features that can be combined into separate related groups.

The oral microflora is represented by numerous types of aerobic and anaerobic bacteria, among which anaerobes dominate (in dental plaque the anaerobic/aerobic ratio is 1000/1) [7]. The permanent oral microflora is composed of representatives of several groups of microorganisms: bacteria, fungi, spirochetes, protozoa, viruses. The role of microorganisms in the development of periodontitis, candidiasis, ulcerative necrotic gingivitis, etc., is undoubtful [5]. The development of oral inflammatory diseases alters composition of the microflora of different biotopes that are part of the oral cavity [10].

The oral cavity can be considered as a complex ecological system in which the external factors (biological, individual, social) interact with internal ones (periodontal, bacterial community, local immune system, oral epithelium) [9]. Similar to the outer environment, all components of the system are in dynamic equilibrium.

In case of favorable conditions, any of the oral diseases, which required treatment, may develop [9]. The drug arsenal is large and requires the dental professional to be expert in their usage and giving recommendations.

Jardin Cosmetics LLC (Ukraine) has developed the oral care product Antiqua Mare MAX that is composed from natural products only: Poltava's Bischofite mineral complex, propolis, decoctions of stevia leaves, liquorice, oak bark (Sanitary-Hygienic Official Letter No. 602-123-20-1/781 as of 21.01.2019).

The spray contains eco-mineral Poltava's Bischofite, which is a bromine chloride-magnesium brine solution with a high content of salts and microelements of magnesium, potassium, calcium, sodium, iodine, copper, iron, etc., which has anti-inflammatory, absorbent and analgesic properties, based on the penetration of micro- and macroelements through the mucous membranes. Propolis has antimicrobial, antioxidant, anti-inflammatory, immunomodulatory and cardioprotective effects. Decoction of stevia leaves is a safe substitute for sugar. Stevia is 10-15 times sweeter than sugar and is low calorie; its intake has no negative effects. It is used as a natural sweetener to reduce blood pressure, increase immunity. Liquorice contains active substances glycyrrhizic acid with its anti-inflammatory, hypo-sensitizing effect; flavonoids, which reduce inflammation, normalize the level of vascular permeability; natural surfactants (saponins) with their anti-inflammatory, disinfectant properties.

The purpose of the work was to study the positive effect of Antiqua Mare MAX oral care product, containing natural mineral Poltava's Bischofite, on the oral bacterial species.

Materials and methods. To gain the objective of the study the museum strains of E. coli ATCC 25922, S. aureus ATCC 25923, S. epidermidis ATCC 14990, E. faecalis ATCC 29212, M. lysodeicticus ATCC 4698 and C. albicans ATCC 10231, obtained from the L.V. Gromashevskiy Institute of Epidemiology and Infectious Diseases of the NAMS of Ukraine (Kyiv) have been used. The above strains were used to prepare daily cultures on an MPA slanting nutrient agar or Sabouraud's slope agar (*"Pharmaktyv*" LLC, Ukraine), which inocula were brought to 0.5 McFarland. The sensitivity of standard strains of microorganisms to the preparations was studied by quantitative method in accordance with the Order of the Ministry of Health of Ukraine No. 167 as of 05.04.2007 "On approval of guidelines: Determination of sensitivity of microorganisms to antibacterial drugs" [4].

The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of Antiqua Mare MAX (*Jardin Cosmetic* LLC, Ukraine) was determined for each test-culture of standard strains of microorganisms [6]. Conventional antimicrobial agent, 0.02% chlorhexidine bigluconate (*Chervona Zirka*, Pharmaceutical Plant, Ukraine) was used as a control. Thereafter, all subsequent dilutions were made from the main solution of the preparation in nutrient broth (LLC "*Pharmaktyv*", Ukraine), adding 10^6 microbial bodies/1 ml of standard strains of microorganisms to each dilution. 1 ml of broth and 0.1 ml of bacterial suspension (CC - culture control) was added into the last test tube. Bacterial inoculations were incubated at + 37 ° C or + 30 ° C for C. albicans during 24 h, after which the results were determined by the degree of turbidity of the nutrient medium. The last test tube with a transparent medium indicated a delay in the growth of microorganisms under the influence of the MIC of the study preparation. To determine the MBC, the above determination of MIC was supplemented with a second step during which inoculation was made onto agar sectors or Sabouraud's medium in Petri dishes from the test tubes with no evidence of bacterial mass accumulation, and after 24 h of incubation, the presence of microbial growth was determined, taking the lowest concentration of the preparation for MBC, which showed bactericidal effect [6]. The above studies were repeated three times. The combined effect of Antiqua Mare MAX and chlorhexidine was studied quintuply by diffusion method [7]. The substance of the stydy preparation was applied onto the clean paper disks to the amount of 25 μg /disk. The antiseptic chlorhexidine bigluconate in the form of 0.02% aqueous solution was applied onto the clean disks to the amount of 25 μg /disk. The disks were dried at a room temperature and used to determine the sensitivity of museum strains. The areas of inhibition of growth of microorganisms around the disks were measured after 24 h. The results obtained by the disk-diffusion method were statistically processed by standard computer programs. The probability of difference between the groups was determined using the Student's t-test.

Results and Discussion. The findings of the study of the effect of Antiqua Mare MAX on museum strains of E. coli, enterococci, micrococci, S. epidermidis and *S.* aureus and yeastlike fungi have shown the ability of the preparation to inhibit the growth of these microorganisms in a liquid medium that completely coincided with the results of three repeated tests (table 1).

Visual accumulation of bacterial mass of *E. coli* ATCC 25922 test-culture was absent in 1:1 dilution. The repeated inoculation onto solid medium showed a complete absence of growth of microorganisms. This meant that MBC of Antiqua Mare MAX for E.coli ATCC 25922 coincided with the MIC. The findings of the study of the effect of the preparation on the *S. aureus* museum strain after incubation have shown no growth of the test-culture in dilutions of 1:1–1:2 (table 1). Under the influence of the preparation, a complete sterility of the medium was achieved in 1:1 dilution. The sensitivity of the museum strain of S. epidermidis to the study preparation was similar to that of S. aureus.

Table 1

The effect of Antiqua Mare MAX on the museum strains of the microorganisms in liquid medium

Museum strain	Dilution, concentration of the preparation, μL								
	1:1/500	1:2/ 250	1:4/125	1:8/62.5	1:16/31.3	1:32/15.7	1:64/7.8	1:128/3.	C/C
E. coli ATCC 25922	–ster	+	+	+	+	+	+	+	+
S. aureus ATCC 25923	–ster	–	+	+	+	+	+	+	+
S.epidermidis ATCC 14990	–ster	–	+	+	+	+	+	+	+
E. faecalis ATCC 29212	–ster	–	–	–	+	+	+	+	+
M. lysodeicticus ATCC 4698	–ster	–	–	+	+	+	+	+	+
C. albicans ATCC10231	–ster	–ster	–	–	–	+	+	+	+

Notes: 1. «–» – no growth of microorganisms; 2. «+» – regular growth of microorganisms; 3. ster. – sterility in repeated inoculation onto solid nutrient medium (bactericidal effect).

E. faecalis ATCC 29212 museum strain was sensitive to Antiqua Mare MAX at a maximum dilution of 1:32; however, the MBC was 1:1. The preparation delayed the growth of the test-culture of M. lysodeicticus ATCC 4698 in 1: 4 titre and showed a bactericidal effect in 1:1 dilution. Antiqua Mare MAX showed inhibition of C. albicans growth in dilutions of 1:1–1:64 (Table 1). The repeated inoculation of the above dilutions onto solid nutrient medium showed no growth of fungi at a maximum dilution of 1:2. Apparently, in our study, slightly higher values of bacteriostatic concentrations can be explained by a visual evaluation of the results, whereas in the works of A.G. Miroshnichenko, et al. hardware densitometric determination of the optical density of bacterial suspensions was used [2]. These authors consider the effect of the preparation to be bacteriostatic and suggest that its mechanism is to inhibit protein synthesis [3]; however, bactericidal property of certain concentrations of the preparation and its effect on both bacteria and fungi is controversial. In our opinion, most likely, in a microbial cell, the preparation acts on the same target as in the cells of a macroorganism, namely, energy processes, structure and functions of membranes.

Thus, Antiqua Mare MAX demonstrated a suppressive effect on museum strains of gram-positive cocci, Escherichia coli and yeastlike fungi, indicating antimicrobial properties and wide range. The most sensitive to the preparation were strains of C. albicans ATCC10231 and E. faecalis ATCC 29212. The MIC of chlorhexidine bigluconate in relation to E. coli ATCC 25922 was 12.5 μg / ml, the MBC was 25 μg / ml (Table 2). Growth of Staphylococcus after incubation of test-cultures was absent in dilutions of 1:1–1:4, which corresponded to 25 μg / ml MIC (table 2). Under the influence of the preparation, complete sterility of the medium was achieved at a dilution of 1: 1, and MBC of chlorhexidine bigluconate was 100 μg / ml.

Museum strain of E. faecalis ATCC 29212 was sensitive to the antiseptic at a maximum dilution of 1: 8, though the MBC was 50 μg / ml. Chlorhexidine delayed the growth of the M. lysodeicticus ATCC 4698 test-culture at 1: 4 titer and showed a bactericidal effect in 1: 1 dilution, similar to Antiqua Mare MAX.

Table 2

The effect of 0.02% chlorhexidine bigluconate on the museum strains of the microorganisms in liquid medium

Museaum strain	Dilution / concentration of the preparation, μL								
	1:1/100	1:2/50	1:4/25	1:8/12,5	1:16/6,25	1:32/3,12	1:64/1,56	1:128/0,78	C/C
E. coli ATCC 25922	– ster	– ster	– ster	–	+	+	+	+	+
S. aureus ATCC 25923	– ster	–	–	+	+	+	+	+	+
S.epidermidis ATCC 14990	– ster	–	–	+	+	+	+	+	+
E. faecalis ATCC 29212	– ster	– ster	–	–	+	+	+	+	+
M. lysodeicticus ATCC 4698	– ster	–	–	+	+	+	+	+	+
C. albicans ATCC10231	– ster	– ster	–	+	+	+	+	+	+

Notes: 1. «–» – no growth of microorganisms; 2. «+» – regular growth of microorganisms; 3. ster. – sterility in repeated inoculation onto solid nutrient medium (bactericidal effect).

Under the influence of antiseptic, inhibition of growth of C. albicans was observed in dilutions of 1: 1–1: 4, which is typical for MIC of 25 μg / ml (Table 2). The repeated inoculation onto solid nutrient

medium showed no growth of fungi at a maximum dilution of 1: 2, corresponding to MBC of 50 μg / ml. After 24 hours of incubation, the zones of absence of growth of all bacteria around the disks with Antiqua Mare MAX had no significant differences compared to the disks with chlorhexidine, except for two cases (Table 3). First, E. coli ATCC 25922 strain was by 3.2 times ($p < 0.001$) more sensitive to chlorhexidine, and, secondly, the antifungal effect of Antiqua Mare MAX exceeded the activity of the conventional antiseptic by 1.4 times ($p < 0.01$).

Table 3

Combined effect of Antiqua Mare MAX and chlorhexidine, (M±m), n=5

Museum strain	The diameter of the zone of growth inhibition, mm		
	Antiqua Mare MAX	Chlorhexidine	Antiqua Mare MAX + Chlorhexidine
E. coli ATCC 25922	7.3±0.8	23.3±2.9*	22.6±3.3
S. aureus ATCC 25923	12.1±2.1	14.2±2.5	25.8±2.8**
S.epidermidisATCC 14990	12.3±2.1	14.6±2.1	15.2±0.8
E. faecalis ATCC 29212	17.0±2.1	20.6±3.3	20.0±3.3
M. lysodeicticus ATCC 4698	11.2±2.5	12.5±0.8	12.2±3.0
C. albicans ATCC 10231	23.4±2.1*	17.2±2.5	23.9±3.4

Notes: 1. * – reliable compared to chlorhexidine, ($p<0,01$); 2. ** – reliable compared to combination of preparations, ($p<0,01$)

The effect of chlorhexidine, supplemented with study preparation, showed that the diameter of the zone of inhibition of Staphylococcus aureus growth increased by 2.1 times ($p < 0.01$) compared to that without Antiqua Mare MAX. The combined effect of the study preparation and chlorhexidine showed no increase in the zones of growth inhibition of other museum strains compared to this antiseptic, not supplemented with Antiqua Mare MAX (table 3). Apparently, the oral care product Antiqua Mare MAX increased the sensitivity of the museum strain of S. aureus ATCC 25923 to 0.02% chlorhexidine bigluconate. Obviously, given the antimicrobial effect of Antiqua Mare MAX, such synergy can be regarded as a summation [8]. Thus, the antimicrobial effect of Antiqua Mare MAX revealed synergy with another antimicrobial agent, chlorhexidine, which is a natural component of the pharmacodynamics of the novel preparation of Antiqua Mare MAX, which should be considered in the clinical use of the preparation, especially in combination therapy of oral infections, which is consistent with other researchers [1].

Conclusion

Fungiostatic activity of the study preparation Antiqua Mare MAX exceeded the effect of 0.02% chlorhexidine bigluconate by 4 times ($p < 0.001$), though with similar fungicidal effect. For the M. lysodeistricus museum strain, the antibacterial effect of both preparations was the same, whereas for museum strains of E. coli, S. aureus and S.epidermidis antibacterial effect of Antiqua Mare MAX was weaker compared to 0.02% chlorhexidine bigluconate. The antifungal activity of AntiquaMareMAX exceeded the activity of the conventional antiseptic to C. albicans ATCC 10231 museum strain by 1.4 times ($p<0.01$), which was demonstrated by the method of paper disks.

The combination of the study preparation with chlorhexidine contributed to the tendency of increase the effect against the museum strain of S. aureus ATCC 25923.

In conclusion, the findings of the study have shown that Antiqua Mare MAX preparation can be recommended for the treatment of fungal stomatitis caused by C. albicans.

Prospects of further research will encompass the use of the Antiqua Mare MAX preparation in the comprehensive treatment of oral mucosa diseases and development of algorithm for its usage.

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Реферати

ВПЛИВ ПРЕПАРАТУ, ЩО ВМІЩУЄ ПРИРОДНИЙ МІНЕРАЛ БІШОФІТ, НА МІКРОФЛОРУ ПОРОЖНИНИ РОТА

Скрипников П.М., Скрипнікова Т.П., Лобань Г.А., Ганчо О.В., Хавалкіна Л.М., Зезекало С.В.

Порожнину рота можна розглядати як комплексну екологічну систему, в якій зовнішні фактори (біологічні, індивідуальні, соціальні) взаємодіють із внутрішніми (пародонт, бактеріальне співтовариство, локальна імунна система, епітелій порожнини рота). При виникненні сприятливих умов може розвинутись те чи інше захворювання яке необхідно лікувати. Ми вивчали ефективність впливу засобу по догляду за ротовою порожниною Antiqua Mare MAX, що вміщує природний мінерал Бішофіт Полтавський, на представників мікрофлори порожнини рота. Для вирішення поставленої мети використовували музейні штами E. Coli ATCC 25922, S. Aureus ATCC 25923, S. Epidermidis ATCC 14990, E. faecalis ATCC 29212, M. Lysodeicticus ATCC 4698 та C. Albicans ATCC1023. У якості контролю використовували відомий антимікробний засіб - 0,02% водний розчин хлоргексидину біглюконат. Фунгіостатична активність дослідного препарату перевищувала дію 0,02% розчину хлоргексидину біглюконату у 4 рази ($p<0,001$) , але фунгіцидна дія не відрізнялась.

Ключові слова: мікрофлора СОПР, хлоргексидин біглюконат, Antiqua Mare MAX.

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ВЛИЯНИЕ ПРЕПАРАТА СОДЕРЖАЩЕГО ПРИРОДНЫЙ МИНЕРАЛ БИШОФИТ НА МИКРОФЛОРУ ПОЛОСТИ РТА

Скрипников П.Н., Скрипникова Т.П., Лобань Г.А. Ганчо О.В., Хавалкина Л.М., Зезекало С.В.

Полость рта можно рассматривать как комплексную экологическую систему, в которой внешние факторы (биологические, индивидуальные, социальные) взаимодействуют с внутренними (пародонт, бактериальное сообщество, локальная иммунная система, эпителий полости рта). При возникновении благоприятных условий может развиться то или иное заболевание слизистой оболочки полости рта которое необходимо адекватно лечить. Мы изучали эффективность воздействия средства по уходу за полостью рта Antiqua Mare MAX, вмещающий природный минерал бишофит Полтавский, на представителей микрофлоры полости рта. Для решения поставленной цели использовали музейные штаммы E. coli ATCC 25922, S. aureus ATCC 25923, S. epidermidis ATCC 14990, E. faecalis ATCC 29212, M. lysodeicticus ATCC 4698 и C. albicans ATCC1023. В качестве контроля применяли известное антимикробное средство - 0,02% водный раствор хлоргексидина биглюконат. Фунгиостатическая активность исследуемого препарата Antiqua Mare MAX превышала действие 0,02% раствора хлоргексидина биглюконата в 4 раза ($p<0,001$), однако, фунгицидное действие не отличалась.

Ключевые слова: микрофлора СОПР, хлоргексидин биглюконат, Antiqua Mare MAX.

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EMG-ACTIVITY OF MUSCLES OF THE CRANIO-MANDIBULAR SYSTEM DURING FUNCTIONS OF THE DENTO-FACIAL REGION

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Electromyographic (EMG) activity of the temporal, masseter, orbicularis oris, mentalis, and sternocleidomastoid muscles was studied in 30 patients aged 20-28 years without somatic pathology, morphological, functional and aesthetic disorders in dento-facial region. The results of the study proved the involvement of the mimic and neck muscles in the teeth clenching, movements of the mandible and swallowing. The obtained data indicated the functional unity of the neuromuscular component of the stomatognathic system and the need to study the bioelectric activity of these muscles in subjects with functional disorders, especially associated with movements of the mandible and tongue at all stages of orthodontic treatment.

Key words: dento-facial region, electromyography, cranio-mandibular muscles, functions.

The work is a fragment of the research project "An interdisciplinary approach to the diagnosis, prevention and treatment of patients with dental malocclusion and jaw deformations", state registration No. 0018U004343.

Within the framework of the modern human functional development during the evolution of functions, such as speech, mental activity, self-awareness and social behavior, we can conclude: Masticatory organ is a highly organized multifunctional cybernetic system that works independently and interacts with various internal and external components, adapts permanently to the changing environmental factors, maintains a constant state of instable homeostasis (R. Slavicek, 2016) [2]. The dento-facial region is an integral part of the whole somatognathic system of the person. The structural components of this cybernetic system are the cranio-mandibular (TMJ), neuro-muscular systems of the dento-jaw area and occlusion. The cranio-mandibular system, as a component of the neuro-muscular system of the human body, consists of the muscular apparatus (temporalis, masseter, lateralis and medialis pterygoideus muscles) and ligaments (spheno-mandibularis, stylo-mandibularis, stylo-hyoideus) [2, 3, 4]. These

components are necessary for human life because of functions, that are perfomed (chewing, swallowing, speech, breathing, etc.), and can be indicators of overall somatic health [5, 7]. That is why, studies of the imbalance of neuromuscular connections between components of the dento-facial region are important for current diagnostic research.

The purpose of the study was to investigate the electromyographic activity of some muscles of the cranio-mandibular system during performing the functions of the dento-facial region.

Materials and methods. A clinical examination and a surface electromyography (EMG) of 30 patients of 20-28 years aged were used to find the peculiarities in the work of muscles of the cranio-mandibular system. The average age of patients was 23.4±2.1 years. 13 (30.0%) were men, 17 (70%) were women. All patients did not have any malocclusion. A clinical examination was carried out according to the standard algorithm (the form of the orthodontic card No. 043-1/o, confirmed by order of the Ministry of Health of Ukraine dated May 29, 2013). All patients were "healthy": without somatic pathology, morphological, functional and esthetic disorders of masticatory system. EMG of anterior temporal, masseter, orbicularis oris, chin (m. mentalis) and sternocleidomastoid muscles was performed according to the recommendations of Sforza et al. and Tartaglia et al [9]. The masseter, anterior temporal, sternocleidmastoid muscles of both sides (left and right) were examined. Disposable silver chloride surface electrodes (diameter 10 mm, Neirosoft, Russia) were positioned on the muscular bellies parallel to muscular fibers [6, 8, 9]. The skin was cleaned with 70% alcohol prior to the placement of the electrodes. The surface electrodes were attached to the skin, according to the relevant anatomical orientation. A disposable reference electrode was applied to the forehead. EMG-activity was recorded using a computerized instrument Synapsis and software by Neirotech (Russia). The analog EMG signal was amplified and digitized. Patients were sitting in a natural position without muscular tension, arms, legs were not crossed, head was held equally without support. Lips were kept closed slightly, tooth – in physiological rest. To avoid the effect of fatigue, there was three minutes-rest between each test.

EMG-activity was recorded in 4 tests, lasted 10s for each one: maximum voluntary clenching, moving the lower jaw forward (protrusion), swallowing of a sip of water and swallowing of saliva ("dry" swallowing). Maximum voluntary clenching was performed in intercuspal position (without any material placed on the molar teeth). The maximum activity of the muscle contractions (μV) was analyzed during the electromyography analysis. EMG data were processed using Neurotech's Synapsis software.

The procedures received approval from the Bioethics Committee of the Ukrainian Medical Stomatological Academy (Poltava, Ukraine). All girls and their parents signed a statement of informed consent.

The obtained data was statistically analyzed using the Student's t-test and the Fisher's criterion X2. The hypotheses were verified at the level of significance $p<0,05$.

Results of the study and their discussion. EMG-activity of muscles in a state of physiological rest was not detected in all tests that were carried out. EMG-activity was registered during muscle work and constrictions. The characteristics of the bioelectric activity of the muscles were different in each test. The EMG-characteristics of the muscles in the tests are presented in table 1.

Table 1

EMG - activity of masticatory, mimic and sternocleidomastoid muscles

Muscles		Maximum amplitude of constriction							
		Maximum teeth clenching test		Movement of the lower jaw forward (protrusion) test		A sip water swallowing test		Salvia swallowing («dry» swallowing) test	
		μV	%	μV	%	μV	%	μV	%
m.masseter	Left	1636,25 ±36,45	36,4	594,09 ±17,43	21,1	366,5 ±9,55	16,9	565,0 ±12,77	23,7
	Right	1722,25 ±38,92		630,0 ±18,76		416,75 11,39		575,25 ±12,85	
m. temporalis	Left	1335,75 ±26,54	27,4	379,75 ±13,28	17,5	392,75 ±10,04	27,3	530,5 ±12,04	21,2
	Right	1474,0 ±28,71		413,5 ±15,44		349,25 ±8,76		441,5 ±11,14	
m. orbicularis oris		839,5 ±15,34	11,4	350,53 ±9,54	15,2	625,0 ±13,45	20,8	498,75 ±11,69	18,2
m. mentalis		999,75 ±20,06	13,2	661,0 ±20,51	28,9	628,5 ±13,98	27,3	557,0 ±12,54	21,5
m. sternocleidomastoideus	Left	838,25 ±16,23	11,5	393,0 ±13,08	17,3	443,25 ±11,34	19,0	384,25 ±8,54	15,5
	Right	898,02 ±17,65		430,65 ±16,75		414,4 ±10,84		423,87 ±10,74	

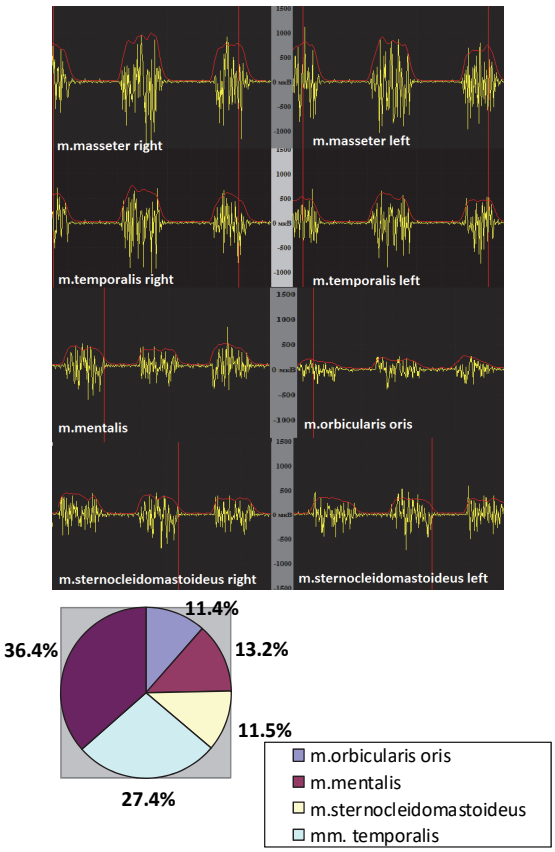

Fig. 1. Fragment of the electromyogram of patient K., 25 years. A graphical representation of the muscle activity in the maximum teeth clenching test.

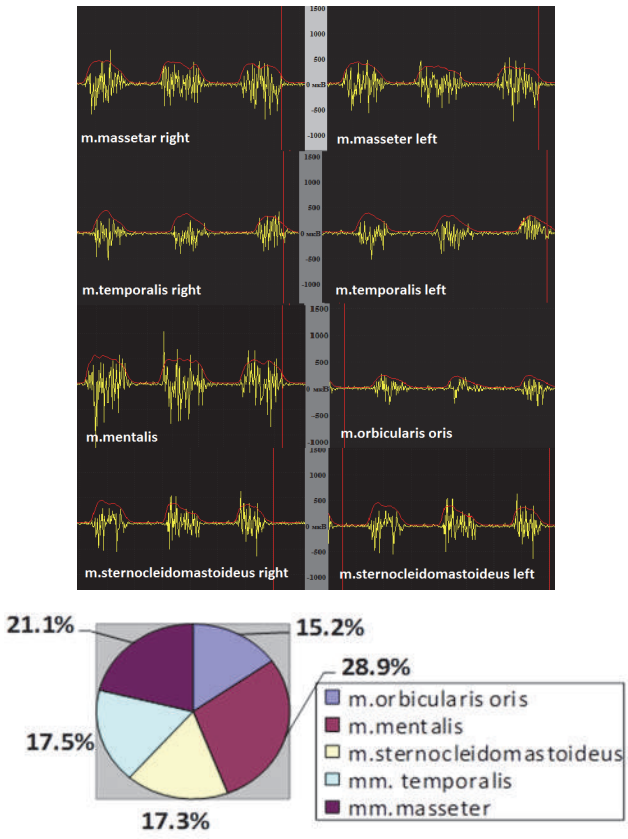

Fig. 2. Fragment of the electromyogram of patient K., 25 years. A graphical representation of the muscle activity in the protrusion test.

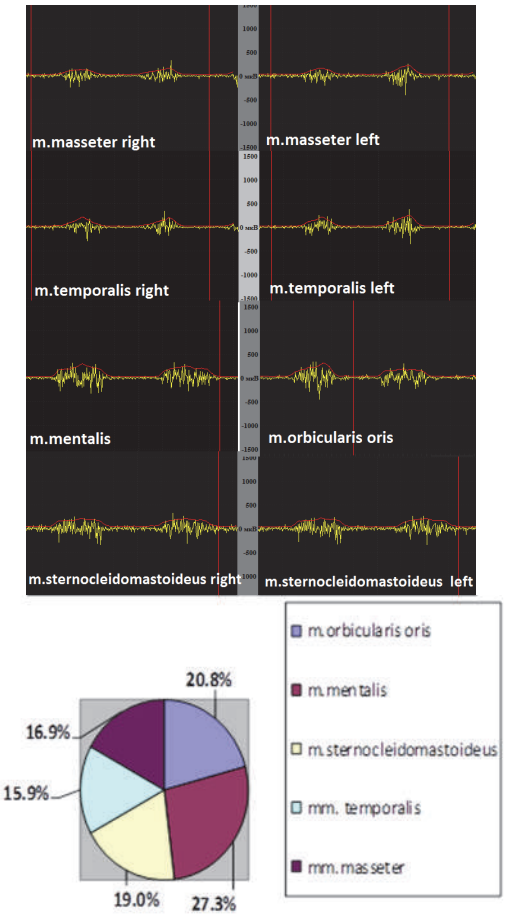

Fig. 3. Fragment of the electromyogram of patient B., 22 years. A graphical representation of the muscle activity in a swallowing test.

In the maximum teeth clenching test the highest EMG-activity was registered in the masticatory muscles (1679,25 μV±37,58), the lowest – in the sternocleidomastoid ($p < 0,05$) and the orbicularis oris muscles ($p < 0.05$) – 868.13±16.94 μV and 839.5±15.34 μV, respectively, as shown in fig. 1.

In the mandibular movements (protrusion) test, the highest EMG-activity was determined in the mentalis (661.8 μV±20.51) and masseter muscles (612.05 μV±18.09). EMG-activity of the temporal and sternocleidomastoid muscles in this test was almost the same (average for the temporalis muscle – 396,62 μV±1436, $p > 0,05$, sternocleidomastoid muscles – 411.82 μV±14.92, $p > 0.05$). An example of the electromyogram in this test is shown in fig. 2.

The orbicularis oris (625.0 μV±13.45) and chin muscles were observed the highest EMG-activity in the swallowing test (628.5 μV±13.98). The EMG-activity of the sternocleidomastoid muscle was significantly less (443.25±11.34 μV, 414.4±10.84 μV on the left and right sides, respectively, $p < 0.05$).

The values of the maximal amplitude of contractions of the temporal and masseter muscles were the lowest and did not significantly differ ($p > 0.05$). An example of the electromyogram in this test is shown in fig. 3.

In the "dry" swallow test, the highest EMG-activity was recorded in the orbicularis oris muscle and masseter muscles, while the values of the temporal,

sternocleidomastoid and mentlis muscles were at the same level and were not statistically different ($p > 0.05$).

We also investigated the symmetry of the EMG-activity of contractions of the muscles of the left and right sides (masseter, temporal and sternocleidomastoid muscles). In the majority of the examined patients (35.0 - 83.3%), symmetrical bioelectric activity of the masseter, temporal, and sternocleidomastoid muscles of the left and right sides was observed, what corresponds to the physiological norm. Asymmetric work of these muscles was determined in 5 (16.7%) patients. Increasing of the maximum amplitude of contractions on one side (in 3 people (10.0%) –EMG-activity of the temporal and masseter muscles was higher on the right, in 2 people (6.7%) – on the left side) was found. The asymmetric work of the sternocleidomastoid muscles was also observed in these subjects. It is important to note that the side with the increased EMG-activity of sternocleidomastoid muscles was opposite to the side with the increased EMG-activity of the temporal and masseter muscles (which can be characterized by the term "cross" activity).

Therefore, the EMG-activity evaluation of the muscles of the dento-facial region should be performed in conjunction with the EMG-activity evaluation of the stomatognathic system muscles, which coincides with other studies [1, 2, 3]. There are data in literature sources about EMG-activity of the upper and lower lip circular muscles, supra-, infragioid muscle during the following tests: physiological rest, pronunciation of certain sounds, swallowing, deep breathing, maximum teeth clenching and chewing [1]. Thus, it was found that the EMG-activity of the orbicularis oris muscle was higher in patients with impaired functions of lip closure and speech in comparison with subjects without such disorders. However, it should be noted that there are no a comparative study of the bioelectric activity of mimic, masticatory, and sternocleidomastoid muscles.

Conclusion

The study allowed us to determine the features of EMG-activity and the proportion of muscle work of the masticatory (masseter, temporal), mimic (chin, orbicularis oris muscles) and sternocleidomastoid muscle during functions of dento-facial region and movements of the mandible. The results of the study proved the involvement of facial and neck muscles in teeth clenching, mandible movements, swallowing. It was found that the EMG-activity of the orbicularis oris muscle during maximum teeth clenching, displacement of the mandible forward (protrusion) and swallowing correlated with the EMG-activity of the sternocleidomastoid muscles. The obtained data indicated the functional unity of the neuromuscular component of the stomatognathic system and the need to study the bioelectric activity of these muscles in subjects with functional disorders, especially associated with movements of the mandible and tongue at all stages of orthodontic treatment.

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Реферати

ЕМГ-АКТИВНІСТЬ М'ЯЗІВ КРАНІО-МАНДИБУЛЯРНОЇ СИСТЕМИ ПІД ЧАС ВИКОНАННЯ ФУНКЦІЙ ЗУБО-ЩЕЛЕПНОЇ ДІЛЯНКИ

Смаглюк Л.В., Смаглюк В.І., Ляховська А.В., Трофименко М.В.

Було проведено дослідження електроміографічної (ЕМГ) активності скроневого, власне жувального,

ЭМГ-АКТИВНОСТЬ МЫШЦ КРАНИО-МАНДИБУЛЯРНОЙ СИСТЕМЫ ВО ВРЕМЯ ВЫПОЛНЕНИЯ ФУНКЦИЙ ЗУБО-ЧЕЛЮСТНОЙ ОБЛАСТИ

Смаглюк Л.В., Смаглюк В.И., Ляховская А.В., Трофименко М.В.

Было проведено исследование электромиографической (ЭМГ) активности височной, собственно

колового, підборідного та грудино-ключично-сосцеподібного м'язів у 30 пацієнтів віком 20-28 років без соматичної патології, морфологічних, функціональних та естетичних порушень зубо-щелепної ділянки. Результати дослідження доводять участь мімічних м'язів та м'язів шиї у стисканні зубів, рухах нижньої щелепи та ковтанні, що вказує на функціональну єдність нейромускулярної складової стоматогнатичної системи. Це обумовлює необхідність вивчення роботи цих м'язів у осіб із порушенням функцій зубощелепної ділянки, особливо тих, що пов'язані із рухами нижньої щелепи та язика на всіх етапах ортодонтичного лікування.

Ключові слова: зубощелепова ділянка, електроміографія, м'язи краніо-мандибулярної системи, функції зубощелепної ділянки.

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жевательной, круговой, подбородочной и грудино-ключично-сосцевидной мышц у 30 пациентов 20-28 лет без соматической патологии, морфологических, функциональных и эстетических нарушений зубочелюстной области. Результаты исследования доказывают участие мимических мышц и мышц шеи в сжатии зубов, движениях нижней челюсти и глотании, что указывает на функциональное единство нейромускулярной составляющей стоматогнатической системы. Это обусловливает необходимость изучения работы этих мышц у лиц с нарушением функций зубочелюстной области, особенно тех, которые связаны с движениями нижней челюсти и языка на всех этапах ортодонтического лечения.

Ключевые слова: зубочелюстная область, электромиография, мышцы краниo-мандибулярной системы, функции зубочелюстной области./

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THE RELATIONSHIP OF MALOCCLUSIONS WITH THE ERUPTION TIME OF PERMANENT TEETH IN CHILDREN LIVING IN DIFFERENT CLIMATIC AND GEOGRAPHICAL CONDITIONS

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The article highlights the prevalence and structure of malocclusion and terms of eruption of the permanent teeth in children living in different climatic and geographical conditions. It has been established that the prevalence of malocclusion and terms of eruption of the permanent teeth in children depends on the geographical and environmental living conditions. It is proved that there is a strong correlation between malocclusions and the number of erupted teeth.

Key words: malocclusions**,** permanent tooth eruption, climatic and geographical conditions.

The work is a fragment of the research project "Assessment of dental morbidity of children with regard to environmental and social aspects and the effectiveness of prevention of dental caries and periodontal diseases", state registration No. 0115U000037.

Dentofacial anomalies, with an average prevalence of 40% to 81%, are among the major dental diseases [3, 8]. The analysis of the literature data shows that there has not been a tendency to a downward trend in this pathology in recent years. Significant increase of dentofacial anomalies, along with other factors, is associated with the negative environmental impact, the presence of somatic diseases, and climatic and geographical living conditions of children [2, 5, 6]. Therefore, the prevalence of dentofacial anomalies can be fully considered as one of the indicators that characterize the health status of children in a particular region.

In addition, it is known that the formation of dentofacial anomalies is significantly affected by the eruption time of permanent teeth, which is an important criterion for indicators of normal development of the dentofacial system. Deviations from the average terms of eruption of permanent teeth serve as one of the prognostic symptoms of the development of the child's organism [4, 7].

Different internal and external factors cause the fluctuations in the time of permanent teeth eruption. Climatic, geographical, ecological, and regional peculiarities of the territory where children live have a significant impact on the term of permanent teeth eruption [1, 8]. In this regard, it is important to study the features of permanent teeth eruption for each individual region, which differ in their conditions and their relationship with the formation of dentofacial anomalies. Epidemiological studies have been devoted to evaluating the eruption time of permanent teeth in Ukraine [8]. In recent years, the issue of terms of permanent teeth eruption, the dynamics of their changes, the regional features of teeth eruption, their relationship with the physical development of children and with dentofacial anomalies have not been covered in the literature, which, in turn, causes difficulties in the choice of treatment and preventive measures. Therefore, it is important to further study the prevalence of dentofacial anomalies, to evaluate the eruption time of permanent teeth at the regional level and to assess their interconnection.

The purpose of the work was to assess the relationship between malocclusions and the eruption time of permanent teeth in children living in different climatic and geographical conditions.

Material and research methods. The total of 333 7-year-old children were examined to assess the prevalence and structure of malocclusions and the eruption time of permanent teeth. Among them, there are 110 children living in the flat terrain, 109 children living in the mountainous terrain and 114 children from the foothills. The nature of dentofacial anomalies was evaluated according to the D.A. Kalvelis classification.

Statistical processing of the research results was carried out using software packages for statistical analysis of Microsoft Excel research data, which is included in the Microsoft Office package and the Statistica program. When performing the statistical processing of the obtained data, the following methods were used: analysis of variational series – since there was Gaussian distribution in the studied groups, the obtained results are presented in the form of arithmetic mean values and their average error (M±m); assessing the estimated probability of differences in the obtained results in the compared groups using the Student t-test; correlation analysis was performed by calculating the paired and linear correlation coefficients using the Pearson method. The difference at $p < 0.05$ was considered significant.

The purpose of statistical data processing was to determine the characteristic quantitative estimates of the studied indicators, to establish the presence or absence of correlation between the obtained indicators, as well as the influence of external factors on them. Correlation analysis was performed between the incidence of malocclusions and the number of erupted permanent teeth.

During the examination all safety measures concerning the children's health, respect for their rights, human dignity and moral and ethical standards were kept in accordance with the principles of the Helsinki Declaration, the Council of Europe Convention on Human Rights and Biomedicine and the relevant laws of Ukraine.

The results of the study and their discussion. The prevalence, structure of malocclusions and permanent teeth eruption in 7-year-old children are shown in table 1. It was found that with the prevalence of deep (40.91±4.69%) and distal occlusion (38.18±4.63%) in children living in the flat territory, only 4.2 and 4.0 teeth were erupted in the upper jaw, respectively, which is significantly less than in children who had malocclusions much less frequently. The largest number of permanent teeth that erupted in the upper jaw in the children living in the flat territory was found in case of the cross bite (5.8 teeth), and the highest number of permanent teeth that erupted in the children in the lower jaw (6.8 teeth) was observed in case of the open bite. Children living in the mountainous area also the most frequently had distal (28.44±4.32%) and deep (16.51±3.56%) malocclusions, in which the number of teeth that erupted in both jaws was 10.6 teeth and 10.9 teeth, respectively.

Analyzing the foothills, on average, we see an increase by one tooth in the number of erupted teeth, and a decrease in the incidence of malocclusions.

Table 1

The prevalence of malocclusions and the number of permanent teeth that erupted in children depending on the area of residence

Children (7-year-old)		Malocclusions									
		Distal Bite		Mesial Bite		Deep Bite		Open Bite		Cross Bite	
		the amount of teeth	%	the amount of teeth	%	the amount of teeth	%	the amount of teeth	%	the amount of teeth	%
Flat Terrain	Upper Jaw	4.0	38.18 ± 4.63	5.1	2.73 ± 1.55	4.2	40.91 ± 4.69	5.4	4.55 ± 1.99	5.8	7.27 ± 2.48
	Lower Jaw	6.2		6.6		6.1		6.8		6.5	
Mountainous Terrain	Upper Jaw	4.2	28.44 ± 4.32	4.6	5.50 ± 2.18	4.4	16.51 ± 3.56	4.8	9.17 ± 2.76	4.6	12.84 ± 3.20
	Lower Jaw	6.4		6.7		6.5		6.6		6.8	
Foothills	Upper Jaw	4.3	11.40 ± 2.98	4.7	7.02 ± 2.39	4.8	12.28 ± 3.07	5.4	4.39 ± 1.92	5.8	6.14 ± 2.25
	Lower Jaw	6,9		6,7		6,1		6,6		6,7	

It was found that in 7-year-old children (table 2) living in the mountainous area there is a statistically significant ($p < 0.05$) inverse correlation between the proportion of permanent teeth in the upper jaw and the prevalence of distal ($r = -0.87$), mesial ($r = -0.78$), deep ($r = -0.79$), and cross ($r = -0.53$) bites.

A similar significant ($p < 0.05$) relationship was found between the proportion of permanent teeth and the prevalence of distal ($r = -0.68$), mesial ($r = -0.60$), and open ($r = -0, 75$) bites in the lower jaw. This means that the higher the prevalence of these types of malocclusions is, the less is the number of permanent teeth that erupted in 7-year-old children living in the mountainous area.

Table 2

Correlation between different malocclusions and the number of permanent teeth that erupted depending on the area of residence of 7-year-old children

Children (7-year-old)		Malocclusions				
		Distal Bite	Mesial Bite	Deep Bite	Open Bite	Cross Bite
Mountainous Terrain	Upper Jaw	-0.87*	-0.78*	-0.79*	-0.46	-0.53*
	Lower Jaw	-0.68*	-0.60*	-0.35	-0.75*	-0.49
Foothills	Upper Jaw	-0.42	-0.63*	-0.47	-0.32	-0.55*
	Lower Jaw	-0.25	-0.31	-0.49	-0.21	-0.24
Flat Terrain	Upper Jaw	-0.45	-0.56*	-0.41	-0.62*	-0.68*
	Lower Jaw	-0.42	-0.44	-0.51*	-0.50*	-0.34
Average	Upper Jaw	-0.61*	-0.70*	-0.52*	-0.45	-0.57*
	Lower Jaw	-0.52*	-0.42	-0.48*	-0.59*	-0.44

Note. * – the correlation coefficient is significant ($p < 0.05$)

In children living in the foothills, a similar significant ($p < 0.05$) inverse correlation was found between the proportion of permanent teeth in the upper jaw and the prevalence of mesial ($r = -0.63$) bite.

Significant inverse correlations were found between the proportion of permanent teeth in the upper jaw and the prevalence of mesial ($r = -0.56$), open ($r = -0.62$) and cross ($r = -0.68$) bites in children living in the flat territory. In the lower jaw, a similar relationship was established with the prevalence of deep ($r = -0.51$) and open ($r = -0.50$) bites. We analysed the relationship between the incidence of malocclusion and the eruption of permanent teeth in children, taking into account the article (table 3). The results of the analysis indicate that the higher the incidence of malocclusions is, the smaller is the number of permanent teeth that erupted.

Table 3

Correlation between different malocclusions and the number of permanent teeth that erupted depending on the area of residence of boys

Boys (7-year-old)		Malocclusions				
		Distal Bite	Mesial Bite	Deep Bite	Open Bite	Cross Bite
Flat Terrain	Upper Jaw	-0.50	-0.47	-0.62*	-0.43	-0.69*
	Lower Jaw	-0.39	-0.58	-0.27	-0.54	-0.47
Mountainous Terrain	Upper Jaw	-0.89*	-0.76*	-0.83*	-0.79*	-0.61
	Lower Jaw	-0.67*	-0.43	-0.39	-0.77*	-0.44
Foothills	Upper Jaw	-0.34	-0.81*	-0.62*	-0.46	-0.57
	Lower Jaw	-0.46	-0.21	-0.54	-0.37	-0.28

Note. * – the correlation coefficient is significant ($p < 0.05$)

Therefore, significant ($p < 0.05$) inverse correlations between the proportion of permanent teeth in the upper jaw and the prevalence of deep ($r = -0.62$) and cross ($r = -0. 69$) bites were found in boys living in a flat terrain. In boys living in the mountainous area, there is a significant ($p < 0.05$) inverse correlation between the proportion of permanent teeth in the upper jaw and the prevalence of distal ($r = -0.89$), mesial ($r = -0.76$), deep ($r = -0.83$) and open ($r = -0.79$) bites. A similar significant ($p < 0.05$) relationship was found between the proportion of permanent teeth and the prevalence of distal ($r = -0.67$) and open ($r = -0.77$) bites in the lower jaw. In boys living in the foothills, a significant ($p < 0.05$) inverse correlation was found between the proportion of permanent teeth in the upper jaw and the prevalence of mesial ($r = -0.81$) and deep ($r = -0.62$) bites.

It was found that with the increase in the incidence of malocclusions, a decrease in the number of permanent erupted teeth is observed (table 4). Therefore, significant ($p < 0.05$) inverse correlations between the proportion of permanent teeth in the upper jaw and the prevalence of mesial ($r = -0.55$) and open ($r = -0, 63$) bites were found in girls living in a flat terrain. A similar significant ($p < 0.05$) relationship was found between the proportion of permanent teeth and the prevalence of distal ($r = -0.78$) and deep ($r = -0.55$) bites in the lower jaw.

Table 4

Correlation between different malocclusions and the number of permanent teeth that erupted depending on the area of residence of girls.

Girls (7-year-old)		Malocclusions				
		Distal Bite	Mesial Bite	Deep Bite	Open Bite	Cross Bite
Flat Terrain	Upper Jaw	-0.46	-0.55*	-0.40	-0.63*	-0.50
	Lower Jaw	-0.78*	-0.43	-0.55*	-0.51	-0.36
Mountainous Terrain	Upper Jaw	-0.88*	-0.83*	-0.43	-0.32	-0.51
	Lower Jaw	-0.65*	-0.84*	-0.41	-0.53	-0.47
Foothills	Upper Jaw	-0.43	-0.54*	-0.31	-0.29	-0.54*
	Lower Jaw	-0.17	-0.38	-0.41	-0.07	-0.22

Note. * – the correlation coefficient is significant ($p < 0.05$)

For girls living in the mountainous areas, there is a significant ($p < 0.05$) inverse correlation between the proportion of permanent teeth in the upper and lower jaws and the prevalence of distal ($r = -0.88$ in the upper and - 0.65 in the lower) and mesial bites ($r = -0.83$ and -0.84, respectively).

In girls living in the foothills, a similar significant ($p < 0.05$) inverse correlation was found between the proportion of permanent teeth in the upper jaw and the prevalence of mesial ($r = -0.54$) and cross ($r = -0.54$) bites. The prevalence of dental jaw abnormalities occupies an important place among the main dental diseases [1, 4, 7]. Several authors link the significant increase of dental jaw abnormalities with the negative impact of the environment, the presence of somatic, climatic and geographical living conditions of children [1, 3, 7]. The prevalence of dental jaw abnormalities can be considered as one of the indicators characterizing the health of children in a particular region [5, 8].

The article highlights the prevalence and structure of malocclusion and terms of eruption of the permanent teeth in children living in different climatic and geographical conditions. It has been established that the prevalence of malocclusion and terms of eruption of the permanent teeth in children depends on the geographical and environmental living conditions [3, 5]. It is proved that there is a strong correlation between malocclusions and the number of erupted teeth.

It was estimated that in the case of frequency of deep bite (40.91±4.69 %) and distal occlusion (38.18±4.63 %) in children living in flat terrain region there were revealed only 4.2 and 4.0 erupted teeth, which is less comparing with children with decreased index of malocclusions frequency. The most high number of the permanent teeth, which are erupted on the upper jaw is revealed in the case of crossbite (5, 8 tooth). in the case of open bite it was noticed the most high number of the permanent teeth that were erupted on the lower jaw (6, 8 tooth).

In children that live in the mountainous terrain the most frequent were diagnosed distal occlusion (28.44±4.32 %) and deep bite (16.51±3.56 %). In that cases number erupted teeth on the both jaws was 10, 6 tooth and 10, 9 tooth.

Conclusion

The examination of children revealed that distal and deep bites were more frequently diagnosed in children living in the flat territory compared with the mountainous area and foothills. It was proved that there is a strong correlation between the number of teeth that erupted in children during the period of an early transitional bite and malocclusions. A relationship between the incidence of malocclusions and the eruption time of permanent teeth was found, taking into account the peculiarities of the residence area.

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Реферати

ЗВ'ЯЗОК АНОМАЛІЙ ПРИКУСУ І ТЕРМІНІВ ПРОРІЗУВАННЯ ЗУБІВ У ДІТЕЙ З РІЗНИХ КЛІМАТО-ГЕОГРАФІЧНИХ УМОВ

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У статті висвітлено поширеність та структуру аномалій прикусу та терміни прорізування постійних зубів у дітей, які проживають у різних кліматогеографічних умовах. Встановлено, що поширеність аномалій прикусу та прорізування постійних зубів у дітей залежать від географічних та екологічних умов проживання. Доведено, що між аномаліями прикусу та кількістю зубів, що прорізалися існує сильний кореляційний зв'язок.

Ключові слова: аномалії прикусу, прорізування постійних зубів, клімато-географічні умови.

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СВЯЗЬ АНОМАЛИЙ ПРИКУСА И СРОКОВ ПРОРЕЗЫВАНИЯ ЗУБОВ У ДЕТЕЙ С РАЗНЫХ КЛИМАТО-ГЕОГРАФИЧЕСКИХ УСЛОВИЙ

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В статье освещены распространенность и структуру аномалий прикуса и сроки прорезывания постоянных зубов у детей, проживающих в различных климато-географических условиях. Установлено, что распространенность аномалий прикуса и прорезывания постоянных зубов у детей зависят от географических и экологических условий проживания. Доказано, что между аномалиями прикуса и количеством зубов прорезались существует сильная корреляционная связь.

Ключевые слова: аномалии прикуса, прорезывание постоянных зубов, климато-географические условия.

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FUNCTIONAL STATE OF CARDIOVASCULAR AND DIGESTIVE SYSTEMS IN THE BODY OF STUDENTS DURING FITNESS TRAINING

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Examination of students engaged in modern fitness technologies is performed in the work and it is established that physical exercises effect the activation of internal systems' work in the body. Analyzing the correlation of recreative fitness with students' nutrition provides an opportunity to identify prospects for improving cardiovascular and digestive systems, improving general condition and achieving the desired student athletic performance. The study found that 92.5% of students were positive about the new content of training in modern fitness technology and only 7.5% said their attitude was uncertain. During the experiment, the dynamics of changes in the parameters of the cardiovascular and digestive systems' functional state (experimental/control groups) were confirmed: the mean body weight decreased by 2.8 kg/1.5 kg, the pulse at rest decreased to 65.25 beats./min.±0.25/74.46 bpm±0.64; systolic pressure decreased to 112.75 mm Hg±0.35/118.21 mm Hg±0.79; diastolic pressure decreased to 72.21 mm Hg±0.39/76.57 mm Hg±0.43; the vital capacity of the lungs increased by 0.4 l/0.2 l, which is evidence of the cardiovascular system's economic activity and confirms the feasibility of the applied methodology of health fitness technologies. Regarding the expediency of dietary change: 77% of students said they needed change, while 21% said they wanted it, and only 2% said they didn't want to change their diet.

Key words: fitness technology, nutrition, physical education, health, cardiovascular and respiratory systems.

The work is a fragment of the research project "Implementation of health-saving technologies in physical education in the context of European integration of Ukraine", state registration No. 0117U 003236.

Modern fitness technology is an aspect of the fitness industry that is related to organizational and methodological support of the process aimed at improving the physical condition of the person. High fitness competitive advantage in comparison with other industries, which provide the sphere of human leisure, causes its rapid development, provides a meaningful filling of fitness technologies and determines their efficiency. The purpose of this study is to systematize organizational forms of work, to analyze the structure and methodological features of the tools, to identify the dynamics of changes in the parameters of the physical state, nutrition recommendations that are used in training of modern fitness technologies. Our study was performed based on the research and methodological literature, pedagogical observations of the course of work at the best fitness clubs in Poltava, analysis of health fitness at the Faculty of Physical Education at the Poltava V.G. Korolenko National Pedagogical University, and studies of physical education classes while training the module "Recreative Gymnastics".

The fitness industry is characterized by a high degree of innovation. Specialists identify a variety of activities that can meet the broadest segments of the population. Despite their differentdirectivity profiles, their belonging is determined by a common goal, which is to promote overall health of the body, the achievement of which is conditioned by the principles of health nutrition [1, 4, 7]. All the accumulated knowledge regarding the organizational and methodological support of fitness requires systematization for

further development of methodological provisions to be used in the process of implementing technologies of health fitness.

The purpose of the work was to analyze the characteristics of the cardiovascular system and The purpose of the work was to analyze the characteristics of the cardiovascular system and the dietary pattern, to systematize organizational forms of work during health fitness classes with students.

Materials and methods. The study was carried out at the Poltava V.G. Korolenko National Pedagogical University during 2018-2019 with students of the 1st year of natural sciences (22), physics and mathematics (26) and history faculties (24).

We have carried out a survey on the attitude to fitness classes and an enquiry of students about their adherence to the day regime and nutrition balance. At the beginning and at the end of the experiment, control measurements of weight, blood pressure (AP), pulse and vital lung capacity (VLC) were performed, comparative characteristics of the experimental and control groups were made.

Methods used in our study consist in theoretical analysis of modern methodological and special literature on health fitness programs, sociological, pedagogical and medical-biological methods, comparative analysis of cardiovascular indices of students engaged in fitness, study of their dietary pattern. They were selected based on the analysis of research and methodological literature and pedagogical observations of the training method during the physical education classes, teaching the subject "Health fitness" at the Poltava V.G. Korolenko National Pedagogical University, studies of the work experience at the leading fitness centers in Poltava.

Results of the study and their discussion. At the first stage of the study we carried out a survey and determined the performance of the cardiovascular and digestive systems in students. At the beginning of the experiment, we suggested to assess our desire to practice traditional physical education and modern fitness technology. Students assessed their desire to be engaged by a 10-point scale, where 10 points is the maximum desire and 1 point is the absence of any desire.

The survey showed that the desire to be engaged in traditional physical education classes was assessed on average by 4 points, but the highest score was rated by the desire to exercise in different types of fitness - an average of 9 points. The survey revealed that only 14% had a positive attitude towards traditional physical education classes, and the number of those with negative attitude was tripled - 57%. Respondents having an uncertain attitude made 29%.

При проведенні аналізу показників фізичного стану студентів були визначені такі показники: вага, пульс у стані спокою і після фізичних навантажень, АТ (систолічний і діастолічний), ЖЄЛ (табл.1).

During the analysis of students' physical condition indices the following indices were determined: weight, pulse at rest and after physical exertion, blood pressure (systolic and diastolic), VLC (table 1).

Table 1

Indices of the cardiovascular and digestive systems functional state

Faculty	Number of students	Body weight (mean) kg	Pulse (at rest) bpm	Pulse (after physical load) bpm	BP (systolic) mm Hg	BP (diastolic) mm Hg	VLC (mean value) L
Faculty of Sciences	22	63.1±2.8	77.38±0.62	125.46±0.24	120.41±0.28	78.31±0.39	2.7±0.4
Mathematics and Physics	26	64.5±3.6	75.43±0.51	121.45±0.71	115.76±0.75	76.24±0.31	2.8±0.2
History	24	62.2±2.5	76.21±0.66	118.4±0.76	112.63±0.24	75.32±0.43	2.6±0.5

After the analysis, it can be concluded that the functional state of the cardiovascular and digestive systems tends to deteriorate, there is a decrease in the body's reserve capacity, which corresponds to a satisfactory level of physical condition in students.

Further we implemented modern fitness technologies into the educational process of the discipline "Physical Education". Fitness was practiced by 48 first-year girls at the Faculty of Sciences and Faculty of Physics and Mathematics, who formed the experimental group. At the same time, other participants of the experiment at the Faculty of History were engaged into the traditional program of physical education. The control group (CG - 24 students) and the experimental group (EG - 48 students) were formed.

The fitness program included five blocks of exercises: the introductory part, the cardio-exercise complex, the strength training, the flexibility exercises and the final part. To implement the shaping program into the educational process of the common higher education (CHE) we used a video software of the international shaping federation "shaping classic" with duration of 55 minutes.

The introductory part is designed for 10 minutes. and aimed at preparing the body to perform the main part of the class, which consisted of 8 blocks of exercises, a sequence that helped to increase the load and consolidate motor skills. The first four blocks of exercises are aimed at correction of the hips; the fifth block is aimed at correction of the buttocks; the sixth one is aimed at correction of the abdominal muscles (waist); the seventh is for the rectus abdominis muscles, and the eighth, final block is for the upper back muscles.

The final part of health fitness is aimed at reducing the activity of the vegetative functions and the gradual bringing of the cardiovascular and respiratory systems to rest.

After the experiment, the survey permitted to clarify the students' attitude to the traditional and updated content of physical education classes: 92.5% of students were positive about the new content of the classes and only 7.5% said their attitude was uncertain. The answers to the questionnaire on the feasibility of changes in the content of physical education training were as follows: 77% said they needed changes, while 21% said changes were desirable and only 2% would like to leave the classes unchanged.

At the end of the academic year, we obtained the following indices of the cardiovascular and digestive systems functional state in students of the experimental groups at the faculties of physics and mathematics and the control group at the history faculty (table 2).

Table 2

Dynamics of cardiovascular and digestive systems functional state indices in EG and CG

Faculty	Number of students	Body weight (mean) kg	Pulse (at rest) bpm	Pulse (after physical load) bpm	BP (systolic) mm Hg	BP (diastolic) mm Hg	VLC (mean value) L
Faculty of Sciences (EG)	22	60.3±2.8	65.25±0.25	138.31±0.29	112.75±0.35	72.21±0.39	3.1±0.4
Mathematics and Physics (EG)	26	61.5±3.6	64.34±0.86	135.23±0.47	110.36±0.74	70.43±0.37	3.2 ±0.2
History (CG)	24	62.1±1.5	74.46±0.64	118.51±0.59	118.21±0.79	76.57±0.43	2.7±0.2

After the experiment, the dynamics of changes in the parameters of cardiovascular and digestive systems' functional state in the experimental group of the Sciences Faculty and Mathematical and Physical Faculty were compared to the control group of the History Faculty, which indicates the cardiovascular system's work economizing. Thus, the mean weight decreased by 2.8 kg / 1.5 kg, the pulse at rest decreased to 65.25 bpm±0.25 / 74.46 bpm±0.6 systolic pressure decreased to 112.75 mm Hg±0.35 / 118.21 mm Hg±0.79; diastolic pressure decreased to 72.21 mm Hg±.39 / 76.57mm Hg±0.43; VCL increased by 0.4 l / 0.2 l, which is an evidence of improved cardiovascular and digestive systems activity, and confirms the feasibility of using health fitness techniques. In the control group of the History Faculty, which was engaged in the traditional system of physical exercises, the parameters of the cardiovascular and digestive systems' functional state have significantly lower values compared to the experimental group.

Results of the studies permitted to distinguish in health fitness: individual, group and independent forms of work. Individual form of work permits to take into account individual psychophysical condition characteristics of the person involved, his motivation, level of physical and coordination fitness, but to the fundamental disadvantages we attribute the lack of social support from other participants of the fitness process, which negatively affects the motivation of training. In such cases, the support is the responsibility of the trainer.

Group form of work is quite widespread in health fitness when carrying out various types of aerobic and aerobic-strength training. Collective action in this case creates social support that enhances emotional background and promotes motivation, but the possibilities of personal control over exercise techniques are limited.

In terms of self-study, students are responsible for their state of health, but negative consequences of training are possible in the case of improper exercise techniques, failure to observe their exercise regimen, etc. This form of training is recommended for experienced athletes, students who have worked for more than 1 year with a fitness trainer and have mastered the technique of performing exercises [3, 5, 8].

We believe that the main advantages of fitness over other programs are:

1. Aerobic exercise will lead to overweight loss.
2. Anaerobic load helps to improve cardiovascular, respiratory and digestive systems.
3. Strength exercises will help to lift muscles and create elastic shapes.
4. Proper nutrition will help to correct weight.
5. The individual selection of exercises, the mode of training depending on the type of figure, health status and the purpose of training will help to achieve the desired result faster.
6. Fitness can be practiced by anyone, regardless of age and physical condition.

Particular attention is paid to a balanced diet when exercising. To achieve the desired positive result, a leading role must be given to the diet. The ideal figure is not a myth or a gift of nature, but the result of hard work on oneself. A person will not acquire the desired physical fitness if he or she eats irregularly. Properly selected diet and constant adherence to it is the key to success. It is rational and healthy nutrition which carries a positive charge and a healthy state of the body that will help to see clearly how your figure is changing, approaching the ideal.

At the beginning of the experiment, we carried out the students' survey of nutrition balance and adherence to the daily regimen. Most students, 74%, do not pay attention to observing the daily regime, eating irregularly malicious food. We have given the following recommendations to the students: it is desirable to eat food at the same time, the amount of food consumed at a single meal should not cause a feeling of heaviness and drowsiness. It is necessary to have breakfast, the food consumed in the morning recharges the body with energy for the whole day. In the morning it is recommended to eat carbohydrates, yoghurts, farm cheese, whole-wheat bread, honey.

The body needs proteins, fats and carbohydrates, as well as vitamins and minerals. All of them should be contained in certain quantities: the daily amount of protein half animal and vegetable origin, vegetables and fruit should make at least 40% of the diet. A daily diet should consist of 4 main types of products:

- fruit and vegetables;
- grits and cereals;
- dairy products;
- meat and fish.

We recommended the following useful foods: veal, chicken breast, fish, cheese, low fat rice, buckwheat, oatmeal, rye bread, potatoes, green fruits and vegetables. Energy income should only cover the body's energy expenditure for all activities. For women, the required amount of calories consumed should be 2000 kcal per day. High-calorie products (sweets, baked goods, sausages, fried foods) should be replaced with low-calorie ones (vegetable dishes, light soups, seafood, dairy products). The main daily diet (up to 70%) should include morning and afternoon meals: second breakfast, lunch and snack. Dinner is easy, no later than 6 pm - 7 pm. The body also wants to have rest at night and not to work hard as a result of a high-calorie dinner. Once a week, one day of fasting is very useful and once a week is two days, three days of fasting. If it is difficult to manage without food at all, arrange an apple-kefir day. These days help get rid of accumulated slag and improve metabolism. [3, 6].

It is important to take into account not only the amount of calories, but also their quality, i.e. the ratio of proteins, fats and carbohydrates contained in the food consumed. "Protein calories" are used by the body immediately, and "fat" is only used by the body partially, and its excess forms fat deposits in the body. Calories also differ in their content of nutrients, the degree of their absorption by the body also depends on it. The most "caloric substances" are fats. For example with protein cleavage in the body 1 g of protein or 1 g of carbohydrates 4.1 kcal are released, and splitting 1 g of fat gives release of 9.3 kcal. It is necessary to observe the usefulness when choosing the fats themselves. Representatives of saturated fats are refined products, fatty meats and dairy products, which are both "poor" in useful fatty acids and used by the body for energy supply of only 5%, the rest of fat goes to "fat depot". Unsaturated fats are nuts, fish, seeds and oils that are rich in unsaturated fatty acids and almost 75% of them is used by the body.

Our students were advised to eat small portions of food 5-6 times a day, replacing all low-calorie diets with regular, balanced meals. We have set the optimal diet for fitness: every 3 hours in small portions, with a third of the daily norm of food being consumed in the first half of the day. This will ensure a constant supply of nutrients to the body, increase the overall intake of natural protein. This principle of nutrition will permit you not to enlarge your stomach and not to feel hungry. It should be noted that people who constantly limit themselves in food often have a strong appetite, so you should eat small portions every 3-4 hours. It is necessary to eat slowly, because the signal of satiety arrives to our brain in 20-30 minutes. According to medical observations, weight loss should not exceed 2-2.5 kg per month. Therefore, we proposed to gradually reduce energy consumption (calories consumed per day) and increase energy expenditure (physical activity).

We do not recommend you to lose weight quickly and use low calorie intake because it not only threatens to reduce the fat layer but also to reduce muscle tissue. Studies have shown that excessively low calorie diet affects stable weight formation (leptin), which further threatens with uncontrolled hunger and activation of the lipase lipoprotein (the enzyme responsible for accumulation of fat).

It is important to choose the time of meal in accordance with the time of training. If a person intends to lose weight, it is necessary to eat food not later than two hours before training and not earlier than three hours after it. Tuck-in before training not only threatens with digestive disorders but also reduces the efficiency of

your training. It is necessary to refrain from eating immediately after the exercise because during this time the body is in the process of recovering substances. During the training, the muscles stop synthesizing the protein, its balance begins to normalize when the class is over. Consumption a protein (protein) cocktail after training will increase muscle protein synthesis by 3 times, which is useful for the musles recovery. To replenish energy after exercise, it is necessary to eat fruit, vegetables, whole-wheat bread and grits [1, 6].

During training, the body works actively and needs food rich in proteins and carbohydrates. Protein is the main building material for the cells of the body, it is necessary for strengthening and enlarging the muscles. Proteins form tissues such as skin, muscles. hair and nails, if it is not enough, then while training, giving it to the muscles, the body will deprive other organs of the protein, which will lead to fatigue, reduce immunity, impair mental capacity. To avoid this, it is necessary to meet the daily demand for proteins, which is 1.5 g per 1 kg of body weight. Protein can be of both plant and animal origin. Animal protein contains a large number of essential amino acids, which source are all kinds of meat, fish, poultry, eggs and dairy products. Vegetable protein has a higher biological value and is found in legumes, rice, and cereals.

For the most efficient training, to activate the metabolic processes, we recommend drinking water during training. Not only will it improve the body's thermoregulation, it will also accelerate the excretion of breakdown products from the body. To properly adjust your water balance, we recommend weighing before and after your training. If the weight after exercise is less than before, it is necessary to fill this amount with water. It is recommended to give up sweet juices and aerated water in favor of clean non-carbonated water.

Therefore, a balanced diet during fitness should be rich in protein, carbohydrates, minerals and vitamins. Lack of vitamins and minerals will lead to muscle weakness, weakening of immunity, and deterioration of physical condition. The diet must include foods containing a lot of potassium, calcium and vitamins A, B, E and C, so it is recommended to include a large amount of fresh vegetables and fruit, meat, fish, wholegrains and dairy products into the diet [1, 3].

Conclusion

Thus, the use of appropriate methods in the health fitness training has a positive effect on the activity of the cardiovascular and digestive systems, which permits to argue for increasing the body's functionality, immunity to diseases, well-being and achieving the desired sports results. Despite the difference in the directivity of the of health fitness means, modes of performance, the expediency of their use is conditioned by their inherent methodological features, among which there are: variety and interchangeability, ability to strictly regulate the load, ability to be transformed in order to differentiate the load, providing a selective effect on the body, simultaneous solving a wide range of issues.

During fitness classes, the CNS discharges endorphins, which cause feelings of pleasure and good mood [2, 6]. We have found that regular exercises from healthy fitness programs lead to recovering and raise the body's resistance to disease, activate the cardiovascular and respiratory systems, and in combination with a balanced diet have a positive effect on the digestive system and the general condition of the body. By combining music and movement, the nervous system is stimulated, the tone of the muscles is increased, the working ability of students and the performance of all the body systems are improved.

The peculiarity of our study was the combination of exercise and rational nutrition, which guarantees a full revitalizing impact on the human body. In our opinion, in order to improve the health system in our country, it is necessary to implement the acquired knowledge in practical activities and to create the necessary conditions for development of health fitness programs in higher education establishments.

Prospects for further research in this field provide for implementation the content module "Health Fitness" in into the practice of physical education in Ukraine.

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Реферати

ФУНКЦІОНАЛЬНИЙ СТАН СЕРЦЕВО-СУДИННОЇ І ТРАВНОЇ СИСТЕМ ОРГАНІЗМУ У СТУДЕНТІВ ПІД ЧАС ЗАНЯТЬ ФІТНЕСОМ

Согоконь О.А., Донець О. В., Донець І. М.

В роботі проведено дослідження студентів, що займаються сучасними фітнес-технологіями та встановлено, що заняття фізичними вправами впливають на активізацію роботи внутрішніх систем організму. Аналіз взаємозв'язку оздоровчого фітнесу з раціональним харчуванням студентів, дає можливість виявити перспективи покращення діяльності серцево-судинної та травної систем, покращення самопочуття та досягнення бажаних спортивних результатів студентів. За результатами дослідження було встановлено, що 92,5 % студентів позитивно віднеслися до нового змісту занять за сучасними фітнес-технологіями і лише 7,5 % своє ставлення назвали невизначеним. Під час проведення експериментальної роботи підтвердилась динаміка змін параметрів функціонального стану серцево-судинної та травної систем (експериментальна /контрольна групи): середній показник маси тіла зменшився на 2,8 кг / 1,5 кг, пульс в стані спокою знизився до 65,25 уд./хвл. ± 0,25 / 74,46 уд./хвл. ±0,64; систолічний тиск знизився до 112,75 мм рт.ст.±0,35 / 118,21 мм рт.ст.±0,79; діастолічний тиск знизився до 72,21 мм рт.ст. ±0,39 / 76,57 мм рт. ст. ±0,43 ; життєва ємність легень збільшилась на 0,4 л / 0,2 л, що є свідченням економічної діяльності серцево-судинної системи та підтверджує доцільність використаної методики оздоровчих фітнес-технологій. Щодо доцільності змін у харчуванні: 77% студентів висловились за необхідність змін, тоді як 21% назвали зміни бажаними і лише 2% виявили небажання змінювати свій режим харчування.

Ключові слова: фітнес-технології, раціональне харчування, фізичне виховання, здоров'я, серцево-судинна і дихальна системи.

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ФУНКЦИОНАЛЬНОЕ СОСТОЯНИЕ СЕРДЕЧНО-СОСУДИСТОЙ И ПИЩЕВАРИТЕЛЬНОЙ СИСТЕМ ОРГАНИЗМА У СТУДЕНТОВ ВО ВРЕМЯ ЗАНЯТИЙ ФИТНЕСОМ

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В работе проведено исследование студентов, которые занимаются современными фитнес-технологиями и установлено, что занятия физическими упражнениями влияют на активизацию работы внутренних систем организма. Анализ взаимосвязи оздоровительного фитнеса с режимом питания студентов, дает возможность выявить перспективы улучшения деятельности сердечнососудистой и пищеварительной систем, улучшения самочувствия и достижения желаемых спортивных результатов. По результатам исследования установлено, что 92,5 % студентов позитивно отнеслись к новому содержанию занятий за современными фитнес -технологиями и только 7,5 % свое отношение назвали неопределенным. Что касается изменений в режиме питании: 77% высказались за необходимость изменений, тогда как 21% назвали изменения желаемыми и только 2% выявили нежелание изменять свой режим питания.

При проведении эксперимента подтвердилась динамика изменений параметров физического состояния организма: средний показатель массы тела снизился на 2,8 кг, пульс в состоянии покоя снизился до 65,25 ± 0,25 уд. /мин.; систолическое давление снизилось до 112,75 мм рт.ст.±0,35; диастолическое давление снизилось до 72,21 мм рт.ст. ±0,39, что является показателем экономной деятельности сердечно-сосудистой системы.

Ключевые слова: фитнес - технологии, рациональное питание, физическое воспитание, здоровье, сердечно-сосудистая и пищеварительная системы.

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EVALUATION OF ORAL HYGIENE AND DENTAL CARIES STATUS IN PATIENTS WITH BETA THALASSEMIA

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The study involved 321 patients with a homozygous form of thalassemia and 382 somatically healthy individuals. For the objective evaluation of teeth hard tissues and oral hygiene, the following clinical tests were performed: Simplified Oral Hygiene Index (OHI-S) (Green J.C., Vermillion, J. R., 1960), index by Yu.A. Fedorov and V.V. Volodkina (1971), DMFT index. Comparative analysis revealed a significant difference between the indices of the DMFT index and the index of OHİ-S in the groups. There was a tendency to deterioration of the hygienic index with advancing age of patients with thalassemia. The highest values were found in the group over the age of 18 (3.60±0.11). Thus, preventive dental care is a top priority for patients with β-thalassemia.

Key words: β-thalassemia, oral hygiene, prevention of dental diseases, dental caries.

The study is initiative.

Thalassemia belongs to the most common genetic diseases in the group of blood pathologies. According to the World Health Organization (WHO), there are more than 250 million thalassemia carriers in the world and about 300,000 thalassemia patients [5, 6, 8]. At present, in Azerbaijan, β-thalassemia major is one of the main medical and social problems of the public healthcare. According to the results of genetic studies presented to "Unisef", the frequency of thalassemia among the population in Azerbaijan is

quite significant, and it occupies one of the first places (15%) among the numerous hemoglobinopathies. Based on genetic heterogeneity, clinical and hematological variability, β-thalassemia can be homozygous (β-thalassemia major), heterozygous or complex heterozygous. The heterozygous form of the disease is the most common form with minimal clinical manifestations [1, 2].

The main pathogenetic factor of the homozygous form - β-thalassemia major - is the reduction or complete inhibition of β-globin chains. The main symptoms of this disease include, first of all, severe anemia with intense but inefficient erythropoiesis, excessive bone marrow activity and extramodular hematopoiesis causing pronounced changes in the development of bones, including those of the face and skull [3, 4].

It should be noted that in the performed studies, the authors observed deforming expansion of the upper jaw, protrusion of the frontal teeth, distal and open bite in patients with β-thalassemia major [5, 11, 13]. A number of studies report that patients with β-thalassemia major have a higher level of tooth demineralization than the normal population. The low concentration of phosphorus and IgA in such patients' saliva makes them more prone to the dental caries development [7, 12, 14].

It should be noted that in modern clinical practice the opinion has arisen that numerous dental problems in patients with β-thalassemia major are due to the lack of proper attention to preventive measures and hygienic care of the oral cavity, the negligence of patients and insufficient attention of their parents to the necessary measures for the main disease [3, 6, 10]. Therefore, it is possible that pathogenetic involmemt of thalassemia major can play an important role in the development of dental deases.

The purpose of the study was to determine the oral hygiene indices and the dental caries intensity, depending on the age of patients with β-thalassemia major.

Materials and methods. The study was carried out at the Department of Dentistry of the Azerbaijan State Medical University and at the Thalassemia Center in Baku.

The study involved 321 patients with β-thalassemia major and 382 healthy persons. The study groups were divided into 4 age groups: 1- group from 3 to 5 years of age; 2- group aged from 6 to 12; 3- group aged from 13 to 17 and group 4 aged from 18 to 35. To determine the oral hygiene status, the Fedorov-Volodkina hygiene index (1971) and the simplified hygiene index (GreenJ.C., VermillionJ.R., 1960) were applied. To assess the caries intensity of tooth with DMFT, deft indices were used. PBI (Papillary Bleeding Index) were used for in assessing changes ingingival health.

The obtained digital data were subjected to statistical processing by the methods of variational (U-Mann-Whitney) and discriminant (Chi-Square) analyzes by the electronic table EXCEL-2010 and SPSS-20.

Results of the study and their discussion. When analyzing the oral cavity hygienic status according to Fedorov-Volodkin in the younger age group (3-5 years), no statistically reliable differences were noted. In the control group, the index was 2.19±0.09 versus 2.25±0.05 in the main group, which indicates unsatisfactory oral hygiene in the both groups of patients (table 1).

Table 1

Oral cavity hygiene index according to Fedorov Volodkin

Indices / Age group	Group under study	hygiene index in points	Index assessment, number in %				
			Good (1.1-1.5)	Satisfactory (0.6-1.5)	Unsatisfactory (2.1-2.5).	Bad (2.6-3.4)	Very bad (3.5-5.0)
3-5 years of age	Main group (n-59)	2.25±0.05	2 (3.4±2.4)	20 (33.9±6.2)	19 (32.2±6.1)	18 (30.5±6.0)	-
	Control group (n-33)	2.19±0.09	2 (6.1±4.2)	15 (45.5±8.7)	11 (33.3±8.2)	4 (12.1±5.7)	1 (3.0±3.0)

Note: * - statistically significant with values ($p < 0.05$); ** - statistically significant with values ($p < 0.01$); *** - statistically significant with values ($p < 0.001$).

In assessment of the deft index, reliably different results were obtained. Thus, the mean value of the index in the main group was by 1.4 times higher than the mean value in the control group ($p < 0.05$).

When assessing the level of oral cavity hygiene in the age group of 6-12 years, a reliable increase of the index in the group of patients with β-thalassemia major ($p < 0.001$) was established. Meanwhile, if a satisfactory oral hygiene index was observed in 12.8% of the patients in the control group, in the main group this index was determined in 4.3% ($x2 = 15.23$, $p < 0.01$); by calculating the same DMFT/deft index, their increase was noted be doubled in patients with β-thalassemia major ($p < 0.001$) (table 2).

Comparing the mean indices of oral hygiene in patients with β-thalassemia major with somatically healthy persons in the third age group (13-18 years), a significant increase in the OHI-S index by 1.9 times ($p < 0.001$) was observed. Meanwhile, satisfactory hygiene in the control group was observed in 54.1%, and in the main group only in 10.5% of the patients. Unsatisfactory oral hygiene in the control group was in 35.3% versus 24.6% in the main group.

Table 2

Simplified Oral Hygiene Index |- OHI-S

Indices / Age group	Group under study	Hygiene index in points	OHI-S assessment, number in %			
			Good (0-0.6)	Satisfactory (0.7-1.6)	Unsatisfactory (1.7-2.5)	Bad (2.6-6.0)
6-12 years	Main group (n-140)	2.98±0.07	-	6 (4.3±1.7)	43 (30.7±3.9)	91 (65.0±4.0)
	Control group (n-179)	2.56±0.07	1 (0.6±0.6)	23 (12.8±2.5)	74 (41.3±3.7)	81 (45.3±3.7)
13-18 years	Main group (n-57)	3.11±0.15***	-	6 (10.5±4.1)	14 (24.4±5.7)	37 (64.9±6.3)
	Control group (n-85)	1.62±0.09	5 (5.9 ±2.6)	46 (54.1±5.4)	30 (35.3±5.2)	4 (4.7±2.3)
18-35 years	Main group (n-65)	3.60±0.11***	-	2 (3.1±2.1)	5 (7.7±3.3)	58 (89.2±3.8)
	Control group (n-85)	2.13±0.10	1 (1.2±1.2)	28 (32.9±5.1)	31 (36.5±5.2)	25 (29.4±4.9)

Note: * - statistically significant with values (p <0.05); ** - statistically significant with values (p <0.01); *** - statistically significant with values (p <0.001).

The "poor hygiene" criterion index was observed in 64.9% in the first group, and in the second group - only in 4.7% cases (x2 = 65.16, p <0.001). The mean value of the DEF index in the group of patients with β-thalassemia major also differed reliably and was by 1.8 times higher than in the healthy group (p<0.001).

When interpreting the OHI-S hygiene index values in the fourth age group (18-35 years), it was found that only 2 patients among 65 of the main group (3.1%) had satisfactory and 5 people (7.7%) unsatisfactory indicators, and the remaining 89.2% showed a poor hygienic condition of the oral cavity, which is by 2.3 times more than in somatically healthy individuals (x2 = 53.72, p <0.001).

As for the DMFT index, its mean value in the main group was 9.18±26, which is by 1.5 times higher than the mean value in the control group (p <0.001). (table 3)

The data obtained indicate a more pronounced degree of oral hygiene index in all the main groups. Thus, it is obvious that one of the factors causing high carious injuries of teeth in talassemic patients is unsatisfactory oral hygiene.

Table 3

Intensity of the carious process

Age groups	deft/DMFT index records	
	Main group	Control group
3-5 (deft)	9.41±0.62***	6.82±0.75
6-12 (DMFT/ deft)	9,75±0,35***	4,84±0,25
13-17 (DMFT)	6.84±0.25***	3.91±0.30
18 -35 (DMFT)	9.18±0.26***	6.31±0.31

Note: * - statistically significant with values (p <0.05); ** - statistically significant with values (p <0.01); *** - statistically significant with values (p <0.001).

The DMFT indices and the index of oral hygiene in the second age group are higher than those of the other age groups. Studies of the age-related dynamics of oral hygiene showed that a more favorable situation was found in somatically healthy individuals.

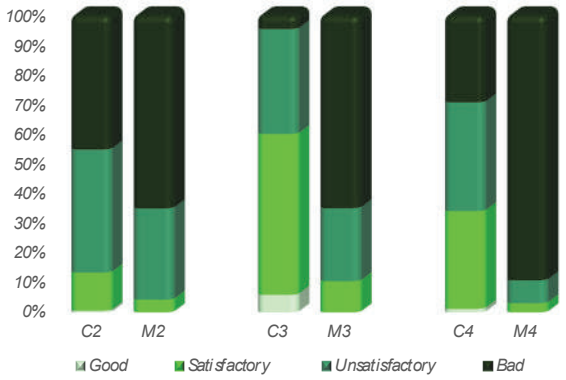

Fig. 1. Values of OHI-S hygiene index depending on age (C-control group, M-main group)

In the group of patients with ß-thalassemia major, the level of individual oral cavity hygiene is decreasing with age (fig. 1).

As it is known, bacterial plaque resulting from poor oral hygiene is the cause of chronic inflammatory periodontal diseases. The earliest sign of inflammatory periodontal disease is the gum bleeding.

A comparative analysis of the results of the bleeding index in patients of the main and control groups aged 6-12 years revealed that mild inflammation was observed in 14.4%±3.0 of the patients of the main, 46.8%±4.0 of the children in the control groups. The moderate degree of

inflammation is present in 52.5±4.2% of the main group and in 46.8±4.0% of the control group. Severe inflammation is observed in the main and control groups, respectively, in 33.1±4.0% and 6.3±1.9%.

At the age of 13-17 years, a mild inflammation was detected in 1.8±1.8% in the main group and 63.4±5.3% in the control group, the moderate degree of inflammation was 25.0±5.84% in the main and 35.4±5.3% in the control while severe degree of inflammation was observed in 73.2±5.9% of the main and 4.3±2.9% of the control groups. In the main group of the adult population of 18-35 years old, mild inflammation was observed in 1.5±1.5%, moderate in 26.2±5.5%, and severe in 72.3±5.6% of patients. In the control group, mild inflammation was observed in 32.9±5.1%, moderate inflammation was observed in 43.5±5.4% of patients, and severe inflammation was detected in 23.5±4.6% of patients.

The results of the work of Yousif A. et al. did not show a statistical difference in the indicators of the hygiene index, the value of the DMFT index and the gingivitis index between thalassemic patients and healthy group in the younger age group [9]. However, these indicators were significantly high in thalassemic patients in the adolescent age group. The results of our study are not consistent with the results of the study by Tirumala K. et al. The study of children with β-thalassemia major revealed a low level of dmft index in young children and a low level of the DMFT index in teenagers [12, 14]. Dama S. et al. also did not reveal a statistically significant difference between the degree of dental caries in patients with β-thalassemia major and healthy group [5]. Authors Karayilmaz H., Manali A. reported higher rates of oral hygiene indices, DMFT in patients with thalassemia major compared with similar readings of the healthy group [11, 12]. The age group range in our work, absorbs shorter ranges of foreign researchers and is distinguished by a larger sample, which obviously explains the different results. Thus, our data suggest that one of the factors of high prevalence of dental caries and inflammation of periodontal tissues in patients with β-thalassemia major is poor oral hygiene. The provision of dental care should be considered as a necessary component of the healing of the body and the favourable course of such a complex pathology as major β - thalassemia.

Conclusion

Thus, the study of the oral hygiene index and the dental caries indices in patients with β-thalassemia major permits to control the level of individual hygienic care, early detection of demineralization and destruction of dental hard tissues, prevention of secondary dental arch deformities and occlusion disorders. In a comprehensive study of patients with β-thalassemia, the importance of dentist involvement and the provision of dental care should be considered a necessary part of the body's recovery and a favorable course of such complex pathology as β-thalassemia major.

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Реферати

ОЦІНКА ГІГІЄНІЧНОГО СТАНУ ПОРОЖНИНИ РОТА ТА ИНТЕНСИВНОСТІ КАРІЄСУ ЗУБІВ У ПАЦІЄНТІВ З В-ТАЛАСЕМІЄЮ

Шадлінська Р.В.

У дослідженні брали участь 321 пацієнта з гомозиготною формою β-таласемії і 382 соматично здорові особи. Для об'єктивної оцінки твердих тканин зубів і гігієни порожнини рота використовувалися клінічні тести: гігієнічний індекс Гріна-Вермільльона (Green J.C., Vermillion J.R., 1960), індекс Ю.А. Федорова і В.В. Володкіної (1971) і показник інтенсивності карієсу КПУ. При порівняльному аналізі в групах виявлена достовірна різниця між показниками індексу КПУ і індексу ОНІ-S. Спостерігалася тенденція до погіршення гігієнічного індексу зі збільшенням віку пацієнтів з β-таласемією. При цьому, найбільше значення виявлено в групі старше 18 років (3,60 ± 0,11). Більш високий ризик розвитку карієсу був виявлений в групі з β-таласемією в порівнянні з обстежуваним контингентом без соматичних захворювань. Профілактична стоматологічна допомога є першочерговою необхідністю для пацієнтів з великою β-таласемією.

Ключові слова: β - таласемія, карієс, гігієна порожнини рота, профілактика стоматологічних захворювань.

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ОЦЕНКА ГИГИЕНИЧЕСКОГО СОСТОЯНИЯ ПОЛОСТИ РТА И ИНТЕНСИВНОСТИ КАРИЕСА ЗУБОВ У ПАЦИЕНТОВ С В–ТАЛАССЕМИЕЙ

Шадлинская Р.В.

В исследовании принимали участие 321 пациента с гомозиготной формой β-талассемии и 382 соматически здоровые лица. Для объективной оценки твердых тканей зубов и гигиены полости рта использовались клинические тесты: гигиенический индекс Грина-Вермилльона (Green J.C., Vermillion J.R., 1960), индекс Ю.А. Федорова и В.В. Володкиной (1971 г.) и показатель интенсивности кариеса КПУ. При сравнительном анализе в группах выявлена достоверная разница между показателями индекса КПУ и индекса ОНІ-S. Наблюдалась тенденция к ухудшению гигиенического индекса с увеличением возраста пациентов с β-талассемией. При этом, наибольшее значение обнаружено в группе старше 18 лет (3,60±0,11). Более высокий риск развития кариеса был обнаружен в группе с большой β-талассемией по сравнению с обследуемым контингентом без соматических заболеваний. Профилактическая стоматологическая помощь является первостепенной необходимостью для пациентов с большой β-талассемией.

Ключевые слова: β – талассемиия, кариес, гигиена полости рта, профилактика стоматологических заболеваний.

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FEATURES OF THE RAYNAUD'S SYNDROME COURSE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Often, patients with rheumatoid arthritis develop secondary Raynaud's syndrome, which is a prognostically unfavorable symptom of its course. Raynaud's syndrome is more common in patients with an existing rheumatoid factor in the blood serum. In patients with rheumatoid arthritis there is an impaired endothelium dependent vasoregulation in the shoulder artery, indicating the endothelial function disorder. In patients with rheumatoid arthritis with secondary Raynaud's syndrome, there are more pronounced signs of endothelial dysfunction, indicating a high risk of atherosclerosis and cardiovascular complications. The index of open capillaries permits to objectively assess the Raynaud's syndrome severity in patients with rheumatoid arthritis.

Key words: rheumatoid arthritis, Raynaud's syndrome, endothelial dysfunction.

The study is a fragment of the research project "Clinical and immunological aspects of the internal organs major diseases course and their correction", state registration No. 0119U002040.

Rheumatoid arthritis (RA) is an autoimmune disease of unknown etiology with the development of symmetrical erosive arthritis (synovitis) and a wide range of extra-articular (systemic) manifestations [9]. This is the most common and disabling connective tissue disease (affects about 1% of the world and 0.4% of Ukrainian population) [10]. In 58.7-72% of patients with RA, comorbid conditions such as Raynaud's syndrome (RS) and arterial hypertension, which can significantly modify the course of the disease, impair the treatment efficacy and reduce the life expectancy of patients [10].

An important pathogenetic link of RA is the microcirculation system impairment, and the microvasculature serves as the target organ in which the immune, inflammatory and metabolic mechanisms of the pathological process are implemented. Disorders in the microcirculation system are associated with the systemacity of lesions, duration of the disease, antioxidant protection disorders, endothelial dysfunction indices and reliably play a leading role in the pathogenesis of RA systemic manifestations. As of today, the endothelium is known to be the target of oxidative stress, which reduces endothelium dependent vasodilatation of blood vessels, promotes the increase of cellular processes course rate and accelerates their apoptosis.

In recent years, the results of numerous studies show that endothelial dysfunction (ED), as well as the increasing intima-media thickness, is a predictor of future cardiovascular morbidity in the general population and one of the diagnostic criteria for early detection of atherosclerotic vascular lesions. This also applies to RA, since the presence of ED is even observed at its early stages and is also interpreted as a sign of accelerated development of atherosclerosis. Thus, the presence of ED is considered to be the first manifestations of atherogenesis in patients with RA [4, 5, 8].

Patients with RA frequently have secondary Raynaud's syndrome (RS), which serves as a prognostically unfavourable sign of its course. Mechanisms of RS development are still insufficiently studied. The nature of the disease is multifactorial, vascular and immune mechanisms playing an important role. Local ischemia of tissues with the possible development of dystrophy, which is observed in RS, may arise either due to the vascular functions regulation impairment caused by the sympathetic nervous system, or due to the increased formation of vasoconstrictor substances in the process of autoimmune inflammation.

Vascular changes in the inflammatory process are proliferation or destruction of the endothelium, hyperplasia and thickening of the intima, which leads to the tissues ischemia [2, 3]. Further study of the clinical-pathogenetic and immunological features of the secondary RS course in patients with RA is relevant and will permit to improve the schemes of its correction in the complex therapy of RA.

The purpose of the work was to study the features of the RS course in patients with RA using laboratory and instrumental research methods.

Materials and methods. The total of 85 patients with RA (12 men and 73 women) were examined, being under inpatient treatment at the rheumatologic department of Ivano-Frankivsk Regional Clinical Hospital. RS was diagnosed in 43 patients (6 men and 37 women). Mean duration of RA was 9.3 ± 2.4 years. The diagnosis of RA was established based on the criteria of the American College of Rheumatology (2010). The criteria by E.Allen and G.Brown were used to diagnose RS [7].

All patients with RA were divided into two groups: group 1 consisted of patients with RA - 38 patients, and group 2 included RA patients with secondary RS - 47 patients. The control group was represented by 25 healthy volunteers whose age and sex corresponded to those in groups 1 and 2.

Endothelin-1 (ET-1) content was determined by immunoassay (ELISA) using a reagent set produced by Peninsula Laboratories Inc. (USA). It is a sandwich ELISA method, which measures “free” forms of human endothelin-1. Concentration of tumor necrosis factor-α (TNF-α) was determined by standardized ELISA using a set of CYTELISA-TNF-α reagents. (USA).

The level of C-reactive protein (CRP) and rheumatoid factor (RF) were determined by the method of latex agglutination. To determine the amount of CRP in mg / l in the sample, the maximum dilution of the blood serum giving visible agglutination should be multiplied by 6 mg / l. The norm is considered to be indices of up to 6 mg / l, sensitivity of the test to be 6 mg / l. To determine the amount of RF in IU/ ml in the sample, the maximum dilution of blood serum, which gave visible agglutination, must be multiplied by 12 IU / ml. Normal values are up to 12 IU / ml, test sensitivity is 12 IU / ml.

The endothelium function was assessed using the so-called endothelium dependent vasodilatation of the brachial artery (EDVBA). The reactive test was carried out using the technique developed by D.S. Celermajer and co-authors (1992). The normal reaction of the brachial artery was considered to be its dilation against the background of reactive hyperemia by 10% or more of the initial diameter, and lower indices were regarded as a pathology [6].

We used capillaroscopy of the nail bed to objectivize the RS assessmenrt in patients with RA. The index of open capillaries (IOC) was calculated reflecting the ratio of functioning and desolate anses capillaires. The IOC normally makes 50-70%.

To study the subjective picture of the peripheral circulation status, we used the assessment scale by A.B. Scherbakov (1987). The scale of the RS attacks severity is a visual 10-point scale, in which 0 is a complete absence of attacks, and 10 points - the presence of gangrene changes in the fingers. The frequency and duration of SR attacks were also assessed.

Statistical processing of the data obtained was performed with the definition of the arithmetic mean, its mean square deviation and the error of the arithmetic mean. The reliability of the differences (p) between the compared groups of patients was established using the t-criterion. To determine the variables interaction, the correlation index (r) was determined.

Results of the study and their discussion. Signs of ED were detected in 76 patients examined, which amounted 89.4% (table 1). All patients with RA in combination with secondary RS have been diagnosed for ED. We found that patients with RA and RA in combination with RS have insufficient EDVBA. In patients of group 2, the EDVBA score was significantly ($p < 0.05$) lower (6.5 ± 0.2%) compared

to patients in group 1 (8.8 ± 0.3%). This is most likely due to constant vasospastic attacks in these patients, which leads to disruption of the endothelium integrity.

In RA patients with secondary RS, the level of endothelin-1 by 1.7 times higher compared to RA patients without RS ($p < 0.05$). It all suggests a greater probability of endothelial damage in patients of group 2. Concentration of ET-1 in RA patients with RS correlated with RA activity ($r = 0.68$, $p < 0.05$).

Table 1

Indices of EDVBA, ET-1, TNF-α and CRP in examined patients

Index	Control group, n=25	All patients, n=85	RA, n=38	RA +RS n=47	Degrees of RA activity		
					Degree I, n=8	Degree II n=25	Degree III n=52
ED	-	76 (89.4%)	29 (34.1%)	47 (55.3%)	1 (1.2%)	24 (28.2%)	51 (60.0%)
EDVBA, %	12.9±0.4	7.5±0.3*	8.8±0.3*	6.5±0.2*•	9.3±0.3*•	7.8±0.2*•°	6.3±0.2*•°'
Endothelin-1, пкг/мл	1.5±0.1	7.0±0.3 *	5.1±0.3*	8.6±0.3*•	4.4±0.2*•	6.4±0.2*•°	9.1±0.3*•°'
TNF-α, pg/ml	24.4±3.1	72.6±7.6*	64.1±5.2*	79.3±6.2*•	50.7±5.1*•	66.1±5.2*•°	82.3±7.2*•°'
CRP, mg/l	6.3±0.3	68.4±7.6*	52.4±7.6*	88.4±7.6*•	24.3±4.5*•	53.2±5.7*•°	86.5±8.5*•°'

Notes: n –number of patients; * - reliable difference from the control group, $p<0.05$; • - reliable difference between RA and RA+RS patients, $p<0.05$; ° - reliable difference between patients with I and II RA activity degrees, $p<0.05$; ' - reliable difference between patients with II and III RA activity degrees, $p<0.05$.

TNF-α belongs to proinflammatory cytokines. Therefore, the inflammatory process activity degree has the most important meaning for assessing the level of TNF-α. In particular, in patients with minimal activity of the pathological process, this index reliably grows by 2.1 times in comparison with healthy donors. With the moderate activity of the inflammatory syndrome, the TNF-α level grows even more (by 23.3% higher than the TNF-α titre with degree I of RA activity). Whereas with maximal activation of the pathological process, the TNF-α value increases to 82.3±7.2 pg / ml. It should be noted that the level of this cytokine is significantly higher in group 2 of patients compared to group 1 (20.0%). A strong correlation between the degree of RA activity and the level of TNF-α ($r = 0.73$; $p < 0.01$) in RA patients with secondary RS was established. Summarizing the above, it can be argued that TNF-α is an important pro-inflammatory agent, which increased production with RA complicates the course of the disease. The revealed correlation between the TNF-α level and the degree of the inflammatory syndrome activity permits to use determined value of this cytokine as a marker of inflammation in RA. Stably high TNF-α concentration in blood serum of patients with secondary RS is a prognostically unfavorable symptom and a predictor of RA progression.

Both CRP and TNF-α serve as a nonspecific markers of inflammation, which were determined at significantly higher concentrations (88.4 ± 7.6 mg / l, $p < 0.01$) in patients with RS, than in patients with pure RA (52.4 ± 7.6 mg / l). This testifies to the high RA activity in patients of group 2.

An important factor in predicting the course of RA and secondary RS is the presence of the RF (RF +) in the blood. In patients of group 2, the concentration of RF was 89.3 ± 7.2 IU / ml and was significantly higher than in group 1 (49.4 ± 5.2 IU / ml, $p < 0.01$). Among the patients of group 2, 43 patients had a seropositive variant of RA (table 2).

Table 2

RF frequency and concentration levels in examined patients

Index	Control group, n=25	All patients, n=85	RA, n=38	RA +RS n=47	Degrees of RA activity		
					Degree I, n=8	Degree II n=25	Degree III n=52
RF+	-	63 (74.1%)	20(23.5%)	43 (50.3%)	2 (2.35%)	18 (21.2%)	43 (50.6%)
RF-	30(100%)	22(25.9%)	18(21.2%)	4 (4.7%)	6 (7.1%)	7 (8.2%)	9 (10.6%)
RF, IU/ml	8.3±1.8	65.3±5.8*	49.4±5.2*	89.3±7.2*•	43.4±3.8*•	55.3±4.6*•°	108.3±8.8*'

Notes: n –number of patients; * - reliable difference from the control group, $p<0.05$; • - reliable difference between RA and RA+RS patients, $p<0.05$; ° - reliable difference between patients with I and II RA activity degrees, $p<0.05$; ' - reliable difference between patients with II and III RA activity degrees, $p<0.05$.

After monitoring the data obtained, it was found that in patients of group 2 with high activity degree, frequency (7.8 ± 0.5), duration (24.7 ± 3.6) and severity (6.6 ± 0.6) of RS attacks was significantly higher ($p < 0.05$) than in patients with activity degree I (3.7 ± 0.5, 12.8 ± 2.1 and 3.1 ± 0.2, respectively).

IOC had a correlation interaction with the frequency ($r = 0.59$; $p < 0.05$), duration ($r = 0.58$; $p < 0.05$) and severity ($r = 0.53$, $p < 0.05$) of RS attacks. The highest values were observed in patients with high RA activity (95.2 ± 5.2) and significantly differed from those in patients with RA activity degree II (76.2 ± 4.2; $p < 0.05$) and the activity degree I (66.3 ± 3.5; $p < 0.05$) (table 3).

Table 3

IOC, frequency, duration and severity of RS attacks in patients with RA

Index	Control group, n=25	RA +RS n=47	Degrees of RA activity		
			Degree I, n=8	Degree II n=25	Degree III n=52
Frequency of attacks	-	6.7±0.5	3.7±0.5	4.7±0.5*°	7.8±0.5*°'
Duration of attacks, min	-	23.7±3.6	12.8±2.1	16.4±3.3*°	24.7±3.6*°'
Severity of attacks, points	-	5.3±0.5	3.1±0.2	4.1±0.5*°	6.6±0.6*°'
IOC, %	54.3±3.5	84.5±4.6*	66.3±3.5*	76.2±4.2*°	95.2±5.2*°'

Notes: n –number of patients; * - reliable difference from the control group, p<0.05; ° - reliable difference between patients with I and II RA activity degrees, p<0.05; ' - reliable difference between patients with II and III RA activity degrees, p<0.05.

Clinical manifestations, features of the inflammatory process and changes in the parameters of the endothelium functional status in RA patients in combination with secondary RS are still understudied and require a targeted study. In general, the results of our study coincide with the literature data. High levels of CRP, TNF-α, and ET-1 in RA patients in combination with RS were presented in domestic and foreign studies [3, 5, 10]. Early development of ED and the presence of high RF titres in RA patients were shown in the studies of I.I. Blahinina [5].

However, in our study for the objective assessment of peripheral blood circulation, a capillaroscopic examination of the patient was used. Capillaroscopy of the nail bed is a highly informative, fast and convenient method for diagnosing and monitoring the RS progression in patients with RA. We first used IOC to objectively assess the peripheral circulation changes and showed its high informational value in the instrumental assessment of RS course in RA patients.

Conclusions

1. In patients with secondary RS, the activity of RA inflammatory syndrome is higher than in patients with RA without RS, as evidenced by higher CRP, RF and TNF-α in the study group 2.

2. The RF presence in the blood serum of patients with RA serves as an unfavourable sign of its course, and more frequently occurs in patients with secondary RS.

3. The ED severity and frequency in patients with secondary RS is higher than in RA patients without RS.

4. In patients with RA in combination with secondary RS, high values of ET-1 and IOC levels, low rates of EDVBA appear to be a prognostically unfavorable sign in the course of this disease.

5. A detailed study of the pathophysiological and immunological features of the secondary RS will improve the treatment regimens in RA patients, reduce clinical and laboratory manifestations of RA, and improve the life quality of these patients.

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Реферати

ОСОБЛИВОСТІ ПЕРЕБІГУ СИНДРОМУ РЕЙНО У ХВОРИХ НА РЕВМАТОЇДНИЙ АРТРИТ

Штефюк О.В., Яцишин Р.І., Герич П.Р., Карпюк Ю.Я.,Бойчук В.Б.

Нерідко у хворих на ревматоїдний артрит розвивається вторинний синдром Рейно, який є

ОСОБЕННОСТИ ТЕЧЕНИЯ СИНДРОМА РЕЙНО У БОЛЬНЫХ РЕВМАТОИДНЫМ АРТРИТОМ

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Нередко у больных ревматоидным артритом развивается вторичный синдром Рейно, который служит

прогностично несприятливою ознакою його перебігу. Синдром Рейно частіше виникає у пацієнтів з наявним ревматоїдним фактором у сироватці крові. У хворих на ревматоїдний артрит має місце недостатня ендотелій залежна вазорегуляція у плечовій артерії, що вказує на порушення ендотеліальної функції. У хворих на ревматоїдний артрит з вторинним синдромом Рейно спостерігаються більш виражені ознаки ендотеліальної дисфункції, що є свідченням високого ризику розвитку атеросклерозу та серцево-судинних ускладнень. Індекс відкритих капілярів дає можливість об'єктивно оцінити вираженість синдрому Рейно у хворих на ревматоїдний артрит.

Ключові слова: ревматоїдний артрит, синдром Рейно, ендотеліальна дисфункція.

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прогностически неблагоприятным признаком его течения. Синдром Рейно чаще возникает у пациентов с имеющимся ревматоидным фактором в сыворотке крови. У больных ревматоидным артритом имеет место недостаточная эндотелий зависимая вазорегуляция в плечевой артерии, что указывает на нарушение эндотелиальной функции. У больных ревматоидным артритом с вторичным синдромом Рейно наблюдаются более выраженные признаки эндотелиальной дисфункции, что свидетельствует о высоком риске развития атеросклероза и сердечно-сосудистых осложнений. Индекс открытых капилляров дает возможность объективно оценить выраженность синдрома Рейно у больных ревматоидным артритом.

Ключевые слова: ревматоидный артрит, синдром Рейно, эндотелиальная дисфункция.

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CARDIOVASCULAR SYSTEM INDICATORS IN THE PRIMARY SCHOOL-AGED CHILDREN DURING THE ADAPTATION TO EDUCATIONAL LOADS IN THE REGION WITH IODINE EFICIENCY

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The purpose of the study was to study the adaptive capacity of the cardiovascular system and to identify changes in the performance of heart rate variability in the primary school-aged children with iodine deficiency during the school year. It was found that among the 1st grade schoolchildren with iodine deficiency, 30% of children had the adaptive strategy tension at the beginning of the school year. The largest share of schoolchildren with low adaption level at the beginning of the school year was revealed. According to the indicators of heart rate variability, in 1-4 grades students with iodine deficiency the sympathetic nervous system influence is prevalent during the school year, while the parasympathetic nervous system is predominant in schoolchildren, properly provided with iodine.

Keywords: adaptation, heart rate variability, autonomic nervous system regulation, children, iodine deficiency.

The study is a fragment of the research project "Biochemical mechanisms of metabolic disorders in the presence of toxins of different origins", state registration No. 0116U003353.

The course of adaptation processes best reflects the functional state of the cardiovascular system (CVS), and the heart rate variability (HRV) allows to speak directly about the involvement of certain levels of the central nervous system (CNS) in the physiological functions regulation, in other words about the level of their centralization. According to the theory of R.M. Baevsky, the heart rate structure allows us to evaluate the state of the autonomic nervous system, the degree of organism adaptive resistance, the possibility of adaptive reserves [1, 5]. It is known that the higher the CNS level involved in the regulation of functional systems, the higher the adaptation tension [4, 9]. At the same time, it has been proved that thyroid hormones are essential for the maturation and functioning of the nervous system. Therefore, iodine deficiency (ID) may indirectly impair the adaptation course because of the negative effect on the nerve cell differentiation. One of the most scientifically based and informative methods of quantitative evaluation of the Autonomic Activity Indices, whose parameters are considered as integral indicators of regulation processes of the organism, is a method of computer cardiointervalography [3].

In this regard, to assess the iodine deficiency effect on the CVS activity, all children underwent cardiointervalography to determine the impact of individual autonomic nervous system sections.

The purpose of the study was to study the adaptive capacity of the child's organism to the school loads and to identify changes in the performance of cardiovascular system using heart rate variability in the primary school-aged children with iodine deficiency during the school year.

Materials and methods. The total of 243 schoolchildren from 1st to 4th grade were surveyed at the beginning, the middle and the end of the school year. In the first grade, 64 schoolchildren were healthy, 29 were with iodine deficiency, in the 2nd grade 34 children were healthy, and 18 were with iodine

deficiency, in 3rd grade 33 schoolchildren were with normal iodine content, and 25 were with iodine deficiency, in the 4th grade 17 schoolchildren were healthy and 23 were with iodine deficiency. Schoolchildren were divided into two groups based on iodine availability. The first group consisted of children with normal iodine content in the urine (control group), the second group – with iodine deficiency in the urine (experimental group).

The adaptive capacity level of the cardiovascular system was determined based on the Functional Status Index (FSI). The character of adaptation was determined by the FSI value [4]. When characterizing adaptation, we considered the child's behavior on the basis of the questionnaire of teachers using the test "Adaptation of children to school". (Kyrylenko M., 2006).

Heart rate variability was studied using the Neurosoft's Poly-Spectrum Computing Diagnostic Tool. In our study we took into account in horizontal – baseline test (b) – and in vertical position – orthostatic test (o) – the following indicators: average heart rate (HR), RR interval arithmetic mean value (M), standard deviation (SD), mode(Mo), amplitude of mode (AMo), RR interval median value (Me), deviation range (DR), vegetative equilibrium index (VEI), regulation adequacy index (RAI), vegetation rhythm index (VRI), tension index (TI), ratio of the tension index in the test to the index in the baseline test (TI_2/TI_1), increase in heart rate in the orthostatic test. The resulting digital material was processed by the Student's method of variational statistics, and also used the program STATISTICA 6.0., non-parametric methods (Mann-Whitney), P (u) = 0.05. Correlation analysis was performed using the program STATISTICA 10.0. To determine ioduria in children, the iodine excretion level in spot urine was examined with Dunn's test, and the thyroid was palpated.

Results of the study and their discussion. The most accurate indicator of the adaptive capacity of the organism, including the child's one, is the so-called "adaptive potential", which is quite often used in scientific studies. It defines the possibility of equilibrium between the child's organism and the environment by mobilizing the functional reserves of the CVS. Assessment of the adaptive potential (AP) changes makes it possible to diagnose prenosological conditions and control the effectiveness of rehabilitation measures [4, 9].

Emphasis should be placed on the leading role of determining the functional state of the circulatory system, both at resting state and during the physical activity in the studying of the health status of primary school-aged children. It should be noted that starting school is one of the critical periods in the life of the child, which is accompanied by a very high level of tension of the cardiovascular and sympathoadrenal systems, as well as a low indicator of the interaction of different systems with each other [10].

In the 1st grade, during a detailed ioduria analysis, 64 schoolchildren (69%) were found to be adequately provided with iodine and 27 schoolchildren (29%) were with mild ID, 1 schoolchild (1%) had moderate iodine deficiency and 1 schoolchild (1%) was with a severe ID.

In terms of urinary iodine excretion in the 2nd grade, 34 schoolchildren (65 %) were properly provided with iodine, 14 schoolchildren (27%) had a mild ID, and 4 schoolchildren (8%) had a moderate ID.

Among third-graders: 33 schoolchildren (57 %) were healthy relative to iodine provision and 25 schoolchildren (43 %) had iodine deficiency in their urine. In 4th grade 17 schoolchildren (42 %) were properly provided with iodine, and 23 schoolchildren (58%) had a mild ID.

Our AP indicators, as a criterion for quantifying health status, indicate that the satisfactory adaptation level in the children under observation is predominant. In particular, it was found that the highest percentage (93%) of first-graders with ID had a satisfactory adaptation level at the end of the school year, which exceeds the same indicator at the beginning and in the middle of the school year, and the highest percentage (30%) of the adaptive mechanisms tension is observed at the beginning of the school year. Such a pattern indicates a relatively higher adaptive capacity of the CVS in children provided with iodine. Changes in FSI (probable increase for almost 10% in children with ID) during the school year indicate comparatively lower adaptive capacity of CVS in schoolchildren with iodine deficiency relative to their peers.

Analyzing the questionnaire "Adaptation of children to school" at the beginning, middle and end of the school year, we have found that the largest share of schoolchildren with low adaptation level (13%) was detected at the beginning of the school year.

According to the results of heart rate variability, it was found that at the beginning of the school year the 1st grade schoolchildren with ID had lower values of VEI(b) by 37% ($p < 0.05$), TI(b) by 39% ($p < 0.05$) in relation to the similar data in healthy peers, which indicates the prevalence of the ANS parasympathetic effect in schoolchildren with iodine deficiency, which is consistent with the established data (Tsiapets G.B., 2010). In the middle of the school year, in children with ID was observed a lower value

of TI(b) by 36% (p <0.05) relative to the control, which indicates that the ANS parasympathetic effect was predominant in the schoolchildren of the experimental group. At the end of the school year, the DR(b) values were found to be lower by 48% (p <0.05) in schoolchildren with reference data, which indicates the dominance of sympathetic ANS in these schoolchildren.

At the beginning of the school year, in the 2nd grade schoolchildren with ID were found lower values of VEI(b) by 44% (p <0.05), TI(b) by 45% (p <0.05) relative to healthy peers, which indicates the prevalence of the impact of the ANS parasympathetic section in these children. In the middle of the school year, schoolchildren with ID had significantly higher DR(o) values (almost twice), which indicates the predominance of the parasympathetic nervous system. A 50% decrease in the TI_2/TI_1 indicator (p <0.05) indicates that there is a certain sympathetic tone in children with ID. However, on the basis of the quantitative correlation between the indicators obtained in the heart rate analysis in 2nd grade schoolchildren with ID in the middle of the school year, the parasympathetic nervous system prevails over the sympathetic one. At the end of the school year, lower values of Me(b) (by 60%, p <0.05), Me(o) (by 72%, p <0.05) and TI_2/TI_1 (by 68%, p <0.05) for similar indicators in the control group indicate a predominance of sympathetic tone in schoolchildren with ID.

In the 3rd grade at the beginning and in the middle of the school year, in schoolchildren with ID there were any significant differences between the studied data of heart rate variability. At the end of the school year there was a decrease in Mo(b).

At the same time, there were no significant differences between the indicators of heart rate variability in the 4-th grade schoolchildren with different iodine provision during the school year.

There was no correlation in the first-grade children between indicators of iodine deficiency, adaptive capacity and the child's age.

Table 1

Correlation between indicators of iodine deficiency, adaptive capacity and the child's age in the second grade schoolchildren

	Adaptive capacity in children	Iodine content in the urine	Age
Adaptive potential in children	-	r =0.0080 p=.955	r=0.1773 p=0.209
Iodine content in the urine	r = 0.0080 p=0.955	-	r = 0.2957 p=0.033
Age	r=0.1773 p=0.209	r = 0.2957 p=0.033	-

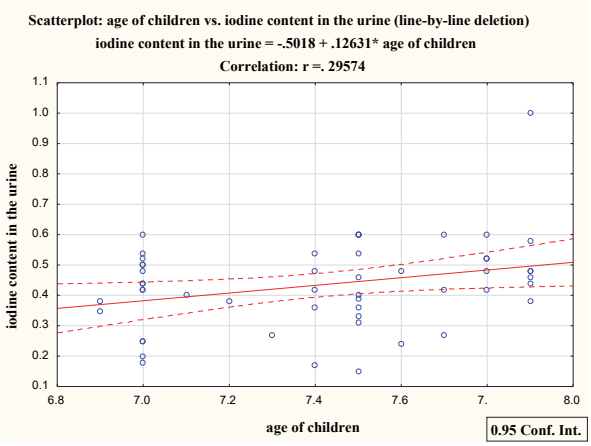

Fig. 1 Correlation between iodine values in the urine and child's age in the second grade schoolchildren

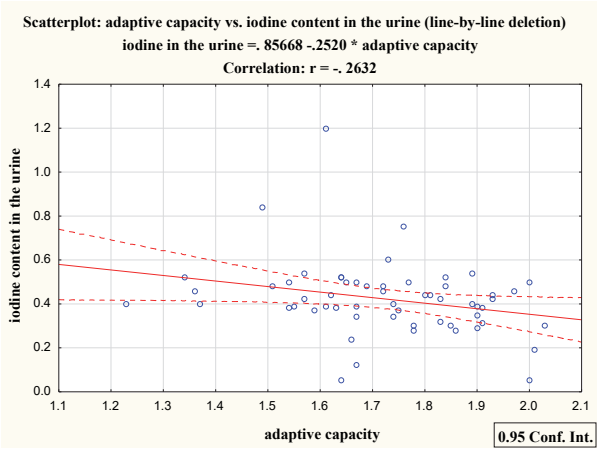

Fig. 2 Correlation between iodine values in the urine and adaptive potential in third grade schoolchildren

Thus, in the 2nd grade schoolchildren, there was a direct weak correlation between the iodine content in urine and the age (r = 0.2957, p = 0.033) (fig. 1).

Table 2

Correlation between indicators of iodine deficiency, adaptive capacity and the child's age in the third grade schoolchildren

	Adaptive potential in children	Iodine content in the urine	Age
Adaptive potential in children		r = 0.2632 p=.046	r = 0.2077 p=0.118
Iodine content in the urine	r = -0.2632 p=0.046	-	r = -.01272 p=0.341
Age	0.2077 p=0.118	r = -0.1272 p=0.341	-

Therefore, in the 3rd grade schoolchildren, there was an inverse weak correlation between the iodine content in urine and the adaptive potential (r = -0.2632, p = 0.046) (fig. 2).

Table 3

Correlation between indicators of iodine deficiency, adaptive capacity and the child's age in the fourth grade schoolchildren

	Adaptive potential in children	Iodine content in the urine	Age
Adaptive potential in children	-	r =-0.2537 p=.114	r =0.3135 p=0.049
Iodine content in the urine	r =-0.2537 p=0.114	-	r =-0,1131 p=0.487
Age	r =0.3135 p=0.049	r =-0,1131 p=0.487	-

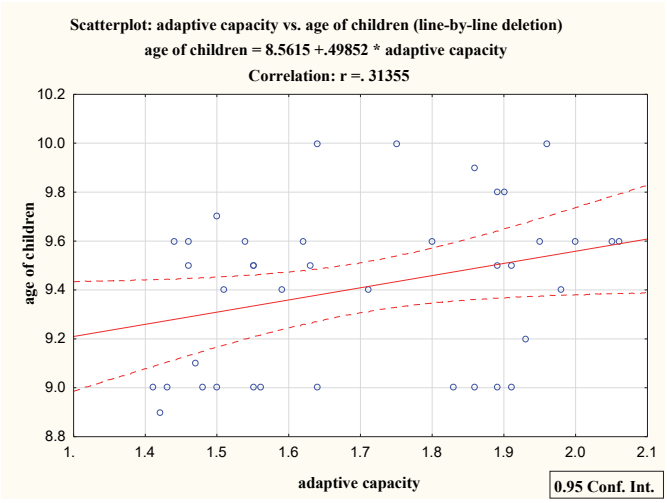

Fig. 3 Correlation between values of children's age and adaptive potential in the fourth grade schoolchildren

There was a direct weak correlation between age and adaptive potential in the fourth grade schoolchildren (r = 0.3135, p = 0.049) (fig.3).

Thus, the frequency of iodine deficiency among schoolchildren in the 1-4 grades is 39 % of children. The results of the study showed that among the 1st grade schoolchildren with ID, a third had the adaptive mechanism tensions at the beginning of the school year, compared with the middle and the end of the school year, and in relation to the similar indicators of the 2-4 grades schoolchildren, which is consistent with the data of other scientists [6, 4, 9]. This can be explained by the fact that starting school inevitably increases the brain load of the child, leads to a decrease in motor activity, changes the usual stereotype; it is an emotional-stress factor for many children and the maximum tension of neuro-psychological adaptive mechanisms. It is known that starting school is characterized by a failure of adaptation and a decrease in the reactivity of the child's organism [2]. It can be argued that younger schoolchildren do not adapt equally to educational loads. This is obviously due to their individual psychophysiological characteristics and environmental impact. According to the literature, reforming the education system has proved inadequate for the physiological capabilities of the child's organism. Thus, almost 30% of the first-graders have adaptation failures in the form of neurovegetative disorders, and an increase in the incidence rate [9].

The data obtained showed that the first-graders have an increase in sympathetic nervous system tone at the end of the school year in children with ID, compared to schoolchildren with normal iodine provision. The identified changes can be considered as a decrease in adaptation reserves of the organism, moderate depletion of regulatory influences, which is consistent with the established data of other authors [4, 9, 10, 11]. The Second- and the third-grade schoolchildren with ID by the end of the school year had an increase in the sympathetic nervous system tone [7, 8, 12]. Correlation analysis revealed that the higher the iodine content in the urine, the better the adaptive capacity in children.

Conclusion

The study results found that the highest levels of tension and the most children with low levels of adaptation were recorded in the first-graders at the beginning of the school year. Primary-aged schoolchildren with iodine deficiency had a higher percentage with the adaptive mechanisms tension, compared to schoolchildren who were properly provided with iodine.

According to the indicators of heart rate variability in the 1-4th grades schoolchildren with iodine deficiency during the school year, the sympathetic nervous system influence is prevalent (decrease of the deviation range index by 52 % ($p < 0.05$) and increase of the tension index by 2.3 times ($p < 0.05$), while in schoolchildren, adequately provided with iodine the parasympathetic nervous system is predominant (an increase of 2.4 times RR interval median value in the baseline test ($p < 0.05$) and 3.5 times in the orthostatic test ($p < 0.05$), ratio of the tension index in the test to the index in the baseline test by 2.3 times ($p < 0.05$).

Prospects of further research lie in assessment of the functional state of the cardiovascular system allows to assess the adaptation state of the child's organism and to predict the possibility of pathology, including the thyroid gland, at the prenosological stage. Children, diagnosed with iodine deficiency using a screening test, need in-depth clinical and laboratory-instrumental examination not only of the thyroid gland but also of other organs.

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Реферати

ПОКАЗНИКИ СЕРЦЕВО-СУДИННОЇ СИСТЕМИ ПІД ЧАС АДАПТАЦІЇ ДО НАВЧАЛЬНИХ НАВАНТАЖЕНЬ ОРГАНІЗМУ ДІТЕЙ МОЛОДШОГО ШКІЛЬНОГО ВІКУ В ЙОДОДЕФІЦИТНОМУ РЕГІОНІ

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Метою дослідження було вивчення адаптаційних можливостей серцево-судинної системи та виявлення змін в показниках роботи варіабельності серцевого ритму в дітей молодшого шкільного віку з йододефіцитом впродовж навчального року. Встановлено, що серед дітей 1-их класів із дефіцитом йоду 30% дітей мали на початку навчального року напруження механізмів адаптації. Виявлено найбільшу частку школярів із низьким рівнем адаптації на початку навчального року. Згідно показників варіабельності серцевого ритму, у дітей 1-4-их класів з дефіцитом йоду впродовж навчального року домінує вплив симпатичної нервової системи, тоді як у школярів, належним чином забезпечених йодом, переважає парасимпатична нервова система

Ключові слова: адаптація, варіабельність серцевого ритму, автономна нервова регуляція, діти, йододефіцит.

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ИССЛЕДОВАНИЕ ИЗМЕНЕНИЙ В ПОКАЗАТЕЛЯХ СЕРДЕЧНО-СОСУДИСТОЙ СИСТЕМЫ ПРИ АДАПТАЦИИ К УЧЕБНЫМ НАГРУЗКАМ ОРГАНИЗМА ДЕТЕЙ МЛАДШЕГО ШКОЛЬНОГО ВОЗРАСТА В ЙОДОДЕФИЦИТНОМ РЕГИОНЕ

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Целью исследования было изучение адаптационных возможностей сердечно-сосудистой системы и выявления изменений в показателях работы вариабельности сердечного ритма у детей младшего школьного возраста с йододефицитом в течение учебного года. Установлено, что среди детей первого классов с дефицитом йода 30% имели в начале учебного года напряжение механизмов адаптации. Выявлено наибольшую часть школьников с низким уровнем адаптации в начале учебного года. Согласно показателям вариабельности сердечного ритма у детей 1-4-х классов с дефицитом йода в течение учебного года доминирует влияние симпатической нервной системы, тогда как у школьников с обеспеченных йодом преобладает парасимпатическая нервная система

Ключевые слова: адаптация, вариабельность сердечного ритма, автономная нервная регуляция, дети, йододефицит.

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MEDICAL, PSYCHOLOGICAL AND LEGAL ASPECTS TO SUBSTANTIATE THE CONCEPT OF REHABILITATION FOR MILITARY PERSONNEL – PARTICIPANTS OF THE ANTI-TERRORIST OPERATION

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The purpose of the work was to substantiate the concept of medical and psychological rehabilitation and legal protection of the military personnel participating in ATO / OOS. The psycho-diagnostic study involved 93 military personnel participating in the ATO / OOS with the mean stay of 12-14 months in the war zone in eastern Ukraine, ranging in age from 20 to 30 years. The results of the study indicate that 53.78% of military participants in the ATO / OOS have certain symptoms of post-stress conditions; partial PTSD was diagnosed in 13.97% of the military; the presence of clinically pronounced disorders of post-stress states is subjectively noted by 19.35% of respondents. Depressive symptoms were recorded in 62.39% of respondents, of which 13.99% were at levels above moderate and high. More than half of the respondents noted the symptoms inherent in post-stress disorders - "invasion" - 59.23% for PTSD and 55.90% for ASD; "Avoidance" - 59.63% with PTSD and 66.27% with ASD; the indicator "Hyperactivation" - 58.21 points for PTSD, and 56.04 for ASD, dissociative symptoms and states of distress and maladaptation - 65.66 points for PTSD and 65.56 for ASD. Given the above, it is necessary to work out at the legislative level the medical-psychological concept of rehabilitation of the military personnel participating in ATO / OOS. Into the program of combat training of military personnel, including commanders of all levels, to introduce a course of the basics of psychological assistance in order to adjust the emotional state by providing self and mutual assistance.

Key words: medical and psychological rehabilitation, participants in ATO / OOS, post-traumatic stress syndrome, acute stress disorder, screening.

The work is initiative.

Medical and psychological rehabilitation and social and psychological adaptation of the military men, who have undergone psycho-traumatic effects caused by a combat situation, are considered to be an extremely pressing problem today. The servicemen who perform combat missions in the ATO / JFO area are constantly confronted with combat stressful situations, which reprogram the organism's resources for survival in life-threatening conditions and are accompanied by the strain of adaptation mechanisms and the obvious signs of psychophysiological changes, which, being very intensive and extended, become the predictors of combat psychotrauma [2, 8, 9]. Post-traumatic stress disorder arises as a deferred or durable response (after a latent period, but not exceeding 6 months) to a stress event (short or long) of threatening or catastrophic character that can cause a deep stress in almost every person. Majority of the military actions participants are able to adapt to new living conditions, but the war effects affect everyone [2, 6].

It is known that over 70% of adults all over the world experience trauma at certain periods of their lives, and 31% have four or more traumatic events. Post-traumatic stress disorder is the most common psychopathological consequence of traumatic events. Duration of post-traumatic stress disorder (PTSD) prevalence varies depending on the social background of an individual and the country of residence, ranging from 1.3 to 12.2%, and the annual prevalence rate ranges from 0.2 to 3.8%. The main features of PTSD are the persistence of stress reactions and fear, avoiding recalls about an alarming event, mood changes, common feeling of imminent threat, sleep disturbance, and hyper-militancy [4, 9, 11].

The most important research achievements in the biological understanding of PTSD are nowadays considered to be the efforts aimed at drawing different conclusions in functionally integrated mechanistic models. Practical biological PTSD correlates today (Pitmanetal) include genes, epigenetic regulations, neuroendocrine factors, inflammatory markers, vegetative risks [11-14]. There is another side connected with the effects of post-stress events. Thus, according to American criminologists, one-third of prisoners serving criminal sentences for committing serious crimes against humans' life and health were veterans of the Vietnam War, many of them had been held captive. According to the experts, 93% of the crimes committed by combatants other than war were connected with their aggression and characterized by unpredictability, impulsiveness, inadequacy with the release of "automated" combat skills. The scholars are concerned that such type of post-traumatic stress has a longer, cumulative nature. In minds of individuals in such a state, devaluation of their own lives as well as the lives of others occurs; fear of death and personal responsibility for social consequences of the committed actions remit [2, 6].

The study of Vietnam, Afghanistan and Iraq war veterans shows that they experience specific types of aggression: fear of attack from behind; feelings of guilt for remaining alive; identifying themselves with the people who were killed [2, 8].

The research findings have shown that the veterans also had the instability of psyche, due to which even the smallest losses, difficulties pushed a person to a suicide [1, 11]. In Ukraine, such studies are only carried out at an early stage, but they are of great importance.

According to the Order of the Ministry of Defense of Ukraine No. 333 dated May 26, 2014 "On Approval of the Instruction on Organizing the Personnel Accounting in the Armed Forces of Ukraine", the list of non-battle irretrievable losses was provided. It said: «the personnel, who irrevocably quitted the ranks of the Armed Forces of Ukraine due to their perish (death), captivity, missed in action or for other reasons, represent irretrievable personnel losses [5]. According to the experts, two-thirds of suicides are committed not in the war zone, but in the permanent disposition points to which the military personnel are sent for recovery. Even more cases of suicide are recorded among those persons who have already completed service in the war zone. In spring 2019, the Head of the Committee on Affairs of Veterans, Combatants, ATO Participants and Disabled People, Verkhovna Rada of Ukraine, O. Tretyakov reported that more than a thousand veterans, with the mean age of about 35 years old, had committed suicide [6]. Thus, despite the measures taken to prevent non-battle losses, the statistics of such events do not decrease. The situation is getting more complicated because of the significant changes in the quality of the military personnel: nowadays the person who serves under the contract often has low cognitive abilities, the lower level of neuro-mental stability and adaptive capacity, that create prerequisites for increasing number of behavioral abnormalities [10]. Currently, a number of foreign scholars propose to supplement the diagnosis of post-stress disorders with one more category – post-traumatic personal disorders (or PTPD), which seems to be quite a logical step, taking into account the fact that the presence of chronic PTSD symptoms is common throughout the whole life of a person who survived a massive psycho-trauma. Undoubtedly, such a trauma can leave an indelible imprint in the soul of a person and lead to a pathological transformation of the personality [15]. Therefore, according to the Military Medical Doctrine of Ukraine, and taking into account the above-mentioned information, we consider it necessary to work out a common position on prevention, diagnosis, medical and psychological assistance, evacuation, treatment, medical and psychological rehabilitation of the wounded (injured, sick). It is very important to understand the reasons for the reduction (loss) of servicemen's combat capability and the ways to increase (or to preserve) it, that requires prevention of combat stress (preventive rehabilitation) [7].

The purpose of this research was to substantiate the concept of medical and psychological rehabilitation and legal protection of the military personnel participating in the anti-terrorist operation (joint forces operation).

Materials and methods. The study involved 93 servicemen, aged 20-30, with a mean duration of staying in the combat zone in the eastern part of Ukraine for 12-14 months. In particular, during the study on the presence of post-traumatic stress disorder and acute stress disorder in the combatants, the survey was carried out to the ATO / JFO military personnel who held full-time positions of the privates, sergeants and sergeant-level positions to determine the combat capability of the military units [12]. In the psychological study, the following scientific methods were applied: observation, testing, systematization, generalization of theoretical and empirical results of the study. The Traumatic Stress Questionnaire for the Diagnosis of Psychological Consequences developed by I. Kotenov was also used to detect PTSD symptom complex (trauma event, "avoidance" symptoms, "invasion" symptoms, hyperactivation, distress and maladaptation); acute stress disorder (ASD) symptom complex (trauma event, dissociative symptoms, "avoidance" symptoms, "invasion" symptoms, hyperactivation, distress and maladaptation, depression). The survey procedure with this questionnaire usage included filling in the questionnaire form and preliminary instructions how to work with it.

Results of the study and their discussion. The questionnaire included the participation of ATO / JFO military personnel with a mean duration of staying in the combat zone for 12-14 months who are at the military service at the present moment. Among this category of respondents, 9 servicemen (9.68%) were injured, 22 servicemen (22.66%) suffered a contusion. In the course of the study, we have obtained the results similar to the guidelines and systematic reviews, which have shown that 53.78% of the military personnel suffered from slight symptoms of post-stress states, 13.97% of the military personnel – combatants suffered from partial PTSD, 19.35% of the respondents had clinically obvious post-stress disorders. Depressive symptoms were recorded in 62.39% of the respondents, 13.99% of whom having depressive symptoms at above moderate and high levels (table 1).

The depression symptoms are very diverse, but the most common ones occur in the form of *emotional* (sadness, anxiety, irritability, self-depreciation, decreased interest to the outside world), *physiological* (sleep disorders, change in appetite, decreased energy, pain and a variety of unpleasant sensations in the body), *behavioral* (passivity, difficulty of person's involvement into the purposeful

activity, contact avoidance, entertainment refusal, alcohol and psychoactive substance abuse) and *mental* manifestations (problems in concentrating, difficulty in decision-making, pessimistic vision of the future, thoughts about suicide, slowness in thinking) [1].

Table 1

Survey results of the military personnel participating in the ATO according to the traumatic events impact assessment scale (%)

No	Assessing the impact of a traumatic event	< 50 points (no symptoms)	50-60 points (certain symptoms)	65-70 points (partial PTSD or ASD)	> 70 points (probability of clinically obvious disorders)
1	Post-traumatic Stress Disorder (PTSD)	12.90	53.78	13.97	19.35
2	Acute Stress Disorder (ASD)	50.53	22.58	9.67	17.22
3	Depression	32.25	53.76	8.62	5.37

The danger of these mental disorders lies in such consequences as: deviant, delinquent and additive behavior. An extreme degree of depression can become a suicide [1].

Qualitative analysis of the statistical data obtained in the study shows that 12.90% of the respondents had a trauma event preceding the development of post-traumatic stress disorder symptoms; in acute stress disorder, the presence of a traumatic event was observed in 50.53% of the respondents. This means that a serviceman encountered or witnessed events related to death, threat of death or a serious injury - a threat to his/her or other people's physical integrity; this event was accompanied by intense emotional experiences (fear, helplessness, horror) (table 2).

Table 2

Results of PTSD and ASD screening in ATO / JFO military personnel (%)

PTSD	Quantitative indices	ASD	Quantitative indicators
Trauma event	12.90	Trauma event	50.53
Invasion	59.23	Dissociative symptoms	60.31
Avoidance	59.63	Invasion	55.90
Hyperactivation	58.21	Avoidance	66.27
Distress and Maladaptation	65.66	Hyperactivation	56.04
–	–	Distress and Maladaptation	65.56

The index of "invasion" according to the events impact scale was 59.23% for PTSD and 55.90% for ASD. This means that the traumatic event is persistently experienced again by unpleasant memories, recurrent dreams or "flashbacks" that are repeated and cause obvious psychological discomfort.

The "avoidance" index according to the events impact scale was 59.63% for PTSD and 66.27% for ASD. It may be manifested in the avoidance of trauma-associated stimuli, attempts to avoid thoughts. feelings or conversations about traumatic events, attempts to avoid activity, places or people who provoke these memories, reduction of interest and active prticipation in meaningful activities.

The "hyperactivation" index was 58.21% for PTSD and 56.04% for ASD. It can be manifested in increased irritability, outbreaks of anger, unmotivated vigilance and exaggerated readiness for "escape reaction", lack of physical fatigue, need for rest. In addition to the "hyperactivation" index, a qualitative analysis of the "over vigilance" index was performed. It had 4.96 points and the scale of "exaggerated response" - 4.85 points (with the highest possible score - 5.0). These data confirm the high pronouncement of psycho-emotional state.

The index of "dissociative symptoms" was 60.31%. It may indicate that in the period of trauma or after trauma an individual may have: a subjective feeling of emotional dependence; "emotional dullness" or lack of emotional response; narrowed awareness of the outside world; derealization; depersonalization; dissociative amnesia (inability to recall some important aspect of a traumatic event). Dissociation can occur in the form of absorption (it is characterized by strain, sense of activity and enthusiasm for activity) and in the form of depersonalization (it is characterized by the loss of individuality, a subjective feeling implying the loss of reality, loss of emotions. feeling of ennui). Dissociation can also lead to the identity changes. In this state, visible violations in the experience of the Self-integrity are marked.

The main concern is connected with the obtained data about distress and maladaptation. According to our study, "distress and maladaptation" with PTSD occurred in 65.66% of the servicemen and in 65.56% with ASD. This index is connected with the violation of psychological adaptation, decreased professional ability to work and worsening the quality of life activity.

Thus, according to the data obtained from the assessment of the traumatic event impact among the interviewed military personnel participating in the ATO / JFO. The majority of respondents had the

symptoms characteristic of post-stress disorders – "invasion", "avoidance", "hyperactivation", dissociative symptoms, distress and maladaptation state.

Consequently, if these symptoms do not receive discharge, i.e. the energy arising from overexitement is immobilized and continues to be accumulated, then a mental disorder gradually develops and transforms into psycho-trauma.

The acquired psycho-trauma becomes a self-acting factor within a person. In this state, a psycho-traumatized person may experience unmotivated and uncontrollable outbreaks of aggression, as well as coldness and indifference towards relatives [3, 8].

That is why, according to the current statistics, 80% of divorces recorded in Ukraine during 2015-2016 occurred in the families of demobilized servicemen, most of them having taken place in the first six months after returning from war. According to other researches, within a year after demobilization, from 35% to 60% of the ATO / JFO participants' families are about to break up. The following example shows that according to the data of Lutsk City Council, in Lutsk every second demobilized soldier has divorced [4].

The main manifestations of post-stress psychological maladaptation in the military personnel - participants of the ATO / JFO are now considered to be the feeling of alienation, "abandonment" and "unnecessariness"; cognitive dissonance due to the indifference of a "peaceful" community to war; the strong belief that civilians can not understand what a military man has endured; social maladaptation. unemployment; an attempt to apply new acquired behavioral strategies in a peaceful life, that is negatively assessed by the relatives; failure to settle family conflicts peacefully, cases of physical, sexual and psychological abuse; over-actualization of the "combat brotherhood" feeling and its opposition to the "peaceful" community; experience of getting rid of psycho-emotional stress with the use of psychoactive substances [4].

One of the main problems in implementing psychological rehabilitation measures for ATO / JFO participants is nonrecognition of the need to undergo psychological examination and rehabilitation by the military personnel themselves that is caused by their unwillingness to be connected with people suffering from psychological (mental) disorders.

Therefore, in order to detect ASD or PTSD in the military personnel, including the servicemen who got injured or had contusions while performing their combat missions, and to provide them with timely medical and psychological assistance, it is necessary to introduce the obligatory psychological examination at the legislative level.

Considering the above-mentioned information, as well as the fact that the health of the population is one of the main factors for achieving national security and welfare of the state as a whole, it is necessary to introduce new approaches to solve public health problems, taking into account the Medium-Term Government Priority Action Plan up to 2020, approved by the Cabinet of Ministers of Ukraine, Decree No. 275-r dated April 3, 2017 [3, 10].

Conclusions

1. According to the performed study, the Traumatic Stress Questionnaire for the Diagnosis of Psychological Consequences developed by I. Kotenov is an efficient screening tool for assessing the presence of post-traumatic stress disorder in the military personnel participating in the ATO / JFO.

2. The results of the study have shown that 53.78% of the military personnel –participants of the ATO / JFO have certain symptoms of post-stress states; 13.97% of the military personnel have partial PTSD; 19.35% of the respondents subjectively assert that they experience clinically obvious disorders of the post-stress states. Depressive symptoms have been recorded in 62.39% of the respondents; 13.99% of them have experienced symptoms at above a moderate and at a high level.

3. According to the obtained data on the assessment of the traumatic event impact, more than half of the respondents experience the symptoms which are characteristic of the post-stress disorders, such as: "invasion" - 59.23% with PTSD and 55.90% with ASD; "avoidance" - 59.63% with PTSD and 66.27% with ASD; "hyperactivity" - 58.21% with PTSD and 56.04% with ASD. Dissociative symptoms and states of distress and maladaptation - 65.66% with PTSD and 65.56% with ASD.

4. It is necessary to enshrine in law medical and psychological support for the military personnel participating in the ATO / JFO starting from the time of screening process and appointment to the position, during the period of military service, as well as during their staying in the reserve (retirement).

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Реферати

МЕДИКО-ПСИХОЛОГІЧНІ ТА ЮРИДИЧНІ АСПЕКТИ ОБГРУНТУВАННЯ КОНЦЕПЦІЇ РЕАБІЛІТАЦІЇ ВІЙСЬКОВОСЛУЖБОВЦІВ-УЧАСНИКІВ АНТИТЕРОРИСТИЧНОЇ ОПЕРАЦІЇ

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Метою роботи було обгрунтування концепції медико-психологічної реабілітації та правового захисту військовослужбовців-учасників АТО/ООС. У психодіагностичному дослідженні взяли участь 93 військовослужбовця-учасника АТО/ООС із середнім терміном перебування в зоні бойових дій на сході України 12-14 місяців у віці від 20 до 30 років. Результати дослідження свідчать, що у 53,78 % військових-учасників АТО/ООС відзначаються окремі симптоми постстресових станів; частковий ПТСР діагностовано у 13,97 % військових; наявність клінічно виражених розладів постстресових станів суб'єктивно відзначають 19,35 % респондентів. Депресивна симптоматика зафіксована у 62,39 % респондентів, з яких 13,99 % на рівнях вище середнього та високому. Більше половини респондентів відзначають симптоми, які притаманні постстресовим розладам – «вторгнення» – 59,23 % при ПТСР та 55,90 % при ГСР ; «уникнення» – 59,63 % при ПТСР та 66,27 % при ГСР; показник «гіперактивація» – 58,21 бали при ПТСР, та 56,04 при ГСР, дисоціативні симптоми та стани дистресу і дезадаптації – 65,66 бали при ПТСР та 65,56 при ГСР. З огляду на вищесказане, необхідно опрацювати на законодавчому рівні медико-психологічну концепцію реабілітації військовослужбовців-учасників АТО/ООС. В програму бойової підготовки військовослужбовців, у тому числі командирів всіх рівнів, ввести курс з основ психологічної допомоги, з метою коригування емоційного стану методом надання само- та взаємодопомоги.

Ключові слова: медико-психологічна реабілітація, учасники АТО/ООС, посттравматичний стресовий синдром, гострий стресовий розлад, скринінг.

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МЕДИКО-ПСИХОЛОГИЧЕСКИЕ И ЮРИДИЧЕСКИЕ АСПЕКТЫ ОБОСНОВАНИЯ КОНЦЕПЦИИ РЕАБИЛИТАЦИИ ВОЕННОСЛУЖАЩИХ-УЧАСТНИКОВ АНТИТЕРРОРИСТИЧЕСКОЙ ОПЕРАЦИИ

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Целью работы было обоснование концепции медико-психологической реабилитации и правовой защиты военнослужащих-участников АТО / ООС. В психодиагностическом исследовании приняли участие 93 военнослужащих-участника АТО / ООС со средним сроком пребывания в зоне боевых действий на востоке Украины 12-14 месяцев в возрасте от 20 до 30 лет. Результаты исследования свидетельствуют, что у 53,78% военных-участников АТО / ООС отмечаются отдельные симптомы постстрессовых состояний; частичный ПТСР диагностирован у 13,97% военных; наличие клинически выраженных расстройств постстресовых состояний субъективно отмечают 19,35% респондентов. Депрессивная симптоматика зафиксирована в 62,39% респондентов, из которых 13,99% на уровнях выше среднего и высоком. Более половины респондентов отмечают симптомы, присущие постстресовых расстройствам – «вторжение» – 59,23% при ПТСР и 55,90% при ГСР; «Избегание» – 59,63% при ПТСР и 66,27% при ГСР; показатель «Гиперактивация» – 58,21 балла при ПТСР, и 56,04 при ГСР, диссоциативные симптомы и состояния дистресса и дезадаптации – 65,66 балла при ПТСР и 65,56 при ГСР. Учитывая вышесказанное, необходимо проработать на законодательном уровне медико-психологическую концепцию реабилитации военнослужащих-участников АТО / ООС. В программу боевой подготовки военнослужащих, в том числе командиров всех уровней, ввести курс основ психологической помощи, с целью корректировки эмоционального состояния методом предоставления само и взаимопомощи.

Ключевые слова: медико-психологическая реабилитация, участники АТО / ООС, посттравматический стрессовый синдром, острый стрессовое расстройство, скрининг.

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FORENSİC ASSESSMENT OF GUNSHOT İNJURİES USİNG MODERN OPTİCAL RESEARCH METHODS

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An increased number of injury cases caused by firearms in Ukraine makes it important to improve the accuracy and objectivity of forensic medical examinations in this type of injury by using modern optical research methods, in particular, autofluorescence spectral analysis. Archival material of the Chernivtsi Regional Bureau of Forensic Medical Examination was used. The material of the study was skin sections of the entrance gunshot wounds caused by the "Fort" traumatic pistol when the muzzle of the weapon was point blank and at a close distance. The studies were performed on a stokes polarimeter modified for autofluorescence studies of biological sections. For each two-dimensional distribution of the intensity values of the laser-induced intrinsic fluorescence in histological skin sections, the statistical moments values of the 1st-4th orders and the statistical processing of the measured indicated moments set of values were calculated. It is proved that the use of modern physical and optical methods improves the accuracy and objectivity of forensic medical examinations regarding gunshot injuries.

Key words: forensic medical examination, X-ray fluorescence spectral.

The work is a fragment of the research project "Development of new methods for diagnosing and treatment of the most common forms of malignancies", state registration No. 0116U002930.

Gunshot wound (including blast one) remains an urgent problem for forensic medicine, in particular, in Ukraine. According to the results of a statistical analysis, since 2014 number of people, who were killed by firearms and explosive devices, increased during the events at the Maidan Nezalezhnosti and war in Eastern Ukraine [2, 9, 6, 7]. The negative role is played by a constant growth of explosive devices and rifles among the population caused by their uncontrolled import into the "peaceful" territory from the war zone. That is the reason, why the number of cases of fatal bullets, debris of grenades and mines has increased and the amount of fire damage caused by means of shock-traumatic ("non-lethal") weapons equipped with elastic bullets has increased, as well [6, 8]. The result of mentioned information was a progressive increase in the number of biological and non-biological objects of gunshot injuries (flaps of skin, clothing, weapons) in the department of forensic medcine of Bureau of Forensic Expertise (FME) of Ukraine. In particular, due to statistics there is a significant increase in the number of cases of gunshot injuries at the Kyiv City Clinical Bureau of FME during 2014-2017 [6]. Therefore, it is future-oriented aim to find the most informative methods for studying both biological and traumatic objects of firearms for their differential diagnosis and identification [5].

Among the numerous factors characterizing the features of a gunshot injury, the detection of metals from bullets and shell casigns of a firearm formed during a shot and the components of the charge gunpowder which in general are defined as "the factors accompanying a shot" or "products of gunshot" [13]. Detection and identification of these factors in the forensic laboratory is a complex of methods and techniques has known since the twentieth century. There are X-ray fluorescence analysis, spark mass spectrometry, atomic absorption analysis, neutron activation analysis, flame photometry, emission spectrographic method, infrared spectrometry etc. [11, 14, 10, 11]. The methods are highly sensitive and able to detect almost the full range of chemical elements in the composition of gunshot products. One of their major drawbacks is the preparation of the sample which is accompanied by the inevitable destruction and loss of the study object.

X-ray spectral analysis is a sufficiently effective and non-destructive method of gunshot products studying, the essence of which is the X-ray irradiation of the object of study and detection of the spectral composition of the secondary radiation, it reflects the quantitative and qualitative indicators of the chemical elements of the studied object [10]. Scientific studies, that were carried out using Ukrainian spectrometers, have revealed a high efficiency of the method, which consisted in the complete conservation of the object and the possibility of repeated studies, the identification of more than 70 chemical elements with high reliability, due to the software of the whole process, it allows computer processing and archiving the

obtained results [1]. Over the last 5 years, the modern M4 TORNADO spectrometer from Bruker (Germany) has been successfully used in Ukraine, in particular, at Kiev City Clinical Bureau of FME which has opened up new possibilities for laboratory diagnostics of gunshot injuries, weapons and ammunition [11]. Using X-ray fluorescence spectral analysis, it was possible to set the position of the muzzle face of the gun relatively to the skin surface with an irregular distribution of layering of Fe, Cu, Zn elements along the edges of the wound. It was possible only due to contact of the muzzle face side with the skin of the wound [4, 5].

The successful use of X-ray fluorescence spectral analysis for the diagnosis of various aspects of gunshot injuries suggests the feasibility of using other fluorescence methods for objective establishing of the circumstances in which the shot was fired.

Optical and physical autofluorescence methods are widely and very effectively used in medical diagnostics. They are based on the use of the phenomenon of fluorescence, which starts to occure in the secondary radiation of various molecular structures, which appears under the influence of short-wavelength optical radiation on biological tissue or fluid. In forensic practice, the effective use of these methods has been reflected in diagnosing of the time of death, identifying the level and effect of ethyl alcohol on the accuracy of determining time of death, diagnosing the cause of death due to acute and chronic myocardial ischemia [3].

The purpose of the work was development and testing of the intrinsic fluorescence two-dimensional mapping method of biological layers (skin sections preparations) for establishing of the distance of a shot by means of statistic analysis of the dynamics of post-mortem changes in the coordinate distributions of the intensity of laser-induced fluorescence in sections of skin preparations from the site of the gunshot wound during a shot from "Fort" traumatic pistol.

Materials and methods. In this work, archival materials from the Chernivtsi Regional Bureau of Forensic Medicine is used. The material on the study was skin sections obtained from the site of the entrance of gunshot wounds resulting from shots from the Fort traumatic pistol when the muzzle of the weapon barrel was positioned close and at close range. It is done by using a microtome knife, layered sections were made parallel to the skin, up to 0.5 cm thick, thus, each of the formed planes of the skin was approached to the subcutaneous fat. Altogether, 42 pathology slides of skin sections (PSSS) were obtained from a section of gunshot wounds with a thickness of 5 μm from different distance shots: close to 8 preparations (19%), 5 cm – 10 preparations (24%), 9 cm – 8 preparations (19 %), 10 cm – 8 preparations (19%), 20 cm – 8 preparations (19%).

The method of laser-induced fluorescence based on the excitation of the own fluorescence of biological molecules by laser radiation was used. The studies were carried out on Stokes Polarimeter modified for studies of autofluorescence of biological sections (fig. 1) [4].

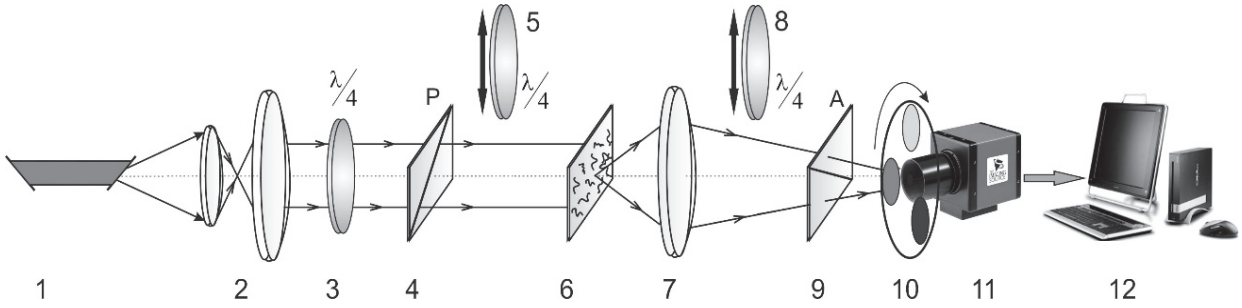

Fig. 1. Optical scheme of an autofluorescence Stokes polarimeter. Further explanations are in the text.

The mode of irradiation of histological preparations of skin section 6 consisted of a parallel (Ø = 2 × 103 μm) beam of "red" (λ2 = 0,405 μm) semiconductor laser 1. The quarter-wave plate 3 and the polarizer 4 are a polarizing irradiator. Image of skin incisions of incoming wound 6 using polarizing micro lens 7 (Nikon CFI Achromat P, focal length - 30 mm, aperture - 0.1, magnification - 4x) was projected into the plane of the photosensitive plane of CCD camera 10 (The Imaging Source DMK 41AU02.AS, monochrome 1/2 "CCD, Sony ICX205AL (progressive scan); resolution is 1280x960; sensitivity of the photosensitive plane – 7600x6200 microns; sensitivity – 0.05 lx; dynamic range – 8 bit). Later on, the polarization analysis of the images of the histological preparations of skin section of entrance wound 6 was performed using a quarter-wave plate 8 and a polarizer 9.

In the irradiation of the samples was applied by radiation of a red semiconductor laser LSR405ML-LSR-PS-II with a wavelength Δλ = 0.58 μm / 0.66 μm and a power W = 50 mW for each histological preparations of skin section in the optical location of the Stokes polarimeter (fig. 1). Spectral-selective two-

dimensional distributions of the intrinsic fluorescence intensities of skin sections were measured using a digital camera. The fluorescence maps of the histological preparations of skin section were determined at each of the above mentioned firing distances.

Later on, for each two-dimensional distribution of the values of the laser-induced intrinsic fluorescence intensity of the skin section, the magnitude of the statistical moments of the 1-4 order (Z1-4) was calculated and statistical processing of the measured set of values of the indicated moments obtained a value of the confidence interval (p <0,005).

Results of the study and their discussion. In the case of a gunshot injury, namely, firing at a distance and at close range, as a result of exposure to such an additional firing factor as a flame, the effect of carbon monoxide resulted in the redness of the skin tissues around the entrance of gunshot wound [9]. This phenomenon is happened due to the formation of carboxyhemoglobin that is a stable compound of blood hemoglobin with carbon monoxide. In general, the hemoglobin molecule is made up of a protein part. Globin is combined with a porphyrin part containing iron, which actually provides hemoglobin and red blood. Iron in the blood has got a divalent form. In the presence of carbon monoxide, it readily binds to it forming a stable carboxyhemoglobin compound which blocks oxygen transport [12].

From the analysis of the obtained data of two-dimensional mapping of the intrinsic fluorescence of human skin section, in the red spectral range, it is seen that the sensitivity of the data on the optical manifestations of molecular complexes of porphyrins in the composition with carbon monoxide decreases with increasing shot distance. Quantitatively, this fact is illustrated by significant changes (4-fold reduction) of the average spread of random values of the intensity of laser-induced fluorescence of porphyrins of histological preparations of skin sections (Fig. 2, Fig. 3, right parts) with increasing firing distance (table 1). Since the obtained results are based on objective data obtained by the method, the mathematical calculation is based on the calculation of the magnitude of the statistical moments of the 1-4 th order and the statistical processing of the measured totality of the values of the indicated moments, the obtained value of the confidence interval is p <0.005, taking into account even a small number of tested samples [3].

Thus, the results of two-dimensional mapping of the intensity values of laser-induced intrinsic fluorescence of the histological preparations of skin section at different firing distances are shown in figs. 2 and 3.

Table 1

Time dependences of the statistical moments magnitudes of the 1st and 3rd orders which characterize the distribution of the values of the intensity of laser-induced fluorescence of porphyrin molecules

L, см	At close range	5	10	20
	0.310.033	0.490.029	0.660.045	0.830.095
	p<0.005	p<0.005	p<0.005	p<0.005
	0.680.077	0.870.055	1.050.091	1.220.087
	p<0.005	p<0.005	p<0.005	p<0.005

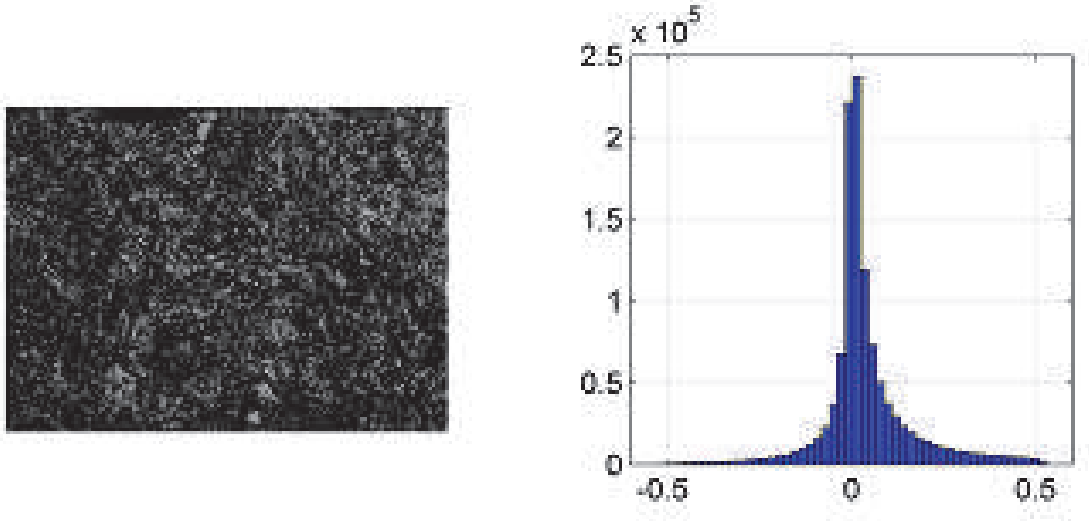

Fig. 2. Coordinate structure (left part) and histogram of the distribution (right part) of the dipole azimuth value of the polarization image of the fluorescence of the skin section in the pre-optical spectrum of the optical range. Distance is 5 cm.

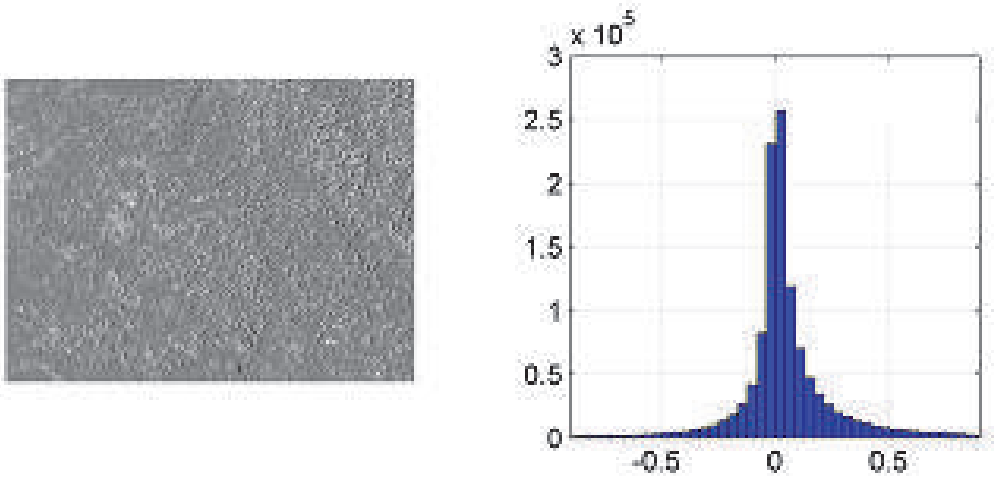

Fig. 3. Coordinate structure (left part) and the histogram of the distribution (right part) of the dipole azimuth value of the polarization image of the self fluorescence of skin section in the pre-optical spectrum of the optical range. Distance is 20 cm.

Thus, forensic assessment of gunshot injuries using modern spectral and optical methods of investigation has revealed new opportunities for laboratory diagnostics of various chemical elements in the composition of tissues of biological and non-biological origin, in particular, gunshot products by creating topography maps as well as common element maps, and individual combination maps [1,4,5]. They are highly accurate, minimally invasive and highly informative, they provide complete preservation of the object and study area, the possibility of repeated investigations, and the availability of software that allows computer processing and archiving of the obtained results [4, 10, 11, 12].

The advantages of the method of laser-induced fluorescence in determining the distance of the shot is that the most pronounced and dynamic temporal changes in the coordinate structure of maps of laser-induced fluorescence of porphyrin images of histological preparations of skin sections are revealed by changes in the values of the statistical moment of the 1st order, which are the mean values of fluorescence intensities in the red region of the spectrum - the range is 2.06 times ($p < 0.005$). The range of change of the values of the statistical moment of the third order which characterizes the asymmetry of the histogram of the distribution of random values of the fluorescence intensity is 1.47 times ($p < 0.005$). This method of accuracy can be approximated by known modern spectral methods of investigation [4, 5, 11, 13, 14].

Therefore, the use of modern fluorescence techniques in forensic practice has got a considerable research interest, worthy of further study. An important aspect of the study is the development of an algorithm for processing and analysis of the obtained results which would provide an increase in the efficiency of differential diagnosis of gunshot damage using modern optical devices such as a laser polarimeter and spectrometer. Further studies will also be devoted to establishing the diagnostic effectiveness of the use of the elemental analysis method in conducting forensic examinations not only in cases of gunshot injuries but also in electric injuries and in causing bodily injuries by shockers.

Conclusion

1. The use of modern physico-optical methods (X-ray fluorescence spectral analysis and laser-induced fluorescence) increases the accuracy and objectivity of forensic examinations of gunshot injuries, since they have got a wide range of detection of chemical and biochemical elements in the composition of gunshot and in composition of biological tissues.

2. Analysis of the temporal dynamics of the autofluorescence of porphyrins compounds with carbon monoxide allows one to set a maximum shot distance of 18 cm for this opto-physical method due to the most rapid decrease in the values of the statistical moments of the 1st and 3rd orders.

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Реферат

СУДОВО-МЕДИЧНА ОЦІНКА ВОГНЕПАЛЬНИХ УШКОДЖЕНЬ З ВИКОРИСТАННЯМ СУЧАСНИХ ОПТИЧНИХ МЕТОДІВ ДОСЛІДЖЕННЯ

Бачинський В.Т., Ванчуляк О.Я., Савка І.Г., Козлов С.В., Зубко М.Д.

Збільшення в Україні кількості випадків уражень, заподіяних вогнепальною зброєю, робить актуальним підвищення точності і об'єктивності судово-медичних експертиз цього виду травми шляхом проведення сучасних оптичних методів дослідження, зокрема – автофлуоресцентного спектрального аналізу. Був використаний архівний матеріал Чернівецького обласного бюро судово-медичної експертизи. Матеріалом дослідження були зрізи шкіри з ділянок вхідних вогнепальних ран, спричинені з травматичного пістолету «Форт» при положенні дульного зрізу зброї упритул та з близької дистанції. Дослідження проводилися на стокс-поляриметрі, модифікованому для досліджень автофлуоресценції біологічних зрізів. Для кожного двомірного розподілу значень інтенсивності лазерно-індукованої власної флуоресценції гістологічних препаратів зрізів шкіри проводилося обчислення величини статистичних моментів 1-4-го порядків та статистична обробка виміряної сукупності значень вказаних моментів. Доведено, що використання сучасних фізико-оптичних методів підвищує точність і об'єктивність судово-медичних експертиз з приводу вогнепальної травми.

Ключові слова: судово-медична експертиза, рентгенфлуоресцентний спектральний аналіз, лазер-індукована автофлуоресценція, вогнепальна травма, продукти пострілу.

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СУДЕБНО-МЕДИЦИНСКЯ ОЦЕНКА ОГНЕСТРЕЛЬНЫХ ПОВРЕЖДЕНИЙ С ИСПОЛЬЗОВАНИЕМ СОВРЕМЕННЫХ ОПТИЧЕСКИХ МЕТОДОВ ИССЛЕНДОВАНИЯ

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Увеличение в Украине количества случаев поражений, нанесенных огнестрельным оружием, обуславливает актуальность повышения точности и объективности судебно-медицинских экспертиз этого вида травмы путем использования современных оптических методов исследования, в частности - автофлуоресцентного спектрального анализа. Проводилось изучение архивного материала Черновицкого областного бюро судебно-медицинской экспертизы. Материалом исследования были срезы кожи с участков входных огнестрельных ран, причиненных травматическим пистолетом «Форт» при положении дульного среза оружия в упор и с близкой дистанции. Исследования проводились на стокс-поляриметре, модифицированном для исследований автофлуоресценции биологических срезов. Для каждого двухмерного распределения значений интенсивности лазерно-индуцированной собственной флуоресценции гистологических препаратов срезов кожи проводилось вычисление величины статистических моментов 1-4-го порядков и статистическая обработка измеренной совокупности значений указанных моментов. Доказано, что использование современных физико-оптических методов повышает точность и объективность судебно-медицинских экспертиз по поводу огнестрельной травмы.

Ключевые слова: судебно-медицинская экспертиза, рентгенофлуоресцентный спектральный анализ, лазер-индуцированная автофлуоресценция, огнестрельная травма, продукты выстрела.

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MORPHOFUNCTIONAL CHARACTERISTIC OF HEMOMICROCIRCULATORY BED IN THE RED BONE MARROW WHEN MODELING AN ACUTE ASEPTIC INFLAMMATION IN RATS

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In modern medicine, the structural components in various organs and tissues have been studied in great detail, but at the same time there are no works which would study hemomicrocirculation in the red bone marrow in the modeling of acute aseptic inflammation in rats, where reactive changes of morphological and functional character take place. The purpose of the work was to study the morphological changes of the components of the hemomicrocirculatory bed in the red bone mrrow of rats when modeling an acute aseptic inflammation. The work was performed on 50 mongrel white rats, divided into 2 groups: Group I–5 intact animals, Group II included 45 animals, which were simulated an acute aseptic peritonitis. In experimental groups of animal, an immediate, but reversible, increase in the penetration of venules and capillaries was observed, due to the active reduction of microfilaments in endothelial cells. In vascular lumens, during the experiment, a sludge syndrome was observed, which led to the difficulty of perfusion of blood corpuscles through the wall of the venule, which is a morphological confirmation of the inflammatory process.

Key words: red bone marrow, hemomicrocirculatory bed, inflammation.

The article is a fragment of the research project "Experimental-morphological study of the influence of cryopreserved preparations of cord blood and embryofetoplacental complex (EFPC), diferelin, ethanol and 1% ester of methacrylic acid on the morphofunctional state of a number of internals", state registration No. 0119U102925.

One of the problems of morphology is the study of the principles of structural components and the functioning of hemomicrocirculatory pathways on the level of the bloodstream, as a link that provides the whole complex of metabolic processes of the organism. In modern medicine, the structural components in various organs and tissues have been studied in great detail[1, 5, 8, 10, 12], but at the same time there are no works which would study hemomicrocirculation in the red bone marrow in the modeling of acute aseptic inflammation in rats, where reactive changes of morphological and functional character take place [3].

The study of the morphology and the functions of a vascular bed in red bone marrow, in normal and in different pathological conditions, allows us to determine which morphological mechanisms occur during blood regeneration, since a large number of blood corpuscles dies in an adult organism daily, while the number of blood cells in the peripheral bed remains quite stable. This is due to the fact that the dead cells are replaced by new ones that are formed in the organs of hematopoiesis [2, 3].

As it is known, the magistral vessels, which provide the trophism of the red bone marrow of the rat's femur, did not undergo a significant change in topographic anatomy in all experimental groups[2]. It is morphologically found that components of the hemomicrocirculatory bed in the red marrow of the rats make a multicomponent system, which consists of a certain set of typical units: arterioles, capillaries and venules. Blood capillaries of the red bone marrow in a rat have distinct differences and are both nonfenestrated and fenestrated. Nonfenestrated blood capillaries that provide the trophism of the red marrow are a continuation of the blood vessels that branch off the precapillary arterioles that adhere sufficiently close to the bone tissue. Sinusoidal (fenestrated) capillaries branch off the somatic capillaries and are located predominantly in cells, perforating the erythroblastic islets [2, 3]. Thus, the fact of the topographic differentiation of a single integral hemomicrocirculatory bed of the red marrow has been established, which results in a peculiar functional distribution.

The purpose of the work was to study the morphological changes of the components of the hemomicrocirculatory bed in the red bone mrrow of rats when modeling an acute aseptic inflammation.

Materials and methods. The work was performed on 50 mongrel white rats, divided into 2 groups: Group I – 5 intact animals, Group II included 45 animals, which were simulated an acute aseptic peritonitis by intraperitoneal administration of 5 mg λ-carrageenan (Sigma, USA) in 1 ml isotonic solution of sodium chloride for one animal.

The animals were withdrawn from the experiment on the 1^{st}, 2^{nd}, 3^{rd}, 5^{th}, 7^{th}, 10^{th}, 14^{th}, 21^{st} and 30^{th} day by an overdose of thiopental anesthesia. The study of red bone marrow was carried out in accordance with the established terms of the experiment.

The material for microscopic study was taken immediately after euthanasia of animals, the femur carefully was separated from soft tissues, followed by its fixation in 10% formalin solution for 24-48 hours. Subsequently, fragments of the femur were subjected to decalcification with ethylenediaminetetraacetic

acid. The material of the red bone marrow was thickened in parafin according to the generally accepted technique and sections were produced on the sliding microtome snuff micro-tissue MC-2 in thickness (4-5) microns, which were stained with hematoxylin and eosin according to Van Gieson[4].

Morphometry and microphotography were performed using Biorex-3 BM-500T microscope with digital DCM 900 photomicrographic attachment with programs adapted for such studies.

Statistical processing of morphometric data was performed using the program Exel [6].

During the experiment, the international principles of the European Convention on "the Protection of Vertebrate Animals used for Experiments and Other Scientific Purposes" (Strasbourg, 1986) were kept [11].

The results of the research and discussion. In the study of histologic preparations, it was found that the red bone marrow of the intact rats consisted of the stromal, vascular and cellular components. The stromal component is represented by the bone lamellae and reticular tissue. The vascular component consisted of arterioles, capillaries of somatic and sinusoidal type, and venules. The cell component is represented by cells: proerythroblasts, basophilic erythroblast, polychromatophilic, and orthochromic erythroblasts, which formed an erythroblastic islet with a centrally located macrophage.

As a result of the morphometric study, the average lumen diameters of the vessels in the hemomicrocirculatory bed of the red marrow in the rats of the intact group were established: for arterioles – 18.47 ± 1.06 μm; for somatic capillaries – 5.71 ± 0.98 μm; for sinusoidal capillaries – 28.53 ± 2.37 μm; for venules – 50.97 ± 3.28 μm. In their lumens, erythrocytes in the form of double-concaved discs were determined predominantly.

The average diameter of the somatic capillaries was 4.9 times smaller than of the sinusoidal capillary, which indicates their different functional significance.

The conducted histological studies showed that the magistral vessels that provide the trophism of the red marrow in the femur of the rats did not undergo anatomically significant changes in all experimental groups.

Having done the morphologic and morphometric analysis of the average lumen diameter of the hemomicrocirculatory bed in the experimental group, it was found that during the whole experiment the mean value was uneven and a vascular reaction of the red marrow was revealed, which was manifested in the form of enlargement of its lumens and spasming at different terms of the experiment.

The analysis of the average diameters of arterioles showed that on the 1st day of the experiment there was a decrease in their lumen, compared with the intact group of animals, which continued to decrease to the 2nd day. From the 3rd and 5th days, an increase in the arterioles' diameter was observed, with $p < 0,05$, in comparison with the previous term. The maximum mean of the average diameters of the arterioles was reached on the 10th day, expanding by 1.17 times, at $p < 0.05$, in comparison with the previous experimental period, from the 14th to the 21st day their expansion was observed. From the 30th day, there was a reliable tendency, at $p < 0,05$, in comparison with the previous experimental period, to the restoration of the parameters of the average lumen diameter in arteriols (table).

Table

Changes' dynamics in the components of the red marrow hemomicrocirculatory bed during experimental inflammation (μm)

Day	Arterioles	Capillaries	Venules
Intact animals	18,47 ± 1,06	28,53 ± 2,37	50,97 ± 3,28
1 day	17,56 ± 1,04*	55,87 ± 2,92*	77,51 ± 2,88*
2 day	15,64 ± 1,08*	52,21 ± 2,94*,*	79,01 ± 2,79*,*
3 day	16,07 ± 1,09*	53,35 ± 2,83*	85,11 ± 2,67*,**
5 day	19,81 ± 1,07*,*	45,46 ± 2,91*,*	89,19 ± 2,29*,*
7 day	28,08 ± 1,06*,*	54,21 ± 2,92*,*	90,21 ± 2,86*,*
10 day	32,73 ± 1,05*	54,73 ± 2,48*	92,14 ± 2,67*,*
14 day	26,12 ± 1,08*	55,34 ± 2,49*,*	58,11 ± 2,92*,*
21 day	20,71 ± 1,05*,*	36,81 ± 2,26*,*	57,08 ± 2,87*,*
30 day	19,21 ± 1,07	29,44 ± 2,92	51,48 ± 3,84

Note 1. * – $p<0,05$ in comparison with the contact group.

Note 2. ** – $p<0,05$ in comparison with the previous observation term.

Histologically, at the light-optical and ultramicroscopic levels, the signs of the inflammatory process were determined even in the wall of the arterioles. It was found that though the wall of the arterioles retained the typical three-layer structure, but the nuclei of the endotheliocytes were intensively protruded into the vessels' lumen, the internal elastic membrane, when stained with a polychrome dye, had the appearance of a basophilic strip that formed numerous tall layers. Such changes in the internal elastic membrane were not observed in the intact group of animals. It was determined that the overwhelming

majority of the nuclei of smooth myocytes in the middle membrane of arterioles acquired various forms, and the arteriol's lumen itself was densely filled with blood corpuscles.

It was established that the metabolic link of the hemomicrocirculatory bed, on the introduction of λ-carrageenan, reacted with a dilation from the 1st to the 3rd day of the experiment, which was conditioned, first of all, by the development of tissue hypoxia in the red marrow due to spasm of resistive vessels, but the wall retained a layered structure. An electron microscopic study of the elements of the hemomicrocirculatory bed has established that from the 3rd day of observation, changes in the luminal circuit of endotheliocytes, which has a non-uniform run, due to numerous protrusions, the basement membrane maintains continuity. On the 5th day, the decrease in arteriol diameter was observed, in comparison with the previous term, but these parameters significantly differ from the intact group at $p < 0.05$. From the 7th to the 14th day, the expansion of the average diameter of the vessels appeared at $p < 0,05$, in comparison with the previous term, and starting from the 30th day of the experiment, their diameter approached to the parameters of the intact group of animals.

It was proved that the average diameter of venules, during the experiment, also significantly increased, the analysis of the parameters of the diameters indicates that the increase was irregular, thus from the 1st to the 7th day, the gradual expansion of the vessels was observed. The maximum value of the venules diameters was reached on the 10th day of observation, with $p < 0,05$, in comparison with the previous experiment term and the indicators of the intact group of animals. The 5th, 7th and 10th days were characterized by expanded venules diameters, whereas from the 21st day, there was a decrease in the diameter of vessels' lumens, with $p < 0.05$ as compared to the previous observation period, and from the 30th day of the experiment their diameter approached the indicators of the intact group of animals.

Morphologically, the wall of the capillaries was thinned, the restoration of the morphofunctional state of metabolic hemomicrovessels in the early stages of the experiment was not observed. Histologically and morphometrically, it was found that capillaries and venules also tended to expand in response to acute aseptic inflammation and remained enlarged to the end of the experiment.

The wall of the venules preserved the typical structure, but it was thinned, hyperemia was observed, and the blood corpuscles densely filled the lumens.

The ultramicroscopic examination revealed changes that were manifested by decompensation processes in the selective penetration and barrier function of the microvascular wall. Endothelial cells became swallen, which led to the formation of folds, lacuna, protrusions, and as a result, the size and shape of the vascular lumen changed significantly, from the right round or oval to the wrong one. Alongside with this, endothelial cells showed a loss of the order and the uniformity of microfilaments and myofilaments in myocytes, as well as the separation of endothelial contacts with the formation of clefts through which an excess fluid penetrated into the parenchyma of the red marrow from the blood plasma. As a result of these pathomorphological changes at the ultramicroscopic level, it is noted that in the areas of folds and protrusions of the endotheliocytes cytoplasm, the merge of pinocytic vesicle and the formation of vacuoles took place, which led to their subsequent separation into vascular lumen and subsequent necrotic and apoptotic changes.

The reaction of the microvessels in the experimental group had a general tendency of development and manifested itself in the form of spasms with subsequent dilation of the arterioles in response to the expansion of the lumen of capillaries and venules and had a gradual nature.

In experimental groups of animal, an immediate, but reversible, increase in the penetration of venules and capillaries was observed, due to the active reduction of microfilaments in endothelial cells (Fig. 1).

In vascular lumens, during the experiment, a sludge syndrome was observed, which led to the difficulty of perfusion of blood corpuscles through the wall of the venule, which is a morphological confirmation of the inflammatory process(Fig. 2).

In the previously conducted experimental studies, on the state of the vessels of the hemomicrocirculatory bed, under the influence of an acute aseptic inflammation, the differentiated response of the vascular system is traced. Thus, the comparative analysis of morphometric parameters of the diameter of the elements in the hemomicrocirculatory bed of the adrenal medulla revealed the following changes: for the 1 day the diameter of the arterioles increased reliably compared to the indicator of the intact group ($p < 0.05$) and decreased unreliably by 7-10 days ($p > 0.05$). The exchange link of the hemomicrocirculatory bed in the adrenal cortex of the IInd group also varied in different directions.

Comparing capillary diameter changes with intact animal data, a significant decrease in capillary diameter was revealed on the 5th and 21st days ($p < 0.05$), with a maximum increase on the 3rd and 14th days of the study, the difference in significance was ($p < 0.05$). In the statistical analysis of the average diameter

of the capacitive link (venules) in the hemomicrocirculatory bed of the adrenal cortex, the following changes were established: a significant decrease of the indicator compared to the intact group ($p < 0.05$) was observed on the 1st day. The same trend preserved for 7 days, within 2-3 and 10-14 days a significant increase in venule diameter was detected ($p < 0.05$).

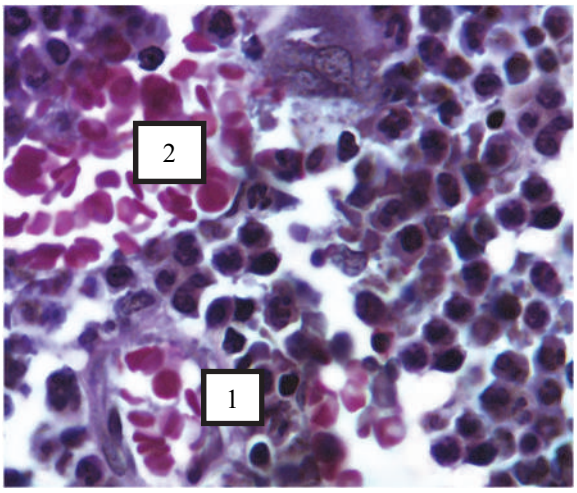

Figure 1. Red bone marrow of rats in the early stages of acute aseptic inflammation. 1– arteriole; 2 – venula. Coloring: polychrome dye. Increase: ocular: 10; object.100 (oil immersion).

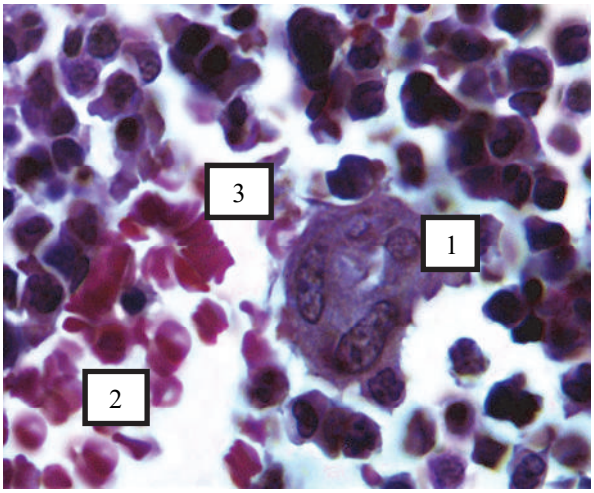

Figure 2 Red bone marrow of rats in the late stages of acute aseptic inflammation. 1 - megakaryocyte; 2 - venules; 3 - sludge-syndrome. Coloring polychrome dye. Increase: ocular: 10; object100 (oil immersion).

On the 5th -7th days and 21-30 days there was a significant decrease in diameters ($p<0.05$). Examining the changes in the diameter of the sinusoidal capillaries and venous sinuses during aseptic inflammation, certain common features were revealed - on the 1st day of inflammation, there was a significant increase in the diameter of sinusoids and venous sinuses ($p < 0.05$). But on the 2nd -3rd days, a sharp decrease in the diameter of both units ($p < 0.05$) was detected, from the 5th day of inflammation, the diameter of sinusoids significantly increased ($p < 0.05$), whereas, from the 7th day, an unreliable increase in the size of venous sinuses was observed ($p > 0.05$) [7].

In the studies of the reaction of the hemomicrocirculatory bed in the mucous membrane of the empty intestine during transplantation of cryopreserved placenta at the acute aseptic inflammation of the peritoneum in rats, it was found that the arterioles and capillaries initially decrease in diameter substantially on the 2nd day, and then increase substantially in diameter on the 3rd-10th day. Thus, with the introduction of cryopreserved placenta on the background of acute aseptic inflammation of the peritoneum, the development of inflammation and its correction is reduced by 4-5 days [9], and at the same time the reaction to the restoration of the blood vessels of the hemomicrocirculatory bed can be traced at the later stages of the experiment.

As a result of complex morphological researches it is found out that in the modeling of an acute aseptic inflammation significant morphological changes of the hemomicrocirculatory bed in the red marrow occur. The capillaries of the sinusoidal type are the main link of the vascular bed, as it is necessary for the organism's vital activity to have daily blood renovation, and this process is provided by the capillary bed of the red bone marrow.

Conclusions

1. At the early stages of the experiment during acute aseptic inflammation (1st - 14th day) there were significant changes of vessels of the hemomicrocirculatory bed in the red marrow. Arterioles spasmed on the 2nd day, their average lumen diameter significantly decreased by 1.18 times. From the 7th to the 14th day, they tended to expand with a reliable maximum value on the 10th day in 1.77 times. The capillaries of the sinusoidal type reached maximal expansion on the 1st day, having increased in 1.96 times, and the venules' lumen on the 3rd day increased in 1.67 times ($p<0.05$), which corresponded to the general principles of vascular reactions in response to the inflammatory process.

2. At the late terms of the experimental inflammation (21st and 30th days) it was found morphometrically that the arterioles were significantly expanded in 1.12 times on the 21st day and till the 30th day they did not acquire the values of the intact group of animals. The capillaries had increased lumens – in 1.29 times on the 21st day, and on the 30th day this figure almost reached the norm. At the late terms of the study venules remained expanded, which confirmed the continuation of the vascular reaction in response to the acute aseptic inflammation.

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Реферати

МОРФОФУНКЦІОНАЛЬНА ХАРАКТЕРИСТИКА ГЕМОМІКРОЦИРКУЛЯТОРНОГО РУСЛА ЧЕРВОНОГО КІСТКОВОГО МОЗКУ ПРИ МОДЕЛЮВАННІ ГОСТРОГО АСЕПТИЧНОГО ЗАПАЛЕННЯ У ЩУРІВ

Борута Н.В.

В сучасній медицині досить докладно досліджені структурні компоненти в різних органах і тканинах, і поряд з тим відсутні роботи в яких розглядаються дослідження гемомікроциркуляції в червоному кістковому мозку при моделюванні гострого асептичного запалення у щурів, де і відбуваються реактивні зміни морфологічного та функціонального характеру

В експериментальній групі тварин спостерігалося негайне, але реверсивне, збільшення проникності венул і капілярів, завдяки активному скороченню мікрофіламентів в ендотеліальних клітинах.

В просвітах судин, під час експерименту, спостерігався сладж-синдром, який призвів до утруднення перфузії формених елементів крові через стінку венул, що є морфологічним підтвердженням запального процесу.

Ключові слова: червоний кістковий мозок, гемомікроциркуляторне русло, запалення.

Стаття надійша 26.06.2019 р.

МОРФОФУНКЦИОНАЛЬНАЯ ХАРАКТЕРИСТИКА ГЕМОМИКРОЦИРКУЛЯТОРНОГО РУСЛА КРАСНОГО КОСТНОГО МОЗГА ПРИ МОДЕЛИРОВАНИИ ОСТРОГО АСЕПТИЧЕСКОГО ВОСПАЛЕНИЯ У КРЫС

Борута Н.В.

В современной медицине достаточно подробно исследованы структурные компоненты в разных органах и тканях, вместе с тем отсутствует работы в которых рассматриваются исследования гемомикроциркуляции в красном костном мозге при моделировании острого асептического воспаления у крыс, где и происходят реактивные изменения морфологического и функционального характера В экспериментальной группе животных наблюдалось реверсивное увеличение проницаемости венул и капилляров, благодаря активному сокращению микрофиламентов в эндотелиальных клетках.

В просветах сосудов, во время эксперимента наблюдался сладж-синдром, который привел к затруднению перфузии форменных элементов крови через стенку венул, что является морфологическим подтверждением воспалительного процесса.

Ключевые слова: красный костный мозг, гемомикроциркуляторное русло, воспаления.

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HISTOLOGICAL CHANGES OF STRUCTURAL COMPONENTS IN LYMPH NODES OF RATS AND CHANGES IN BIOCHEMICAL BLOOD INDICES IN EXPERIMENTAL OBESITY

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The article analyses the results and data of experimental study performed on white female and male rats of reproductive age (2.5-3.5-months). The purpose of the study was to establish the histological changes of rat lymph nodes structural components and changes in biochemical blood parameters through different terms of experimental obesity. The biochemical analysis of white male and female rats' blood for the level of glucose, ALT, AST, cholesterol and triglycerides was carried out throughout the experiment. After one week of experiment, there is an insignificant expansion of the marginal and cortical lymphatic sinuses. With the experiment duration increase all pathological changes exacerbate.

Key words: obesity, experiment, rat, lymph node, lymphocytes

This study is a part of complex projects «Morphological characteristics of internal organs and vascular bed in ontogenesis in the norm and patterns of their restructuring in obesity and effects on the body of physical factors», state registration number 0119U102059.

One of the most topical problems of modern society is the body overweight [6-9]. Obesity is a chronic recurrent disease manifested by excessive accumulation of adipose tissue and is the result of energy intake and discharge imbalance in individuals with hereditary predisposition or in the absence of it [10-11]. According to recent calculations, every third inhabitant of the Earth has overweight, and every tenth one is suffering from obesity [4].

An important role in the whole body homeostasis is played by lymphoid (immune) organs. The secondary lymphoid (immune) organs include lymph nodes. In secondary lymphoid organs, antigen-dependent proliferation is taking place together with differentiation of T-B-lymphocytes entering the blood from the primary lymphoid organs. It provides an adequate immune response of the body to foreign antigens. Changes in lymphoid organs after affecting the body of various harmful factors, including drugs have been studied for a long time [1-3, 5, 10]. In experimental obesity, the results obtained by the authors showed that the thymus and spleen react differently to the long-term use of a high-calorie diet. Changes in the mass and cellularity of the thymus and the spleen were of a multi-directional nature. High-calorie daiet resulted in a decrease in the mass of thymus, cell growth. In the spleen, on the contrary, there was an increase in the mass, a decrease in cellularity [5].

However, there is not enough data on the lymphoid organs changes under the obesity conditions.

The purpose of the work was to study histological changes in rat lymph nodes structural components; to study the biochemical blood indices changes through different terms of experimental obesity.

Materials and methods. We carried out the study on 50 white rats of reproductive age (2.5-3.5 months) weighing 150-180 g. Microanatomy of the lymph nodes structural components in white rats under conditions of physiological norm was studied on 10 intact animals. Experimental animals were divided into 4 groups: the first group (10 animals), being fed a high-calorie diet for one week; the second group (10 animals), fed high-calorie diet for two weeks; the third group (10 animals), fed high-calorie diet for three weeks; the fourth group (10 animals), fed the same diet for four weeks.

Each group included 5 male and 5 female rats. High-calorie diet was achieved due to the fact that glutamate sodium was added into food in a dose of 0.07 g / kg of rat body weight.

The experiment was performed according to the agreement on scientific cooperation between the Department of Human Anatomy and Histology of the Faculty of Medicine of Uzhhorod National University and the Department of Normal Anatomy of Danylo Halytsky National Medical University on November 18, 2013 at the Department of Normal Anatomy of the Danylo Halytsky Lviv National Medical University. The study was performed in accordance with the provisions of the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes (Strasbourg, 1986), Council of Europe Directives 86/609 / EEC (1986), Law of Ukraine No. 3447-IV "On the Protection of Animals from Cruelty", the general ethical principles of experiments on animals adopted by the First National Congress of Ukraine on Bioethics (2001).

Images from the histological preparations of the club-shaped and mesenteric lymph nodes in the computer monitor were displayed from the MICROmed SEO SCAN microscope by means of the Vision

CCD Camera. The studies were carried out within the established schedule of the trial in samples stained with hematoxylin, eosin and azane.

To control the state of the liver, blood vessels, capillaries and heart, a biochemical analysis of the white male and female rats' blood was performed to determine the glucose, ALT, AST, cholesterol and triglycerides content throughout the experiment.

Results of the study and their discussion.

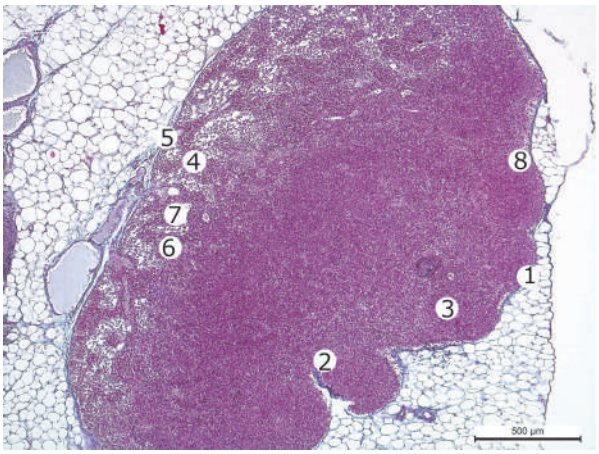

Fig. 1. A mesenteric lymph node of an intact white rat male. Azane stained. Magnif: obj. × 5, ocul. × 10. Designation: 1 - capsule; 2 - trabecula; 3 - cortical substance; 4 - medullary substance; 5 - the hilum of the node; 6 - lymph cord; 7 - medullary lymph sinus 8 - marginal sinus.

In animals of the intact and control groups, according to our histological studies, the structure of the iliac and mesenteric lymph nodes was compliant with the species norm. Externally, the lymph nodes are surrounded by a connective-tissue capsule, from which numerous trabeculae lead inside the node's parenchyma. On the node's concave side a hilum is located. Parenchyma consists of a cortical substance located on the node's periphery, and is closer to the gate of the medullary substance. Under the capsule there is a marginal sinus. In the cortical substance there are primary and secondary lymphoid follicles. The secondary ones contain clearing centers: germinal centers. There is a marginal layer around them. The medullary substance contains lymph cords and medullary intermediate lymph sinuses (fig. 1).

After 1-2 weeks of experiment, both in male and in female rats, the general structure of the lymph node corresponds to that of the intact animal group. There is a slight increase of the marginal and the cortical lymph sinuses (fig. 2A). Two weeks after, the medullary lymph sinuses get expanded. The veins and arteries are full-blooded (fig. 2B). The capsule is somewhat thickened.

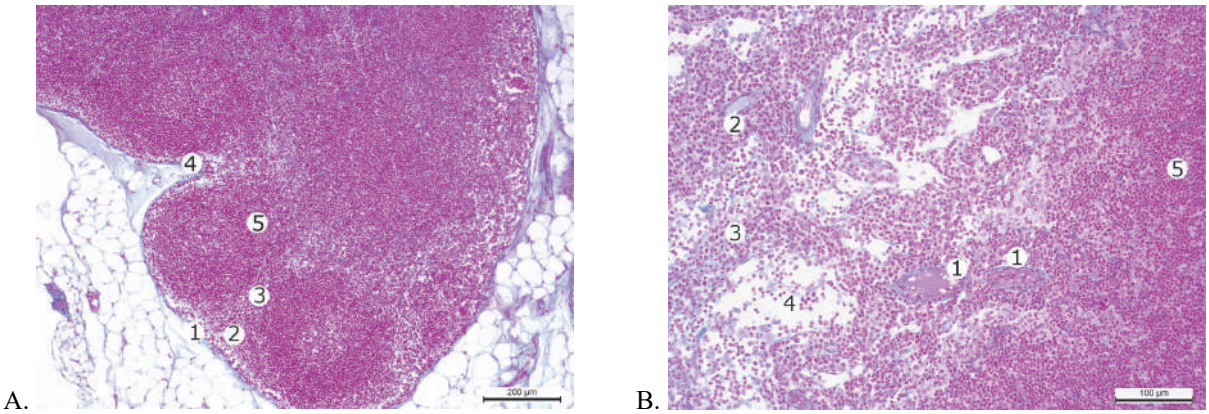

Fig. 2. A fragment of a mesenteric lymph node of a white female rat (A) and white male rat (B) after one (A) and two (B) weeks of the experiment. Azane stained. Magnif: A - obj. × 10, ocul. × 10; B - obj. × 20, ocul. × 10. Designation: A. 1-capsule; 2 - slightly expanded marginal sinus; 3 - expanded cortical lymph sinus; 4 - trabecula; 5 - secondary lymphoid follicle. B. 1 - varicose and full-blooded veins in the paracortical region; 2 - varicose and full-blooded vein in the medulla; 3 - medulla lymph cord; 4 - expanded medullary lymph sinus; 5 - cortical substance.

The level of glucose in the blood of white male rats grows to its maximum after two weeks of the experiment by 72.3%, then gradually reduces and after four weeks it exceeds the intact animals' indices by 16.7%. The level of glucose in the blood of white female rats grows to its maximum after one week of the experiment by 67.7%, then gradually reduces and four weeks after it is lower by 13.7% than in the intact animals (table 1).

Table 1

Indices of blood glucose levels in white rats, mmol/l (M ± m)

Group name	White male rat	White female rat
Intact animals	5.9±0.09	6.0±0.08
Group I	6.14±0.1	10.06±0.11
Group II	10.58±0.12	9.56±0.1
Group III	7.9±0.08	5.76±0.05
Group IV	7.08±0.12	5.18±0.09

The ALT level in the blood of white male and female rats grows to its maximum after two weeks of experiment, which exceeds the rate of intact animals by 57.3% and 40.4% respectively. During the experiment, it gradually reduces and four weeks after it is by 18.2% and 11.6% less than that of intact animals (table 2).

The AST level in the blood of white male rats grows to its maximum after one week of the experiment by 44.2% and 40.4% respectively, exceeding that of intact animals. During the experiment it fluctuates, and four weeks after it exceeds by 8.0% the intact animals' index. The AST level in the blood of white female rats does not change significantly during the experiment (table 2).

Table 2

Indices of ALT and AST levels in the blood of white rats, U/L (M ± m)

Group name	White male rat	White female rat	White male rat	White female rat
	ALT		AST	
Intact animals	76.5±0.2	67.5±0.18	175.7±0.35	168±0.49
Group I	93.4±0.3	58.9±0.21	253.4±0.39	148.7±0.7
Group II	120.3±0.31	94.8±0.29	172.4±0.33	167.8±0.67
Group III	96.7±0.4	61.3±0.22	240.8±0.77	172±0.56
Group IV	62.8±0.08	59.7±0.09	189.7±0.45	168.2±0.44

The level of cholesterol in the blood of white male rats and white feline rats increases as much as two weeks of the experiment, which is 2.5 and 2.9 times correspondingly higher than the rate of intact animals. During the experiment, it decreases somewhat and in four weeks it is 56.7% and 82.8% higher than the rate of intact animals (table 3).

The level of triglycerides in the blood of white male rats at the beginning of the experiment decreases, and from the second week begins to increase and in four weeks it is 11.6% less than the rate of intact animals. The level of triglycerides in the blood of white female rats increases as much as 2.9 times in two weeks of the experiment, then gradually decreases and returns to the level of intact animals four weeks later (table 3).

Table 3

Indices of cholesterol (mmol/l) and triglycerides (mmol/l) in blood of white rats (M ± m)

Group name	White male rat	White female rat	White male rat	White female rat
	cholesterol		triglycerides	
Intact animals	0.9±0.01	0.87±0.02	0.69±0.009	0.67±0.01
Group I	2.22±0.011	2.54±0.011	0.28±0.006	0.96±0.01
Group II	1.77±0.013	1.16±0.01	0.29±0.09	1.92±0.011
Group III	1.95±0.01	1.63±0.013	0.53±0.008	0.62±0.009
Group IV	1.41±0.01	1.59±0.011	0.61±0.007	0.68±0.01

After three weeks of the experiment, the capsule of the lymph nodes is thickened, containing a large amount of adipose tissue. Arteries in the node parenchyma and its hilum with a thickened wall, full blooded; vessels, veins and venules are deformed, dilated and full-blooded (fig. 3). The number of secondary lymphoid follicles in the cortical substance of the mesenteric and iliac lymph nodes grows both in male and in female rats.

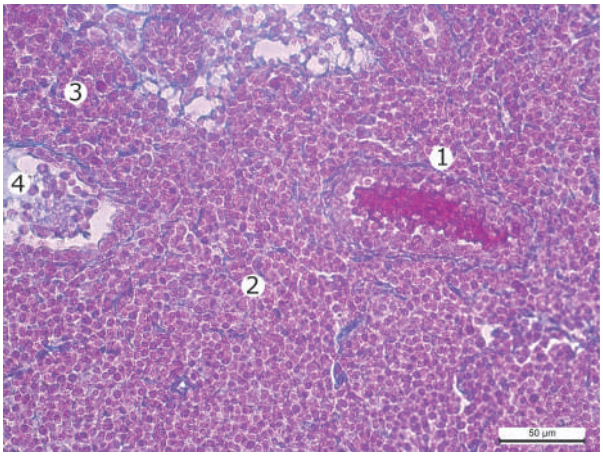

Fig. 3. Venule (1) with a thickened swollen wall in the paracortical region (2) of a white female rat's mesenteric lymph node after three weeks of experiment. Azane stained. Magnif.: obj. × 40, ocul. × 10. Designation: 2 – medullary lymph cord; 3 - a slightly enlarged medullary lymph sinus.

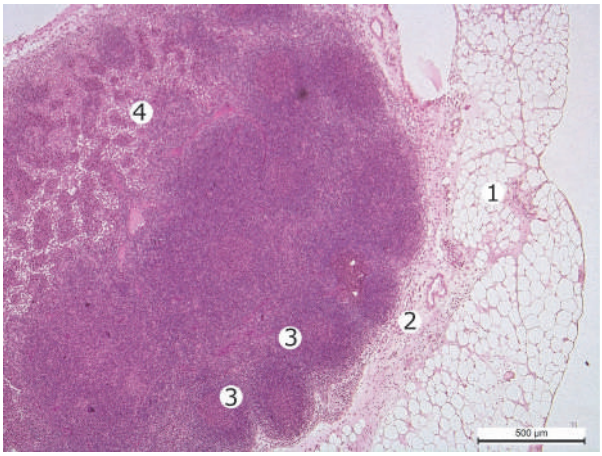

Fig. 4. White female rats' mesentery lymph node after four weeks of the experiment. Stained with hematoxylin and eosin. Magnif.: obj. × 5, ocul. × 10. Designations: 1 - accumulation of adipose tissue around and in the thickness of the capsule; 2- thickened capsule; 3- secondary lymphoid follicles in the cortical substance; 4 – medullary substance.

After four weeks of the experiment, the number of secondary lymphoid follicles in the cortical substance of the mesentery and iliac lymph nodes continues to grow both in male and in female rats. The germinal center is cleared, enlarged (fig. 4). The amount of adipose tissue grows around the body. Trabeculas leaving the capsule are pronounced, thickened. The area of cortical substance reduces, and that of medulla, respectively, grows, which is more pronounced in male rats. Arteries have thickened walls, full-blooded. Veins are varicose, deformed, full-blooded. The marginal sinus is unevenly enlarged. Medullary lymph nodes are enlarged, tortuous (fig. 4). B-lymphocytes, plasmacytes and macrophages are densely located in the medullary lymph cords.

In female rats, a large proportion of adipose tissue has been found around the organ. In male rats, destructurization in the cortical substance is more frequently observed: the integrity of the mantle zone is lost, the elongated germinal center is expanded. There is a large number of vacuole-like structures in the capsule.

As a result of the analysis of modern literature, it has been found that the development of obesity causes pathological changes in the lymphatic system, such as an increase in the average size of the spleen in animals was found to be 38%, indicating splenomegaly. In the study of histological preparations of the spleen there was a significant expansion of venous sinuses (sinusoids), macrophages filled with drops of hemosiderin were revealed, on some sections, especially around small vessels, eosinophilic aggregations and accumulation of lipids in the extended sinusoid were revealed. Consequently, a high-fat diet resulted from splenomegaly, which the authors associate with sinusoidal dilatation and intracellular and intercellular deposits [7].

Expansion of lymph sinuses, expansion and full blooded of vessels is also noted in studies of other authors [5, 7].

With the help of light and electron microscopy of liver preparations of the experimental group of animals, the expression of enlarged sinusoidal capillaries, microvessicular steatosis, an increase in the proportion of connective tissue in the liver, hepatocytes with an excessively extended smooth endoplasmic net, altered mitochondria and signs of necrosis have been revealed [7].

Thus, adipose tissue is a complex endocrine organ whose action on organs and tissues is weighty and diverse, increasing the likelihood of multiple diseases. The study of the dynamics of changes in the structural organization of organs and tissues, as well as possible methods for their correction, remain relevant and important for both theoretical and practical medicine. According to the results of our study, we showed an increase in the relative area of the B-dependent zone and a decrease in the T-dependent. Similar changes can lead to redistribution of activity in the direction of humoral immune response. There are signs of constant immune activity.

Conclusion

As a result of the study performed on male and female rats, we found that histological changes in the structural components of the iliac and mesentery lymph nodes were already observed after a week: a slight expansion of the marginal and cortical lymph nodes. With the duration of the experiment increasing, all changes are worsened. In the cortical substance, the number of secondary lymphoid follicles grows, the marginal sinus expands, the capsule thickens, accumulation of adipose tissue around the organ is gradually increasing.

In female rats, a large proportion of adipose tissue is found around the organ. In male rats, destructurization of cortical substances is more frequently observed.

In the biochemical analysis of the experimental animals' blood, after four weeks of high-calorie diet, it was found that the level of glucose in white male rats exceeds the indices of intact animals by 16.7%, and in female rats it is lower by 13.7%; ALT reduces by 18.2% and 11.6% respectively; AST in the white male rats' blood grows by 8.0%; cholesterol level grows by 56.7% in white male rats and by 82.8% in white female rats; the level of triglycerides in the white male rats' blood grows by 11.6%.

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Реферати

ГІСТОЛОГІЧНІ ЗМІНИ СТРУКТУРНИХ КОМПОНЕНТІВ У ЛІМФАТИЧНИХ ВУЗЛАХ ЩУРІВ ТА ЗМІНИ БІОХІМІЧНИХ ПОКАЗНИКІВ КРОВІ ПРИ ЕКСПЕРИМЕНТАЛЬНОМУ ОЖИРІННІ

Гарапко Т.В.

У даній статті наведені та проаналізовані результати експериментального дослідження, яке проводилося на білих щурах, самках і самцях репродуктивного віку (2,5-3,5 місяці). Метою дослідження було встановлення гістологічних змін структурних компонентів лімфатичних вузлів щурів і зміни біохімічних показників крові в різні терміни експериментального ожиріння. Проведено біохімічний аналіз крові білих щурів-самців і білих щурів-самок на рівень глюкози, АЛТ, АСТ, холестерину і тригліцеридів протягом всього експерименту. Через один тиждень експерименту спостерігається незначне розширення крайової і коркових лімфатичних пазух. При збільшенні тривалості експерименту всі патологічні зміни поглиблюються.

Ключові слова: ожиріння, експеримент, щур, лімфатичний вузол, лімфоцити.

Стаття надійшла 10.03.2019 р.

ГИСТОЛОГИЧЕСКИЕ ИЗМЕНЕНИЯ СТРУКТУРНЫХ КОМПОНЕНТОВ В ЛИМФАТИЧЕСКИХ УЗЛАХ КРЫС И ЗМЕНЕНИЯ БИОХИМИЧЕСКИХ ПОКАЗАТЕЛЕЙ КРОВИ ПРИ ЭКСПЕРИМЕНТАЛЬНОМ ОЖИРЕНИИ

Гарапко Т.В.

В данной статье приведены и проанализированы результаты экспериментального исследования, которое проводилось на белых крысах самках и самцах репродуктивного возраста (2,5-3,5 месяца). Целью исследования является установление гистологических изменений структурных компонентов лимфатических узлов крыс и изменения биохимических показателей крови в различные сроки экспериментального ожирения. Проведен биохимический анализ крови белых крыс-самцов и белых крыс-самок на уровень глюкозы, АЛТ, АСТ, холестерина и триглицеридов в течение всего эксперимента. Через одну неделю эксперимента наблюдается незначительное расширение краевой и корковых лимфатических пазух. При увеличении продолжительности эксперимента все патологические изменения усугубляются.

Ключевые слова: ожирение, эксперимент, крыса, лимфатический узел, лимфоциты.

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THE NATURE OF ULTRASTRUCTURAL CHANGES INDUCED BY ORCHIEPIDIDYMITIS IN THE MEN'S TESTES AND EJACULATE

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In 14 testicular biopsy specimens of men with male infertility, who had orchiepididymitis, aged 22-35 years we studied the nature of ultrastructural changes and their effect on ejaculate values. There were determined: deformity and pycnosis of nuclei, uneven expansion of perinuclear space, cytoplasm vacuolization, homogenization of mitochondrial cristae, expansion of endoplasmic reticulum cisterns and elements in the Golgi apparatus in endothelial cells of the hemocapillaries, peritubular myoid cells of the coiled seminiferous tubules lining, Sertoli cells, spermatocytes and spermatids, which were complemented in the ejaculate with reducing twice the sperm concentration in 1 ml, increasing 3 times the number of pathological forms and reducing the sperm motility.

Key words: testis, orchiepididymitis, germinal epithelium cells, ejaculate.

The work is a fragment of the research project "Topical aspects of andrology and correction of spermatogenesis", state registration No. 0119U103671.

Acute orchiepididymitis is one of the most common genital diseases of men of all ages, and the most common one among the complications of transurethral surgical and instrumental interventions [3, 7]. Half of orchiepididymitis cases involve sexually transmitted infections. Pathogens: Gonococci, Chlamydia, Streptococci, Escherichia coli, etc. penetrate the testis and epididymis through the vas deferens [2, 7]. According to the literature data [3, 6], the sperm pathology was found in all patients with orchiepididymitis,

which leads to infertility in 50-80% of cases. The study of ejaculate in infertile men is one of the main examinational methods, but the nature of ultrastructural changes in the testis in orchiepididymitis remains poorly studied.

The purpose of the study was to determine the nature of cytological and ultrastructural changes in the testis and ejaculate of infertile mature men (aged 22-35 years), who had orchiepididymitis.

Materials and methods. The study material included 14 testicular biopsy specimens from men with a history of orchiepididymitis sampled at the urology hospital. Laboratory analysis of ejaculate in this group of men was performed before surgical intervention. The Medical Ethics Committee of Ivano-Frankivsk National Medical University did not find any violations of moral and ethical standards during the study (Protocol No. 3 of 16.10.2018).

In the studied ejaculate was determined its volume, color, pH, sperm count in 1 ml, the content of living, motile and pathological forms. The calculations were performed in the Goryaev chamber at x400 magnification [6]. Statistical analysis of the obtained indicators was performed using the Stat. Soft. Inc., Tulsa, OK, USA; Statistica 6 software.

Electron microscopic study of testicular biopsy specimens was performed according to the conventional method. Ultrathin sections were studied in the PEM-125k electron microscope [4].

Results of the study and their discussion. According to electron microscopy in the testis of men with orchiepididymitis, the basement membrane of the coiled seminiferous tubules was unevenly thickened and twisted (fig. 1).

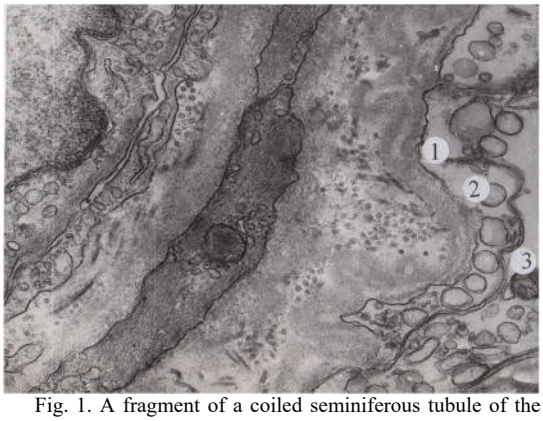

Fig. 1. A fragment of a coiled seminiferous tubule of the 30 years-old man's testis after having orchiepididymitis. x16000.
1 – twisting of basement membrane of the germinal epithelium;
2 – cytoplasm vacuolization in the peritubular myoid cell;
3 – homogenization of mitochondrial cristae.

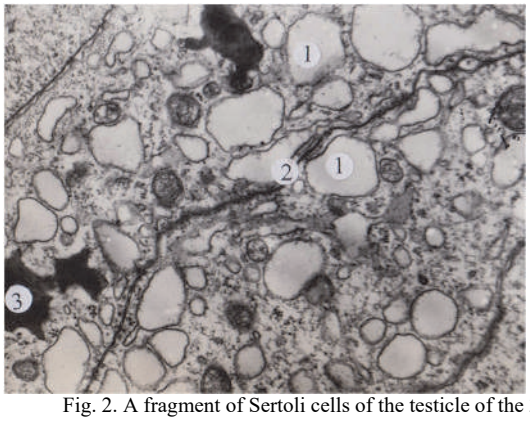

Fig. 2. A fragment of Sertoli cells of the testicle of the 30 years-old man's testis after having orchiepididymitis. x16000.
1 – significant cytoplasm vacuolization;
2 – convergence of the cell membranes of Sertoli cells;
3 – lipid droplets.

Peritubular myoid cell nuclei are hyperchromic with unevenly spaced chromatin. Micropinocytotic vesicles are predominant in the cytoplasm; myofilaments are not found (fig. 2). The cell membrane integrity of the Sertoli cells is impaired, the nucleus is impaired by deepened nuclear envelope invaginations, and the chromatin is rarefied. The cytoplasm of these cells is cleared out and vacuolated, with a large number of lysosomes and lipid inclusions. The mitochondria are small, their matrix is homogenized, the endoplasmic reticulum tubules and elements in the Golgi apparatus are unevenly expanded. In the connective apparatus, the cell membranes of Sertoli cells are converged, the filiform filaments are reduced, and the endoplasmic reticulum tubules are significantly expanded (fig. 2).

Karyorrhexis, uneven expansion of perinuclear space, cytoplasm vacuolization, homogenization of mitochondrial cristae were found in spermatids (fig. 3). The nuclei in the Leydig's cell are deformed, with peripheral chromatin condensation (fig. 4). The cell membrane contours are not clear, the cytoplasm is cleared-out, and the mitochondria have reduced cristae and a vacuolated matrix. The basement membrane of testicular blood capillaries is thickened, the cytoplasmic matrix is vacuolated, and macroclasmatosis is present. Nuclei are with peripheral chromatin condensation.

During the study of the ejaculate, in 20% of men who had orchiepididymitis, any sperm cells were not detected. In other men, the ejaculate volume was reduced to 2.57±0.24 ml, and the sperm concentration was decreased five times in 1 ml to 21.6±3.70 million/ml. It has a 67% and 73% reduction in the number of live and actively motile sperm. At the same time in the ejaculate the content of pathological forms of sperm was increased by 72%, in 90% of them the combined pathology (head, middle piece and flagellum) was detected. The content of fructose in the ejaculate decreased by 2 times. The number of white blood cells in the ejaculate increased significantly (up to 100 per field of view).

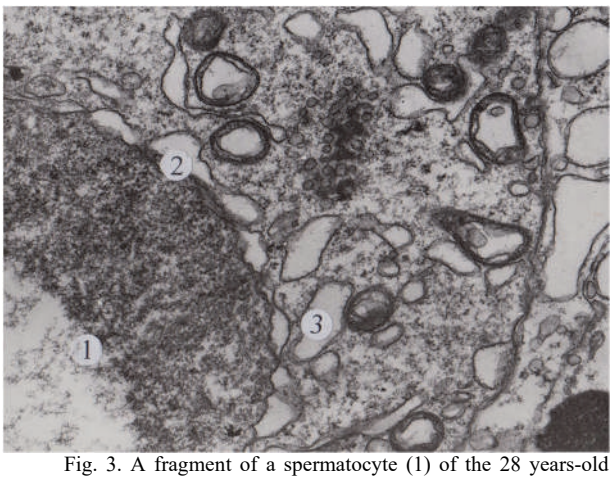

Fig. 3. A fragment of a spermatocyte (1) of the 28 years-old man's testis after having orchiepididymitis; 2 – uneven expansion of the perinuclear space; 3 – cytoplasm vacuolization. x16000.

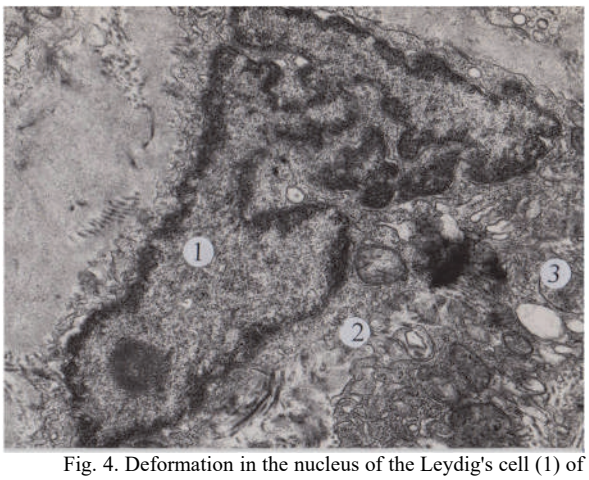

Fig. 4. Deformation in the nucleus of the Leydig's cell (1) of the 28 years-old man's testis after having orchiepididymitis; 2 – cytoplasmic reduction; 3 – homogenization of mitochondrial cristae. x16000.

In our previous studies of testicular blood vessels in men who had orchiepididymitis [3], the microvasculature blood vessel wall was deformed. Blood capillaries have an uneven lumen, their inner diameter was reduced to 4.0±0.3 μm, and focal reduction of capillaries was detected.

Diameter of the coiled tubules in the studied testicular biopsy specimens of men who had orchiepididymitis, was reduced to 156.15±5.0 μm. Counting the germ cells number revealed that only 5.6% of the seminiferous tubules retained their normal structure. Severe degree of damage to the germinal epithelium was found in 44.3%, and 31.2% of the tubules were emptied [3].

Along with atrophic changes in the testicular parenchyma, there was revealed pathology in the interstitium, which consists in the proliferation of connective tissue elements with local lymphocytic infiltration, hyalinosis and sclerosis of the fibrous connective tissue. The volume of the Leydig's cell nuclei decreased to 68.49±3.6 μm^3 versus 97.56±1.60 μm^3 in the control with a parallel decrease in testosterone concentration in the blood. Thus, the ultrastructural changes revealed in the hemocapillaries wall, the coiled seminiferous tubules lining and Sertoli cells with their connective apparatus, which are the components of the blood–testis barrier [1, 2], have led to disorders of spermatogenesis in the testis of men who had orchiepididymitis.

According to other authors, in acute orchiepididymitis was recorded thermal asymmetry, the difference in temperature between the affected and contralateral testis was $2\,^0C$, which also adversely affected spermatogenesis and, in particular, spermogram [5, 7]. In our study, there was a sharp decrease in the concentration of spermatozoa, an increase in the number of pathological forms and a decrease in their motility.

Conclusions

1. Past orchiepididymitis leads to profound ultrastructural changes in the endothelial cells of the testicular hemocapillaries, peritubular myoid cells of the coiled seminiferous tubules lining, Sertoli cells and Leydig's cells with damage to their cytoplasmic organelles.

2. In the ejaculate of men with this testicular pathology decreases the spermatozoa concentration, decreases the number of living and actively mobile spermatozoa, increases the number of dead and pathological spermatozoa forms.

Prospects for further research are to find the means of stimulating spermatogenesis in infertile men who had orchiepididymitis.

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Реферати

ХАРАКТЕР УЛЬТРАСТРУКТУРНИХ ЗМІН, ЗУМОВЛЕНИХ ОРХОЕПІДИДИМІТОМ, В ЯЄЧКУ І ЕЯКУЛЯТІ ЧОЛОВІКІВ
Глодан О.Я., Грицуляк Б.В., Грицуляк В.Б., Івасюк І.Й.

В 14 біоптатах яєчка неплідних чоловіків віком 22-35 років, що перенесли орхоепідидиміт, досліджено характер ультраструктурних змін та їх вплив на показники еякуляту. Встановлено деформацію і пікноз ядер, нерівномірне розширення перинуклеарного простору, вакуолізацію цитоплазми, гомогенізацію крист мітохондрій, розширення цистерн ендоплазматичної сітки та елементів комплексу Гольджі в ендотеліоцитах гемокапілярів, міоїдних клітинах власної оболонки звивистих сім'яних трубочок, підтримувальних епітеліоцитах, сперматоцитах і сперматидах, які супроводжувались в еякуляті зменшенням вдвічі концентрації сперматозоїдів в 1 мл, збільшенням у 3 рази кількості патологічних форм та зниженням їх рухливості.

Ключові слова: яєчко, орхоепідидиміт, клітини сперматогенного епітелію, еякулят.

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ХАРАКТЕР УЛЬТРАСТРУКТУРНЫХ ИЗМЕНЕНИЙ В ЯИЧКЕ И ЭЯКУЛЯТЕ МУЖЧИН, ОБУСЛОВЛЕННЫХ ОРХОЭПИДИДИМИТОМ
Глодан О.Ya., Hrytsuliak Б.В., Грицуляк V.В., Ивасюк И.И.

В 14 биоптатах яичка бесплодных мужчин в возрасте 22-35 лет, перенесших орхоэпидидимит, исследован характер ультраструктурных изменений и их влияние на показатели эякулята. Установлены деформация и пикноз ядер, неравномерное расширение перинуклеарного пространства, вакуолизация цитоплазмы, гомогенизация крист митохондрий, расширение цистерн эндоплазматической сети и элементов комплекса Гольджи в эндотелиоцитах гемокапилляров, миоидных клетках собственной оболочки извитых семенных трубочек, поддерживающих эпителиоцитах, сперматоцитах и сперматидах, которые сопровождались в эякуляте уменьшением концентрации сперматозоидов вдвое в 1 мл, увеличением в 3 раза количества патологических форм и снижением их подвижности.

Ключевые слова: яичко, орхоэпидидимит, клетки сперматогенного эпителия, эякулят.

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EXPERIMENTAL MORPHOLOGICAL STUDY OF DENTAL PULP LESIONS AT DIFFERENT STAGES OF DENTAL CARIES

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Numerous studies show that in the structure of the affection of deciduous teeth by dental caries, a high percentage of complicated dental caries is observed. Paper was aimed at the study of morphological lesion of the dental pulp in experimental dental caries of various severity in rats with theoretical rationale of the principles of treatment of pulpitis. 50 outbred albino male rates were involved into study. Experimental dental caries in rats was induced by special cariesogenic diet. At the first stage, the depth of carious lesions of the enamel and dentin was measured. The second stage was performed on decalcified blocks of teeth, serial sections were made from the resulting blocks, stained with hematoxylin and eosin. It revealed the potential occurrence of more frequent complications in the conservative treatment of deep carious lesions of approximal surfaces in comparison with deep lesions of chewing surfaces. Dental pulp carious lesion depends not only on the degree of carious process, but also on its localization, which should be taken into account when choosing the optimal method of treatment of dental caries, which also prevents the development of its complications.

Key words: experimental caries, tooth pulp, morphology**.**

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Notwithstanding the rapid development of dental science, the emergence of the advanced technologies and capabilities, the high prevalence of dental caries, especially in childhood, has prompted the WHO to include it into the six global contemporary diseases. Numerous studies show that in the structure of the affection of deciduous teeth by dental caries, a high percentage of complicated dental caries is observed [2, 3].

The main feature of the dental caries occurrence in deciduous teeth is rapid development of the pathological process. This is due to a thin enamel of deciduous teeth, a smaller volume of dentin, the presence of low-mineralized zones in it, which reach the pulp by broad bands in the form of interglobular dentin.

The dentin pulp complex responds to the microorganism's invasion into deep layers of the dentin by the formation of tertiary dentine, which is a protective barrier, since it reduces the diffusion of the latter in the direction of the pulp [7, 10]. However, the feature of the pulp of deciduous teeth is in its insignificant functional ability to produce dentin substitute, due to the minimum expressed protective and adaptive properties. At the same time, according to [9] the deciduous teeth pulp is quite often in a state of chronic

inflammation, which is represented by a chronic inflammatory exudate, including lymphocytes, macrophages and plasma cells. In some cases pulp recovery is possible, which, however, is a long-term process and depends on many factors, such as the overall state of the child's health, virulence of microorganisms, the possibility of the regenerative potential of the pulp, etc. Therefore, predicting lesions in pulp in the presence of dental caries, especially in the deciduous teeth, is quite difficult [1, 12].

The purpose of the paper was to study morphological lesion of the dental pulp in experimental dental caries of various severity in rats with theoretical rationale of the pulpitis treatment principles.

Materials and methods. The total of 50 outbred albino male rates aged ≈30 days weighing 35-40 g were involved into the study. Experimental dental caries in rats was induced by special cariesogenic diet, including: 54.0% saccharose, 18.5% cow cheese, washed under tap water and dried to solid state; 18.5% white bread crackers; 5% sunflower oil; 4 g sodium chloride and 1 dragee of the multivitamin complex "Undevit" per 100 g of feed. Under conditions of the diet, the animals were kept for 168 days with a gradual withdrawal from the experiment by the method of chloroform anesthesia overdose. The biological material was taken on the 28, 42, 56, 84, 98, 112, 126, 140, 154 and 168th day of the experiment and in the amount of 5 animals at each stage. Animal housing and experiments on them have been carried out in compliance with requirements of international principles of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg , 1985), and "General Ethic Rules for Conducting Experiments on Animals", adopted by the I National Congress on Bioethics (Kyiv, 2001).

Determination of morphological changes in different parts of the tooth was carried out in two stages. At the first stage, the depth of carious lesions of the enamel and dentin was measured, which was carried out on the removed non-decalcified jaws with molar and premolar, affected by caries. At the same time a crown of the tooth was cut with a special diamond cutter and stained histochemically with PAS-Alcian blue. This method enables clear distinction between the enamel, dentin and carious lesions. The second stage was performed on decalcified blocks of teeth. After fixation in 10% neutral formalin and paraffin, serial sections were made from the resulting blocks, stained with hematoxylin and eosin. The obtained preparations were used for study of morphological changes of the dental pulp which were observed at superficial, medium and deep dental caries. Decalcified, not affected by dental caries teeth of 5 rats served as the controls.

Results of the study and their discussion. The carious process was observed mainly on molars of experimental animals with varying degrees of damage to enamel and dentin. The enamel caries at the stage of the spot developed mainly on 28-56 days, the medium dentin caries on 70-98 days, deep dentin caries without perforation of the pulp chamber on 112-140 days, deep dentin caries with perforation of the pulp chamber on 154-168 days. The caries process developed on both proximal and chewing surfaces of the molars.

In superficial caries in the coronal region of the pulp a capillary hyperemia in the subodontoblastic plexus was noted with sporadic stasis. The main substance of the loose connective tissue of the central region of the pulp adjacent to the vessels was somewhat loosened, swollen. Between the odontoblasts small gaps were found, which were formed due to moderate edema of the stroma of the peripheral region of the pulp. In the root part of the pulp a moderate hyperemia in capillaries was noted without stasis. No pronounced structural changes in the odontoblasts of the root pulp that were located at the root of the pulp were found (fig. 1).

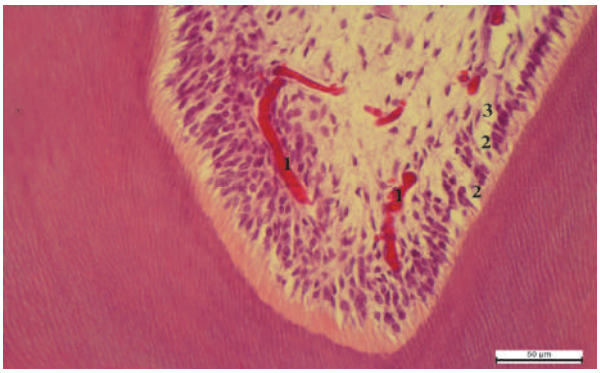

Fig. 1. Coronal pulp lesions in superficial dental caries. H&E stain.400× magnification.

1 – hyperemia in capillaries; 2 – edema in the interodontoblastic space; 3 – edema in subodontoblastic layer of the pulp.

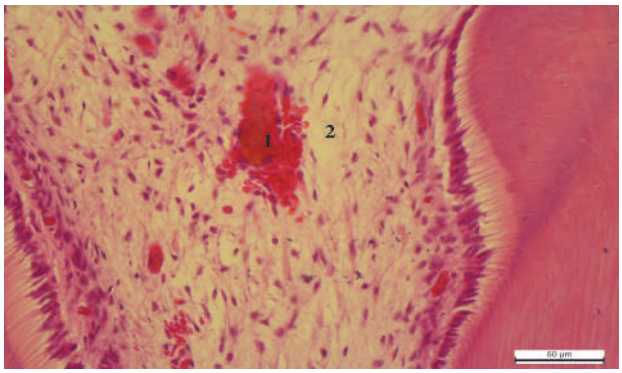

Fig. 2. Coronal pulp lesions in medium dental caries. H&E stain.400× magnification.

1 – hemorrhage in the central region of the pulp; 2 – edema of the main substance of the central region of the pulp; 3 – moderate edema of the supraodontoblastic space.

Histological changes in the pulp in medium caries were manifested by vascular hyperemia and stasis. In some vessels of the central region of the coronary pulp the hyaline, less often erythrocytic thrombi, were formed. In addition, in the central and peripheral region of the pulp diapedetic hemorrhages were visualized.

The main substance of the loose connective tissue of the pulp was swollen, especially in the coronal part. Moreover, in this part sporadic minor cellular infiltrations were visualized, mainly by lymphocytes, plasmacytes and single neutrophils. A significant amount of transsudate was accumulated in the supraodontoblastic space, between individual odontoblastic processes. In the areas of the projection of carious cavity the odontoblasts underwent necrotic lesions, localized in separate groups. The predentin was loosened, the odontoblastic processes were often destroyed (fig. 2).

A moderate vascular hyperemia, a minor mixed-cell inflammatory infiltration with no stasis was observed in the root pulp. Slightly pronounced proliferative odontoblastic processes and an increase in the number of preodontoblasts were detected. The remaining odontoblasts had an oblique or vertical orientation.

In deep caries of the approximal surfaces (without perforation), signs of acute serous pulpitis, accompanied by severe necrotic lesions of the odontoblasts, with disorganization of the peripheral layer of the pulp were revealed in the pulp. Inflammatory hyperemia, stasis, marginal standing of the neutrophilic granulocytes, hyaline, erythrocytic thrombi, extensive hemorrhages, edema of the supraodontoblastic space with the destruction of the odontoblastic processes was found in the vessels. Mainly hyperemia, stasis, isolated erythrocytic or hyaline thrombi, diapedetic hemorrhages were found in the root pulp. The coronal and root pulp stroma was focally infiltrated with lymphocytes, plasma cells, neutrophilic granulocytes, macrophages. In addition, deep carious lesions of the approximal surfaces of molars without perforations of the pulp cavity, inflammation in the pulp and sites, adjacent to the zone of carious destruction of the dentin were more pronounced in comparison with the level of inflammation, which was observed in the deep carious lesions of the occlusive surfaces of the molars (fig. 3).

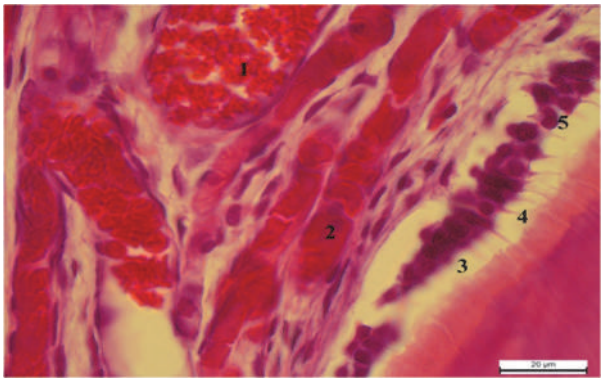

Fig. 3. Root pulp lesions in deep approximal caries. H&E stain. 1000×magnification.

1 – vascular hyperemia; 2 – stasis; 3 – edema of the supraodontoblastic space; 4 – destruction of the odontoblastic processes; 5 – necrobiotic lesions of the odontoblasts.

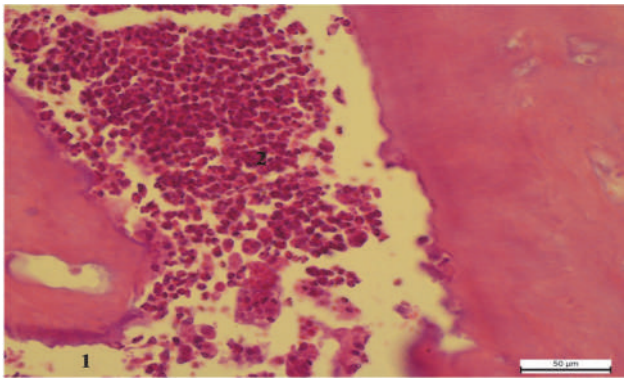

Fig. 4. Pulp lesions in deep dental caries with perforation. H&E stain. 400× magnification.

1 – the zone of dentin destruction; 2 – necrosis and diffuse leukocytic infiltration of the pulp.

On 154-168 days, a deep caries with perforation in the pulp chamber developed, accompanied by the development of purulent inflammation, passing from the coronal part of the pulp to the root part of the pulp and resulted in pulp gangrene (fig. 4).

The findings of the present experimental study are in concordance with the findings of the study [8], which compares the level of inflammatory pulp reaction in occlusal and deep approximal caries in deciduous molars of children.

Currently, pulp-preserving methods of treating deep carious lesions [7] by partial dentin excavation and indirect pulp coverage is tending to increase globally, therefore, it is recommended to take into account the localization of carious lesion, its depth and the state of the dental pulp. The latter criterion can be judged by the findings of our experimental study.

The resulting data on the experimental animals have found that in the deep carious lesions of molars without perforation of the pulp cavity, morphological changes in the pulp of molars were more pronounced in the presence of deep carious lesions of approximal surfaces in comparison with morphological changes observed in the presence of deep caries of chewing surfaces. This indicates the potential occurrence of more frequent complications in the conservative treatment of deep carious lesions of approximal surfaces in comparison with deep lesions of chewing surfaces.

In most studies, the method of indirect coating of dental pulp with sparing preparation of caries-modified dentin (one-stage or two-stage) is considered to be more rational and predictable approach to preserving the vitality of pulp tissues in the long term than the method of radical preparation of carious cavity, in which the opening of a horn of pulp occurs in most cases. Some publications report even about the possibility of almost complete preservation of caries-modified dentin with the isolation of the carious cavity only within the limits of the enamel [5, 11]. However, basically, these studies were conducted with the localization of carious cavities of Blake's Class I, which doubts the success and rationality of using this approach in the localization of deep carious lesions on the approximal surfaces, especially when it comes to deciduous teeth [6].

In this connection, when choosing the method of treatment of deep carious lesions of deciduous teeth, it is necessary to take into account the localization of the carious process and reasonably choose the method of treatment.

Conclusion

The intensity of dental caries and localization of deep carious lesions are important factors in the prediction of the effectiveness of conservative treatment of deep carious lesions. Dental pulp carious lesion depends not only on the degree of carious process, but also on its localization, which should be taken into account when choosing the optimal method of treatment of dental caries, which also prevents the development of its complications.

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Реферати

МОРФО-ЕКСПЕРИМЕНТАЛЬНЕ ДОСЛІДЖЕННЯ ЗМІН ПУЛЬПИ ЗУБА НА РІЗНИХ СТАДІЯХ КАРІЄСУ

Гринишин О.Б., Дидик Н.М., Филенко Б.М.

Чисельні дослідження свідчать, що у структурі ураженості карієсом тимчасових зубів спостерігається високий відсоток ускладненого карієсу. Метою дослідження було вивчення морфологічних змін пульпи зуба при експериментальному карієсі різної стадії у щурів з теоретичним обґрунтуванням принципів лікування пульпіту. Дослідження виконані на 50 білих безпородних щурах-самцях у яких викликали експериментальний карієс спеціальною карієсогенною дієтою. Спочатку визначали глибину каріозного ураження емалі та дентину на видалених недекальцинованих щелепах з подальшим виготовленням гістологічних препаратів на яких вивчалиль морфологічні зміни пульпи. Виявлено потенційну можливість виникнення більш частих ускладнень при глибоких каріозних ураженнях апроксимальних поверхонь у порівнянні із глибокими

МОРФО-ЭКСПЕРИМЕНТАЛЬНОЕ ИССЛЕДОВАНИЕ ИЗМЕНЕНИЙ ПУЛЬПЫ ЗУБА НА РАЗНЫХ СТАДИЯХ КАРИЕСА

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Многочисленные исследования показывают, что в структуре пораженности кариесом временных зубов наблюдается высокий процент осложненного кариеса. Целью исследования было изучение морфологических изменений пульпы зуба при экспериментальном кариесе различной стадии у крыс с теоретическим обоснованием принципов лечения пульпита. Исследования выполнены на 50 белых беспородных крысах-самцах в которых вызвали экспериментальный кариес специальной кариесогенной диетой. Сначала определяли глубину кариозного поражения эмали и дентина на удаленных недекальцинованих челюстях с последующим изготовлением гистологических препаратов на которых изучались морфологические изменения пульпы. Выявлено потенциальную возможность возникновения более частых осложнений при глубоких кариозных поражениях апроксимальных поверхностей по сравнению с

ураженнями жувальних поверхонь зубів. Отже, ураження пульпи зуба при карієсі залежить не лише від ступеня каріозного процесу, але й від його локалізації, що потрібно враховувати при виборі оптимального методу лікування карієсу, що також попередить розвиток його ускладнень.

Ключові слова: експериментальний карієс, пульпа, морфологія.

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глубокими поражениями жевательных поверхностей зубов. Итак, поражения пульпы зуба при кариесе зависит не только от степени кариозного процесса, но и от его локализации, что нужно учитывать при выборе оптимального метода лечения кариеса, также предупредит развитие его осложнений.

Ключевые слова: экспериментальный кариес, пульпа, морфология.

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INFLUENCE OF INHIBITORS OF TRANSCRIPTION FACTOR KAPPA B ON DEPOLIMERIZATION OF BIOPOLYMERS IN PERIODONTAL CONNECTIVE TISSUE UNDER SYSTEMIC INFLAMMATORY RESPONSE IN RATS

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The article presents the results obtained in the experiment on 40 white rats aimed at investigating the influence of ammonium pyrrolidine dithiocarbamate (APDTC), an inhibitor of the nuclear translocation of the transcription factor κB (NF-κB), on the depolymerization of collagen, proteoglycans and sialoglycoproteins in extracellular matrix of soft and osseous tissues under modeled systemic inflammatory response (SIR). The latter was induced by intraperitoneal administration of lipopolysaccharide Salmonella typhi (pyrogenalum) in a dose of 0.4 μg/kg of weight 3 times during the first week, and once a week for the following 7 weeks. It has been shown the SIR simulation is accompanied by activation of the collagenolysis as well as depolymerization of proteoglycans and sialoglycoproteins in the tissues of the gum, periodontal ligament and alveolar process of the jaws as evidenced by a considerable increase in the concentration of free hydroxyproline, glycosaminoglycans and N-acetylneuraminic acid. The application of APDTC during SIR significantly reduces the depolymerization of collagen, proteoglycans and sialoglycoproteins in soft and bone periodontal tissues, and limits the degree of resorption of the jaw alveolar process. This allows us to conclude the use of this compound during SIR is an effective means to correct disruption the periodontal connective tissue in rats.

Key words: nuclear factor kappa B, systemic inflammatory response, connective tissue biopolymers, collagen, proteoglycans, glycoproteins, periodontium.

The work is a part of the research project "The role of reactive oxygen species, nitric oxide system and transcriptional factors in the mechanisms of pathological systemogenesis", state registration No. 0114U004941.

Depolymerization of periodontal connective tissue biopolymers is considered to be an important link in the pathogenesis of chronic periodontitis under the influence of general (emotional and pain stress) [14] and local factors [10] that impedes its treatment by means of regenerative therapy [5]. Previously, we have shown that the modeling of lipopolysaccharide (LPS)-induced systemic inflammatory response (SIR) in periodontal tissues is accompanied by an increase in production of reactive oxygen and nitrogen species by mitochondria, endoplasmic reticulum and NO synthase (NOS), as well as NADPN-oxidase of white blood cells. The progression of oxidative-nitrosative stress results in the collagenolysis and the depolymerization of proteoglycans and sialoglycoproteins, both in the connective tissue of the gums and the periodontal ligament and in the bone tissue of the alveolar process [1]. It is noteworthy that most of the activators of NF-κB as bacterial LPS, proinflammatory cytokines, E2 prostaglandins, stress, viruses, etc. are involved in the pathogenesis of chronic periodontitis [3].

However, the relevant literature presents contradictory information regarding the effect of NF-κB on connective tissue status during inflammation [2, 6]. Solving this problem is of exceptional importance in searching new approaches towards the pathogenetic therapy of inflammatory and dystrophic periodontal diseases.

The purpose of the study was to investigate the effect of ammonium pyrrolidine dithiocarbamate (APDTC), an inhibitor of the nuclear translocation of the transcription factor κB (NF-κB), on the depolymerization of collagen, proteoglycans and sialoglycoproteins in extracellular matrix of soft and osseous tissues in periodontium of rats under modeled systemic inflammatory response induced with LPS Salmonella typhi.

Materials and methods. The series of the experiment were performed on 30 white male Wistar rats weighing 180-220 g, which were divided into 3 groups (with 10 animals in each group): the 1st group included intact animals, the 2nd group included rats, which were subjected to the systemic administration of LPS (pyrogen, Medgamal, Russia), and the 3rd group consisted of the animals, which received APDTC (manufactured by Sigma-Aldrich, Inc., USA) intraperitoneally in a dose of 76 mg/kg 3 times a week,

starting with the 30th day of the LPS experiment [12]. The latter was administered in a dose of 0.4 μg/kg of body weight 3 times through the 1st week, and then for the next 7 weeks once a week [15]. The animals were decapitated under light ether anesthesia, following the principles of biomedical ethics.

The level of collagenolysis was assessed by the content of free hydroxyproline (FHP) [13]. The level of depolymerization of proteoglycans and sialoglycoproteins was evaluated by determining their monomers, glycosaminoglycans (GAGs) [11] and N-acetylneuraminic acid (NANA) [9], respectively. Using the light microscope with an eyepiece micrometer, we measured the distance from the edge of the dental alveolar socket to the lower edge of the crown of the third molar (L_0) and the distance from the edge of the dental alveolar socket to the upper edge of the dental crown (L_1), followed by the calculation of the molar root exposure coefficient (C) using the formula (C) = L_0 / L_1.

Statistical calculations were performed using "StatisticSoft 6.0". To check the distribution for normality, the calculation of the Shapiro-Wilk test was applied. If the series corresponded to the normal distribution, then the Student's t test for independent samples was used to compare them. When the data were not subject to normal distribution, statistical processing was performed using a non-parametric method, the Mann-Whitney test.

Results of the study and their discussion. The LPS administration led to a significant increase in the concentration of collagen monomers, proteoglycans and sialoglycoproteins of the connective tissue of the gums and periodontal ligament (table 1). FHP content increased by 66.2% ($p<0.01$), GAGs by 66.8% ($p<0.05$), and NANA by 62.9% ($p<0.001$) that indicates the activation of the processes of collagenolysis and depolymerization of proteoglycans and glycoproteins in soft tissues of periodontium under this condition.

Table 1

Effect of APDTC on the indices of biopolymer depolymerization in connective tissues of gingival and periodontal ligament under SIR conditions (M±m, n = 30)

Experimental groups	FHP, μmol /g	GAGs, μmol /g	NANA, μmol /g
Intact animals	4.08±0.48	1.93±0.34	4.56±0.17
Systemic LPS administration	6.78±0.35 *	3.22±0.34 *	7.43±0.33 *
Applying APDTC under systemic LPS administration	4.89±0.30 **	2.03±0.26 **	5.67±0.17 */**

Notes (in Table 1-2): * - p <0.05 compared with the results of the intact group, ** - p <0.05 compared with the results of the second group.

The APDTC administration reduced the FHP concentration by 27.9% ($p<0.01$), GAGs by 37.0% ($p<0.05$), and NANA by 23.7% ($p<0, 01$) in the soft tissues of periodontium compared to the values of the 2nd group.

Systemic LPS administration also resulted in the marked changes in the biopolymer composition of extracellular matrix in bone tissues of the alveolar process (table 2): the FHP content increased by 69.9% ($p <0.001$), the GAGs increased by 72.4% ($p<0.02$), and NANA by 115.0% ($p<0.01$).

Using APDTC led to the lowering of FHP concentration by 29.2% ($p<0.001$), GAGs by 42.3% ($p<0.01$), and NANA by 50.3% ($p<0.01$) compared with the values in the 2nd group.

Table 2

Effect of APDTC on the indices of depolymerization of periodontal bone biopolymers and the molar root exposure coefficient (C) under SIR condition (M±m, n = 30)

Experimental groups	FHP, μmol /g	GAGs, μmol /g	NANA, μmol /g	C
Intact animals	3.06±0.28	1.70±0.30	2.01±0.35	25.0±1.4
Systemic LPS administration	5.20±0.19 *	2.93±0.22 *	4.33±0.37 *	37.5±2.2 *
Using APDTC under systemic LPS administration	3.68±0.22 **	1.69±0.16 **	2.15±0.32 **	27.8±1.6 **

As it has been demonstrated previously, NF-κB activation enhances the expression of collagenase 3 (matrix metalloproteinase 13) genes [8]. The activation of NF-κB has been found to be an important link in the pathogenesis of free radical lesions of periodontium, collagenolysis and depolymerization of proteoglycans of its connective tissue in experimental metabolic syndrome, where SIR is an inseparable component. And the administration of a nuclear translocation inhibitor NF-κB 4-methyl-N- (3-phenylpropyl) benzene-1, 2-diamine under these conditions lowers the amount of FHP and GAGs in periodontium tissues [7].

According to our data obtained, depolymerization of periodontal connective tissue biopolymers caused the changes in the dental root exposure coefficient (C), characterizes the intensity of the alveolar process resorption (see Table 2). Under SIR conditions, the C value increased by 50.0% ($p<0.01$). APDTC administration decreased this index by 25.9% ($p<0.01$).

The study has revealed that in the osseous tissues of periodontium, NF-κB-dependent processes associated with NF-κB receptor activator (RANK), its ligand (RANKL), and an erroneous receptor, osteoprotegerin, play an important role in regulating osteoclast resorptive activity [4]. This can be considered as an additional mechanism of destructive changes in osseous tissue of periodontium.

Conclusion

The use of ammonium pyrrolidine dithiocarbamate (APDTC), an inhibitor of the nuclear translocation of the transcription factor κB (NF-κB), under the conditions of systemic administration of Salmonella typhi lipopolysaccharide is an effective means in correction of periodontium connective tissue disorganization of the periodontium in rats, reduces depolymerization of collagen, proteoglicans and sialoglycoproteins in soft and osseous tissues of periodontium, as well as decreases alveolar process resorption.

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Реферати

ВПЛИВ ІНГІБІТОРА ТРАНСКРИПЦІЙНОГО ФАКТОРА КАППА В НА ДЕПОЛІМЕРИЗАЦІЮ БІОПОЛІМЕРІВ СПОЛУЧНОЇ ТКАНИНИ ПАРОДОНТА ЩУРІВ ЗА УМОВ СИСТЕМНОЇ ЗАПАЛЬНОЇ ВІДПОВІДІ

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В експерименті на 40 білих щурах досліджено вплив інгібітора ядерної транслокації транскрипційного фактора каппа В (NF-κB) амонію піролідиндітіокарбамату (APDTC – ammonium pyrrolidinedithiocarbamate) на деполімеризацію колагену, протеогліканів та сіалоглікопротеїнів позаклітинного матриксу м'яких і кісткової тканин пародонта за умов експериментальної системної запальної відповіді (СЗВ). Останню моделювали шляхом внутрішньочеревного введення ліпополісахариду Salmonella typhi (пірогенал) у дозі 0,4 мкг/кг маси протягом 1-го тижня 3 рази, протягом наступних 7-ми тижнів – 1 раз у тиждень. Показано, що моделювання СЗВ супроводжується активацією процесів колагенолізу, а також деполімеризації протеогліканів та сіалоглікопротеїнів у тканинах ясен, періодонтальної

ВЛИЯНИЕ ИНГИБИТОРА ТРАНСКРИПЦИОННОГО ФАКТОРА КАППА В НА ДЕПОЛИМЕРИЗАЦИЮ БИОПОЛИМЕРОВ СОЕДИНИТЕЛЬНОЙ ТКАНИ ПАРОДОНТА КРЫС ПРИ СИСТЕМНОМ ВОСПАЛИТЕЛЬНОМ ОТВЕТЕ

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В эксперименте на 40 белых крысах исследовано влияние ингибитора ядерной транслокации транскрипционного фактора каппа В (NF-κB) аммония пирролидиндитиокарбамата (APDTC - ammonium pyrrolidinedithiocarbamate) на деполимеризацию коллагена, протеогликанов и сиалогликопротеинов внеклеточного матрикса мягких и костной тканей пародонта в условиях экспериментального системного воспалительного ответа (СВО). Последний моделировали путем внутрибрюшного введения липополисахарида Salmonella typhi (пирогенала) в дозе 0,4 мкг/кг в течение 1-й недели 3 раза, в течение следующих 7-ми недель - 1 раз в неделю. Показано, что моделирование СВО сопровождается активацией процессов коллагенолиза и деполимеризации протеогликанов и сиалогликопротеинов в тканях десны, периодонтальной

зв'язки та альвеолярного відростку щелеп, що підтверджується суттєвим збільшенням концентрації вільного оксипроліну, глікозаміногліканів та N-ацетилнейрамінової кислоти. Застосування APDTC за умов СЗВ істотно зменшує у м'яких і кістковій тканинах пародонта деполімеризацію колагену, протеогліканів та сіалоглікопротеїнів, обмежує ступінь резорбції альвеолярного відростка щелеп. Зроблено висновок, що застосування цієї сполуки при СЗВ є ефективним засобом корекції дезорганізації сполучної тканини пародонта щурів.

Ключові слова: ядерний фактор каппа В, системна запальна відповідь, біополімери сполучної тканини, колаген, протеоглікани, глікопротеїни, пародонт.

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связки и альвеолярного отростка челюстей, что подтверждается существенным увеличением концентрации свободного оксипролина, гликозаминогликанов и N-ацетилнейраминовой кислоты. Применение APDTC при СВО существенно уменьшает в мягких и костной тканях пародонта деполимеризацию коллагена, протеогликанов и сиалогликопротеинов, ограничивает степень резорбции альвеолярного отростка челюстей. Сделан вывод, что применение этого соединения при СЗВ является эффективным средством коррекции дезорганизации соединительной ткани пародонта крыс.

Ключевые слова: ядерный фактор каппа В, системный воспалительный ответ, биополимеры соединительной ткани, коллаген, протеогликаны, гликопротеины, пародонт.

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EFFECTIVENESS OF THE PLATELET-RICH PLASMA APPLICATION AT DIFFERENT SIMULATION PERIODS OF DEGENERATIVE DISC DISEASE IN RATS

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The article describes the study of the platelet-rich plasma application effectiveness for tissue regeneration of intervertebral discs in rats with simulated degenerative disk disease of the caudal vertebrae for 60 and 90 days. The experiment involved 80 rats, which were divided into four groups: Group I – rats with a simulated pathology without correction for 60 days, Group II – rats with a simulated pathology without correction for 90 days, Group III – rats with a pathology and its correction for 60 days, Group IV – rats with a pathology and its correction for 90 days. The described morphological changes in the invertebral disk tissue suggest that the application of platelet-rich plasma in the pathology simulation for 60 days leads to the degenerative process inhibition and restores the invertebral disk structure. The application of platelet-rich plasma for 90-day pathology simulation is less effective.

Key words: degenerative disk disease, intervertebral disc, fibrous ring, nucleus pulposus, platelet-rich plasma.

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Spinal diseases take the second place among the causes of temporary disability, and, eventually, often lead to permanent disability [2]. In 90% of cases, spinal diseases are based on degenerative disk disease (DDD) [3]. At the age of 30 years, signs of DDD are detected in 57% of cases, and at the age of 60 years and older – in 100% [3]. In Ukraine, annually about 1 million patients with DDD seek medical help, more than 16 thousand of them subsequently become disabled. Thus, this pathology is of great importance not only for the medical, but also for the socio-economic sphere.

Currently, the study of the effectiveness of tissue therapy application to regenerate the intervertebral disc (IVD) structure after DDD is a promising area. The literature data indicate the effectiveness of using some growth factors for the intervertebral disk morphology regeneration after DDD in the experiment [9]. The use of platelet-rich plasma (PRP) on IVD tissues in laboratory rats after the acute IVD injury in the early stages of the DDD formation has a positive effect [7, 8]. However, often DDD-associated visits to medical institutions for qualified care occur after the first clinical manifestations, when the pathological process is already expressed.

The purpose of work was to study the efficiency of using PRP in the DDD simulation for 60 and 90 days.

Materials and methods. The study was carried out on Whistar rats of both sexes aged 4-6 months (80 animals), which were divided into four groups: Group I – animals with DDD for 60 days, without correction; Group II – animals with DDD for 90 days, without correction; Group III – animals with DDD for 60 days, which were injected with PRP; Group IV – animals with DDD for 90 days, which were injected with PRP. A separate group (10 animals) studied as intact animals. Animal preparation, anesthesia, surgery, postoperative care and terminal sacrifice were carried out in accordance with the Law of Ukraine "On protection animals from brutal treatment" No. 27, Art. 230 of 2006, and the general principles of ethics of experiments on animals and the Code of Ethics for Ukrainian Scientists.

The experiment was performed in the research laboratory of the Department of Normal and Pathological Clinical Anatomy of Odessa National Medical University (ONMedU) by forming static compression-distension of the caudal vertebrae of spinal column [5]. The surgical procedure took place under general ether anesthesia. 2% lidocaine solution was used for pain relief. The procedure was carried out in two stages. First, a stump was formed by the tail resection at the level of CcXIV-CcXV. Then the stump was sutured to the muscles and ligaments of the lumbosacral spine. After treating the surgical wound with an antiseptic and applying the postoperative dressing, the animals were placed in a warm container until awakened, and then transferred to the cells. Pathology was simulated within 60 and 90 days after surgery. Then, animals of Groups III and IV were injected subcutaneously in the base of the tail with 0.1 ml of PRP twice with an interval of seven days. PRP was obtained immediately before administration, by isolating it from whole blood on a SmartPrep preparation (manufactured by Harvester Corp, USA). The first day of the experiment was considered the day after the last PRP injection. Animals were sacrificed on the 14th and 28th day of the experiment via ether overdose inhalation.

After the experiment, a section with two adjacent vertebrae in the area of the greatest tail flexure was excised for the pathomorphological study. The obtained objects were formalin-fixed, decalcified, and further prepared and stained with hematoxylin-eosin according to standard methods [1]. Histologic specimens were studied using a Leica DM750 light microscope using standard microscopy and morphometric methods [1]. The significance of differences between the two samples was determined using Student's parametric criterion. The Student's coefficient value was determined with the number of degrees of freedom equal to (n1+n2-2). The significance of the differences between the two samples (p) was calculated using the distribution table. The difference was considered significant if the probability of a random difference did not exceed 0.05 ($p \leq 0.05$).

Results of the study and their discussion. The intervertebral discs of intact animals consisted of a centrally located nucleus pulposus, which was surrounded on the periphery by a fibrous ring with an almost symmetrical shape. The nucleus pulposus (NP) had a regular oval shape, consisted of large notochordal cells and small chondrocytes. Notochordal cells were located mainly in the central parts of the nucleus in clusters of 4-6 cells, and chondrocytes were located on the periphery. The fibrous ring (FR) was represented by plates of collagen fibers of the longitudinal direction with fibroblasts and chondrocytes located between them. At the border of the IVD with the epiphysial cartilage of neighboring vertebrae, end plates consisting of round and spindle-shaped basophilic cells located in 1-2 layers were located parallel to each other. The IVD thickness of intact animals on both sides was almost the same and averaged 1.75±0.09 mm. The NP cross-section area in the central part of the disk was equal to 4.21±0.16 mm^2 (table 1).

Table 1

Morphometric indicators of intervertebral discs in rats

Parameter	Control	Group I	Group II	Group III		Group IV	
				in 14 days	in 28 days	in 14 days	in 28 days
FR on compression side (mm)	1.75±0.11	1.22±0.12*	0.62±0.05*	1.61±0.13	1.59±0.12	0.78±0.05*	0.76±0.05*
FR on distension side (mm)	1.75±0.11	2.14±0.15	1.48±0.05	2.16±0.22	2.02±0.19	1.76±0.08	1.70±0.08
NP area (mm^2)	4.21±0.16	2.37±0.21*	0.91±0.12*	2.97±0.19*	2.96±0.19*	1.18±0.05*	1.17±0.05*

* - $p \leq 0.05$ – the difference is significant relative to the control

Histological examination of IVD in Group I (simulation of DDD for 60 days) revealed the asymmetry of its structures. On the compression side, a decrease in the thickness of the fibrous ring was observed. Its plates were flattened and stratified. In the central areas of compression, ruptures of collagen fibers with the presence of polymorphic fissures and foci of fibrinoid necrosis were noted. Between the fibers were single fibrocytes with signs of dystrophy. The thickness on the compression side was 1.22±0.12 mm, and on the distension side – 2.14±0.15 mm. The nucleus pulposus was reduced in size and displaced towards distension. Its area in the central part of the disk was 2.37±0.21 mm^2. The nuclear matrix was heterogeneous, consisting of complexes of 3-4 notochordal cells of preserved structure and areas without cells. There were signs of vacuole dystrophy in the nucleus cells. The end plate consisted of predominantly preserved cells located in 1-2 rows, and contained areas of necrosis (fig. 1).

On histological preparations of IVD in animals of Group II, a sharp asymmetry of their structures was noted. The IVD thickness on the compression side was 0.62±0.05 mm. The FR collagen fibers on the compression side were sharply compressed, and in some places they were broken. Among them are single fibrocytes and chondrocytes with signs of dystrophy. On the distension side, the FR collagen fibers were stretched, stratified, and contained polymorphic fissures and multiple ruptures. The IVD thickness on the

distension side was 1.48±0.05 mm. There were signs of vacuole dystrophy in the FR cells. The nucleus pulposus was irregular in shape, sharply reduced in size and displaced towards distension. Its matrix contained significant cell-free foci. Notochordal cells were located singly and in groups of 2-3 cells, forming clusters. Most of the cells were in the stage of hydropic degeneration. The end plate contained numerous foci of necrosis and ossification (fig. 2).

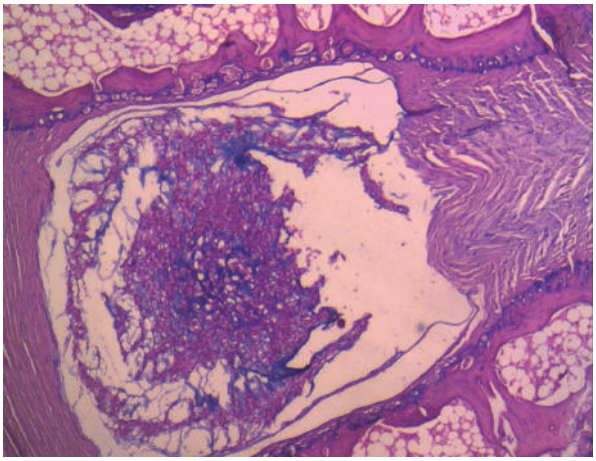

Fig. 1. Morphology of the intervertebral disc of a rat with simulated DDD for 60 days. Staining: hematoxylin, eosin, x 40

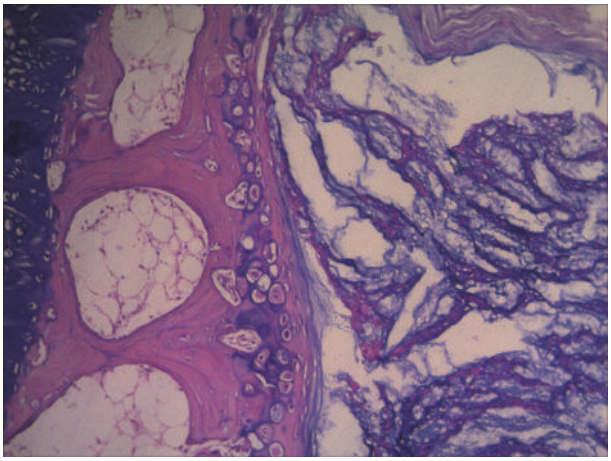

Fig. 2. Morphology of the intervertebral disc of a rat with simulated DDD for 90 days. Staining: hematoxylin, eosin, x 100

The study of preparations of the Group III showed the restoration of the invertebral disk structure, mainly due to the fibrous ring tissues. 14 days after the PRP administration, the restoration of the fibrous ring thickness (1.61±0.13 mm) was observed on the compression side. The fibers were less flattened and stratified than in a group without correction. Chondrocytes of 2-4 cells with signs of proliferation were located between the fibers. There were no foci of fibrinoid necrosis. The FR thickness on the distension side was 2.16±0.22 mm. The nucleus pulposus was displaced towards distension and reduced in volume. Its cross-sectional area was 2.97±0.19 mm^2. The nuclear matrix contained clusters of 3-4 notochordal cells with moderate polymorphism and vacuolated cytoplasm. Signs of synthetic activity were occured in the cells. An increase in the chondrocytes number is noted near the EP, and in the plate itself the number of necrosis foci is reduced and there are signs of synthetic cell activity. 28 days after the PRP administration, signs of synthetic activity of the disk cells persisted. The fibrous plates of the FR outer layer were stratified with breaks. The inner layers of the FR were without breaks. Pockets of fibrinoid necrosis were absent or were very isolated. Between the fibers were located chondrocytes with signs of proliferation. The thickness of the fibrous ring on the compression side was 1.59±0.12 mm, on the distension side – 2.02±0.19 mm. The nucleus pulposus retained a displaced position in the disk; its area in the central part of the disk remained almost unchanged (2.96±0.19 mm^2). In the nuclear matrix, against the background of large cells with signs of dystrophy collected in groups, the number of small single cells visually increased.

In the IVD tissues of animals of Group IV, the nucleus pulposus asymmetry and a decrease in the disk thickness on the compression side were preserved. On the 14th day after the PRP administration, in the outer layers of the FR there are signs of structure restoration against the background of a long degenerative process. The plates of the FR outer layer were stratified, contained longitudinal fissures and single breaks. Foci of fibrinoid necrosis of 10-30 μm, reaching up to ½ of the fibrous ring thickness, were noted in the compression area. The plates of the FR inner layer were more preserved and organized. Hypertrophic fibrocytes with signs of synthetic activity were found between the fibers and near the foci of necrosis. The disk thickness on the compression side was 0.78±0.05 mm, and on the distension side – 1.76±0.08 mm. The nucleus pulposus cut area in the central part of the disc was 1.18±0.05 mm^2. Its matrix was heterogeneous and contained cell-free areas and cavities. Notochordal cells were located singly or clustered in 2-3 cells. Some cells were in a state of vacuole dystrophy, while others formed a heterogeneous matrix around themselves. The end plates were thinned and contained single cells with signs of synthetic activity. Numerous cells with a preserved structure of various sizes were observed near the EP.

On the 28th day of the experiment, the positive effect of PRP on the disc tissue was observed. The plates of the FR outer layer were disorganized and stratified, contained longitudinal fissures 20–40 μm in size. The fiber ruptures in the inner layers of the FR were single. Foci of fibrinoid necrosis were noted on the compression side. Fibroblasts with signs of synthetic activity were located between the FR plates. The

disk thickness on the compression side was 0.76±0.05 mm, and on the distension side – 1.70±0.08 mm. The nucleus pulposus cut area in the central part of the disc was 1.17±0.05 mm^2. The matrix of the nucleus pulposus was compacted and contained cell-free areas. Notochordal cells of the nucleus pulposus were represented by solid clusters and elongated complexes. Against the background of notochordal cells in the stage of vacuole dystrophy and necrobiosis, smaller cells were determined. The end plates contained chondrocytes with signs of synthetic activity.

Studying the histological preparations of animals of Group I and II, and comparing them with the control, revealed the occurrence and progression of degenerative changes in the tissues of FR and NP. This is evidenced by increasing the FR fibrinoid necrosis foci and polymorphic fissures, clusters destruction and an increase in the NP cell-free areas, an increase in the EP necrotic sections, as well as signs of hydropic degeneration of the disk cells. Morphometric analysis revealed a decrease in the fibrous ring thickness on the compression side to 69.7% (Group I) and 35.4% (Group II) of the intact disk thickness. The nucleus pulposus was displaced toward distension, its area in the central part of the disk decreased to 56.3% (Group I) and 21.6% (Group II) of the intact disk.

A study of the intervertebral discs of animals of the Groups III and IV revealed the effectiveness of the PRP administration for the regeneration of degenerative discs. This is evidenced by an improvement in the structure of the fibrous ring plates, a decrease in the number and size of fibrinoid necrosis foci, as well as signs of fibrocyte proliferation. Matrix restoration, the appearance of synthetic activity of notochordal cells and an increase in the number of chondrocytes are noted in the NP tissues. Near the EP, there is an increase in the chondrocytes number, and in the plates themselves – a decrease in the number of necrosis foci and a high synthetic activity of the cells.

After 14 days, the PRP administration in Group III contributed to the restoration of the 92% FR thickness of the intact disc on the compression side. On the distension side, the thickness of the fibrous ring was 23% greater than the intact discs. The nucleus pulposus area after correction amounted to 70.5% of intact discs. A comparison of disk preparations after 14 and 28 days from the PRP administration did not reveal statistically significant differences, which can indicate a prolonged effect of growth factors.

14 days after the PRP administration to the Group IV of animals, the fibrous ring thickness on the compression side was 44.6%, and the NP area was 28% of intact discs. This indicates a lower effect with the PRP administration in the late terms of DDD simulation.

PRP is a small fraction of plasma with a high concentration of platelets. The regenerative effect of PRP is based on the effect of a cocktail of growth factors [11, 12]. With the PRP administration into degenerative discs at the early stages of DDD simulation (60 days), a lot of biologically active growth factors are released that contribute to tissue repair by activating the regenerative potential of disk cells [11]. The effect of the PRP administration is observed after two weeks and persists for at least another four weeks. Against the background of a longer DDD simulation (up to 90 days), when the number of disc cells and their regenerative potential are reduced, the PRP administration has a lower effect.

Of course, we cannot say that our experimental DDD simulation in rats fully reflects the natural course of spinal diseases, if only because of the presence of ongoing compression on the discs in case of illness. However, the literature data indicate that this is one of the closest morphological manifestations of the options for DDD simulation [4].

Obviously, the PRP administration has an active regenerative effect on the IVD tissues for 28 days, and possibly longer, which can be revealed in the course of further experiments. It should be remembered that the quality of PRP, prepared using commonly used laboratory centrifugation procedures may vary [13].

Conclusions

1. The formation of static compression-distension of the caudal vertebrae of spinal column in rats for 60 days leads to a pronounced degenerative disk disease, which is manifested by mechanical displacement and damage to the tissues of the intervertebral disc, resizing of the disc components, as well as the occurrence of degenerative processes in the cells themselves.

2. The formation of static compression-distension of the caudal vertebrae of spinal column in rats for 90 days leads to the progression of degenerative disk disease in the intervertebral discs and the development of irreversible tissue changes.

3. The administration of platelet-rich plasma during the DDD simulation for 60 days is effective in tissue regeneration and helps to restore the disk structure.

4. The use of platelet-rich plasma during the DDD simulation for 90 days has a positive effect on the inhibition of the pathological process in the disks, but, however, a significant restoration of morphology is not observed.

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Реферати

ЕФЕКТИВНІСТЬ ЗАСТОСУВАННЯ ЗБАГАЧЕНОЇ ТРОМБОЦИТАМИ ПЛАЗМИ ПРИ РІЗНИХ ТЕРМІНАХ МОДЕЛЮВАННЯ ДЕГЕНЕРАТИВНО-ДИСТРОФІЧНОГО УРАЖЕННЯ ХРЕБТА У ЩУРІВ

Запорожан В.М., Аппельханс О.Л., Цюрупа О.В.

У статті описано дослідження ефективності застосування збагаченої тромбоцитами плазми для відновлення тканин міжхребцевих дисків щурів з модельованим дегенеративно-дистрофічним ураженням хвостового відділу хребта протягом 60 та 90 днів. В експерименті брали участь 80 щурів, які були розподілені на чотири групи: I група – щури з модельованою патологією протягом 60 днів без корекції, II група – щури з модельованою патологією протягом 90 днів без корекції, III група – щури з патологією 60 днів та корекцією, IV – щури з патологією 90 днів та корекцією. Описанні морфологічні зміни тканин дисків дають змогу стверджувати, що застосування збагаченої тромбоцитами плазми при моделюванні патології 60 днів призводить до гальмування дегенеративного процесу та відновлює структуру диску. Застосування збагаченої тромбоцитами плазми при моделюванні патології 90 днів має менший позитивний ефект.

Ключові слова: дегенеративно-дистрофічне ураження хребта, міжхребцевий диск, фіброзне кільце, драглисте ядро, збагачена тромбоцитами плазма.

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ЭФФЕКТИВНОСТЬ ПРИМЕНЕНИЯ ОБОГАЩЁННОЙ ТРОМБОЦИТАМИ ПЛАЗМЫ ПРИ РАЗЛИЧНЫХ СРОКАХ МОДЕЛИРОВАНИЯ ДЕГЕНЕРАТИВНО-ДИСТРОФИЧЕСКОГО ПОРАЖЕНИЯ ПОЗВОНОЧНИКА У КРЫС

Запорожан В.Н., Аппельханс Е.Л., Цюрупа А.В.

В статье описано исследование эффективности применения обогащенной тромбоцитами плазмы для восстановления тканей межпозвонковых дисков крыс с моделируемым дегенеративно-дистрофическим поражением хвостового отдела позвоночника в течение 60 и 90 дней. В эксперименте участвовали 80 крыс, которые были разделены на четыре группы: I группа – крысы с моделируемой патологией в течение 60 дней без коррекции, II группа – крысы с моделируемой патологией в течение 90 дней без коррекции, III группа – крысы с патологией 60 дней и коррекцией , IV – крысы с патологией 90 дней и коррекцией. Описанные морфологические изменения тканей дисков позволяют утверждать, что применение обогащенной тромбоцитами плазмы при моделировании патологии 60 дней приводит к торможению дегенеративного процесса и восстанавливает структуру диска. Применение обогащенной тромбоцитами плазмы при моделировании патологии 90 дней менее эффективно.

Ключевые слова: дегенеративно-дистрофическое поражение позвоночника, межпозвоночный диск, фиброзное кольцо, студенистое ядро, обогащенная тромбоцитами плазма.

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EXPERIMENTAL AND MORPHOLOGICAL SUBSTANTIATION OF TUBULAR BIOLOGICAL STRUCTURES OBLITERATION BY MEANS OF HIGH-FREQUENCY ELECTRIC WELDING OF TISSUES

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We investigated the effect of high-frequency electric current on the simulated fistula of the digestive canal. We have identified the optimal parameters of the generator necessary for the destruction of the mucous membrane. Morphological methods confirmed the effectiveness of the current in destroying the tunica serosa of the fistula.

Key words: electric welding of biological tissues, morphological changes, intestinal fistula.

The work is a fragment of the research project "Development of new techniques for the operative integrity restoration of vessels and elements in the gastrointestinal tract by means of electric welding and convection-infrared processing of live tissues", state registration No. 0116U004903.

Live Tissue Electric Welding (LTEW) was developed at the E.O. Paton NAS of Ukraine, by specialists of the experimental department at the Institute of Surgery and Transplantation, NAMS of Ukraine with the participation of "Welding" International Association and the CSMG company (USA). [1, 4] Some authors believe that due to the specially selected parameters of high-frequency current and the features of its technique's influence on the tissues, the connection of tissues is performed, which does not lead to the formation of coagulation scab, necrosis and loss of tissue's living activity. [1, 2, 3] Others claim that when used in the electrode area, a coagulation film or coagulation scab is formed, which perform the function of tissue fixation and sealing. [4, 5] The opinion of all authors agrees on the size of tissue damage within the range of high-frequency current, which does not exceed 1-2 mm from the applied electrodes.

LTEW is used in abdominal, thoracic, vascular surgery, oncology, neurosurgery, otolaryngology, gynecology and urology [2, 3, 4] Bipolar spherical or oval-shaped electrodes are used for endovascular obliteration of superficial veins of the lower extremity in varicose vein disease. [3] Optimal parameters for using a welding probe for vein obliteration were developed: the extraction rate was 0.5–1.0 cm/s, depending on the vein diameter, current power being 50%. [3]

This work was performed for experimental and morphological substantiation of the possible applying endoscopic high-frequency current welding of the hollow organs fistulas in the digestive tract. Fistulas account for 1-2% of all abdominal surgical pathology. Mortality in surgical treatment remains high, so the development of new minimally invasive therapies is relevant.

The purpose of the work was to study the nature of morphological changes in the vermiform appendix and small intestine tissues during endoscopic welding with a spherical electrode, under different modes of exposure to high-frequency electric current, to determine the optimal conditions for the mucous membrane destruction.

Materials and methods. The study was carried out in the pathoanatomical department of the Alexander Clinical Hospital in Kyiv on 106 fragments of the small intestine and vermiform appendix of the dead for the period from 01.02 to 30.12. 2018. The material was obtained in compliance with the rules of bioethics in the absence of the digestive tract pathology, during dissection, within 6-12 hours after death. The fistulous passage of various diameters was simulated by imposing a direct Bilroth clamp parallel to the antimesenteric margin of the dissected small intestine through all the layers of opposite walls (82 cases).

A spherical bipolar electrode was introduced into the lumen at the depth of the formed passage. While pulling the electrode, the passage welding was performed from inside. In the second series of the experiment, the lumen of the blindgut vermiform appendix (24 cases) was welded. To do this, the top of the appendix was cut off. An electrode was introduced into the blindgut lumen and the vermiform appendix was welded during the electrode pulling out. For high-frequency biological tissue welding, "EKWZ-300 Patonmed" generator and special spherical electrodes consisting of a spherical shaped working part with two S-shaped electrodes were used. Welding was performed in the "manual mode of the machine", at 50% of its power and at the maximum power, with the drawing speed of 0.5-2mm/s.

The electrodes used were of different diameters from 4 to 8 mm, depending on the vermiform appendix lumen diameter, reaching a firm adherence of the electrode to its wall. Macroscopic changes of the organ's wall during welding were determined, as well as changes of the mucous membrane after opening the modeled small intestine passage. The dependence of macroscopic and microscopic changes on

the electric current power, the electrode drawing speed, integrity of the electrode adhesion to the wall were studied. The organ fragments were excised and fixed in 10% formalin solution, embedded into paraffin blocks. The 5 μm thick sections were stained with hematoxylin and eosin.

Results of the study and their discussion. At the stage of working out the methodology and developing the acceptable parameters, the necessity was established to achieve a firm adherence of the electrode to the wall of the welded organ. When welding is performed with a smaller diameter electrode there is a point, abrupt welding of the wall through. The vermiform appendix, or fragment of the formed gut canal, is deformed in the shape of beads in an irregularly shaped necklace. During the gut opening, the mucosa is mosaically damaged, the sites of coagulation alternate with the intact ones. This indicates unacceptability of using smaller diameter electrodes (than the canal lumen) to destroy its inner layer. Therefore, an electrode of 4-8 mm in diameter was used for the vermiform appendix, and a canal corresponding to the 8 mm diameter electrode was formed from the gut.

While stretching the electrode, the operator feels the moment of its ejection from the canal. But, if the electrode is retained for a longer time, coagulation occurs around and in front of the electrode ball. This resists its stretching and prevents it from moving evenly. Therefore, it the speed was selected at which the operator feels light resistance when stretching the electrode, that is, pulls it out with little effort at smooth advancing. In our case, the optimum mean electrode advance velocity was 1.45 mm/s. Macroscopically, when stretching the electrode, there is a blanching of the appendix or gut wall, contraction and reduction of their diameter.

When removing the clamp from the wall of the canal formed from the gut, the welding of the mucous membrane edges was determined in the closure area, which was torn with little effort. The canal's lumen was preserved and equalled 2-3 mm. The internal surface of the welded canal was dark gray, dry, wrinkled, and the mucous membrane was not identified. Thus, it can be concluded that endoscopic welding of the canal lined by the mucous membrane does not cause its complete welding and elimination of the lumen, but significantly reduces its diameter (from 8 to 2 mm) due to the coagulation and constriction of tissues.

When using the maximum power (100%) of the apparatus, a more pronounced deformation of the wall occurs both behind and before the electrode's movement, the evaporation of fluid is taking place from the surface of the intestine and the vermiform appendix. The resistance to the electrode was significantly increased. It was almost impossible to achieve smooth passage through the canal. This can indicate high temperature on the outer surface of the organ's wall and its severe damage. Therefore, we have limited the power of the device to 50%.

In microscopic study of the vermiform appendix walls, when using an electrode smaller than the diameter lumen, mosaic alternative changes are observed, which mainly concern the walls of blood vessels, individual bundles of collagen fibers in the submucous layer and in the mucous membrane itself, where focal destructive changes are detected with the glandular structures being preserved (fig. 1).

Morphological changes in the use of the electrode corresponding to the diameter of the canal at 50% of the apparatus power and the determined mean speed of stretching are characterized by different changes in the layers of the studied organs' wall. The mucous and submucous membranes are destructed, exfoliated and are not detected in histological slides (fig. 2).

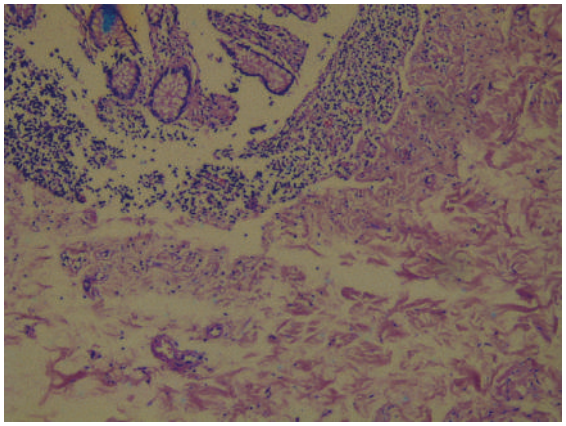

Fig. 1. Mosaic alternative changes in the vermiform appendix sites when using a small diameter electrode. Hematoxylin and eosin, X100.

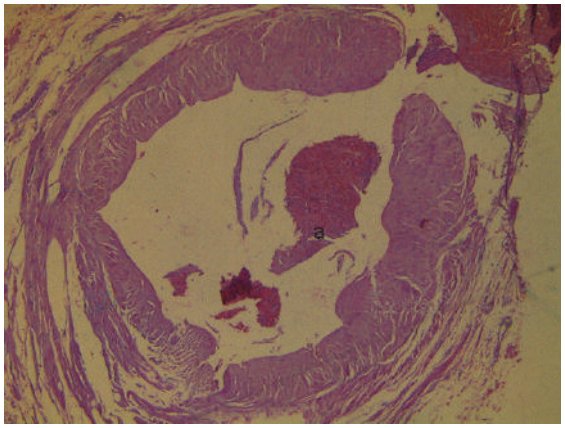

Fig. 2. Destruction and elimination of the vermiform appendix mucous membrane (a) in the site of electric welding endoscopic exposure. Hematoxylin and eosin, X40.

The most preserved is the vermiform appendix myenteron, where only individual myocytes undergo coagulation changes. Smooth muscle cells retain their peculiar structure, but there is interstitial

edema due to the formation of small vacuole-like structures; the nuclei of cells are compacted and acquire a single-vector orientation.

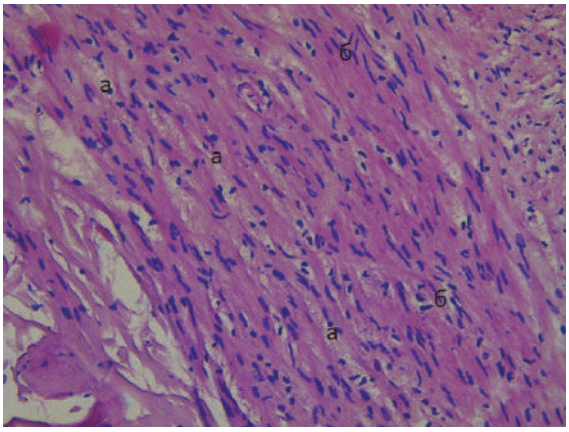

Fig. 3. Dystrophic changes in the muscular cells of the vermiform appendix with the formation of small vacuole-like structures in the cytoplasm (a), compaction of nuclei, and changes in their spatial reorientation (b). Hematoxylin and eosin, X200.

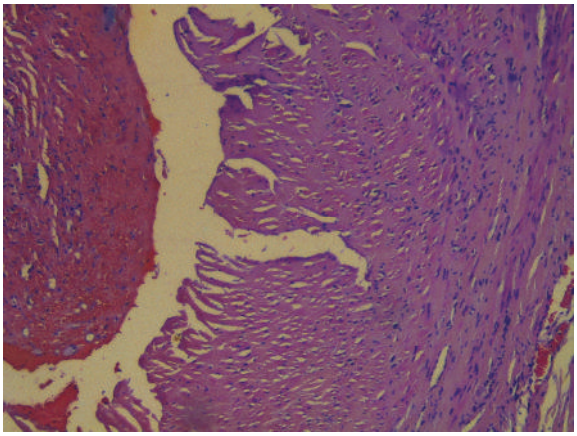

Fig. 4. Coagulation necrosis of the vermiform appendix tissue, which extends through the entire thickness of the wall and covers the structural elements of the mesentery. Hematoxylin and eosin, X100.

Small blood vessels, arterioles, venules of the muscular layer undergo coagulation with the preservation of the contours, destructively altered hemocytes can be detected in the lumens. Thus, using the developed optimal parameters of the high-frequency current influence histologically confirms the mucous membrane destruction of the canal created from the intestine and the vermiform appendix and the morphological preservation of the muscular layer with vascular damage phenomena.

When using 100% of the apparatus power, tissues of the vermiform appendix and small intestine undergo coagulation necrosis, which extends through the entire thickness of the wall and covers structural elements of the mesenterium (fig. 4). The walls of the vermiform appendix mesenterium blood vessels, including the appendicular artery, also undergo coagulation changes, overlap and become empty.

In our opinion, this indicates that the power of the electric current and the time of action affect the depth of the damage caused to the small intestine and the vermiform appendix tissues up to the formation of coagulation necrosis through the entire thickness of the wall. [1]

We have obtained results that correlate with the data of the authors who report the presence of coagulation necrosis in the electrode action zone. The spread and prevalence of the coagulation zone depends on the current capacity and the time of tissues exposure. The mechanism of a spherical electrode action differs from that used by the authors of bipolar clamp electrodes, where the coagulation zone is located between the clamp branches and does not extend more than 2 mm laterally. [2]

On a spherical tool, the distance between the electrodes is constant, and the tissues adhere to the electrodes rather than being compressed between them. Therefore, the severity of coagulation depends on the degree of the electrode adhesion to the tissues. This correlates with studies on the use of a spherical electrode for obliteration of lower extremities varicose veins, where the electrode adhesion is provided by filling of the space around the vein with fluid. [4] Our data suggest that using the apparatus at its maximum power causes deep necrosis of the tissues in the intestine and the vermiform appendix, and 50% power is sufficient to destroy the mucous membrane, as in the case of vein obliteration, where this power ensures the integrity of the surrounding tissues.

Conclusion

High-frequency electric current with using a spherical bipolar electrode causes the destruction of the mucous membrane of the simulated fistulous passages in endoscopic application. Optimal parameters of the impact are: 50% of the device power when welding in the “manual” mode with an electrode advance rate of 1.45 mm/s, which is confirmed by macro and microscopic data. At endoscopic welding with the use of a spherical electrode a residual cavity is formed, which needs to be filled to facilitate its elimination. Based on the data obtained, further studies can be carried out to use endoscopic welding for treatment of the hollow organs’ fistulas in the digestive tract.

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Реферати

ЕКСПЕРИМЕРТАЛЬНО-МОРФОЛОГІЧНЕ ОБГРУНТУВАННЯ ОБЛІТЕРАЦІЇ ТРУБЧАСТИХ БІОЛОГІЧНИХ СТРУКТУР ШЛЯХОМ ВИСОКОЧАСТОТНОГО ЕЛЕКТРОЗВАРЮВАННЯ ТКАНИН

Кобзар О.Б., Дорошенко С.В., Пархоменко М.В., Хворостяна Т.Т., Примаченко В.І.

В експерименті на трупному матеріалі проведено дослідження впливу високочастотного струму ендоскопічним способом на змодельований канал нориці травного каналу. Визначені оптимальні параметри генератора ЕКВЗ-300 Патонмед необхідні для руйнування слизової оболонки. Морфологічними макро- та мікроскопічними методиками підтверджено ефективність впливу струму для руйнування слизової оболонки нориці.

Ключові слова: електрозварювання біологічних тканин, морфологічні зміни, кишкова нориця.

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ЕКСПЕРИМЕРТАЛЬНО-МОРФОЛОГИЧЕСКОЕ ОБОСНОВАНИЕ ОБЛИТЕРАЦИИ ТРУБЧАТЫХ БИОЛОГИЧЕСКИХ СТРУКТУР ПУТЕМ ВЫСОКОЧАСТОТНОЙ ЭЛЕКТРОСВАРКИ ТКАНЕЙ

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В эксперименте на трупном материале проведено исследование влияния высокочастотного тока эндоскопическим воздействием на смоделированный канал свища пищеварительного тракта. Определены оптимальные параметры генератора ЕКВЗ-300 Патонмед необходимые для разрушения слизистой оболочки. Морфологическими макро- и микроскопическими методиками подтверждена эффективность воздействия тока для разрушения слизистой оболочки свища.

Ключевые слова: электросварка биологических тканей, морфологические изменения, кишечные свищи.

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INVESTIGATION OF CALCIUM- AND HYALURONIC ACID-CONTAINING DRUGS OSTEOPLASTIC ACTIVITY IN RATS WITH PERIODONTITIS

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The aim of the research was to investigate the effect of subgingival injection of the solutions of calcium and hyaluronic acid on the condition of the bone tissue of the alveolar process of the lower jaws of rats with experimental periodontitis. The conducted experimental trials confirmed the intensification of the resorption processes in the jaw bone tissue of rats, which were fed peroxidized oil for a long time. Thus, the alimentary intake of lipid peroxides led to an increase in atrophy of the alveolar process of the lower jaw of rats and the loss of calcium in the bones of the jaws. Hydroxyapatite injections had a slight effect on the studied parameters, since the atrophy of the alveolar bone could not be slowed down, and the biochemical indicators, despite some improvements, did not reach normal values. Calcium in combination with unstabilized hyaluronic acid turned out to be much more effective. The authors insisted that further experimental trials are required in order to determine the frequency of subgingival calcium injections of calcium hydroxyapatite with non-stabilized hyaluronic acid.

Key words: experimental periodontitis, bone tissue, blood, hyaluronic acid, calcium hydroxyapatite, subgingival calcium injections.

This work is a fragments of the research project "To study disorders of mineralization and collagen formation in oral cavity in dental pathology and to improve the methods of these disorders early diagnosis and correction", state registration No. 0116U004077.

The bone tissue is a special type of connective tissue and the main component of human bones [9, 10]. The body is constantly undergoing renewal processes and the bone tissue is not an exception. Diseases, injuries or age-related changes can disrupt these processes and lead to the changes in the bone tissue, which can adversely affect the quality of life. For example, resorption of the bone tissue of the facial skeleton with age progression leads to changes in the individual bone structures and to a shift in the attachment of muscles and ligaments and, as a result, to the age-related changes in the face [14].

The possibility of strengthening the structure of the bone tissue would solve many questions in various fields of medicine (traumatology, dentistry, aesthetic medicine, and others). Is there any opportunity to strengthen the bone structure from the outside? Let us try to figure it out.

The inorganic composition of bone tissue includes hydroxyapatite and calcium phosphate crystals, and the composition of the organic matrix of the bone tissue includes collagen and glycosaminoglycans. It is believed that glycosaminoglycans are directly related to the ossification [7].

The purpose of the work was to study the effect of subgingival injection of the solutions of calcium and hyaluronic acid on the state of the bone tissue of the alveolar process of the lower jaws of rats with experimental periodontitis.

Materials and methods. The study was conducted on 63 Wistar rats of the herd breeding, females aged 6-7 months with an average weight of 285±34 g. The animals were randomized into 4 groups:

1. Intact rats
2. Rats with periodontitis
3. Rats with periodontitis who received calcium hydroxyapatite injections
4. Rats with periodontitis who received "calcium hydroxyapatite + non-stabilized hyaluronic acid" injections

Experimental periodontitis was reproduced by adding peroxidized sunflower oil to the rats' meal at the rate of 1 ml per animal per day [12].

The following medications were used in the experiment:

• Calcium hydroxyapatite - Crystalys ("Luminera" company, Israel)

• Calcium hydroxyapatite and non-stabilized hyaluronic acid - Crystalys + Luminera Hydryal 2% (("Luminera" company, Israel).

The medications were administered once a day at a dose of 0.1 ml on the 21st day of modeling of the pathology of periodontitis in the gums of the lower molars of rats.

The rats were removed from the trials with the use of thiopental anesthesia by heart bleeding in three stages: 2 weeks, 4 weeks and 6 weeks after the medications' injections. The lower jaw was allocated and thoroughly cleaned of soft tissues. The method of biometrics was used to calculate the degree of atrophy of the alveolar process by determining the linear dimensions of the exposure of the roots of molars [6].

The determination of the calcium content in the jaw bone hydrolyzate (50 mg/25 ml 0.2 n HCl) was carried out via the use of arsenase reagent according to [12]. In bone homogenates (75 mg / ml 0.1 n citrate buffer pH 6.1), elastase activity was determined via hydrolysis of N-t-BOC-L-alanin-p-nitrophenyl ester [11].

The data obtained were analyzed and calculated via One-way Analysis criteria (standard ANOVA method) [3]. $P<0.05$ was used as the statistically significant difference criteria.

Results of the study and their discussion. First of all, it should be noted that the duration of the full cycle of "resorption-formation" of bone tissue, including jaws, takes about 150 days, i.e. 2-3 cycles per year, while in rats the duration of this cycle is 40 days (9 cycles per year), i.e. three times as intense. As a result, 2 months of modeling of periodontal pathology in rats is equivalent to the semiannual duration of the same process in humans.

Table 1 shows the data for determining the degree of atrophy of the alveolar process of rats. The assessment of the dystrophic process in the alveolar bone of experimental animals showed a significant increase in the degree of atrophy in the group with peroxide periodontitis by 38.5% after 7 weeks ($p<0.05$) and by 47.2% after 10 weeks ($p<0.001$). The obtained results allow us to make conclusions about the activation of resorption processes in the bone tissue of the lower jaws of rats under the influence of lipid peroxides obtained from food, which is aggravated over time (table 1).

Table 1

Effect of calcium and hyaluronic acid on the degree of atrophy of the alveolar process of the lower jaw of rats with peroxide periodontitis (%)

N	Groups	4 weeks after injections (7 weeks of periodontitis)	6 weeks after injections (9 weeks of periodontitis)
1	Intact	26.5±2.2	
2	Periodontitis	36.7±1.9 $p<0.05$	39.0±2.0 $p<0.001$
3	Periodontitis + hydroxyapatite	33.2±2.2 $p<0.05$ $p_1>0.05$	36.3±2.0 $p<0.01$ $p_1>0.05$
4	Periodontitis + calcium + HA non-stabilized	30.2±1.8 $p>0.05$ $p_1<0.05$	32.6±1.4 $p<0.05$ $p_1<0.05$

Notes: p – represents the significant differences on the investigated indexes in comparison with the intact group; p_1 – represents the significant differences on the investigated indexes in comparison with the group of rats with periodontitis (ANOVA statistical criteria).

Hydroxyapatite injections had no significant effect on the degree of atrophy of the jaws of rats of the 3rd group. This indicator remained high and corresponded to the level in animals of the second group with peroxide periodontitis ($p_1>0.05$ after 4 weeks and $p_1>0.05$ – 7 weeks after injections).

Intensification of resorption processes in the mandible bone tissue of rats with periodontitis prevented one-time subgingival administration of calcium in combination with non-stabilized hyaluronic acid to rats of the 4th group. This fact contributed to the inhibition of resorption of the alveolar process 4 weeks after the injection: the rate of atrophy corresponded to that of healthy animals ($p>0.05$ and $p_1<0.05$).

Taking the above data into consideration, the study on the 9th week of periodontitis modeling or 6 weeks after the injection of calcium and non-stabilized hyaluronic acid showed the inability of this composition to completely prevent the active resorption of the jaw bone tissue induced by the alimentary intake of lipid peroxide. It is worth noting that the index of the degree of atrophy of the alveolar process in rats of the 4th group at the final stage of the study was significantly lower than that of the rats with periodontitis by 19.6% ($p<0.05$).

At the same time it exceeded the values in intact animals by 18.7% ($p_1<0.05$), which allowed us to speak about the frequency of such injections once every 4 weeks in rats to get the best result. Nevertheless, the indicator of the degree of atrophy of the alveolar process in rats of the 4th group at the final stage of the study was significantly lower than that of the rats with periodontitis by 19.6% ($p<0.05$), while at the same time exceeding the values in intact animals by 18.7% ($p_1<0.05$). The abovementioned data allowed us to speak about the frequency of such injections to rate once in every 4 weeks in order to get the best result (fig. 1).

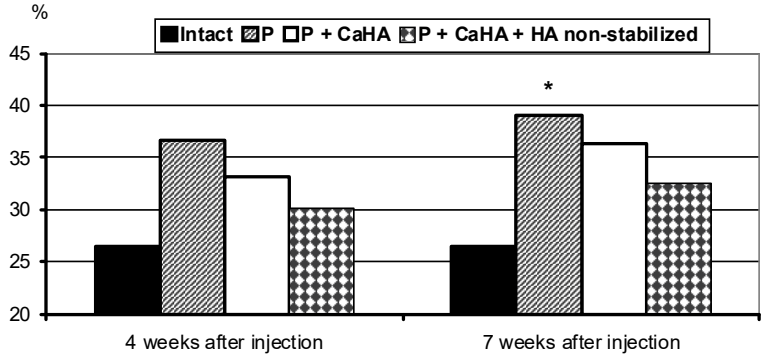

Fig. 1. The value of rats alveolar processes atrophy.

The modeling of periodontitis with the help of an alimentary excess of peroxides leads not only to atrophy of the alveolar bone, but also to a sharp decrease in the level of calcium in the bone tissue of the lower jaws of rats. Consequently, this indicator is decreased by 21.6% after 5 weeks ($p<0.02$), by 31.2% – after 7 weeks ($p<0.01$) and by 48.4% – after 9 weeks of pathology modeling ($p<0.001$, table 2). These results confirm the intensification of the resorption processes in the bone tissue of the jaws of rats, which had been fed peroxidized oil for a long time.

Table 2

Calcium content in the bone tissue of the lower jaws of rats with peroxide periodontitis after administration of calcium and unstabilized hyaluronic acid (mol/kg)

N	Groups	2 weeks after injections (5 weeks of periodontitis)	4 weeks after injections (7 weeks of periodontitis)	6 weeks after injections (9 weeks of periodontitis)
1	Intact	2.547±0.100		
2	Periodontitis	1.996±0.130 p<0.05	1.750±0.143 P<0.01	1.314±0.151 p<0.001
3	Periodontitis + hydroxyapatite	2.260±0.191 p>0.05 p_1>0.05	2.175±0.085 p<0.05 p_1<0.05	1.907±0.184 p<0.05 p_1<0.05
	Periodontitis + calcium + HA non-stabilized	2.357±0.223 p>0.05 p_1> 0.05	2.228±0.052 p<0.05 p_1<0.05	2.174±0.269 p>0.05 p_1<0.05

Notes: p – represents the significant differences on the investigated indexes in comparison with the intact group; p_1 – represents the significant differences on the investigated indexes in comparison with the group of rats with periodontitis (ANOVA statistical criteria).

Injection of hydroxyapatite to rats of group 3 somewhat inhibited the loss of calcium by the alveolar bone. 2 weeks after the injections with this medications, the calcium level corresponded to normal values, but also did not differ significantly from that of the rats with periodontitis ($p>0.05$ and $p_1>0.05$, table 2).

4 and 6 weeks after the administration of hydroxyapatite, the calcium content in the alveolar bone significantly exceeded that of the rats with periodontitis ($p_1<0.05$) but did not reach the values of intact animals ($p<0.05$, table 2).

Effective prevention of calcium loss by the jaw bone tissue was registered after subgingival calcium injections in combination with unstabilized hyaluronic acid in rats of group 4. 2 weeks after the injection, this indicator had an intermediate value between the level in healthy rats and animals with periodontitis (p>0.05 and p>0.05).

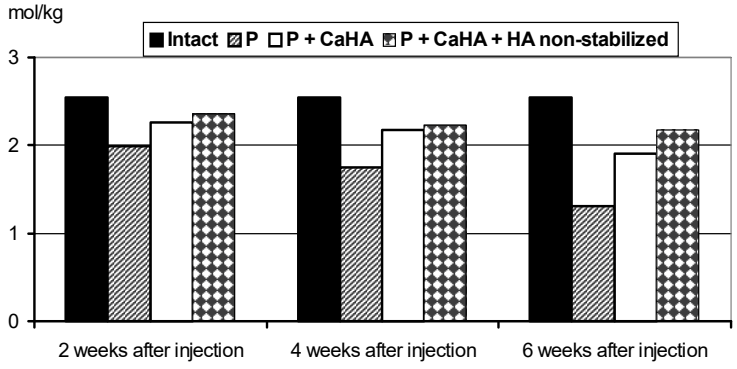

Fig. 2. The calcium content in the bone tissue of the lower jaws of rats.

It also worth mentioning that after 4 and 6 weeks after administration of the compositions of calcium with non-stabilized hyaluronic acid, the calcium content in the jaw bone tissue of rats significantly exceeded that of the rats with periodontitis (p_1<0.05) with no difference from normal values (p>0.1; fig. 2).

Biochemical study of enzymes in the jaws of experimental animals revealed metabolic disorders in the bone tissue of rats with periodontitis.

Elastase is the most active enzyme involved in the degradation of bone collagen. In addition, it is known that elastase activates procollagenase, turning it into the active form of the enzyme - collagenase, which greatly increases the intensity of destruction of bone collagen [1, 2, 4, 5]. The results of the study of the activity of elastase in the bone tissue of the jaws of rats with peroxide periodontitis are shown in the table 3.

Table 3

Effect of calcium-containing medications and non-stabilized hyaluronic acid on the activity of elastase in the bone tissue of the lower jaw of rats with peroxide periodontitis (mkkat/kg)

N	Groups	2 weeks after injections 5 weeks of periodontitis)	4 weeks after injections (7 weeks of periodontitis)	6 weeks after injections (9 weeks of periodontitis)
1	Intact	15.26±1.09		
2	Periodontitis	24.98±1.36 p<0.01	28.83±1.89 p<0.001	26.96±2.96 p<0.001
3	Periodontitis + hydroxyapatite	18.91±2.82 p>0.05 p_1> 0.05	27.20±2.89 p<0.01 p_1>0.05	20.03±1.82 p<0.05 p_1>0.05
4	Periodontitis + calcium + HA non-stabilized	16.98±2.12 p>0.05 p_1<0.05	23.28±1.31 p>0.05 p_1<0.05	18.55±1.67 p>0.05 p_1<0.01

Notes: p – represents the significant differences on the investigated indexes in comparison with the intact group; p_1 – represents the significant differences on the investigated indexes in comparison with the group of rats with periodontitis (ANOVA statistical criteria).

5 weeks after consumption of peroxidized oil by rats, elastase activity in the jaw bone tissue increased by 63.7% (p<0.01). Over the subsequent periods of observation, the activity of this destructive bone tissue enzyme increased to a greater extent - by 88.9% (p<0.001) – after 7 weeks and by 76.7% (p<0.001) – after 9 weeks of pathology modeling (table 3).

The injection of hydroxyapatite prevented an increase in the activity of elastase in the jaw bone tissue of rats with periodontitis only 2 weeks after the injection itself: this indicator corresponded to the level in healthy animals (p>0.05), but did not differ significantly from the values in rats with periodontitis (p_1>0,05). On subsequent periods of the study, the activity of elastase in the jaw bone tissue of rats that were injected with hydroxyapatite was high and corresponded to the level in animals with periodontitis (p_1>0.05), which indicates the low ability of hydroxyapatite to inhibit the destruction of bone tissue (table 3).

Calcium injections with non-stabilized hyaluronic acid had a prominent inhibitory effect on the destruction of bone collagen in the jaws of rats with periodontitis. The elastase activity in rats of the 4th group did not exceed the values in healthy animals (p>0.05) and was lower than that of rats with periodontitis (p_1<0.05). This fact indicates a more pronounced ability of the calcium composition with non-stabilized hyaluronic acid to inhibit the elastase activity, and hence the destruction of bone collagen induced by lipid peroxidation (table 3, fig. 3).

Therefore one can conclude that this research confirmed the intensification of the resorption processes in the jaw bone tissue of rats, which were fed peroxidized oil for a long time. Thus, the alimentary intake of lipid peroxides led to an increase in atrophy of the alveolar process of the lower jaw of rats and the loss of calcium in the bones of the jaws.

Our results are comparable with similar data obtained in studies [2] in which the degree of periodontal bone tissue atrophy (the lower jaw alveolar process) was investigated during the acute inflammatory process in animals modeling. The integrative indicators of periodontal atrophy in these rats (calculated by the acid/base phosphatases ratio activities and calcium concentration in the bone tissue) and the number of decay-induced lesions increased significantly (approximately per 2.5-2.7 times) and were equal to 27.9±1.0% and 5.9±0.5 (for decay rate). Therefore, one could say that, firstly, the model we used is adequate to analogous clinical condition. Secondly, we obtained the comparable data in experimental conditions of the bone tissue destruction. Finally, the subsequent results showed rat's lower jaw bone tissue functional activity normalization under the influence of calcium-containing drugs.

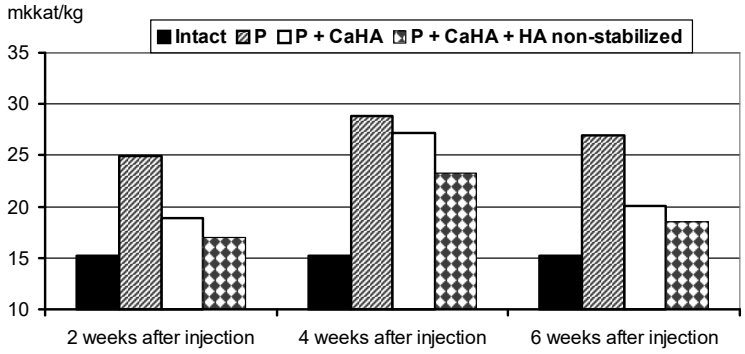

Fig. 3. The expression of elastase in the bone tissue of the lower jaws of rats.

It is also of interest that equivalent data were obtained in conditions of prednisone-induced periodontitis in rats. These data revealed the index of bone tissue mineralization in the experimental conditions was reduced on 39% and equal to 51.0±1.1%. The degree of bone tissue mineralization in such experimental conditions was equal to 4.62±0.37 g/g that was approximately 9% less pertaining with the same control index [10, 13]. Our results nevertheless showed an expressed calcium-containing drugs osteotropic efficacy if compared with the data in case of bioflavanoid quertulin administration.

Our data revealed slight effect of hydroxyapatite injections on the investigated parameters since the atrophy of the alveolar bone could not be slowed down, and the biochemical indicators, despite some improvements, did not reach normal values.

The administration of calcium in combination with unstabilized hyaluronic acid had much better effects. Despite the fact that the degree of atrophy of the alveolar process decreased only at the initial stage after injection, the calcium content was brought to almost normal values. Apparently, the calcium level was restored due to the inhibition of the activity of destructive enzymes of the jaw bone elastase under the influence of calcium in combination with unstabilized hyaluronic acid.

Calcium-containing drugs injection with aim of periodontal bone tissue mineralization increase can also have a clinical perspective in the conditions of metabolic syndrome since it has been shown the significant bone tissue reduce due to an approximately twofold increase of the connective tissue density [8]. In this case one could conclude that our experimental trials have a clinical prospect for patients with expressed osteodestruction phenomena in conditions of diabetes mellitus, obesity and in other symptom complexes combined into the metabolic syndrome concept.

Conclusions

1. Long-term alimentary intake of peroxidized oil led to the activation of resorption processes in the jaws: an increase in atrophy of the alveolar process, loss of calcium and an increase in the activity of destructive bone tissue enzymes elastase.

2. Injection of calcium hydroxyapatite to rats with periodontitis did not significantly affect the pathological processes in the jaw bone tissue.

3. According to the results of our research, the single injection of calcium with unstabilized hyaluronic acid was a much more effective method of inhibiting the atrophy of the alveolar process and normalizing the intensity of the processes of mineralization and destruction of the jaw bone of rats with periodontitis.

4. We consider it necessary to conduct additional studies to determine the frequency of subgingival calcium injections of calcium hydroxyapatite with non-stabilized hyaluronic acid.

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Реферати

ДОСЛІДЖЕННЯ ОСТЕОПЛАСТИЧНОЇ АКТИВНОСТІ ЛІКАРСЬКИХ ЗАСОБІВ, ЯКІ МІСТЯТЬ КАЛЬЦІЙ І ГІАЛУРОНОВУ КИСЛОТУ, У ЩУРІВ З ПЕРІОДОНТИТОМ

Ларкіна С.О., Макаренко О.А., Вастьянов Р.С., Єрмуракі П.П.

Метою дослідження було дослідження впливу субгінгівального введення розчинів кальцію і гіалуронової кислоти на стан кісткової тканини альвеолярного відростка нижньої щелепи щурів при експериментальному періодонтиті. Проведені експериментальні дослідження підтвердили інтенсифікацію процесів резорбції в кістковій тканині щелепи щурів, яким давали в їжу перекисну олію протягом тривалого часу. Таким чином, харчове споживання перекисів ліпідів призводило до збільшення атрофії альвеолярного відростка нижньої щелепи щурів і втрати кальцію в кістках щелеп. Ін'єкції гідроксиапатиту надали невеликий вплив на досліджувані параметри, оскільки атрофію альвеолярної кістки не можна було уповільнити, а біохімічні показники, незважаючи на деякі поліпшення, що не досягли нормальних значень. Кальцій в поєднанні з нестабілізованою гіалуроновою кислотою виявився набагато більш ефективним. Автори наполягають на необхідності подальших експериментальних досліджень для визначення частоти субгінгівальних ін'єкцій гідроксиапатиту кальцію з нестабілізованою гіалуроновою кислотою.

Ключові слова: експериментальний періодонтит, кісткова тканина, кров, гіалуронова кислота, гідроксиапатит кальцію, субгінгівальние ін'єкції кальцію.
Стаття надійшла 12.04.2019 р.

ИССЛЕДОВАНИЕ ОСТЕОПЛАСТИЧЕСКОЙ АКТИВНОСТИ ЛЕКАРСТВЕННЫХ СРЕДСТВ, СОДЕРЖАЩИХ КАЛЬЦИЙ И ГИАЛУРОНОВУЮ КИСЛОТУ, У КРЫС С ПЕРИОДОНТИТОМ

Ларкина С.А., Макаренко О.А., Вастьянов Р.С., Ермураки П.П.

Целью работы было изучение влияния субгингивального введения растворов кальция и гиалуроновой кислоты на состояние костной ткани альвеолярного отростка нижней челюсти крыс при экспериментальном периодонтите. Проведенные экспериментальные исследования подтвердили интенсификацию процессов резорбции в костной ткани челюсти крыс, которым давали в пищу перекисное масло в течение длительного времени. Таким образом, пищевое потребление перекисей липидов приводило к увеличению атрофии альвеолярного отростка нижней челюсти крыс и потере кальция в костях челюстей. Инъекции гидроксиапатита оказали небольшое влияние на исследуемые параметры, поскольку атрофию альвеолярной кости нельзя было замедлить, а биохимические показатели, несмотря на незначительные улучшения, не достигли нормальных значений. Кальций в сочетании с нестабилизированной гиалуроновой кислотой оказался гораздо более эффективным. Авторы настаивают на необходимости дальнейших экспериментальных испытаний для определения частоты субгингивальных инъекций гидроксиапатита кальция с нестабилизированной гиалуроновой кислотой.

Ключевые слова: экспериментальный периодонтит, костная ткань, кровь, гиалуроновая кислота, гидроксиапатит кальция, субгингивальные инъекции кальция.
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DETERMINATION OF ACUTE TOXICITY OF OINTMENT WITH PINUS SYLVESTRIS EXTRACT

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The necessity of search for new biologically active substances among the medicinal plants of Pinus species does not cause any doubts in it. Promising outlook of Pinus sylvestris application is confirmed by many publications of both domestic and foreign researchers. Post the performed study it is known that the obtained dry extract is practically non-toxic and has a wide range of biological effects. One of the main priorities of the new dosage form implementation is its low toxicity. Therefore, purposeful technology of ointment based on dry extract and controlled trial of acute toxicity are the priorities in the pharmacological studies. The purpose of the work was to study the acute toxicity of the ointment based of the Pinus sylvestris dry extract, which was first performed. The acute toxicity was studied on white mice with a single oral administration of the drug. The mice were observed for 14 days. The animals' general condition, mortality, body mass dynamics before and after the experiment were studied. Macroscopic assessment of the internal organs status was performed and their histological structure was studied. As studies have shown, after oral administration of the ointment with the Pinus sylvestris extract in the dose of 0.5 ml, signs of toxicity in mice were not revealed. According to the classification by K. K. Sidorov, the ointment with the Pinus sylvestris extract belongs to practically non-toxic compounds. Thus, the ointment with Pinus sylvestris extract belongs to the fifth class - practically non-toxic when administered orally.

Key words: acute toxicity, ointment with Pinus sylvestris extract, macroscopic analysis of internal organs.

The work is a fragment of the research project "Study of wild and cultivated medicinal plants in the Western region of Ukraine and development of their application technologies with therapeutic purposes", state registration No. 018U003809.

Qualitative therapy requires the deliberate search and creation of new, highly effective medicines without side-effects.

The main task of pharmacy is to find new, modern and high-quality medicines.

A promising group is herbal drugs that are widely used in the medicines market. Broad-spectrum of these drugs is enhanced by the multicomponent composition of biologically active substances and simultaneous presence of different nature compounds. Mild therapeutic effects, low toxicity and minimal side effects, cost-effectiveness are just some of the plant-based drugs benefits.

Pine (Pinus sylvestris L.) of the Pinaceae family is an unofficial medicinal plant in Ukraine. The plant has long been used in medicine in the form of infusion, tincture, decoction, extract, as a diuretic, antiseptic, wound-healing and anti-inflammatory agent. Needles, buds, galipot of Pinus sylvestris L. are used as medicinal plant raw material [2]. Pinus sylvestris L. contains resin, essential oil, vitamins C, B_{12}, K, R, phytoncides, tannins, starch, carotene, mineral salts, turpentine. In general, due to the accumulation of different groups of biologically active substances aerial parts of the plant is promising for integrated pharmacognostical and pharmacological studies aimed at establishing new domestic phytopreparations. Because search and creation of effective and affordable new medicines of plant materials is an important task of the domestic pharmaceutical science and practice, an important step in the new drugs development is to study their safety, namely to establish their class of toxicity and impact on the animals' internal organs [2].

The purpose of the work is to study acute toxicity of the ointment based on the Pinus sylvestris dry extract.

Materials and methods. The study was carried out on outbred white mice males. The experiments were carried out at the Pharmacy Department, Human Anatomy Department, academician G.A. Babenko Biological and Medical Chemistry Department and Bioelementology Center at the Ivano-Frankivsk National Medical University. To study the acute toxicity we selected the methodology approved by the State Pharmacopeia and the MOH of Ukraine on white mice with a single oral administration of the drug. The animals were kept in the same standard conditions and feeding. The mice were observed for 14 days and the animals' general condition, mortality, body mass dynamics before and after the experiment were assessed. Macroscopic assessment of the internal organs status was performed and their histological structure was studied.

The object of research was the ointment with thr Pinus sylvestris extract, obtained on base of the Ivano-Frankivsk National Medical University. As the studies have shown, after oral administration of the ointment with the Pinus sylvestris extract in the dose of 0.5 ml, signs of toxicity in mice were not revealed: the animals were neat and tidy, they reacted to sound and light stimuli, processes of urine and defecation were normal, respiratory failure and convulsions were not observed, eye fissures were narrowed. According to the classification by K. K. Sidorov, the ointment with the Pinus sylvestris extract belongs to practically

non-toxic compounds. Therefore, in the study on acute toxicity of ointment with Pinus sylvestris extract, in the dose of 0.5 ml, signs of toxicity were not revealed.

All manipulations were carried out in compliance with the International Convention of working with animals and the Law of Ukraine "On protection animals from brutal treatment".

Data processing calculations were performed using Statistica 6.0.

The instrumental methods of study were applied. The obtained histological sections were studied in light MC300 Micros Austria microscope and photographed with ToupCam figure 5.1 UHCCD M C-Mount camera with Sony adapter ToupTek Photonics AMA075 using ToupView software v3. (at magnification ×400).

Results of the study and their discussion. Acute toxicity ointment with extract of Pinus sylvestris was studied by the method of State Pharmacopeia of Ukraine and the MOH of Ukraine. According to the classification by K.K. Sidorov they are practically non-toxic [6].

As our studies have shown, after oral administration of the ointment with the Pinus sylvestris extract in the dose of 0.5 ml, signs of toxicity in mice were not revealed: the animals were neat and tidy, reacted to sound and light stimuli, processes of urine and defecation were normal, respiratory failure and convulsions were not observed, eye fissures were narrowed. The reflex excitability of all the animals was preserved. Death of animals during the whole observation period was not registered.

The results of acute toxicity studies on Pinus sylvestris ointment with a single intragastric administration to white mice are presented in table 1.

Table 1

Studies on acute toxicity of Pinus sylvestris ointment with a single intragastric administration to white mice

Group of animals	Body weight, g, $\bar{x} \pm \Delta\bar{x}$, n = 10	
	Before the experiment	After the experiment
Group 1, intact animals	18.0 ± 0.548	19.0±0.508
Group 2, ointment with Pinus sylvestris extract	19.0 ± 0.507	20.0±0.358
Group 3, the ointment base	18.0±0.547	19.0±0.359

After 14 days of the experiment a macroscopic analysis of the animals' internal organs was carried out. In the thorax cavity, all organs were anatomically correct. The form, color, size were regular. The surface of the kidney, liver and adrenal glands was smooth, the spleen was full and elastic. The pancreas had a grayish-pink color.

The stomach mucous membrane had a pronounced relief of folds, the intestine mucous membrane was not changed. The heart muscle is dark red colored in the cross-section, lungs airness was observed, and the pulmonary pleurae was not changed.

At the Department of biological and medical chemistry named after academician G. A. Babenko and Center bioelementology Ivano-Frankivsk national medical University in the serum of mice blood: leukocytes, erythrocytes, hemoglobin, cholesterol, total protein were determined. Biochemical and hematological parameters of animals are given in table. 2.

Table 2

Biochemical and hematological parameters of mice blood in acute intoxication

The studied parameters	Group of animals		
	Intact animals	Ointment basis	Ointment with Pinus sylvestris extract
Leukocytes, × 10^9/l	7.60 ± 0.33	7.40 ± 0.38	7.60 ± 0.24
Erythrocytes, × 10^{12}/l	8.10 ± 0.24	8.00 ± 0.32	8.10 ± 0.32
Hemoglobin, g/l	130.8 ± 0.61	130.1 ± 3.31	132.2 ± 2.47
Cholesterol, mmol/l	2.78 ± 0.13	2.81 ± 0.15	2.83 ± 0.22
Total protein, g/l	54.5 ± 0.95	55.1 ± 0.80	56.2 ± 0.72

Thus, the experimental results show that the ointment with the extract of of Pinus sylvestris needles shows no toxic effect on the white mice body. Organs were prepared to the study using conventional methods in morphology. The sections were stained with hematoxylin and eosin (fig. 1).

14 days after the oral administration, in the histological structure of the kidneys (fig. 1 A) moderate blood filling of intraorganic blood vessels was revealed, epithelial cells of the proximal convoluted tubules were slightly swollen. Increased blood filling of the glomeruli capillaries, expansion of Boumen's spaces were observed. The tubules epitheliocytes' cytoplasm was granular. There were no specific findings in distal tubules, only in some of them isolated vacuoles were present.

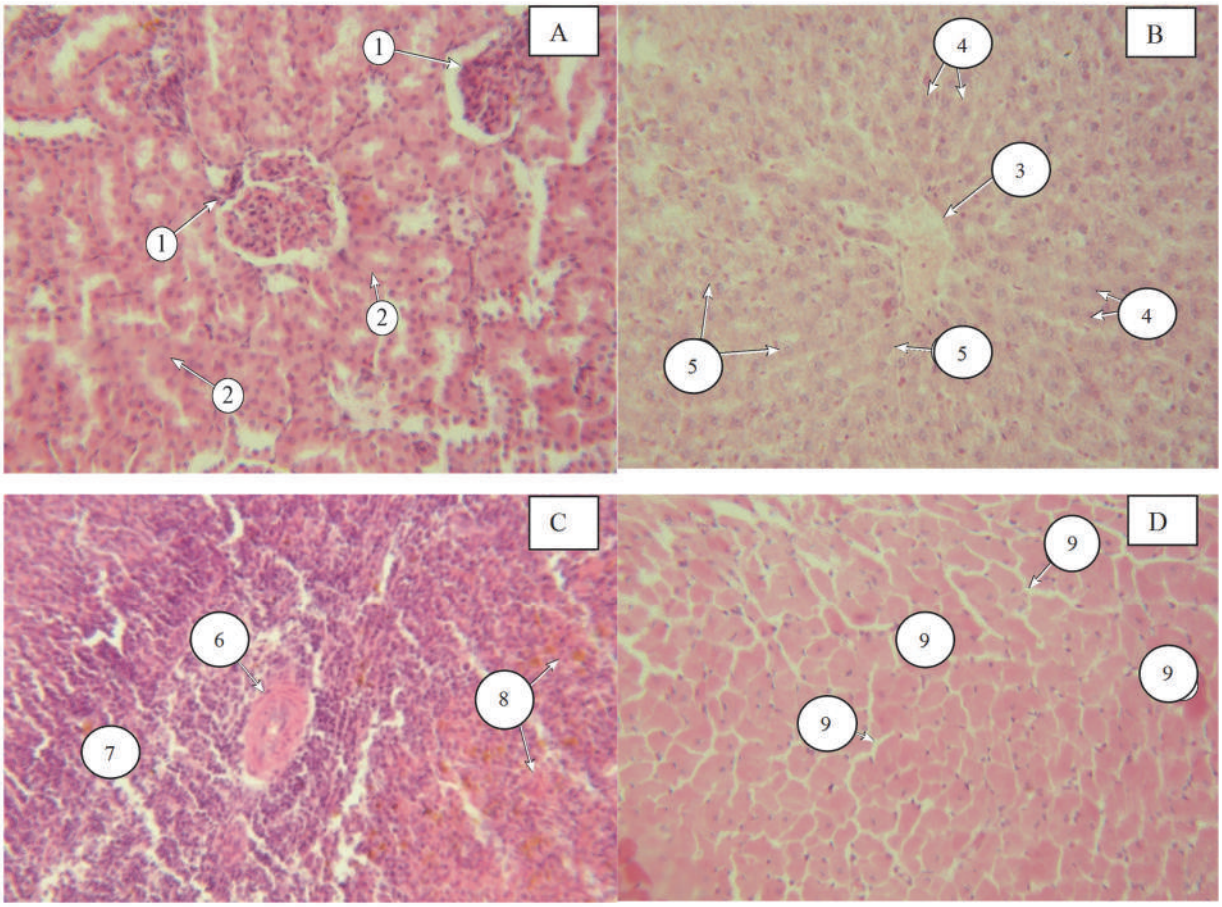

Fig. 1. Histological examination of tissues after 14 days: A - the kidney histological structure (1 – many cells vascular pole, 2 – single cleared epithelial cells of the tubules), B – histological structure of the liver (3 – the central vein of liver, 4 – hepatic plates, 5 – single burned-out hepatocytes), C – the histological structure of the spleen (6 – the central artery, 7 – lymph follicles, 8 – red pulp), D –histological structure of the heart (9 – cardiomyocytes). Staining: hematoxylin and eosin. Increase.: ×400.

Morphological features of the liver (fig. 1 B) under these conditions are characterized by a slight impairment of the hepatic lobules protein structure. Notable alternative processes (signs of protein dystrophy, small vacuolar hydropic vacuolization and pyknosis of nuclei). There are hepatocytes with hypertrophied nuclei. Expansion of Disse's spaces and the plethora of the central veins were observed, sinusoid hemocapillaries having a sludge of erythrocytes in them. There is a moderate lympho-, macrophage infiltration.

The structuredness of lymphatic nodules is traced in the spleen (fig. 1 C). However, the boundaries between the periarterial and marginal zones of the periarteriolar sheath are sporadically erased. In lymph nodules the germinative center is small. Central arteries have narrow lumen and thickened walls. Trabecular vessels are plethoric.

In the study of histological heart sections (fig. 1 D), cross-striation was well pronounced in most fields of vision. A slight dissection of muscle bundles is only observed in the papillary muscles, here the sarcoplasm of cardiomyocytes is unevenly stained with eosin. Blood vessels of the same localization have the deformed wall. Thus, the performed study (table 1, 2 and Fig. 1) indicate that the ointment with the Pinus sylvestris L. extract refers to the V class of toxicity “Practically non-toxic”, as confirmed histologically. Our results are consistent with data obtained by other authors [3, 4 - 9], but in this aspect, our results do not coincide with them.

Conclusions

1. In oral administration of the ointment with pine extract in conventional doses any negative effects of their toxicity were not revealed.

2. The ointment with Pinus sylvestris extract was assessed according to the classification by K.K. Sidorov and belongs to the V class of toxicity – “practically non-toxic”.

3. The histological structure of internal organs confirms the nontoxicity of the ointment with the Pinus sylvestris extract.

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Реферати

ВИЗНАЧЕННЯ ГОСТРОЇ ТОКСИЧНОСТІ МАЗІ З ЕКСТРАКТОМ СОСНИ ЗВИЧАЙНОЇ

Мандзій Т.П., Попадинець О.Г., Грицик А.Р.

Пошук нових біологічно-активних речовин серед лікарської рослинної сировини видів роду Сосна не викликає жодних сумнівів щодо її дослідження. Перспективність застосування сосни звичайної підтверджена багатьма публікаціями як вітчизняних, так і закордонних вчених. Після проведеного дослідження відомо, що отриманий сухий екстракт є практично нетоксичним та володіє при цьому широким спектром біологічної дії. Одним з основних пріоритетів впровадження нової лікарської форми є її незначна токсичність. Отже, цілеспрямована технологія з отримання мазі на основі сухого екстракту та орієнтоване вивчення гострої токсичності є першочерговими завданнями на шляху фармакологічних досліджень. Метою роботи було вивчення гострої токсичності мазі на основі сухого екстракту з сосни звичайної, яке було проведено вперше. Гостру токсичність вивчали на білих мишах при одноразовому пероральному застосуванні препарату. За мишами спостерігали протягом 14 днів. Було вивчено загальний стан тварин, смертність, динаміка маси тіла до і після експерименту. Було проведено макроскопічну оцінку стану внутрішніх органів і вивчено їх гістологічну структуру. Як показали дослідження, після прийому всередину мазі з екстрактом Pinus sylvestris в дозі 0,5 мл ознак токсичності у мишей не виявлено. Відповідно до класифікації К.К. Сидорова, мазь з екстрактом Pinus sylvestris належить до практично нетоксичних сполук. Таким чином, мазь з екстрактом Pinus sylvestris відноситься до п'ятого класу - «практично нетоксична при пероральному застосуванні».

Ключові слова: гостра токсичність, мазь з екстрактом Pinus sylvestris, макроскопічний аналіз внутрішніх органів.

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ОПРЕДЕЛЕНИЕ ОСТРОЙ ТОКСИЧНОСТИ МАЗИ С ЭКСТРАКТОМ СОСНЫ ОБЫКНОВЕННОЙ

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Актуальность поиска новых биологически активных соединений среди лекарственного растительного сырья не вызывает никаких сомнений по ее исследованию. Перспективность применения сосны обыкновенной подтверждена многими публикациями как отечественных, так и иностранных ученых. После проведения исследования известно, что полученный сухой экстракт практически нетоксичный и обладает при этом широким спектром биологического действия. Одним из основных приоритетов внедрения новой лекарственной формы является ее незначительная токсичность. Итак, целенаправленная технология по получению мази на основе сухого экстракта и ориентированное изучение острой токсичности - первоочередные задачи на пути фармакологических исследований. Целью работы было изучение острой токсичности экстракта из сырья сосны обыкновенной. Острую токсичность изучали на белых мышах при однократном пероральном применении препарата. За мышами наблюдали в течение 14 дней. Было изучено общее состояние животных, смертность, динамика массы тела до и после эксперимента. Была проведена макроскопическая оценка состояния внутренних органов и изучена их гистологическая структура. Как показали исследования, после приема внутрь мази с экстрактом Pinus sylvestris в дозе 0,5 мл признаков токсичности у мышей не обнаружено. Согласно классификации К.К. Сидорова, мазь с экстрактом Pinus sylvestris относится к практически нетоксичным соединений. Таким образом, мазь с экстрактом Pinus sylvestris относится к пятому классу - «практически нетоксична при пероральном применении».

Ключевые слова: острая токсичность, мазь с экстрактом Pinus sylvestris, макроскопический анализ внутренних органов.

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MACROSCOPIC AND MICROSCOPIC CONDITIONS OF THE SINGLE KIDNEY AND URETEROPELVIC JUNCTION AFTER THE CONTRALATERAL NEPHRECTOMY

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To date, there is no single concept on the patterns of morphogenesis of a single kidney compensatory hypertrophy. The purpose of the work is to give macroscopic and microscopic characteristics of the single kidney and the ureteropelvic junction structure after nephrectomy in the experiment. The experimental study was performed on 84 sexually matured white male rats weighing 180-200 g. All animals of the experimental group underwent surgery: nephrectomy of the left kidney. Statistical processing of the obtained results was carried out by means of the "Statistica 5.5" license package using non-parametric methods of assessing the results. It is established that in a single kidney there are processes of gradual developing compensatory hypertrophy of the organ. The sequential periods of postoperative changes were identified.

Key words: single kidney, ureteropelvic junction, nephrectomy, morphology.

The work is a fragment of the research project "Features of compensatory-adaptive processes with various diseases and damages of the human and animal body and clinical-experimental substantiation of new surgical treatment methods", state registration No. 0118U007342.

Today it is proved that in patients with a single kidney the rates of filtration-excretory function [1] and glomerular hyperfiltration [2] are significantly lower, which prognostically indicates a high risk of rapid progression of chronic kidney disease. Recent data indicate that after unilateral nephrectomy, the risk of chronic renal failure is by 3-5 times higher than in people with two kidneys [9]. Patients with a single kidney are most vulnerable to end-stage renal failure [8]. A potential risk of developing renal failure has also been established in donors, especially those who lost the kidney at a young age (18-24 years) [4]. A single kidney after contralateral removal may be more vulnerable to additional stress than congenital single kidney forms. Researchers [10] have shown that patients with a congenital single kidney with a kidney length of less than 120 mm or with proteinuria had a higher risk of renal failure.

We have found that the deterioration of the nitrogen excretion function in the single kidney and the increase in blood pressure correlated with the stage of renal ptosis [3], which is naturally due to changes in the topography of the single kidney after contralateral removal.

The pathogenesis of renal failure in patients with a single kidney may be significantly different from the pathogenesis of renal failure in the absence of nephrectomy. During the compensatory renal reaction remaining after nephrectomy, a greater tendency to develop chronic kidney disease and progression of terminal renal failure was detected [9].

However, to date, there is no single concept on the patterns of morphogenesis of a single kidney compensatory hypertrophy.

The purpose of the study was to establish the macroscopic and microscopic characteristics of the single kidney and the ureteropelvic junction structure after nephrectomy in the experiment.

Materials and methods. The experimental study was performed on 84 adult white male rats weighing 180-200 g, which were kept on a standard diet at the vivarium of Vinnytsya Pirogov Memorial National Medical University. The keeping and manipulation of animals was carried out in compliance with the "General Ethical Principles of Animal Experimentation", approved by the First National Congress on Bioethics (Kyiv, 2001), and was also guided by the recommendations of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1985) and the provisions of the "Preclinical Pharmacological Safety Assessment (GLP) Rules".

All animals were divided into two groups (42 in each): the first was the control, the second was the experimental group. In the control group under the ketamine analgesia opening of the abdominal cavity was performed, after which the abdominal wall was sutured in layers.

All animals of the experimental group were performed nephrectomy of the left kidney. Rats under general intramuscular analgesia (aminazine 10 mg/kg and ketamine 20 mg/kg) underwent left nephrectomy by cutting the renal hilum between the two ligatures with subsequent removal of the organ. Animals were sacrificed by intra-pleural administration of sodium thiopental at the dose of 50 mg/kg in 7, 14, 21 and 30, 60 and 90 days after the nephrectomy. Macroscopic assessment and description of the animals' kidneys were performed after their removal. Their weight was determined with VLR-200 laboratory scales to the accuracy of 0.1 mg, the length, width and thickness of the organ were measured using a caliper to the

accuracy of 0.05 mm. The kidney volume was calculated by the formula: V = 0.523 × a × b × s, where a is the length, b - the width, c - the thickness of the kidney.

A single kidney was removed for histological examination together with the ureteropelvic junction to detect compensatory and pathological changes in these structures that occurred within the specified time intervals. Pieces of 1 x 1 cm were cut from the renal parenchyma, and pieces of the same size were cut from the ureteropelvic junction so that 1/3 of the kidney pelvis and the ureteral section up to 1 cm in length got into the histological section. The material was fixed in 10% neutral formalin solution (pH 7.2-7.4) for 24-48 hours, then it was treated with alcohols of increasing concentration and embedded in paraffin. The resulting sections were stained with hematoxylin-eosin. Semifine sections were stained with toluidine blue.

Study of the ureteropelvic junctions and renal parenchyma microscopic structure was performed using an OLIMPUS BX41 light microscope at 100, 200, 400 and 800 magnifications. The morphometric parameters of structural changes were determined using a microscope graticule and Image Tools 3.6 software.

In the course of histometric studies, a series of images were obtained, which were used for linear measurements of each layer in the walls of ureteropelvic junctions. The thickness of the walls, perimeters and diameters of different sections of the ureteropelvic junctions' walls were determined. The percentage of structural elements in the muscular layer was also determined.

Statistical analysis of the obtained results was performed by means of "STATISTICA 5.5" software using non-parametric methods of the obtained results assessment.

Results of the study and their discussion. In the morphological study it was found that in the control group rats at the optic level in the renal cortex renal corpuscles were observed, which were round or oval structures. They have a vascular glomerulus and a Shumlyansky-Bowman capsule. The capsule consists of two epithelial leaflets, with a small space between them. Vascular glomerulus is formed of capillaries between the afferent and the efferent arterioles. The organ's stroma is represented by thin layers of loose connective tissue, which is located between the tubules and surrounds the vessels.

The outer leaflet of the renal corpuscle's capsule is formed by flat cells that had elongated nuclei and narrow cytoplasmic areas. The inner capsule leaflet tightly covered the glomerular capillaries on all sides. It is formed by irregular shaped epitheliocytes - podocytes. From their bodies several long broad processes proceeded - cytotrabecules. The latter were in contact with the basement membrane, and on the opposite side of this membrane there were endothelial cells of the glomerular hemocapillaries, which had narrow cytoplasm (fig. 1).

Morphometrically, the mean values of renal corpuscles' areas in the control group of white rats on the seventh day of the experiment were 4813±109 μm², the mean values of vascular glomeruli - 4308±94 μm², and the mean values of the capsule's lumen - 505±13 μm². After experimental nephrectomy, changes in all the nephron's components are present in the kidneys of immature animals against the background of vascular reorganization. In the cortex, most of the renal corpuscles are hypertrophied, blood filling of vascular glomeruli hemocapillaries was observed in them. The capsules' lumens are also increased compared to renal corpuscles of the control group animals.

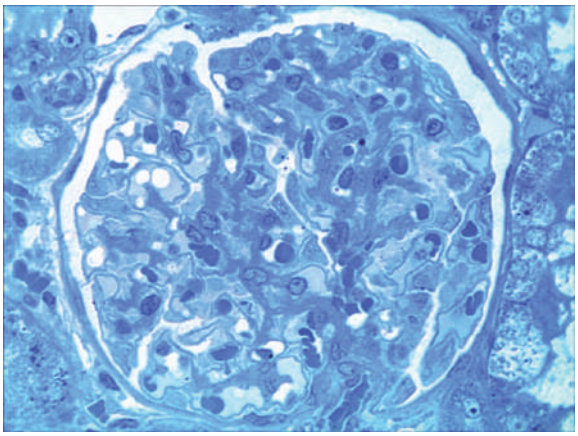

Fig. 1. Microscopic organization of nephron components in the renal cortex of a mature animal in the control group. Semifine section, staining with toluidine blue. x 800.

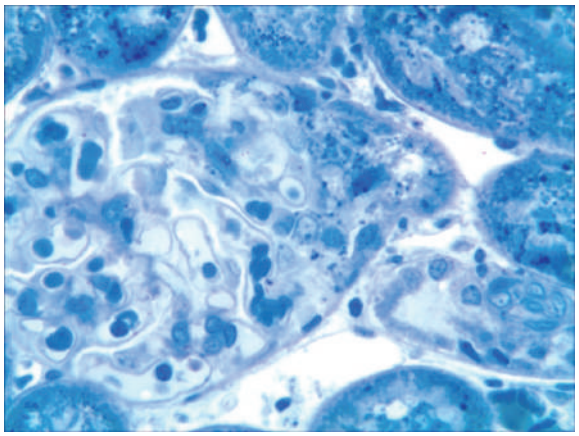

Fig. 2. Microscopic changes of the renal nephron corpuscle's cortex on the 7th day after contralateral nephrectomy. Semifine section, staining with toluidine blue. x 800.

Morphological examination of the ureteropelvic junction revealed that in the control group rats, the wall of the ureter was formed by the mucous, muscular, and serous (adventitial) layers. The structural features of each layer and their ratio were established in microscopic examination. The mucous membrane

of the ureter is formed by two layers - the epithelial and proper mucous plate of the mucous membrane. No peculiar features were noted.

Macroscopically, in the experimental group animals on the 7th day after removal of the contralateral kidney, the single right kidney was enlarged, the normal anatomical shape and surface of the kidney was preserved. The kidney weight was by 4.9% larger than the kidney weight of the control group in the same period and amounted to 0.98±0.01g, the kidney cubic capacity enlarged by 19.9% compared to the data at the beginning of the study and amounted 646.04±15.05 mm^3. Renal parenchyma retained differentiation into cortical and medullar zones. The topographic structure of the ureteropelvic junction was similar to that in the control group. It was found that the mean value of renal corpuscles area were by 15.8% higher than in the control group animals. The growth rate was an average of 2.3% per day.

The mean values of vascular glomeruli and capsule lumens' areas also increased significantly by 14.9% and 25.3%, respectively, compared to the control group animals with the mean growth rate of 2.1% and 3.6% per day, respectively. The mean area of the proximal renal nephron tubules increased to 1075±31 μm², and the mean lumen area was 428±12 μm². The mean values of the areas of the distal renal nephron tubules in this period of the experiment were 834±20 μm², and the mean values of their lumen areas were 395±11 μm². These values were by 52.5% and 45.8%, respectively, higher than in the control group animals. Microscopically, hypertrophied renal corpuscles were observed in semifiine sections of the renal cortex. In their vascular glomeruli, some of the blood capillaries had wide lumens (fig. 2).

The convoluted tubules of the nephrons are enlarged in size, both proximal and distal. The nuclei of the epitheliocytes had a circular, light karyoplasm with small basophilic blobs of heterochromatin. Protein inclusions in the form of rounded, dark, different size structures were observed in the cytoplasm of proximal cells. They are located mainly in the basal parts of the epitheliocytes cytoplasm. Closer to the basement membrane, there is striation, and the apical areas are optically lighter and have a brush-like border.

Two weeks after removal of the contralateral kidney, macroscopically, the single kidney was even larger than 7 days after, its capsule was shiny, tense. The kidney's weight was by 13.6% greater than that of the control group in the same period and amounted to 1.08±0.02 g, the kidneys cubic capacity increased by 47.7 % compared to the data at the beginning of the study and made 989.61±18.24mm^3.

Histological studies showed that on the 14th day after the experimental nephrectomy in the animals' kidneys there were greater changes of the vascular bed and parenchyma than in the previous term of the experiment. Hypertrophied renal corpuscles dominated the cortex. Lumens of the capsules was increased compared to the renal corpuscles of the control group animals. The area of the vascular glomerulus increased by 15.7% in comparison with that in the control group, and by 4.1% in comparison with the seven-days term, which made 0.6% per day. The lumen area of the Shumlyansky-Bowman capsule increased by 23.4% compared to the control and by 1.8% compared to the seven-days term. The growth rate during this period averaged 0.3% per day.

In the course of the compensatory response in the kidney remaining after unilateral nephrectomy, the area of the proximal convoluted tubules also increased. After 14 days it was larger by 11.67% compared to the animals of the seven-days experiment. The rate of the proximal convoluted tubules' area increase was 1.7%.

Three weeks after the surgery, the kidney weight was by 25.5% larger than that of the control kidney in the same period and amounted to 1.17±0.04 g, the kidney's cubic capacity was greater by 55.5 % compared to the data at the beginning of the study and was 1162.73±27.80 mm3.

Histologically, in addition to hypertrophied renal corpuscles in the cortex, the number of atrophied, diminished renal corpuscles increased. The capsule lumens were enlarged and uneven (fig. 3).

Destructive changes in the proximal and distal convoluted tubules of nephrons increased. Tubules with significant lumens were detected. Morphometrically, it was found that the mean value of the renal corpuscles area during this period of study was by 16.14% larger than in the control group animals. Compared to the previous term of the study, the area of the renal corpuscles was only by 2.9% larger. The mean daily growth was 0.4%. Indices of the proximal convoluted tubules area in the single kidney increased by 7.5% compared to the animals on the 14th day of the study.

The performed histological studies showed that on the 30th day after the experimental nephrectomy, the destructive changes in the kidneys are similar to the previous term of the experiment. Edema of the stroma connective tissue was accompanied by focal leukocyte infiltration. In the cortex there are both hypertrophied and atrophied, reduced in size renal corpuscles. The lumens of the capsules are enlarged and uneven (fig. 4).

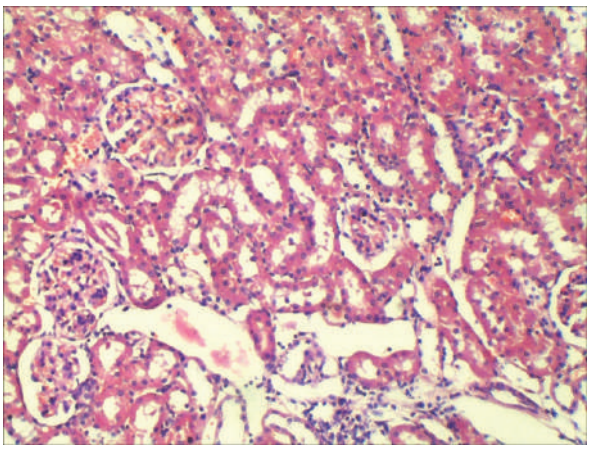

Fig. 3. Microscopic condition of the kidney cortex on the 21st day after the contralateral nephrectomy. Renal corpuscles and nephron tubules are altered. Staining with hematoxylin and eosin. x 200.

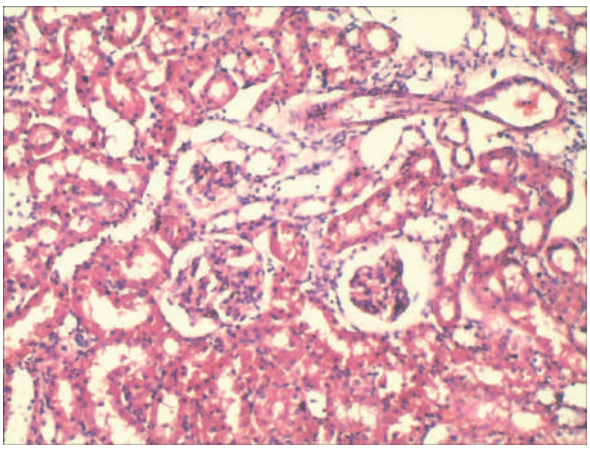

Fig. 4. Microscopic condition of the renal cortex on the 30th day after the contralateral nephrectomy. Renal corpuscles and nephron tubules are altered. Staining with hematoxylin and eosin. x 200.

On the 30th day postoperatively, the mean renal corpuscles area increased by 15.2% compared to the control group animals. Compared to the previous term of the experiment, the area of the renal corpuscles was only by 2.1% larger. The mean daily growth was 0.3%. The mean values of vascular glomeruli are by 13.5% higher than in the animals of the control group and by 1.6% higher than in the previous period. The mean daily growth was 0.2%. The lumen area of the capsule was reliably greater by 5.5% than in the animals of the previous experimental period. Compared to the animals in the control group it was greater by 26.4%. The mean daily growth in this period was 0.8%. The proximal convoluted tubules area was larger by 3.1% compared to the animals on the 21st day of study, but the rate of increase was smaller.

On the 60th day of the postoperative period after nephrectomy, besides hypertrophied, atrophied, reduced renal corpuscles are observed. In their vascular glomeruli, the blood capillaries had mostly small lumens, made by erythrocytes. In the Shumlyansky-Bowman capsules small lumens were noted. The mean value of the renal corpuscles area during this period of study is by 17.1% larger than in the control group animals. Compared to the previous term of the experiment, the renal corpuscles area was by 3.9% larger. The mean daily growth was 0.1%.

The mean values of vascular glomeruli area were by 16.8% higher than in the control group animals and by 6.4% higher than in the previous period. The mean daily growth was 0.2%. The lumen area of the capsule was reliably larger by 8.0% than in the animals of the previous experimental period. Compared to the animals of the control group it was by 28.5% higher. The mean daily growth during this period was 0.3%.

On the 90th day after the experimental nephrectomy, it was found morphometrically that the mean value of renal corpuscles area was by 16.6% higher than in animals of the control group. Compared to the previous term of the experiment, the area of the renal corpuscles was only by 1.8% larger. The mean daily growth was 0.06%. The mean values of vascular glomeruli area were by 15.7% higher than in the control group animals and by 2.8% higher than in the previous period. The mean daily growth was 0.09%. The lumen area of the capsule was reliably larger by 6.2% than in the animals of the previous experimental period. The mean daily growth in this period was 0.2%.

Thus, the morphometric analysis showed that the highest growth rate of the structural components of the renal corpuscles in the single kidney after the contralateral nephrectomy was observed in the near postoperative period until the seventh day, and subsequently it decreased. The growth rates of the proximal and distal convoluted tubules were greater than those of the renal corpuscles components.

In the later period after the kidney removal (60 and 90 days), more pronounced destructive and sclerotic changes occurred. Morphological changes in the wall of the ureteropelvic junction and ureters lied in the increased amount and expansion of intermuscular collagen fibers.

Atrophic processes were followed by further fibrotic degeneration. Against the background of progressing sclerosis, phenomena of deep destruction and dissociation were observed in the elastic frame, particularly in the submucous membrane. The performed microscopic studies of the renal cortex in semifine sections showed that on the 60th and 90th days (long terms after nephrectomy) there were signs of compensatory hypertrophy and destructive changes were revealed in the components of nephrons. Many renal corpuscles are hypotrophic, some podocytes have basophilic, pycnotically altered, irregular nucleus. In their vascular glomeruli, blood capillaries have mainly small lumens that are filled with red blood cells.

According to the literature, intraglomerular hypertension caused damage to podocytes and loss of selective permeability of the slit diaphragm filtration function between the processes of podocytes, causing proteinuria [5], which led to renal failure progression [6]. Studies on the animals kidneys have shown that glomerular hyperfiltration was a key risk factor for chronic kidney disease in nephrectomy-exposed rats [7].

Conclusion

In the single kidney there were processes of the organ's compensatory hypertrophy gradual development. Sequential periods were established: the period of early postoperative changes (in the experiment - 7-14 days after the contralateral kidney removal); the recovery period (from 14 days to 1 month in the experiment). In these terms, there took place the initial compensatory changes, the initial phenomena of hypertrophy, which testified to the strengthening of all functions in the single kidney. In later periods of the study (60-90 days postoperatively), some nephrons developed destructive changes.

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Реферати

МАКРОСКОПІЧНИЙ І МІКРОСКОПІЧНИЙ СТАН ЄДИНОЇ НИРКИ І МИСКОВО-СЕЧОВІДНОГО СЕГМЕНТУ ПІСЛЯ НЕФРЕКТОМІЇ КОНТРАЛАТЕРАЛЬНОЇ

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До теперішнього часу немає єдиної концепції про закономірності морфогенезу компенсаторної гіпертрофії єдиної нирки. Метою роботи було дати макроскопічну і мікроскопічну характеристику структури єдиної нирки і мисково-сечовідного сегмента після нефректомії в експерименті. Експериментальне дослідження виконано на 84 статевозрілих білих щурах-самцях масою 180-200 грамів. Всім тваринам дослідної групи виконували оперативне втручання - нефректомію лівої нирки. Статистична обробка отриманих результатів проведена в ліцензійному пакеті "Statistica 5.5" з використанням непараметричних методів оцінки результатів. Встановлено, що в єдиній нирці відбуваються процеси поетапного розвитку компенсаторної гіпертрофії органу. Виділили послідовні періоди післяопераційних змін нирки.

Ключові слова: єдина нирка, мисково-сечовідний сегмент, нефректомія, морфологія.

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МАКРОСКОПИЧЕСКОЕ И МИКРОСКОПИЧЕСКОЕ СОСТОЯНИЕ ЕДИНСТВЕННОЙ ПОЧКИ И ЛОХАНОЧНО-МОЧЕТОЧНИКОВОГО СЕГМЕНТА ПОСЛЕ НЕФРЭКТОМИИ КОНТРАЛАТЕРАЛЬНОЙ

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К настоящему времени нет единой концепции о закономерностях морфогенеза компенсаторной гипертрофии единственной почки. Целью работы было дать макроскопическую и микроскопическую характеристику структуры единственной почки и лоханочно-мочеточникового сегмента после нефрэктомии в эксперименте. Экспериментальное исследование выполнено на 84 половозрелых белых крысах-самцах массой 180-200 граммов. Всем животным опытной группы выполняли оперативное вмешательство - нефрэктомию левой почки. Статистическая обработка полученных результатов проведена в лицензионном пакете "Statistica 5.5" с использованием непараметрических методов оценки результатов. Установлено, что в единственной почке происходят процессы поэтапного развития компенсаторной гипертрофии органа. Выделили последовательные периоды послеоперационных изменений почки.

Ключевые слова: единственная почка, лоханочно-мочеточниковый сегмент, нефрэктомия, морфология.

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PECULIARITIES OF PORCINE PERIODONTIUM IN NORMAL CONDITION AND IN GENERALIZED PERIODONTITIS DURING DENTAL RESTORATION OF VARIOUS TYPES

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The paper was aimed at determining the structural features of porcine gums in normal conditions and experimental generalized periodontitis in the presence of adhesive bridges and dental implants. It is established, that impaired differentiation in the form of dyskeratosis occurs in the epithelium of the gingival mucosa of pigs with generalized periodontitis; it is manifested by the appearance of basal cells in the cytograms that are absent in the control group of animals, and 4-fold increase in the number of parabasal epitheliocytes. Histological study of the mucous membrane of the epithelial plate revealed vacuolar dystrophy of the cells in the spinous layer and local phenomena of spongiosis. In their lamina propria, disorders of microcirculation and connective tissue edema were noted. Changes in the lamina propria during dental restoration of different types were common. In the epithelium, during restoration with dental implant, the changes corresponded to the control group: vacuole dystrophy and local spongiosis. Marked hyperkeratosis in the epithelial plate was noted in restoration with bridge denture.

Key words: experimental generalized periodontitis, adhesive bridge-like structures, dental implants, cytograms, gums, pigs.

The work of the fragment of research project «Mechanisms of influence of pathogenic factors on the dental status of persons with somatic pathology, ways of their correction and blocking», State registration number 0115U001138.

Currently, periodontal diseases are referred to the most prevalent conditions. [6, 9, 11, 12]. The most common is generalized periodontitis, ranking first among all dental diseases at the age of 40 and above. [1, 2, 5].

Publications report, that prolonged inflammatory process in periodontium causes disturbances in keratinization of the gingival epithelium, manifested by the altered cell ratio. The above indicates about strong correlation between the cellular and humoral immunity of periodontal pockets, primarily due to polymorphonuclear leukocytes and macrophages. These cells play a leading role in inflammatory responses and in protecting the body from the effect of foreign factors, including bacteria and their toxins [7, 8, 10].

The main symptoms of generalized periodontitis are the presence of symptomatic gingivitis, periodontal pockets, traumatic occlusion, and progressive resorption of bone tissues of the alveolar process. All this in turn leads to the loss of teeth and dentition defects. The restoration of the dentition in the presence of the bounded edentulous space can be done using the adhesive bridge and dental implantation method.

The purpose of the work was to determine the structural features of porcine gums in normal conditions and in experimental generalized periodontitis in the presence of adhesive bridges and dental implants.

Materials and methods. The study was carried out on 10 castrated male pigs of the Ukrainian Large White breed, weighing 70+4,5 kg, aged 6±1 month old, kept individually on the conventional system of breeding at the Institute of Pig Breeding and Agricultural Production of the National Academy of Agrarian Sciences of Ukraine.

The experimental study was performed in several stages. At the first stage generalized periodontitis was simulated by destruction of the dentogingival junction using micro-abrasor and insertion of crushed tartar into the created periodontal pocket with its subsequent closure with liquid composite material. Following three weeks the development of generalized periodontitis in pigs was verified.

Before modeling generalized periodontitis and following three weeks thereafter two smears per animal were collected for cytological examination. The samples were obtained by the scraping from the mucous membrane of the gums of the lower and upper jaws using a sickle burnisher.

Subsequently, the collected material was applied to a sterile slide. Drying of the smears was performed by the method of dry fixation at room temperature with open air access. The smears were stained using May-Grünwald method [10]. Cytograms were analyzed using the Biorex–3 BM–500T microscope equipped with DCM-900 digital microphoto attachment with software adapted for the studies in 1000×magnification. Quantitative parameters were determined by counting cellular elements in 5 FOV [10]; the amount was recorded in absolute figures and mean values were calculated in Exel software [3]. The latter were used to determine the ratio of different classes of epithelial cells to establish the reference values.

At the next stage, following three weeks, tooth extraction was performed in a pig with simultaneous replacing the missing tooth with *Alpha dent active* dental implant. Following 3 months, the animals were sedated with ketamine (5 mg / kg intramuscularly). The mucous membrane was separated from the extracted fragments of jaws, where edentulous space was restored with dental implant or adhesive bridge,

as well as from the portion of jaw with preserved dentition, and placed in 10% buffered formalin for 24 hours. The material was embedded in paraffin according to the conventional technique and sections of 5 μm thick were made and stained with hematoxylin and eosin.

All animals had no clinical signs of infection or any other oral diseases. Experimental manipulations have been made in compliance with the requirements of international principals of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1986), the "General Ethic Rules for Conducting Experiments on Animals", adopted by the I National Congress on Bioethics [4] and the requirements of the "Procedure for conducting tests, experiments on animals by research institutions" (2012).

The study and imaging of the sections was made on the Biorex–3 BM–500T microscope equipped with DCM-900 digital microphoto attachment with software adapted for the studies in 400×magnification.

Results of the study and their discussion. The study of the scrape smears of mucous membranes of porcine gums in experimental generalized periodontitis has found that cells of the intermediate layer prevailed in the cytograms, similar to the control group of animals, though their average number in the field of view significantly decreased by 29.25% compared to controls (table).

Table

Changes of the ratio of different classes of cells of stratified squamous epithelium of porcine gums in generalized periodontitis

	Types of cells in the cytograms				
	basal	parabasal	intermediate	superficial	horny scales
Control	0	3.43	6.24	89.55	0.78
Generalized periodontitis	2.10*	12.41*	24.63*	60.30*	0.56

The number of intermediate cells increased by 18.39% and was by 4 times significantly higher than in the control group. The average number of parabasal cells also increased by 8.98% (Table). On the part of the horny scales a decrease by 0.22% was established. In contrast to cytograms in the control group of animals with generalized periodontitis, we found basal cells, the average number of which was 2.10%.

The established changes in the ratio of the epithelial cells in the porcine gums indicate a disorder of the processes of differentiation of the epithelium in the form of dyskeratosis due to inflammatory changes of the mucous membrane of the gums caused by experimental generalized periodontitis. The increase in number of parabasal cells reflects an increase in mitotic activity in the epithelial plate as the manifestation of the activation of adaptive mechanisms. The appearance of basal epitheliocytes indicates impaired epithelial barrier function due to hyperhydration and inflammatory changes in the lamina propria.

Cytological study showed that the basal cells had a rounded shape and small size, compared to other elements of the epithelial diferon. Their cytoplasm was basophilic, lumpy condensed chromatin was clearly visualized in the nuclei. The nuclear to cytoplasmic ratio was high.

A significant number of microorganisms, detected in the cytograms, led to the development of necrobiosis of epitheliocytes. Coccal flora and sporadic filaments of fungi were mainly detected in scrape smears (fig. 1a).

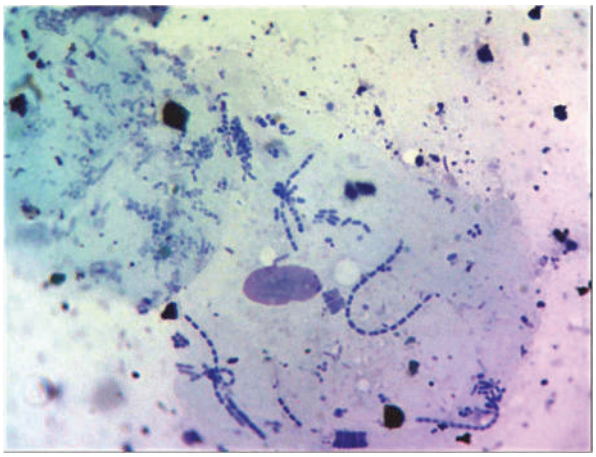

Fig. 1a. Contamination of microorganisms on superficial epitheliocytes of porcine gums in generalized periodontitis. May-Grünwald stain. Lens: 100×magnification, ocular lens: 10× magnification.

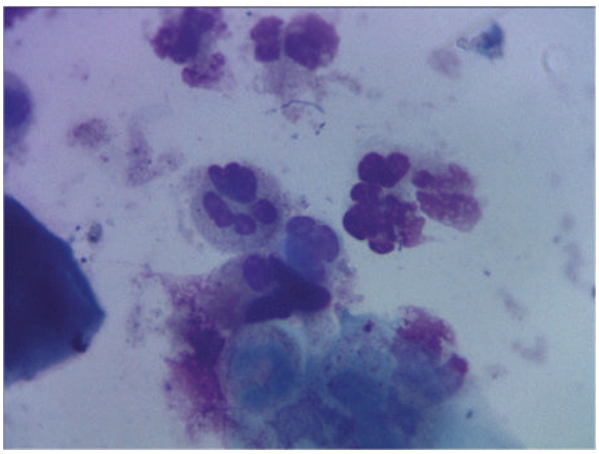

Fig. 1b. Segmentonuclear neutrophils in the cytograms of the porcine gingival mucosa in generalized periodontitis. May-Grünwald stain. Lens: 100×magnification, ocular lens: 10× magnification.

Coccal flora contaminated on segmentonuclear leukocytes. Thus, the activity of phagocytosis of segmentonuclear neutrophils increased, which led to incomplete phagocytosis and the formation of pyocytes (fig. 1b).

Epitheliocytes with signs of irritation were found in the cytograms of the gingival mucosa of pigs with generalized periodontitis. By morphological features, they referred to the cells of the intermediate layer. In this case, enlargement of the cells was observed; vacuoles filled with optically clear content were detected in the cytoplasm (fig. 2a).

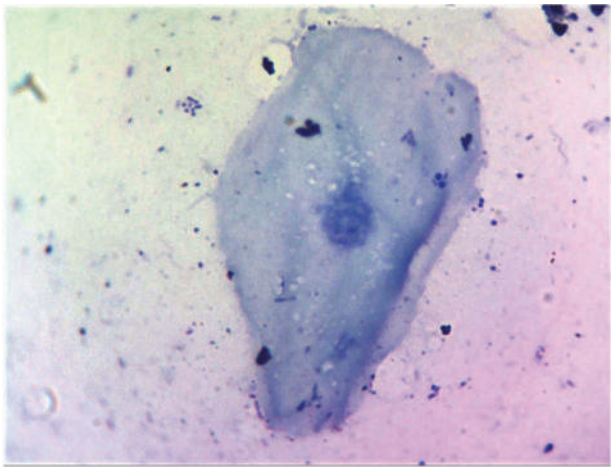

Fig. 2a. Intermediate epitheliocyte of porcine gingival mucosa in generalized periodontitis. May-Grünwald stain. Lens: 100×magnification, ocular lens: 10× magnification.

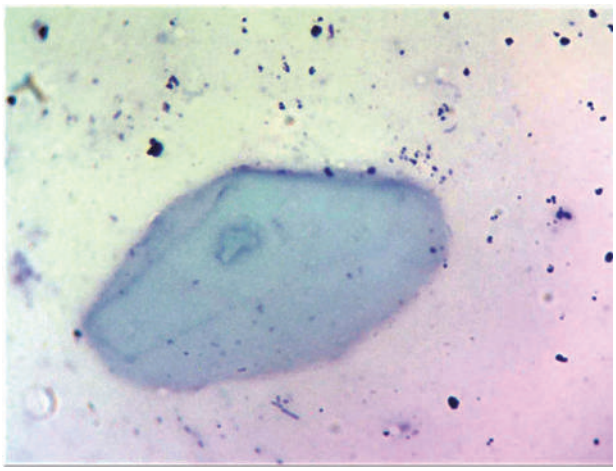

Fig. 2b. Karyopyknosis of the nucleus of the superficial epitheliocyte of the porcine gingival mucosa in generalized periodontitis. May- Grünwald stain. Lens: 100×magnification, ocular lens: 10×magnification.

In some epithelial cells the nuclei were eccentric, shrink, being at the initial stages of karyorhexis (fig. 2b). These changes are the manifestation of the metabolic disorders of cells, resulted from inflammatory changes caused by inflammatory generalized periodontitis.

The analysis of the cytograms has established that epithelial cells of the gums were exposed to higher destruction, accompanied by karyopyknosis and karyorhexis of the nucleus as well as homogenization of the cytoplasm.

The number of horny scales decreased compared to intact cytograms. They had a polygonal shape and were sporadic.

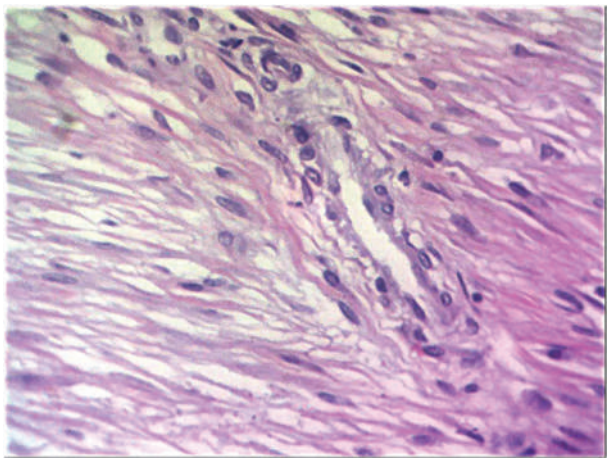

Fig. 3a. Arteriola in the lamina propria of the porcine gingival mucosa in generalized periodontitis. H&E stain. Lens: 40×magnification; ocular lens: 10×magnification.

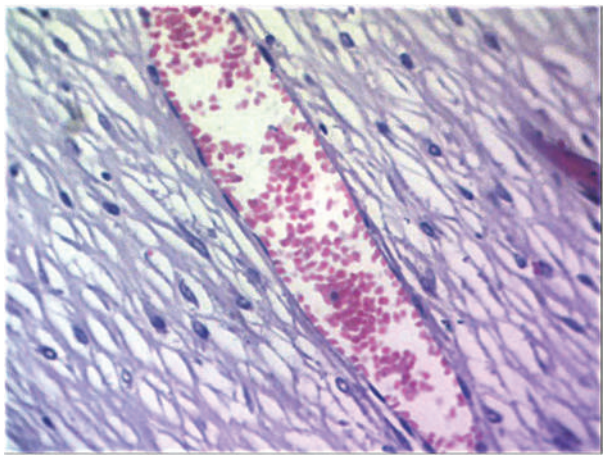

Fig. 3b. Venula in the lamina propria of the porcine gingival mucosa in generalized periodontitis. H&E stain. Lens: 40×magnification; ocular lens: 10×magnification.

The analysis of histological sections of the gingival mucosa of gums of pigs with generalized periodontitis, when the edentulous space was restored by dental implant, has found the impaired epithelial differentiation in the epithelial plate in the form of dyskeratosis. In the spinous layer epitheliocytes showed signs of vacuolar dystrophy, manifested by their enlargement, presence of numerous vacuoles in the cytoplasm, and shrink nuclei. The phenomena of spongiosis were visualized locally. The basement membrane was thickened. The above changes of the epithelial plate were caused by the disorders of

microcirculation with its subsequent reduction and the phenomena of hypoxia. Perivascular edema was developed due to dyscirculatory disorders and increased vascular-tissue permeability. The arteries were spasmodic; no blood corpuscles were detected in the lumina (Fig. 3a). The lumina of venules were enlarged and filled with red blood cells. Adhesion of erythrocytes and sludge syndrome was established (Fig. 3b). Collagen fibers of lamina propria were stratified by edema fluid; lysis and destruction of fibrous structures, as well as diffuse leukocytic infiltrations were locally visualized.

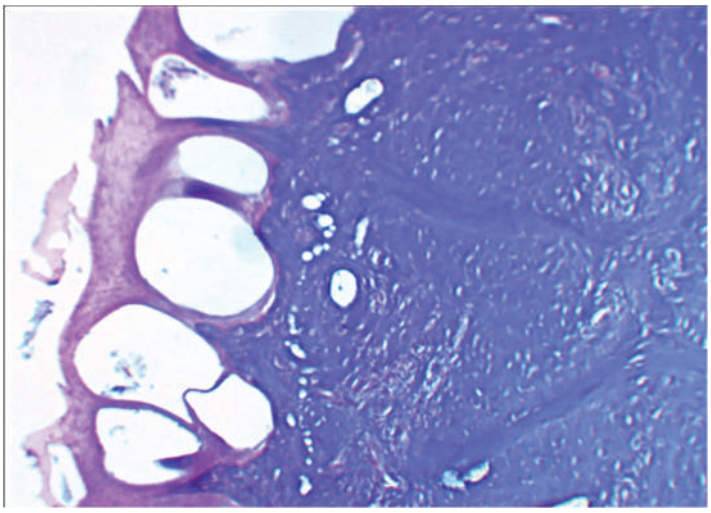

Fig. 4. Epithelium of the porcine gingival mucosa in generalized periodontitis. H&E stain. Lens: 10×magnification; ocular lens: 10×magnification.

The study of the peculiarities of the structural organization of the mucous membrane of the gums of pigs after restoration with adhesive bridge construction has found that changes in the lamina propria were similar to restoration with dental implant. However, marked hyperkeratosis was noted in the epithelial plate. The horny layer was significantly thickened. The basal, spinous and granular layers were thinned and pressed to the basement membrane. Between the above layers and the horny layer, balloon-shaped hollow spaces were identified, which were joined by thin strands of the horny scales (fig. 4).

The established changes in the cellular composition of cytograms in generalized periodontitis are caused by the intensity of inflammatory-dystrophic processes in periodontal tissues. The obtained digital data are significantly different from the ratio of epithelial cells of the stratified squamous epithelium of the gums in pigs of the control group and correlate with the data of other researchers in the study of cytograms of patients with periodontitis [10]. Desquamation disorders of the epitheliocytes, which provide barrier function of the gums are caused by impaired blood microcirculation. The appearance of basal and parabasal cells in the cytograms can be explained by the activation of adaptive mechanisms due to enhanced mitotic activity of the gingival epitheliocytes. Thus, chronic inflammation in the periodontium is the entry of infection that can infect not only the tissues of the maxillofacial area, but also lead to infection of the whole organism, contributing to the formation of foci of chronic infection and intoxication in organs of different systems [2].

Conclusion

Impaired differentiation in the form of dyskeratosis occurs in the epithelium of the gingival mucosa of pigs with generalized periodontitis; it is manifested by the appearance of basal cells in the cytograms that are absent in the control group of animals, and 4-fold increase in the number of parabasal epitheliocytes. Histological study of the mucous membrane of the epithelial plate revealed vacuolar dystrophy of the cells in the spinous layer and local phenomena of spongiosis. In their lamina propria, disorders of microcirculation and connective tissue edema were noted. Changes in the lamina propria during dental restoration of different types were common. In the epithelium, during restoration with dental implant, the changes corresponded to the control group: vacuole dystrophy and local spongiosis. Marked hyperkeratosis in the epithelial plate was noted in restoration with bridge denture.

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Реферати

ОСОБЛИВОСТІ ПАРОДОНТУ СВИНЕЙ В НОРМІ ТА ПРИ ГЕНЕРАЛІЗОВАНОМУ ПАРОДОНТИТІ ЗА УМОВ ВІДНОВЛЕННЯ ВКЛЮЧЕНИХ ДЕФЕКТІВ ЗУБНИХ РЯДІВ РІЗНИМИ СПОСОБАМИ

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Метою роботи було встановити структурні особливості ясен свиней в нормі та при експериментальному генералізованому пародонтиті за умов наявності адгезивних мостоподібних конструкцій та дентальних імплантатів. Встановлено, що при генералізованому пародонтиті в епітелії слизової оболонки ясен свиней визначається порушення диференціювання у вигляді дискератозу, яке проявляється появою базальних клітин в цитограмах, які в контрольній групі тварин відсутні, та збільшенням в 4 рази кількості парабазальних епітеліоцитів. При гістологічному дослідженні слизової оболонки в епітеліальній пластинці виявлена вакуольна дистрофія клітин шипуватого шару і локальні явища спонгіозу. У власній пластинці визначались розлади мікроциркуляції на набряк сполучної тканини. При відновленні дефектів зубних рядів різними способами зміни у власній пластинці були стереотипними. В епітелії, за умов відновлення дефекту зубного ряду за допомогою дентального імпланту, зміни відповідали контрольній групі – вакуольна дистрофія і локальний спонгіоз. При відновлення дефекту зубного ряду за допомогою мостоподібною конструкції в епітеліальній пластинці встановлений виражений гіперкератоз.

Ключові слова: експериментальний генералізований пародонтит, адгезивні мостоподібні конструкції, дентальні імплантати, цитограми, ясна, свині.

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ОСОБЕННОСТИ ПАРОДОНТА СВИНЕЙ В НОРМЕ И ПРИ ГЕНЕРАЛИЗОВАННОМ ПАРОДОНТИТЕ ПРИ УСЛОВИИ ВОССТАНОВЛЕНИЯ ВКЛЮЧЕННЫХ ДЕФЕКТОВ ЗУБНЫХ РЯДОВ РАЗНЫМИ СПОСОБАМИ

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Целью работы было установить структурные особенности десен свиней в норме и при экспериментальном генерализованном пародонтите при наличии адгезивных мостовидных конструкций и дентальных имплантатов. Установлено, что при генерализованном пародонтите в эпителии слизистой оболочки десны свиней определяется нарушение дифференцировки в виде дискератоза, которое проявляется появлением базальных клеток в цитограммах, которые в контрольной группе животных отсутствуют, и увеличением в 4 раза количества парабазальных эпителиоцитов. При гистологическом исследовании слизистой оболочки в эпителиальной пластинке обнаружена вакуольная дистрофия клеток шиповатого слоя и локальные явления спонгиоза. В собственной пластинке определялись расстройства микроциркуляции на отек соединительной ткани. При восстановлении дефектов зубных рядов различными способами изменения в собственной пластинке были стереотипными. В эпителии, в условиях восстановления дефекта зубного ряда с помощью дентального импланта, изменения соответствовали контрольной группе – вакуольная дистрофия и локальный спонгиоз. При восстановления дефекта зубного ряда с помощью мостовидных конструкции в эпителиальной пластинке выявлен выраженный гиперкератоз.

Ключевые слова: экспериментальный генерализованный пародонтит, адгезивные мостовидные конструкции, дентальные имплантаты, цитограммы, десна, свиньи.

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INFLUENCE OF HIGH ADRENALIN DOSES ON THE MORPHOFUNCTIONAL STATUS OF RATS EPIPHYSIS UNDER THE CONDITION OF ITS HYPOFUNCTION

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The work highlights the effect of adrenaline on morphology and functional activity of epiphysis in the conditions of its hypofunction. The study was performed on 24 sexually mature males of Wistar rats, with a body weight of 150-220 g. Animals were simulated hypofunction of epiphysis and administered a single dose of adrenaline hydrochloride (0.5 mg/kg) intraperitoneally. It is established that the effect of a high dose of adrenaline is accompanied by the development of destructive processes in the epiphysis cells and is characterized by vacuolization of the cytoplasm with further development of the intracellular structures lysis. These morphological features indicate the development of necrotic processes and, accordingly, the loss of pinealocytes.

Key words: epiphysis, pinealocytes, adrenaline, vacuolization.

The work is a fragment of the research project "Comparative morphology of the cranial dura mater sinuses of vertebrates", state registration No. 0115U000176.

Adrenaline is the main hormone of the adrenal medulla. By its chemical nature, it belongs to catecholamines, which are stress hormones, which, under the influence of adverse environmental factors, mobilize all the forces and resources of the body, changing the morpho-functional state of almost all organs of the visceral systems [5]. Due to the wide range of physiological and pharmacological properties, the adrenaline hormone in therapeutic doses has been successfully used as a drug in various fields of medicine [9, 10-12]. Administration of large doses of adrenaline hydrochloride is recommended for use in many emergency conditions [7, 8]. However, data on the response of the body's functional systems to high, almost toxic doses of adrenaline are scarce in the literature [4]. There is no information at all on the morpho-functional changes in the epiphysis which is responsible for triggering the stress response.

The purpose of the study was to perform histological analysis and to clarify features of the morpho-functional state of the rat epiphysis under its hypofunction and after a single exposure to a high dose of adrenaline hydrochloride.

Materials and methods. The experimental studies involved 24 adult male Wistar rats, with the body weight of 150-220 g in the autumn and winter. Animals were kept under standard vivarium conditions. Hypofunction of the epiphysis was caused by round-the-clock illumination with intensity of 1000-1500 lx with two lamps, which were located on both sides of the cage for 10 days. On the 10th day of the experiment, rats were administered adrenaline hydrochloride intraperitoneally with the single dose of 0.5 mg/kg. The experimental animals were euthanized 2 hours after adrenaline administration, which corresponds to the onset of necrosis [6]. The animals were sacrificed in strict compliance with the provisions of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1986), as well as the "General Ethical Principles for Experiments on Animals" approved by the First National Congress on Bioethics (Kyiv, 2001). The permission to carry out the research was given by the Ethics and Bioethics Commission of the Mykolayiv V.O. Sukhomlinsky National University.

After removal of the epiphysis, together with the adjacent blood vessels, the obtained complex was immersed into a fixing solution of 10% neutral formalin. Using standard methods, the material was embedded in paraffin blocks, of which sections were made with the thickness of 4 μm and stained with hematoxylin and eosin. The histological slides obtained in this way were studied at various magnifications with the "PrimoStarZeiss" microscope, followed by photographing the microslides with a "Canon" digital SLR camera.

Results of the study and their discussion. Histological examination of the experimental animals slides with a small magnification of the microscope revealed the particulate structure of the organ (fig. 1). Particles detected in the sections are mostly round-shaped. There are different numbers of pineal cells in each epiphysis segment, mostly from 2 to 4.

Analysis of the epiphysis parenchyma structural elements state in the animals which were under the adrenaline exposure conditions indicates specific changes. We have established a general clarification of histological sections. In most cases, they look pale and slightly basophilic. And only in certain places small aggregates of parenchyma cellular elements can be found, having a more intense basophilic staining.

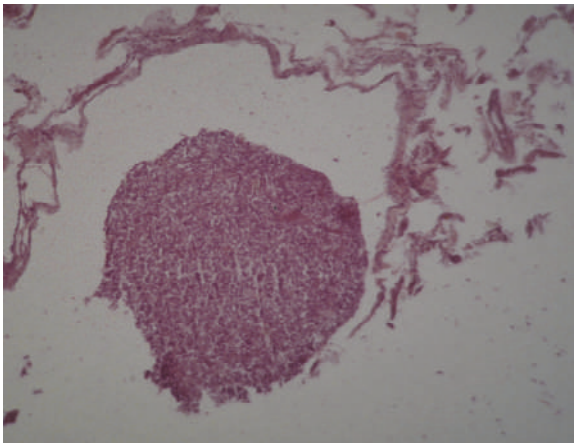

Fig. 1. Micrograph shows the particle structure of the rat epiphysis parenchyma: Approx. oc. × 10, ob. × 10. Staining: hematoxylin and eosin.

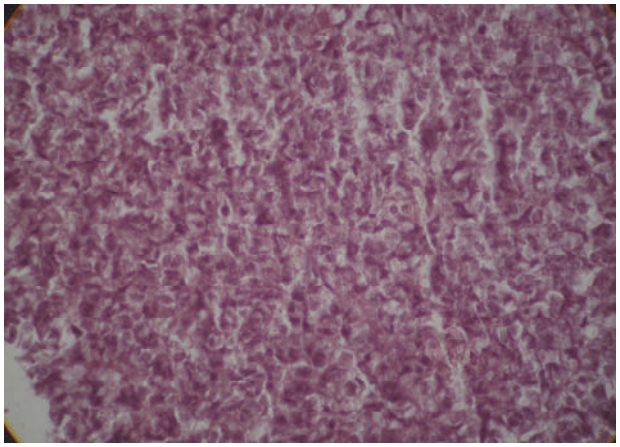

Fig. 2. Micrograph of the cellular composition in the central region of the rat epiphysis parenchyma. Approx.: oc. × 10, ob. × 40. Staining: hematoxylin and eosin.

Clarification of histological slides occurs for two reasons. First, this can be due to the increase in the number of active light pinealocytes. Secondly, by reducing the amount of heterochromatin in the nuclei of pineal cells.

It is established that in histological sections the absolute majority are light pinealocytes, which are large cells the major volume of which cytoplasm is occupied by the nucleus. It should be noted that the cytoplasm of light pineal cells looks transparent, virtually unstructured, except in some cases where a small amount of the basic substance can be seen. The nuclei of the light pinealocytes in the sections are predominantly round-shaped. Only occasionally there occur oval nuclei. It is established that the nuclei of light pinealocytes are characterized by unequal degree of basophilicity, which depends on the amount of basophilic substance in the karyoplasm. Thus, along with very light cells (light nucleus cells), we found more intensely colored (dark nucleus cells) light pinealocytes, which indicates a different degree of the light cells' functional activity (fig. 2). The nucleoli of light pinealocytes are round-shaped and mostly occupy a central position in the karyoplasm. Along with the described structure of the light cells nuclei, nuclei devoid of nucleoili are found quite frequently. With regard to dark pinealocytes, it is established that their number in histological sections is rather limited and they are located mainly in the central regions of the organ's parenchyma (fig. 2). This morphological feature indicates an increase in the functional activity of the epiphysis and the transition of inactive dark cells to the light population. Dark pinealocytes are much smaller in size than light cells. The nuclei of the dark pinealocytes are characterized by a very dark karyoplasm filled with a dense, unstructured mass of condensed chromatin. Due to this, the nucleoli are virtually undetermined in such cells.

It is revealed that in histological sections of epiphysis parenchyma, phenomena of light cells cytoplasm vacuolization of different degree are observed. Some of them are characterized by an enlarged light cytoplasm; in place of other cells, vacuoles of irregular shape and different caliber filled with cytoplasmic fluid can be seen, indicating the death of the cell and the gradual loss of the cellular composition in the epiphysis parenchyma.

It is established that similar vacuolization foci are expressed both in the central part and on the periphery of the organ. It should be noted that almost all pineal cells began to undergo vacuolization processes. Only occasionally, light pinealocytes with basophilic nuclei and non-vacuolated cytoplasm come into the field of view. It was found that in cells subjected to the process of vacuolization, the degree of nuclei basophilia is significantly reduced. Vacualization of cellular elements causes an increase in the cytoplasm volume and, due to this, the cytolemma stretching. Subsequently, the lysis of intracellular structures develops, primarily the nuclei, which is manifested by the gradual discoloration of the nuclear substance and nucleoli.

Information on the effect of high doses of adrenaline on the morphology and functional status of the epiphysis in available to us domestic and foreign literature sources is almost absent. However, our findings regarding the morphofunctional status of the epiphysis correlate with the results of studies by other authors who have studied changes in the morphology and functional status of the epiphysis in response to the influence of many other endogenous and exogenous factors [1, 3]. Thus, the revealed morphological disorders, according to literature, can be described as manifestations of parenchymal hydropic degeneration, indicating the development of necrotic processes and, accordingly, death of pinealocytes [2, 4].

Conclusions

1. The histological examination revealed a significant decrease in the number of inactive dark pinealocytes, and an absolute predominance of light pineal cells, which indicates a high functional activity of the organ.

2. The presence of two types light pinealocytes is established, which indicates the asynchrony of metabolic processes.

3. It was found that pinealocytes undergo processes of vacuolization with the subsequent development of intracellular structures lysis, indicating the development of hydropic degeneration, cell death and gradual loss of the cellular composition in the epiphysis parenchyma.

Prospects for further research *mean that in the future it is planned to study the status of the epiphysis structural elements after a single injection of adrenaline hydrochloride and euthanasia 24 hours after injection, which corresponds to the peak of necrosis.*

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Реферати

ВПЛИВ ВИСОКИХ ДОЗ АДРЕНАЛІНУ НА МОРФОФУНКЦІОНАЛЬНИЙ СТАН ЕПІФІЗУ ЩУРІВ ЗА УМОВ ЙОГО ГІПОФУНКЦІЇ

Пшиченко В.В., Черно В.С., Давиденко Р.М., Гаврилюк І.М., Кучер О.О.

В роботі висвітлено дані щодо впливу адреналіну на морфологію та функціональну активність епіфізу за умов його гіпофункції. Дослідження було проведено на 24 статевозрілих самцях щурів лінії Wistar, з масою тіла 150-220 г. Тваринам моделювали гіпофункцію епіфізу та одноразово вводили адреналін гідрохлорид внутришньобрюшинно у дозі 0,5 мг/кг. Встановлено, що вплив високої дози адреналіну супроводжується розвитком деструктивних процесів у пінеальних клітинах, що характеризуються вакуолізацією цитоплазми з подальшим розвитком лізису внутрішньоклітинних структур. Дані морфологічні особливості свідчать про розвиток некротичних процесів і відповідно загибель пінеалоцитів.

Ключові слова: епіфіз, пінеалоцити, адреналін, вакуолізація

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ВЛИЯНИЕ ВЫСОКИХ ДОЗ АДРЕНАЛИНА НА МОРФОФУНКЦИОНАЛЬНОЕ СОСТОЯНИЕ ЭПИФИЗА КРЫС В УСЛОВИЯХ ЕГО ГИПОФУНКЦИИ

Пшиченко В.В., Черно В.С., Давиденко Р.Н., Гаврилюк И.М., Кучер О.О.

В работе освещены данные о влиянии адреналина на морфологию и функциональную активность эпифиза крыс в условиях его гипофункции. Исследование было проведено на 24 половозрелых самцах крыс линии Wistar, с массой тела 150-220 г. Животным моделировали гипофункцию эпифиза и однократно вводили адреналин гидрохлорид внутрибрюшинно в дозе 0,5 мг / кг. Установлено, что влияние высокой дозы адреналина сопровождается развитием деструктивных процессов в пинеальных клетках, характеризующихся вакуолизацией цитоплазмы с последующим развитием лизиса внутриклеточных структур. Данные морфологические особенности свидетельствуют о развитии некротических процессов и соответственно гибели пинеалоцитов.

Ключевые слова: эпифиз, пинеалоциты, адреналин, вакуолизация

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ULTRASTRUCTURAL CHANGES IN THE LUNGS OF 1-2 MONTHS-OLD RATS IN THE CONDITIONS OF HYPERHOMOCYSTEINEMIA

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A detailed electron microscopic study on structural components in the lungs of 1-2 months-old rats under the conditions of hyperhomocysteinemia was performed. Experiments were performed on 64 white nonlinear male rats. Attention is drawn to the presence of large amount of fibrin and erythrocytes in the lumen of the alveoli surrounded by an electron-dense substrate, which is similar to the blood plasma consistency, which is obviously due to the surfactant film thinning in the alveoli and the increase in fluid transduction from the capillaries placed in the interalveolar septum. Specific features of the study were the presence of transudate in the alveolar space containing blood plasma proteins and fibrin fibers, sludge phenomenon, which prevented blood flow and edema of respiratory alveolocytes. In young animals, changes occur in the blood-air barrier. They are associated with endothelial dysfunction, which in turn is due to local endothelial cells desquamation, changes in the structure of the basement membranes, their loosening, as a result of their layered structure disturbance and obturation of the capillaries' lumen by the blood formed elements. Damage of the endothelial lining integrity leads to permeation of plasma, fibrin and formed elements into the lumen of the alveoli. The process is accompanied by edema of the respiratory epithelium, which is the result of increased vascular permeability and intravascular pressure.

Keywords: homocysteine, hyperhomocysteinemia, lungs, alveolocytes, mitochondria.

The work is a fragment of the research project "The role of exogenous and endogenous sulfur-containing compounds in the mechanisms of affection of internal organs and cytoprotection under various pathological conditions", state registration No. 0119U001142.

Homocysteine is a non-proteinogenic sulfur-containing amino acid formed as a result of the metabolism of an essential amino acid of methionine [11]. Normally, its amount in the human body is ranging from 5 to 15 μmol /L. An elevated homocysteine level in blood plasma above 15 μmol / L is called hyperhomocysteinemia syndrome and is dangerous to the human body [3, 12]. The relationship between disorders in the homocysteine metabolism and numerous pathological conditions remains inadequately studied in our time. Studies of recent years confirm that increased concentration of homocysteine in the blood is an independent risk factor for cardiovascular and cerebrovascular diseases [6, 10]. There is also a strong correlation between hyperhomocysteinemia and neurological disorders, chronic kidney disease, osteoporosis, disorders in the gastrointestinal tract, cancer, congenital defects [5].

However, the relationship between the high concentration of plasma homocysteine and the structure and functions of the respiratory system remains inadequately studied. Existing researches do not fully disclose morphological changes in the structure of the lungs at the optical and electron-microscopic levels.

The **purpose** of the study was to establish ultrastructural changes in the lungs of 1-2 months-old rats under the conditions of hyperhomocysteinemia and to compare the findings to the group of intact rats.

Materials and methods. Experiments were carried out on 22 white nonlinear male rats at the age of 1-2 months. During the experiment animals are divided into two groups – the control (11 animals) and the experimental (11 animals) group [4, 7]. The simulation of the stable hyperhomocysteinemia state was achieved by administering to the rats a research group of thiolactone homocysteine in the dose of 200 mg / kg of body weight intragastrically for 60 days [8]. Animals were sacrificed by decapitation under thiopental anesthesia. The extracted pieces of lungs sizing 0.5-1 mm were fixed in 2.5% glutaraldehyde solution with the pH7.2-7.4 phosphate buffer. It was embedded into a mixture of epon-araldit, according to the generally accepted method [2]. Thinwalled sections were made of the obtained blocks, and then stained with toluidine blue and Hayat. After focusing on the thinwalled sections, ultrathin sections were made using LKB III (Sweden) and Reihart (Austria) ultramicrotomes, which were contrasted with 2% solution of uranyl acetate and lead citrate. The sections were studied and photographed under the PEM-125K electron microscope with magnitudes of 6-20 thousand times.

Results of the study and their discussion. In the parenchyma of young animals' lungs, under the conditions of hyperhomocysteinemia, changes in both alveoli and blood capillaries were observed. In alveoli, almost all respiratory alveolocytes (pneumocytes I) are swollen. Against the background of blisters

with edema fluid, in other areas, there was a significant thinning of the cytoplasm (fig. 1 A, B; fig. 2 A) compared to the control group (fig. 2A). Significant thinning led to a decrease in the number of organelles at the metabolic level, in particular, mitochondria lost crysts and were swollen.

Our results are consistent with the data of D.V. Medvedev's et al. study on metabolic changes in the lungs mitochondria with experimental hyperhomocysteinemia in rats. In the conditions of severe hyperhomocysteinemia, homocysteine accumulates in mitochondria and has a direct toxic effect on them. This fact can be due to the presence of a special S-adenosylmethionine transporter on the mitochondria internal membrane, which carries the latter into the matrix of organelles [9].

There was a sharp thinning of epithelial lining, which led to the protrusion of respiratory epithelial cells, their rupture, and facilitated permeation of blood plasma with protein conglomerates of homocysteine into the lumen of the alveoli (fig. 1A, B, C, D). Between respiratory epitheliocytes secretory cells (pneumocytes II) are detected that produce surfactant. We have found that the number of plate cells contained in it (the membrane and the liquid phase, respectively: phospholipids, proteins and glycoproteins) was twice lower than that in the control group rats (experimental animals - 0.2 in 1 μm; control animals - 0.4 in 1 μm). The foregoing facts about the damage of the blood-air barrier in the conditions of hyperhomocysteinemia are described by us for the first time, there are no data about it in the scientific literature.

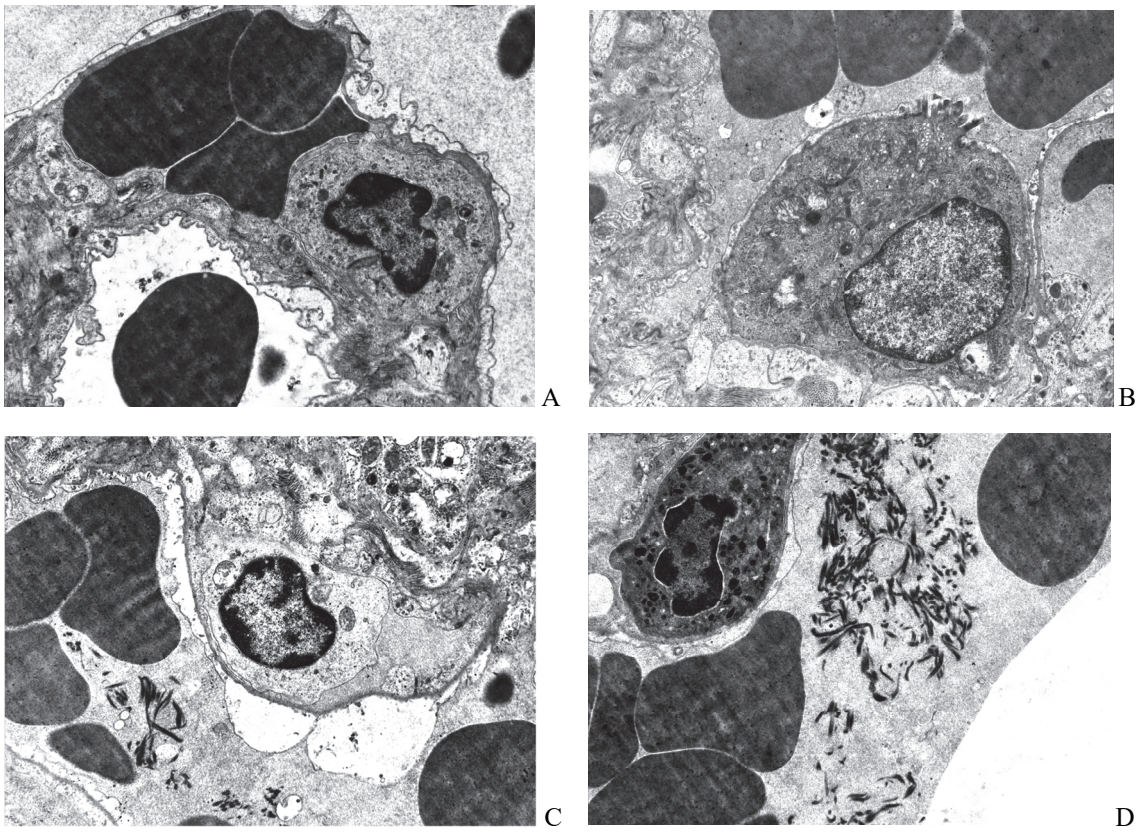

Fig. 1. Respiratory portion of lungs of young rats under conditions of hyperhomocysteinemia: swelling of the cytoplasm of respiratory alveolocytes, red blood cells in the lumen of the alveoli, lymphocytes and neutrophils in the lumen of capillaries; alveolar macrophage, fibrin and blood plasma in the lumen of the alveoli, mitochondria, nucleus. × A- 16000; B - 14000, C-12000; D – 12000 magnification.

In most cells, plate bodies are similar to vacuoles, in which electron-dense substrate is located, formed as a result of the plates disaggregation (fig. 2B). The mitochondria of the secretory cells were observed in small numbers with slight destruction of crysts (fig. 2B). In addition to the respiratory and secretory alveolocytes, there were “wandering” macrophages in the lumen of the alveoli and placed in the wall of the alveoli.The latter, like the secretory cells, had a little amount of small mitochondria with destructively altered crysts and electron-light matrix, microvilli, and protrusion of cytoplasm, which number is significantly increased in experimental animals. The content of these protrusions was electron-dense mass similar to the blood plasma and it was detected in the cytoplasm of the respiratory and secretory cells. (fig. 2A, B). Obviously, transudate from the lumen of capillaries permeates not only through intercellular contacts, but also through the cytoplasm of all cells lining the alveolus.

Attention is drawn to the presence of large amount of fibrin and erythrocytes in the lumen of the alveoli surrounded by electron-dense substrate, which is similar in its consistency to the blood

plasma, which is obviously due to the thinning of the surfactant layer in the alveoli and to the increase in the fluid transduction from the capillaries placed in the interalveolar septum (fig. 1A, B; 2A, B). In this case, in the lumen of capillaries blood plasma has a similar consistency and contains neutrophils, lymphocytes and erythrocytes. Cytoplasm of the endothelial cell is considerably thin, especially in the peripheral zone, which leads to thinning of the blood-air barrier, which can be considered as a manifestation of compensatory and adaptive processes (fig. 1, 2). Lumen of the capillaries, as a rule, is plugged with formed blood cells (erythrocytes, macrophages, lymphocytes, neutrophils). An increase in the content of formed elements and transudate in the alveoli led to the decline of the lumen in some capillaries.

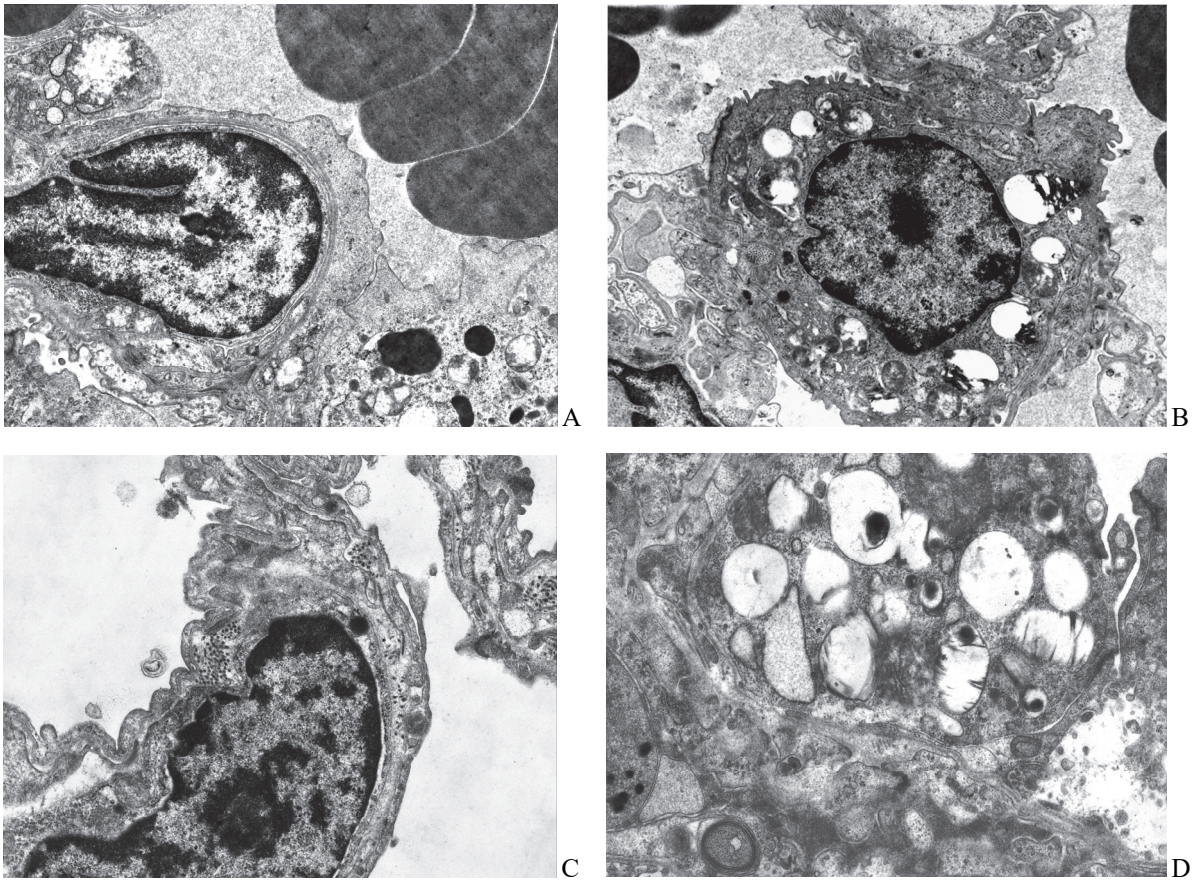

Fig. 2. The respiratory portion of the lungs of young rats under conditions of hyperhomocysteinemia: blood plasma in the lumen of the alveoli, red blood cells in the lumen of the alveoli, secretory alveolocyte, lumbar corpuscles, mitochondria, nucleus cytoplasm. B, G – Respiratory portion of lungs of young control rats. × A-16000; B - 14000; C - 12000; D -16000 magnification.

The foregoing results of our work coincide with the studies of L. P. Voroninet al: significant changes in the vascular epithelium in patients with bronchial asthma under the conditions of hyperhomocysteinemia are determined, while the severity of endothelial dysfunction strongly correlates with the level of homocysteine in the blood plasma [1].

Specific features for this term of the study were the presence of transudates in the alveolar space containing blood plasma proteins and fibrin fibers, slag phenomenon, which prevented blood flow and edema of respiratory alveolocytes.

Conclusion

In young animals, primarily, changes occur in the blood-air barrier. They are associated with endothelial dysfunction, which in turn is due to local desquamation of the endothelial cells, changes in the structure of the basement membranes, their loosening, as a result of their layered structure disturbance and obturation of the capillaries' lumen by the formed elements. Damage to the integrity of endothelial lining leads to permeation of plasma, fibrin and formed elements into the lumen of the alveoli. Secondly, the process is accompanied by edema of the respiratory epithelium, which is the result of the increased vascular permeability and intravascular pressure.

Prospects of further research *will encompass the study of the morphological changes in the structural components of the lungs in mature and old rats under the conditions of hyperhomocysteinemia.*

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Реферати

УЛЬТРАСТРУКТУРНІ ЗМІНИ В ЛЕГЕНЯХ ЩУРІВ ВІКОМ 1-2 МІСЯЦІ В УМОВАХ ГІПЕРГОМОЦИСТЕЇНЕМІЇ

Самборська І.А., Маєвський О.Є., Агафонов К.М., Ковальчук О.І.

Проведене детальне електронномікроскопічне дослідження структурних компонентів легень щурів віком 1-2 місяці в умовах гіпергомоцистеїнемії. Звертає на себе увагу, наявність у просвітах альвеол великої кількості фібрину та еритроцитів у оточенні електроннощільного субстрату, по консистенції аналогічного плазмі крові, що, очевидно, пов'язано зі зменшенням сурфактантної плівки у альвеолах та підвищенню транссудації рідини з капілярів, що містяться у міжальвеолярних перегородках. Специфічними ознаками для цього терміну є наявність у альвеолярному просторі транссудату, який містив білки плазми крові та фібринові волокна, сладж-феномен, що перешкоджає кровотоку та набряк респіраторних альвеолоцитів. У молодих тварин, перш за все, зміни відбуваються у аерогематичному бар'єрі. Вони пов'язані з ендотеліальною дисфункцією, яка в свою чергу обумовлена локальною десквамацією ендотеліоцитів, змінами у структурі базальних мембран, їх розпушуванням, у результаті порушення їх пошаровості та обтурації просвітів капілярів форменими елементами крові. Ушкодження цілісності ендотеліального вистелення призводить до просякнення плазми, фібрину і формених елементів крові у просвіт альвеол. По-друге, процес супроводжується набряком респіраторного епітелію, що є результатом підвищення проникності стінки судин та підвищенням внутрішньокапілярного тиску.

Ключові слова: гомоцистеїн, гіпергомоцистеїнемія, легені, альвеолоцити, мітохондрії.

Стаття надійшла 12.05.2019 р.

УЛЬТРАСТРУКТУРНЫЕ ИЗМЕНЕНИЯ В ЛЕГКИХ КРЫС В ВОЗРАСТЕ 1-2 МЕСЯЦА В УСЛОВИЯХ ГИПЕРГОМОЦИСТЕИНЕМИИ

Самборская І.А., Маєвский А.Е., Агафонов К.М., Ковальчук А.И.

Проведено детальное электронномикроскопическое исследования структурных компонентов легких крыс в возрасте 1-2 месяца в условиях гипергомоцистеинемии. Обращает на себя внимание, наличие в просветах альвеол большого количества фибрина и эритроцитов в окружении электронноплотного субстрата, по консистенции аналогичного плазме крови, что, очевидно, связано с уменьшением сурфактантной пленки в альвеолах и повышению транссудации жидкости из капилляров, расположенных в межальвеолярных перегородках. Специфическими признаками для этого срока – наличие в альвеолярном пространстве транссудата, содержащий белки плазмы крови и фибриновые волокна, сладж-феномен, который препятствует кровотоку и отек респираторных альвеолоцитов. У молодых животных, прежде всего, изменения происходят в аэрогематический барьере. Они связаны с эндотелиальной дисфункцией, которая в свою очередь обусловлена локальной десквамацией эндотелиоцитов, изменениями в структуре базальных мембран, их разрыхлением, в результате нарушения послойности их строения и обтурации просветов капилляров форменными элементами крови. Повреждения целостности эндотелиального слоя приводит к пропотеванию плазмы, фибрина и форменных элементов крови в просвет альвеол. Во-вторых, процесс сопровождается отеком респираторного эпителия, является результатом повышения проницаемости стенки сосудов и повышением внутрикапиллярного давления.

Ключевые слова: гомоцистеин, гипергомоцистеинемия, легкие, альвеолоциты, митохондрии.

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ANTIINFLAMMATORY ACTIVITY OF LEFLUNOMIDE FOR COMBINED APPLICATION WITH CELECOXIB AND AMLODIPINE IN ADJUVANT ARTHRITIS AGAINST THE BACKGROUND OF ARTERIAL HYPERTENSION

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The purpose of the work was to study the anti-edema activity of leflunomide in combination with celecoxib and amlodipine under the conditions of experimental rheumatoid arthritis associated with arterial hypertension. Experiments were carried out on sexually mature nonlinear white rats of both sexes with a starting weight of 201.56 ± 2.42; (n = 174). Experimental RA was induced by subcutaneous injection of the complete AF into the plantar part of the posterior (left) limb. The drugs under study were: leflunomide (LF), 20 mg tablets; celecoxib (CC), 100 mg capsules, and amlodipine (AM), 10 mg tablets. Under the conditions of experimental RA that developed against the background of AH, there was a significant increase in the foot volume by 136-147 % (from 1.16 RU to 2.74 RU) compared to the values in animals of the intact group. Combined application of CC with LF against the background of the combined pathology led to a significant, compared to data in animals with a combined pathology and in rats treated with LF only, reduction in foot volume by 14.4-45.2 % and by 18-41.4 % respectively at all terms of observation. Particularly significant this effect was in the acute development of AA against the background of hypertension. With combined use of leflunomide, celecoxib and amlodipine only in the acute period of inflammation that develops against the background of arterial hypertension, an anti-edema effect is recorded at the level of 12%, which is significantly reduced in other observation periods.

Key words: leflunomide, anti-edema, rheumatoid arthritis, arterial hypertension, comorbid pathology.

The work is a fragment of the research project "Efficacy of cardioprotective and gastrointestinal immunity of immunosuppressants and calcium antagonists of dihydropyridine series in combination with rheumatoid arthritis against the background of arterial hypertension", state registration No. 0117U006446.

Treatment of comorbid states, which prevalence reaches over 60% in young patients and grows with age, is one of the most urgent tasks of modern medicine. Pharmacological correction of rheumatic diseases associated with cardiac pathology, namely with rheumatoid arthritis (RA), combined with arterial hypertension (AG), involves the use of drugs belonging to various pharmacotherapeutic groups [2, 4, 6]. For treatment of RA itself, the disease-modifying agents (gold preparations, cytostatics, antibiotics, sulfonamides, medicinal immuno-biological preparations - immunosuppressors of synthetic and biological origin) and symptomatic medicinal products (non-steroidal anti-inflammatory drugs (NSAID) and glucocorticoids) are used [2, 14]. For the purpose of pharmacological correction of hypertension, antihypertensive drugs of various pharmacological groups, namely beta blockers, diuretics, angiotensin II receptor antagonists, ACE inhibitors, calcium channel blockers are used. It is known that one of the promising fields of RA therapy is the use of immunobiological drugs [5, 11, 14].

Cytostatic drugs, or so-called immunosuppressants (methotrexate, azathioprine, cyclophosphan, chlorobutin, leukeran, etc.) are used in patients with progressive severe RA [11, 13]. Methotrexate in rheumatoid arthritis has become the gold standard of treatment in many countries, because it quickly stops the effect of hyperactive immunity on the joint elements, inhibits the development of acute rheumatism, helps maintain the limbs function. At the same time, its insufficient efficacy in numerous patients, a number of side effects, in many cases intolerance, as well as complications due to interaction with drugs of other pharmacotherapeutic groups used concomitantly for the treatment of associated pathology, in particular cardiac, justified the expediency of searching new drugs. Thus, specifically for the RA treatment, leflunomide (LF) immunosuppressor was developed and implemented [1, 3, 4, 15].

As a rule, using immunosuppressors of synthetic origin is accompanied by the assignment of NSAID. The combination of analgesic, anti-inflammatory and antipyretic effects in NSAID provides them with one of the first places in the clinical application rate for pain syndromes of different genesis and justifies the feasibility of their assignment in RA. Significant progress in RA pharmacotherapy is due, in particular, to the introduction of selective cyclooxygenase inhibitors (COX-2) in the clinical practice. Special attention shoud be paid to preparations of the coxibs group. Celecoxib (CC) is the most commonly used for treatment of the pain syndrome (including RA) and is quite safe in compliance with the dosage and regimen. Its efficacy has a high degree of evidence obtained in clinical trials. At the same time, data on the pharmacodynamic interaction of synthetic origin immunosuppressors and coxibs against the background of RA, as well as in combined pathology - RA and AH - is not sufficient.

In the world, the most extensive combined use of NSAID with antihypertensive drugs is observed. This is due to various reasons: NSAID is characterized by pro-hypertensive effect [2] and more than half of patients with RA who use NSAID are registered with AH; arterial pressure destabilization is often recorded against the background of RA; actually pain syndrome on the background of RA can lead to hypertension; RA often occurs against the background of AH [11, 12].

Amlodipine (AM) has the widest use in cardiology as a hypotensive drug. It leads to a smooth decrease in blood pressure without changing the heart rate, it is metabolically neutral and reduces endothelial dysfunction due its effect on the NO system [3, 7].

Studies devoted to determination of the efficacy and safety of immunosuppressors used in combination with calcium antagonists of the dihydropyridine series and selective cyclooxygenase 2 inhibitors at different phases of the inflammatory process development under the conditions of combined pathology (RA with AH) were not carried out.

The purpose of the work was to study the anti-edema activity of leflunomide in combination with celecoxib and amlodipine against the background of experimental rheumatoid arthritis associated with arterial hypertension.

Materials and methods. The experiments were carried out on sexually mature non-linear white rats of both sexes with the starting weight of 201.56 ± 2.42 g (n = 174), which were kept on a standard balanced diet in vivarium under the conditions of free access to food and water at the temperature 20-22º C and the relative humidity of 40-60 %. The studies were carried out in compliance with the requirements of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1986).

Animals were divided into 8 groups: group 1 (n = 10) - intact animals kept in the laboratory in cages during the same period as animals of other groups. The rest of the animals (n = 164) were modeled AH, or experimental RA - adjuvant arthritis (AA), or comorbid pathology - AG + AA. Thus, group 2 (n = 15) were rats, which reproduced the RA model by a single administration of the Freund's complete adjuvant (AF, control for AA), and animals of this group were not subject to saline loading at all.

In animals (n = 134) AH was induced by salt loading in the conditions of drinking water replacement with 1% solution of sodium chloride with free access to it during 21 days [30, 33, 36, 43]. After 21 days the registration of the blood pressure was performed by means of the sphygmomanometric method using Ugo Basile sphygmomanometer (Italy), blood pressure was determined in animals subjected to saline loading (n = 134). For the next study, only those rats (n = 90) who demonstrated hypertension (elevated blood pressure above 10-12% of the baseline value) were selected.

Following randomization of rats with AH, appropriate groups of animals were formed, each including 8 female and 7 male rats. Group 3 included 15 rats with AH, which were continued salt loading and were not apply any treatment to (control for AH). Group 4 consisted of 15 specimens who, against the background of AH (21 days after the beginning of AH model formation), were given a single dose of complete AF, thus forming a comorbid state - AH + AA under prolonged salt loading (control of the comorbid pathology). Therapeutic measures for animals of group 4 were not taken.

The fifth, sixth, seventh and eighth groups included animals (15 rats in each group), which, against the background of the comorbid state development and salt loading prolongation, were administered LF, LF and AM (LF + AM), LF and CC (LF + CC) and LF, CC and AM (LF + CC + AM) respectively. The ninth group included 15 rats, which were injected LF against the background of AA (animals without AH).

Experimental RA was induced by subcutaneous administration of complete AF into the plantar part of the posterior limb (left), which is one of the most adequate agents capable of reproducing the above mentioned pathological condition, reflecting the immune mechanisms of RA pathogenesis [6, 15]. The mechanism of development of AA induced by administration of complete AF, clinical symptoms, and effects of drugs are most similar to those observed in humans in RA [11, 15].

The studied drugs were: leflunomide (LF), 20 mg tablets; celecoxib (CC), 100 mg capsules and amlodipine (AM), 10 mg tablets.

CC and AM medicinal products were used daily in therapeutic doses, in terms of animals: for CC - 15 mg / kg, for AM - 1.5 mg / kg of the animal body weight. The use of LF was as follows: the first three days - at the dose of 15 mg / kg (shock dose), and then - daily at the dose of 1.5 mg / kg (therapeutic dose). All drugs were injected through a special metal probe into the stomach in 1% starch mucilage 1 time per day (from 10 to 13 o'clock).

Treatment of animals began 7 days after the introduction of AF (acute period of AA). Under the conditions of combination therapy using drugs of various pharmacotherapeutic groups (LF with AM, or LF with CC, or LF with CC and AM), drugs were also administered daily, once a day, but one by one, at

the intervals of 30 min. The LF use duration is due to the fact that the first clinical effect of this drug should be expected in 2-4 weeks, and the pronounced effect - in 6-8 weeks.

Registration of the foot volume was performed with Ugo Basile plethysmometer (Italy) in intact rats (animals of all groups, basal data), 21 days after the beginning of salt loading (in rats with pre-formed AH), and also after 1, 2, 4, 6 , 8, 9 weeks after AF administration and the use of drugs.

Anti-exudative (anti-edema) activity (AEA) of LF, CC, AM for independent and combined use was calculated as the ratio of the difference between foot volume in untreated and treated animals with comorbid pathology to the foot volume in untreated rats and was expressed as a percentage.

Data Processing. Normality of distribution was assessed by the Shapiro-Wilk (W) criterion. The data is presented as a mean arithmetic and standard error of the mean value representativeness. The reliability between the mean values in two samples was determined by the Student's t-test in normal distribution. Statistically significant differences were considered at a significance level of at least 0.05.

Results of the study and their discussion. In the process of AH formation by salt loading (during 21 days), the volume of foot in rats was gradually growing by 11-14.9 % (table 1) compared to the initial data. In the intact animals, the similar degree changes of the studied index were registered. In fact, the same increase in the foot volume of intact animals and in rats in the AH formation can testify to the rats growth. Under the conditions of AA development, a significant increase in the volume of the injured (left) foot of rats was registered, starting from the 1st day after the AF administration. 7 days after the inflammatory process induction, the foot volume in rats increased by 91% as to this index, which was inherent in intact animals (table 1), and was twice as large during the entire observation period (table 2).

Table 1

Volume of foot (RU, M ± m) in white rats in arterial hypertension formation (within 21 days) and in experimental rheumatoid arthritis development

Group, number of animals (n)	Term of observation, day			
	initial data	7	14	21
Intact	1.03±0.04	1.12±0.09	1.13±0.10	1.15±0.04
AH	1.01±0.03	1.12±0.06	1.14±0.05*	1.16±0.05*
AA	1.03±0.07	2.14±0.12*	2.25±0.15*	2.30±0.15*

Note. * - p <0.05 compared to the given index in intact animals for the corresponding period of observation.

In the animals of group 3 (AH control) during the following 60 days, under the conditions of the saline load continued, the foot volume was gradually growing and exceeded the values recorded in the intact group animals by 14% after 80 days from the beginning of the salt loading and by 25.9 % of the value registered on the 21st day of AH (table 2). Consequently, hypertension leads to edema of limbs in rats, which increases with the duration of saline loading.

Under the conditions of experimental RA that developed against the AH background, there was a significant increase in foot volume by 136-147 % (from 1.16 RU to 2.74 RU) compared to values in the intact group animals, and these changes were observed in all periods of the actual inflammatory process development, even in the period of its extinction, which indicates an increase of the limbs edema in the comorbid state (table 2). It is likely that AH contributed to a more significant increase of the limb edema just in the acute period (up to 14 days) since AA induction, indicating an increase of this index by 20.7% compared to that registered in animals with AA only within the same period.

The CC drug did not completely eliminate the limbs edema in rats, but significantly reduced it - by 16-21 % (from 2.74 to 0.93 RU) compared to the data recorded in the control animals with the combined pathology and those with AA only. The anti-inflammatory effect of CC was characterized by stability throughout the observation period.

In general, the results of our study are consistent with the data of other researchers.

LF immunosuppressor against the background of a comorbid state showed significant anti-edema activity compared to this index in animals with AA and lost it in the combined pathology, as evidenced by the foot volume increase within the period from 28 to 60 days. [1, 4, 13].

Combined application of the CC with LF against the background of a combined pathology led to a significant, compared to data in animals with a combined pathology and in rats treated with LF only, reduction in the foot volume by 14.4-45.2 % and by 18-41.4 % respectively at all terms of observation. This effect was particularly significant in the acute development of AA against the background of AH. Thus, in the conditions of pharmacodynamic interaction of NSAID and immunosuppressors against the background of AH associated with AA, a growth of the anti-edema activity is recorded. Obviously, LF potentiates the anti-edema activity of CC. Probably, in the combined of LF and CC the anti-edema activity of LF is “recovered”, which did not manifest itself against the background of a comorbid state. [2, 3]. Under the conditions of comorbidity, AM

did not exhibit anti-edema activity, but, on the contrary, substantially increased the edema of the limbs in rats compared to unlabeled animals with a comorbid state and with AA (table 2). An unexpected result was obtained by the interaction of LF with AM in the context of associated pathology. In spite of the fact that LF lost its anti-edema activity and, like AM, increased the limb edema in animals due to associated pathology, the combined use of these agents resulted in an anti-edema effect characterized by a decrease in foot volume by 9-18 % compared to values in animals treated with LF only [5]. Combined use of the three studied drugs did not normalize the foot volume in animals with associated pathology - AH with AA, although it reduced the foot volume by 9-14 % compared to the rate recorded in animals treated with LF only. Strengthening the anti-edema effect due to the use of three drugs was not observed. On the contrary, it was significantly lower than that recorded in animals treated with CC only in the period from the 28th to the 60th day. Probably, the use of LF and AM decreased the anti-edema effect of CC, and CC contributed to the manifestation of anti-edema effect of LF and AM. Mechanisms of LF interaction with CC and LF with AM on the background of AA associated with AH are currently unknown and require special further studies [2, 7].

Table 2

Foot volume in rats (RU, M ± m) under the conditions of mono- and combination therapy with Leflunomide, Celecoxib and Amlodipine and anti-edema activity (%) of drugs against te background of rheumatoid arthritis associated with arterial hypertension

Group, index	Term of observation, days&				
	Data on the 21st day ‴	14 (21+14)	28 (21+28)	42 (21+42)	60 (21+60)
1	2	3	4	5	6
Intact	1.15±0.04	1.16±0.07	1.18±0.05*	1.20±0.03*	1.28±0.10*
AH, % (до інт.)	1.16±0.10	1.19±0.04* +2.6	1.23±0.05* +3.5	1.32±0.08* +14	1.46±0.1* +26
AA, % (до інт.)	2.30±0.15*	2.27±0.07* +98.3	2.50±0.09* +111.9	2.44±0.14* +103.3	2.40±0.11* +87.5
AH+AA, % (to int.) % (to AA)	1.16±0.10	2.74±0.11* +136 +20.7	2.52±0.15* +147 +0.8	2.44±0.2* +141.6 0	2.43±0.09*♯ +140.6 +1.25
AH+AA+CC AEA	1.16±0.10	2.30±0.1*ƛ 16	2.10±0.1*♯ƛ 17	1.93±0.04*♯ƛ 21	2.0±0.07*♯ƛ 17
AA+LF AEA (to AA)	1.16±0.10	2.11±0.10* 7.0	2.08±0.12*♯ 16.8	1.99±0.11*♯ 18.4	2.08±0.09*♯ 13.3
AH+AA+LF AEA	1.16±0.10	2.56±0.09* 6.6	2.63±0.11* +4.4	2.84±0.12* +16.4	2.54±0.10* +4.5
AH+AA+LF +CC AEA	1.16± 0.10	1.5± 0.02*♯ƛQ 45.2	1.99± 0.07*ƛQ 21	1.93± 0.07*ƛQ 20.9	2.08± 0.05*ƛQ 14.4
AH+AA+AM AEA	1.16±0.10	3.51±0.1*♯ƛ +28.1	2.9±0.2* +15.1	2.9±0.12* +18.9	5.1±0.3*♯ƛ +109.9
AH+AA+LF+ +AM AEA	1.16± 0.10	2.33± 0.02*ƛQ 15	2.38± 0.07* 5.6	2.44± 0.08*Q 0	2.08± 0.05*♯ƛQ 14.4
AH+AA+LF+ +CC+AM AEA	1.16± 0.10	2.41± 0.15*∂ 12.0	2.37± 0.12*ά 6.0	2.44± 0.08*άQ 0	2.3± 0.15*∂ά 5.4

Notes: 1) - values registered at 21 days from the beginning of the salt loading (i.e., animals with pre-formed AH) and registered at the same time in animals with AA only; 2) & - in brackets - the general term of observing animals (from the beginning of the AH formation) is indicated; outside brackets - numbers indicate the time period after the AF administration; 3) * - p≤0.05 compared to the initial index value; 4) ♯ - p≤0.05 compared to the values in animals with AA only within the corresponding observation period; 5) º - p≤0.05 compared to the values in animals with a combined pathology; 6) Q - p≤0.05 compared to the values under the conditions of using LF only against the background of a combined pathology; 7) ∂ - p≤0.05 compared to the values in animals with a combined pathology, treated with AM; 8. ά - p≤0.05 compared to the values in animals with a combined pathology treated by CC only.

The obtained results may be an experimental justification for initiating a clinical study on the feasibility of the combined use of drugs belonging to various pharmacotherapeutic groups in order to optimize the pharmacotherapy of RA associated with AH [7].

Conclusions

1. Under the conditions of experimental rheumatoid arthritis, leflunomide exhibits anti-edema activity at the level of 13-18 %, which is lost in the conditions of arterial hypertension associated with the rheumatoid process.

2. Celecoxib exhibits pronounced anti-edema activity within 16-21 % in different periods of the comorbid state, which is significantly enhanced in combination with leflunomide, especially in acute inflammation against the background of associated pathology.

3. Pharmacodynamic interaction of leflunomide with amlodipine manifests an anti-edema activity of the immunosuppressor, while the independent application of amlodipine results in the edema growth under the conditions of arterial hypertension associated with adjuvant arthritis.

4. Combined administration of leflunomide, celecoxib and amlodipine only in the acute period of inflammation developing on the background of arterial hypertension, an anti-edema effect is recorded at the level of 12%, which is significantly reduced in other observation periods.

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Реферати

ПРОТИЗАПАЛЬНА АКТИВНІСТЬ ЛЕФЛУНОМІДУ ЗА КОМБІНОВАНОГО ЗАСТОСУВАННЯ З ЦЕЛЕКОКСИБОМ І АМЛОДИПІНОМ НА ФОНІ АД'ЮВАНТНОГО АРТРИТУ, ПОЄДНАНОГО З АРТЕРІАЛЬНОЮ ГІПЕРТЕНЗІЄЮ

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Метою роботи було дослідити протинабрякову активність лефлуноміду за комбінованого застосування з целекоксибом та амлодипіном на тлі експериментального ревматоїдного артриту, асоційованого з артеріальною гіпертензією. Досліди проведено на статевозрілих нелінійних білих щурах обох статей з вихідною масою (201,56±2,42; n=174) г. Експериментальний РА викликали за підшкірного уведення в підошовну частину задньої кінцівки (лівої) повного АФ. Досліджувані лікарські засоби: лефлуномід (ЛФ), таблетки по 20 мг; целекоксиб (ЦК), капсули по 100 мг та амлодипін (АМ), таблетки по 10 мг. За умов експериментального РА, що розвивався на тлі АГ, спостерігалося суттєве зростання об'єму стопи на (136-147) % (з 1,16 у.о. до 2,74 у.о.) порівняно до значень у тварин інтактної групи. Комбіноване застосування ЦК з ЛФ на тлі поєднаної патології призводило до суттєвого, відносно даних у тварин з поєднаною патологією та у щурів, лікованих лише ЛФ, зниження об'єму стопи на (14,4-45,2) % і на (18-41,4) % відповідно у всі терміни спостереження. Особливо значущим цей ефект був у

ПРОТИВОВОСПАЛИТЕЛЬНАЯ АКТИВНОСТЬ ЛЕФЛУНОМИДА ПРИ КОМБИНИРОВАННОМ ПРИМЕНЕНИИ С ЦЕЛЕКОКСИБОМ И АМЛОДИПИНОМ НА ФОНЕ АДЪЮВАНТНОГО АРТРИТА, В СОЧЕТАНИИ С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ

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Целью работы было исследование противоотечного действия лефлуномида за комбинированного применения с целекоксибом и амлодипином на фоне экспериментального ревматоидного артрита, ассоциированного с артериальной гипертензией. Опыты проведены на половозрелых нелинейных белых крысах обоего пола с исходной массой (201,56 ± 2,42; n = 174) г. Экспериментальный РА вызвали по подкожного введения в подошвенную часть задней конечности (левой) полного АФ. Лекарственные средства: лефлуномид (ЛФ), таблетки по 20 мг целекоксиб (ГК), капсулы по 100 мг и амлодипин (АМ), таблетки по 10 мг. В условиях экспериментального РА, развивался на фоне АГ, наблюдалось значительное увеличение объема стопы на (136-147)% (с 1,16 у.е. до 2,74 у.е.) по сравнению со значениями у животных интактной группы. Комбинированное применение ЦК по ЛФК на фоне сочетанной патологии приводило к существенному, относительно данных у животных с сочетанной патологией и у крыс, леченных только ЛФК, снижение объема стопы на (14,4-45,2)% и на (18-41 4)% соответственно во все сроки наблюдения. Особенно

гострий період розвитку АА на тлі АГ. За комбінованого застосування лефлуноміду, целекоксибу та амлодипіну лише у гострий період запалення, що розвивається на тлі артеріальної гіпертензії, реєструється протинабряковий ефект на рівні 12 %, що суттєво знижується в інші періоди спостереження.

Ключові слова: лефлуномід, протинабрякова дія, ревматоїдний артрит, артеріальна гіпертензія, коморбідна патологія.

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значимым этот эффект был в острый период развития АА на фоне АГ. При комбинированном применении лефлуномида, целекоксиба и амлодипина только в острый период воспаления, развивается на фоне артериальной гипертензии, регистрируется противоотечный эффект на уровне 12%, что существенно снижается в другие периоды наблюдения.

Ключевые слова: лефлуномид, противоотечное действие, ревматоидный артрит, артериальная гипертензия, коморбидной патологии.

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CORRECTION OF BREAST ASYMMETRY: STRUCTURAL CHANGES OF ADIPOSE TISSUE IN AUTOLOGOUS FAT GRAFTING

The purpose of the work was to determine the structural features of adipose tissue during auto transplantation of a fat transplant. It was found that changes in aspirated adipose tissue indicate partial trauma and violation of the integrity of individual adipocytes in preparation for transplantation. However, an analysis of the structural organization of adapted adipose tissue found that the decrease in adipocyte volume was 19,4 % - 23,1%. Thickening of the layers of connective tissue in adapted adipose tissue is due to compensatory-reparative processes and the maturation of the fibrous component and the amorphous substance of the connective tissue during transplant engraftment. These phenomena are accompanied by an increase in the number of migrant cells in perivascular tissue. On the part of the blood vessels of the hemomicrocirculatory bed, changes were found to have a stereotypic nature on the action of exogenous factors.

Key words: adipose tissue, fat transplant, breast volum asymmetry.

Autologous fat grafting (AFG) technique, used for augmentation of the breast or correction of breast asymmetry is becoming more popular for several reasons. First, fat is autologous and, in most cases, abundant. Second, it is malleable material with the ability to naturally integrate into tissue at the site of injection and is widely used in correction of breast asymmetry. Another advantage of AFG is the possibility of removing excess fat from the areas of the inner surface of the knees, the inner surface of the thigh, the anterior abdominal wall, thus, reducing fat in these areas. Owing to these positive properties autologous fat grafting is increasingly being used as an alternative to commercial fillers, if necessary, for soft tissue expansion and correction of aesthetic defects [4]. According to the report of International Society of Aesthetic Plastic Surgery (ISAPS), in 2009, the frequency of use of autologous fat grafting technique accounted for 5.9% in the structure of aesthetic procedures [6]. The effectiveness of the autologous fat transplantation has improved significantly after the development and standardization of lipoaspiration techniques. The refined techniques have led to reduction of injury to adipose tissue during liposuction and preservation of the graft survival [7]. The basic standards for increasing the autologous fat graft survival are the safe lopoaspiration and non-traumatic processing of the fat graft. Lipofilling should be made by tunnel method, without the formation of bulk cavities [9]. I.V. Kraiinik reports that the use of autoplasma proteins with centrifugation, and the formation of a single protein-fat conglomerate and injection of the material through cannulas with a diameter of 2 mm provides high survival rate, and the rate of graft resorption is not more than 15% [2]. According to the publications, autologous graft retention varies from 40 to 90% [5]. Such variability of results suggests that there is no objective method for evaluation the viability of a fat autograft. Moreover, estimation of lipofilling results is subjective, often made “by eye” or by photos before and after surgery, which is not objective. There is no method that determines how much volume is added to donor sites. That is, the volume in the donor site was augmented due to the quantitative increase in adipocytes due to transplantation or due to the qualitative increase in the volume of old adipocytes through weight, gained by a patient. Therefore, determination of the major changes that occur in lipoaspirate and integrated fat, compared to the intact one, is crucial in the state-of-the-art reconstructive surgery.

The purpose of the study was aimed at determination of the structural features of the adipose tissue during autologous fat grafting.

Methods and Material. Flaps of the adipose tissue were used in the primary correction of breast asymmetry (intact group), lipoaspirate (fat from the anterior abdominal wall) and fragments of oleomas were taken during re-correction. Flaps of adipose tissue and lipoaspirate were placed in 10% buffered

formalin for 24 hours. The material was embedded into paraffin, using conventional technique and sections of 5 μm were made, which were stained with hematoxylin and eosin [1].

Migroimaging and morphometric study was performed using the Biorex-3 BM-500T microscope with digital DCM 900 microphotohead with software, adapted to these studies. The average number of adipocytes in the field of view, area, perimeter and radius of the cells, measured in μm, was determined. Statistical processing of the morphometric data and quantitative analysis were performed by conventional statistical methods using the Exel program [3].

Results and Discussion. Histological study of the specimens of the intact adipose tissue, stained with hematoxylin-eosin, revealed the particles formed by adipocytes, surrounded by the layers of connective tissue, where vessels of the microvasculature and nerve fibers were visualized. The layers of loose connective tissue inside the particles were thin and formed by basophilic collagen fibers. Between the adjacent 3-4 adipocytes, capillary-type vessels, free from red blood cells in the lumens were detected; consequently, trophic processes in the tissue were provided by the flow of blood plasma in the capillaries. Arteries and veins, containing blood corpuscles were determined in the interparticle layers (Fig. 1).

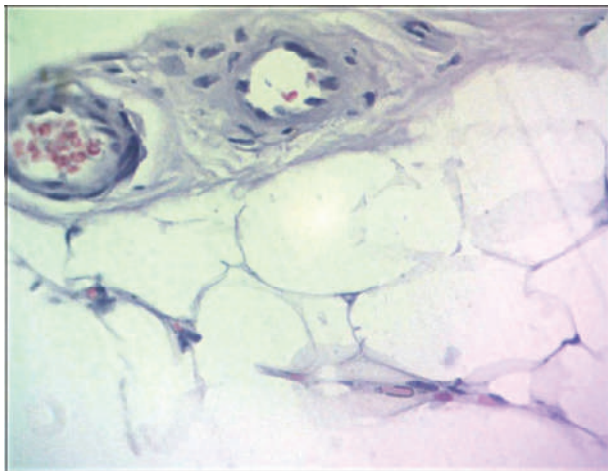

Fig. 1. Adipocytes and vessels of the microvasculature in the particles of the intact adipose tissue. Microimage. H&E stain. 400×magnification.

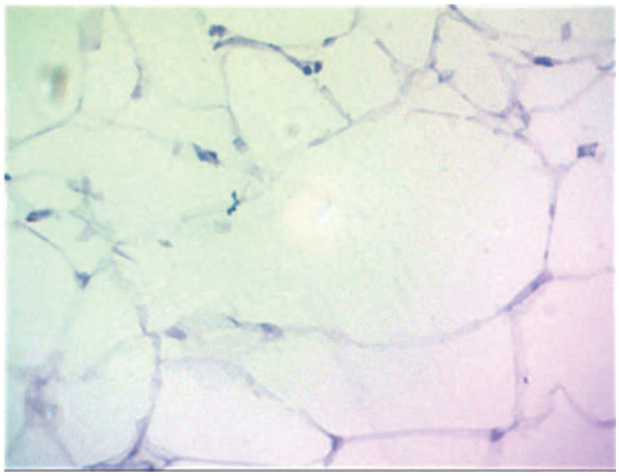

Fig. 2. Adipocytes in the lipoaspirate. Microimage. H&E stain. 400×magnification.

The analysis of the structural features of the lipoaspirate has shown disintegration of the plasmalemma in the majority of adipocytes. This phenomenon is caused by injury and partial destruction of individual adipocytes during lipoaspiration.

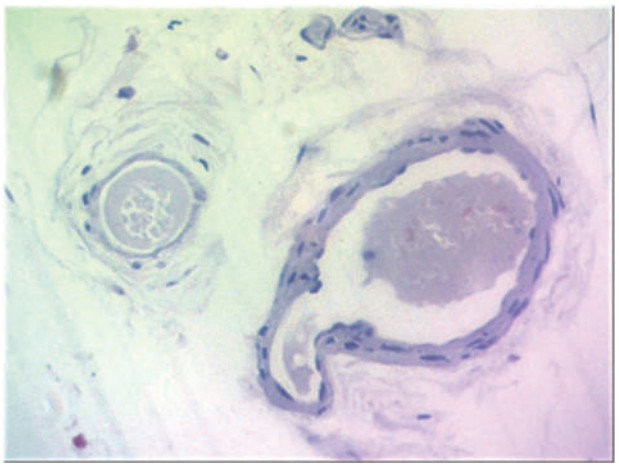

Fig. 3. Vessels of the microvasculature and leukocyte-type cells in the integrated adipose tissue. Microimage. H&E stain. 400×magnification.

Histological study of the integrated fat has established that the layers of connective tissue between the particles were thickened, similarly to the loose connective tissue between the individual adipocytes. Perivascularly, young oxyphilic collagen fibers and the leukocyte-type cells, namely, macrophages, lymphocytes, and plasmocytes were detected in the interparticle septa (Fig. 3).

Adipocytes were predominant in the particles of intact adipose tissue and their average number accounted for 28.4 ± 0.19 FOV. The analysis of the features of the lipoaspirate has shown that the average number of cells was 22.8 + 0.03 FOV that was significantly lower than the value in the intact group. The findings of the morphometric study of specimens of integrated adipose tissue has established that the number of cells in the field of view was significantly less by 10.74% compared to intact adipose tissue (25.35 + 0.15).

The analysis of the qualitative indices of adipocytes in the samples has found that the largest and smallest average area was occupied by the cells of the lipoaspirate and adipocytes of integrated adipose tissue, respectively. The values were significantly smaller at $p<0.05$ (see the Table). In determining the mean perimeter of the cells it was found that adipocytes of intact adipose tissue and integrated adipose tissue had significantly lower values compared to the lipoaspirate, but did not differ significantly. We obtained similar results for the values of cell radius (Table).

The comparison of the metric data of the intact adipose tissue and integrated adipose tissue has found that the values of the latter were by 10.48% lower compared to intact adipose tissue values.

Table

Metric data of adipocytes (μm)

	Lipoaspirate	Intact adipose tissue	Integrated adipose tissue
Area	17459,08±2562,37	11536,19±236,12 *	10071,09±150,98 *, **
Perimeter	139,56±9,27	113,38±6,74 *	98,98±10,43 *
Radius	22,21±1,48	18,29±1,42 *	16,33±1,25 *

Note * - the difference is reliable at p<0,05, compared to the lipoaspirate, ** - the difference is reliable at p<0,05, between the values on the intact and integrated adipose tissues.

Thus, the established changes in the lipoaspirate indicate its partial injury and disintegration of the individual adipocytes during preparation for transplantation. However, the analysis of the structural organization of the integrated adipose tissue has found that the resorption was less than 15% that was consistent with the data of other researchers [2].

The thickening of the layers of connective tissue in the integrated adipose tissue is caused by compensatory-reparative processes and maturation of the amorphous substance and the fibrous component of the connective tissue during autologous graft retention. These phenomena are accompanied by an increase in the number of migrant cells in perivascular tissue. Regarding the vessels of the microvasculature, the established changes have stereotyped character due to the effect of exogenous factors [8].

Conclusion

It was found that in auto-transplantation of adipose tissue for the purpose of breast asymmetry correction adipocyte volume loss does not exceed 19.4% - 23.1% and depends on the peculiarities of the microcirculatory bed of the donor region of each individual patient. This phenomenon is due to the processes of restructuring of the adipose tissue and vessels of the hemomicrocirculatory bed and is a manifestation of compensatory-restorative processes and processes of aseptic inflammation. The adaptive ability of the fat graft in invasive methods of fat preparation (centrifugation) is somewhat diminished, because the centrifugal force during rotation partially emulsifies the fat aspirate, which, when introduced, is replaced by unformed connective tissue. Methods of non-invasive fat preparation (applique - upholding) increase the ability to adapt fat, because tissue fragments with their microcirculatory bed in the aspirate - are not injured.

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Реферати

СТРУКТУРНІ ОСОБЛИВОСТІ ЗМІН ЖИРОВОЇ ТКАНИНИ ПРИ АУТО ПЕРЕСАДЦІ ЖИРОВОГО ТРАНСПЛАНТАТА З МЕТОЮ КОРЕКЦІЇ ОБ'ЄМНОЇ АСИМЕТРІЇ МОЛОЧНИХ ЗАЛОЗ

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Метою роботи було визначити структурні особливості зміни жирової тканини при аутопересадці жирового трансплантата. Встановлено, що зміни в аспіруваній жировій тканині свідчать про її часткову

СТРУКТУРНЫЕ ОСОБЕННОСТИ ИЗМЕНЕНИЙ ЖИРОВОЙ ТКАНИ ПРИ АУТО ПЕРЕСАДКЕ ЖИРОВОГО ТРАНСПЛАНТАТА С ЦЕЛЬЮ КОРРЕКЦИИ ОБЪЕМНЫХ АСИММЕТРИИ МОЛОЧНЫХ ЖЕЛЕЗ

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Целью работы было определить структурные особенности изменения жировой ткани при аутопересадке жирового трансплантата. Установлено, что изменения в аспирированной жировой ткани свидетельствуют о ее

травматизацію і порушення цілісності окремих адипоцитів при підготовці до трансплантації. Однак, аналіз структурної організації адаптованої жирової тканини встановив, що зменшення об'єму адипоцитів при цьому склало 19,4 % - 23,1%. Потовщення прошарків сполучної тканини в адаптованій жировій тканині обумовлено компенсаторно-репаративними процесами і дозріванням волокнистого компоненту і аморфної речовини сполучної тканини при приживлені трансплантата, асептичним запаленням . Означені явища супроводжуються збільшенням кількості клітин-мігрантів в периваскулярній тканині. З боку судин гемомікроциркуляторного русла встановлені зміни мають стереотипний характер на дію екзогенних чинників.

Ключові слова: жирова тканина, ауто пересадка, асиметрія молочних залоз.

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частичной травматизации и нарушении целостности отдельных адипоцитов при подготовке к трансплантации. Однако, анализ структурной организации адаптированной жировой ткани установил, что уменьшение объема адипоцитов при этом составило 19,4 % - 23,1%. Утолщение слоев соединительной ткани в адаптированной жировой ткани обусловлено компенсаторно-репаративными процессами и созреванием волокнистого компонента и аморфного вещества соединительной ткани при приживлении трансплантата. Указанные явления сопровождаются увеличением количества клеток-мигрантов в периваскулярной ткани. Со стороны сосудов гемомикроциркуляторного русла установлены изменения имели стереотипный характер на действие экзогенных факторов.

Ключевые слова: жировая ткань, аутопересадка, асимметрия молочных желез.

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MORPHOFUNCTIONAL FEATURES OF RAT TESTES INTERSTITIAL ENDOCRINOCYTES AND SUSTENTOCYTES AFTER 90 DAYS OF CENTRAL TESTOSTERONE SYNTHESIS DEPRIVATION

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With the social system development, there is a tendency to change attitudes towards family and family values. In developed European countries, there is a trend towards high sexual activity in elderly men and late creation of a family with children, which undergoes certain difficulties in connection with a decreased testosterone production in later years. The purpose of the study was to establish the microscopic organization of rat interstitial endocrinocytes and sustentocytes, to determine the sources of nitric oxide production and the intensity of oxidative stress in the testes with experimental central deprivation of testosterone synthesis with diphereline on the 90th day of the experiment. The experiments were carried out on 20 sexually mature male white rats of the Wistar line. Rats were divided into 2 groups: the control group (10) and the experimental group (10), which were injected subcutaneously with diphereline (Triptorelin embonate) at a dose of 0.3 mg / kg of the active substance for 90 days. Prolonged central deprivation of testosterone synthesis in animals leads to emergence of functional stress structural signs in population of sustentocytes and interstitial endocrinocytes, which are aimed to support testicular secretion. Central deprivation of testosterone synthesis within 90 days causes oxidative stress development owing to reactive oxygen species hyperproduction and nitrite accumulation in testicular tissue due to increased inducible NO-synthase activity.

Key words: testes, interstitial endocrinocytes, sustentocytes, NO-synthase, iNOS, cNOS, L-arginine, superoxide dismutase, rats.

The study is a fragment of the research project "Experimental morphological study of cryopreserved placenta transplants action diphereline, ethanol and 1% methacrylic acid on the morphofunctional status in a number of internal organs", state registration No. 0119U102925.

With the development of the social system, there is a tendency to change attitudes towards family and family values. In developed European countries, there is a trend towards high sexual activity in elderly men and late creation of a family with children, which causes certain difficulties in connection with a decreased testosterone production in older age [2]. Testosterone deficiency leads to infertility and redox imbalance, which further downgrades sperm quality and even causes inflammation in different organs [3, 4]. Besides inflammation and redox imbalance testosterone deficiency may lead to apoptosis in testicular tissues [5].

At the same time, the use of testosterone drugs in uncontrolled quantitative doses may worsen spermatogenesis by suppressing the components of the hypothalamic-pituitary system according to the feedback principle [11].

In our previous article, we showed that 30-days central deprivation of testosterone synthesis had led to the development of compensatory reactions in sustentocytes and interstitial endocrinocytes, which had been accompanied by morphological signs of functional overstrain. Development of oxidative stress and a change in the source of nitric oxide production from constitutive forms of NO synthase (cNOS) to an inducible form (iNOS) were also reported [12].

The effect of a longer central testosterone synthesis deprivation on the testes structure and functional status is not studied sufficiently at the moment.

The **purpose** of the study was to establish the microscopic organization of rat interstitial endocrinocytes and sustentocytes, to determine the sources of nitric oxide production and the intensity of oxidative stress in the testes in experimental central deprivation of testosterone synthesis with diphereline on the 90th day of the experiment.

Materials and methods. The experiments were carried out on 20 sexually mature male white rats of the Wistar line. Rats were divided into 2 groups: the control group (10) and the experimental group (10), which were injected subcutaneously with diphereline (Triptorelin embonate) at a dose of 0.3 mg of the active substance / kg of body weight for 90 days [9]. Animals were kept in standard vivarium conditions of the Ukrainian Medical Stomatological Academy. Experimental animals were sacrificed in strict compliance with the provisions of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1986), as well as with the “General Ethical Principles of Animal Experiments” adopted by the First National Congress on Bioethics (Kyiv, 2001).

After an overdose of ketamine, the animals were decapitated, the prepared small pieces of the testes were fixed in a 2.5% glutaraldehyde solution (pH=7.2-7.4). Postfixation of the material was carried out with 1% solution of osmium (IV) oxide, followed by dehydration in propylene oxide and sample was embedded into the epoxy resins mixture. Ultrathin sections made with an ultramicrotome were contrasted with a 1% aqueous solution of uranyl acetate and lead citrate according to the Reynolds method and studied with an electron microscope [1]. Using standard methods, the material was imbedded in paraffin blocks, of which sections 4 μm thick were made and stained with hematoxylin and eosin. Histological preparations were examined using Olympus C 3040-ADU light microscope with digital microfilter with software adapted for these studies (Olympus DP - Soft, license No. VJ285302, VT310403, 1AV4U13B26802) and Biorex 3 (serial No. 5604).

All biochemical studies were carried out in 10% homogenate of testis tissue using Ulab 101 spectrophotometer.

General NO-synthase activity (gNOS), cNOS, iNOS and nitrite concentration was determined according to the method described by Akimov O.Ye., Yelinska A.M. and Kostenko V.O. [14]. Activity of arginases was determined by the increase in the concentration of L-ornithine after a 20-hour incubation in phosphate buffer medium (pH = 7.0) in the presence of a 24 mM solution of L-arginine [14].

General activity of NO-synthase (gNOS), cNOS, iNOS and the activity of arginases was determined by the increase in the concentration of L-ornithine after a 20-hour incubation in phosphate buffer medium (pH = 7.0) in the presence of a 24 mM L-arginine solution [12].

Basic production of superoxide anion radical ($O_2^{\bullet-}$), its production by the mitochondrial electron transport chain (ETC) and microsomal ETC was determined by the growth of diformazan concentration, formed in the reaction of $O_2^{\bullet-}$ with nitro blue tetrazolium [14]. Superoxide dismutase (SOD) and catalases activity was determined according to guidelines [14]. The concentration of free malondialdehyde (MDA) was determined by reaction with 1-methyl-2-phenylindole [14].

Statistical processing of the research results was carried out using the Microsoft Office Excel software and the Real Statistics 2019 extension to it. The nonparametric Mann-Whitney test was used to determine the statistical significance of differences between the groups. The difference was considered statistically significant at $p<0.05$.

Results of the study and their discussion.

In a micropreparation of the rat seminiferous tubules in the control group, all cellular associations characteristic of spermatogenic epithelium were noticeable: spermatogonia are located on the basal membrane, farther from it spermatocytes are located, spermatids and spermatozoa are located in the lumen of the tubules. Their cellular composition indicated various stages of normal spermatogenesis. In the cross section of the rats’ testes in the control group, the seminiferous tubules had a rounded shape. Closer to the basal membrane, the nuclei of the sustentocytes were well visualized. The testicular stroma was represented by loose fibrous connective tissue, in which groups of interstitial endocrinocytes of 3-5 cells in the field of vision, blood vessels and cellular elements were clearly distinguished.

In the experimental group of animals (on the 90th day of the experiment), we found that the testes interstitial space was represented by loose fibrous connective tissue, which between the convoluted seminiferous tubules was enlarged in comparison with the control group. The vessels were full-blooded, the leukocytes margination was determined inside the vessels with elements of migration activity through the vessel wall into the space of interstitial tissue (fig. 1a).

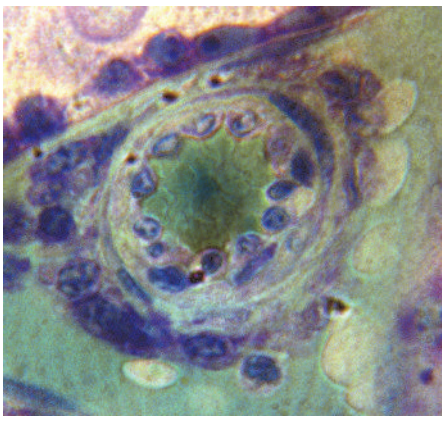

Fig. 1a. Blood vessel of experimental rat on the 3rd month. Microimage. H&E stain: Lens: 80: Ocular lens:15.

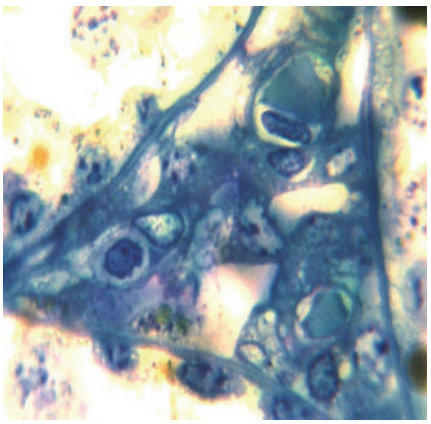

Fig. 1b. Interstitial space of experimental mouse on the 3rd month. Microimage. H&E stain: Lens: 80: Ocular lens:15.

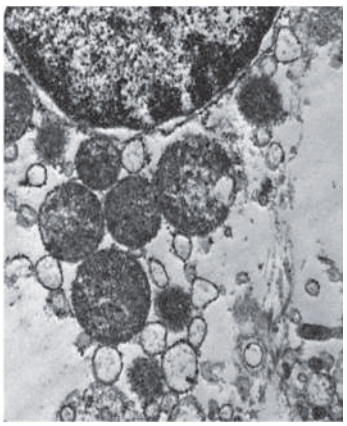

Fig. 1c. Electron micrograph of interstitial endocrinocytes of experimental rat on the 3rd month. Exp. x 12000.

Fig. 1. Blood vessels, interstitial space and interstitial endocrinocyte after 90 days central deprivation of testosterone synthesis.

Around the blood vessels, groups of interstitial endocrinocytes of 1-3 cells were determined in the field of vision (in the control group 3-5 in the field of vision). Interstitial endocrinocytes had round or oval shaped nuclei, 1-2 nucleoli were clearly distinguished (fig.1.b). In the cytoplasm of endocrinocytes, smooth endoplasmic reticulum was determined, which was represented by numerous tubules that branched and were filled with a fine fiber substance, on the membranes of which there were numerous ribosomes. Mitochondria were small, with dense matrix and a small number of cristae. A characteristic feature was the presence of secretory granules of various sizes and electron densities in the cytoplasm; they were localized in a well-developed plate apparatus of the Golgi cytoplasmic complex. Most cells developed destructive disorders in the ultrastructural organization of the plate cytoplasmic Golgi complex, which could be well seen in electron micrographs in comparison with the control group of animals (fig.1.c). In some interstitial endocrinocytes, the smooth membranes of the Golgi complex were randomly oriented and surrounded by single large electron-transparent vacuoles, lipid inclusions and secretory granules. Most interstitial endocrinocytes had fragmented smooth endoplasmic reticulum. The hyaloplasm of glandulocytes was significantly cleared and contained very few free ribosomes and polysomes, compared to the control group of animals. The cytoplasmic membrane of glandulocytes is dissolved, thickened, has high electron density.

In the interstitial space of the experimental group of animals well visualized macrophages were determined. In a micropreparation, two populations of macrophages could be easily distinguished. Depending on the location, macrophages could be divided into parietal (near the convoluted tubule) and actually interstitial, which were located individually or in groups of 1-3 in the field of vision near the blood vessel. Parietal macrophages had a flattened nucleus and cytoplasm, while interstitial macrophages, on the contrary, had a large nucleus of a round or oval shape (fig. 1.b).

When we studied micropreparations of the convoluted seminiferous tubules in the experimental group, it was found that the wall of the tubules is compacted, swollen, with large number of parietal macrophages in comparison with the control group of animals.

Two populations of cells were determined in the lumen of the convoluted tubules: the sustentocytes and cells of the spermatogenic series at different stages of differentiation (fig. 2a, 2b).

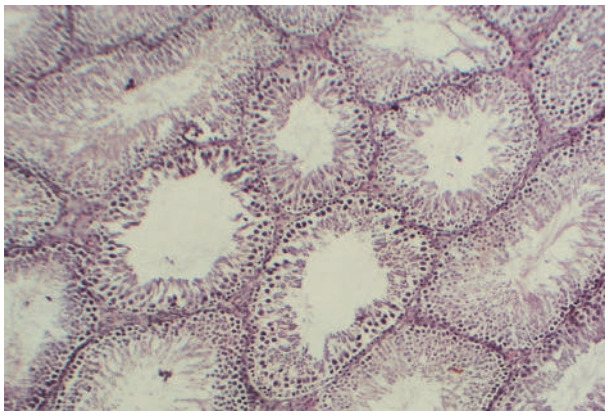

Fig. 2.a. Seminiferous tubules of experimental rat on the 3rd month. Microimage. H&E stain: Lens: 10: Ocular lens: 15.

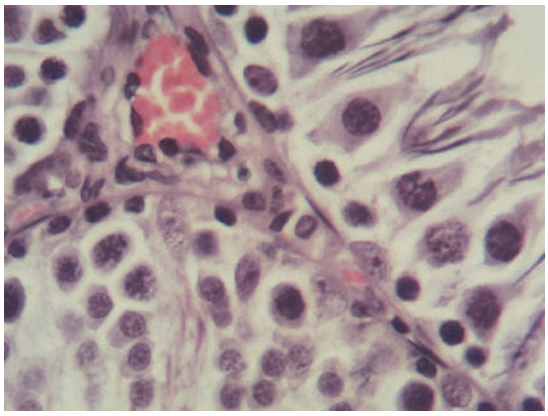

Fig. 2.b. Seminiferous tubules of experimental rat on the 3rd month. Microimage. H&E stain: Lens: 40: Ocular lens: 15.

Fig. 2.

When we studied the structural organization of rat sustentocytes in the experimental group, it was found that most of the cells experienced adaptive reactions, which should be discussed in more detail.

Sustentocytes with hyperplasia of the elements of the smooth endoplasmic reticulum in the cytoplasm, the morphological equivalent of which are numerous small and large dilated round vesicles, localized mainly in the apical sections of cells, were visualized. The heads of maturing spermatids with the impaired structures of the tubulo-bulbar complex with primary signs of degeneration were also found in these fragments of sustentocytes. Quite large phagosomes containing fragments of dead cells occurred in the cytoplasm of the sustentocytes. The intercellular contacts between the round spermatids and sustentocytes were not broken, but the deformation of the inner membranes and vacuolization of mitochondria occurred in the cytoplasm of some spermatocytes, round and maturing spermatids. The number of mitochondria in the cytoplasm of the sustentocytes decreased, electron density of the mitochondrial matrix decreased. Ultrastructural signs of cytoplasm membrane structures degradation in the form of concentric electron-dense formations were found in the cytoplasm of vacuolated sustentocytes, protein structures were present either inside the vacuoles or independently located in the cell cytoplasm. The number of lipid droplets in the cytoplasm of sustentocytes was significantly increased compared to the control group.

In the structure of convoluted seminiferous tubules, an increase in the height of the spermatogenic layer was detected. The presence of small and medium vacuoles, with a tendency to increase and merge in the contact zone between the spermatogonia and the basal membrane of the convoluted seminiferous tubules, was observed.

In some convoluted seminiferous tubules, first there was discomplexation and disorientation, and then desquamation of spermatids. The volume of their cytoplasm decreased in comparison with the control group. Hypochromia and pycnosis were observed in the nuclei. There was also disorientation, discompletion of second-order spermatocytes, then those of the second order, and sometimes their desquamation. Due to the complete or partial desquamation of the sperm layer cells from the basement membrane, “seed layers” were formed in the lumen of the tubules. The number of type A and B spermatogonia decreased.

Table 1

Oxidative stress markers in rat testes during 90-day central testosterone synthesis deprivation (M±m)

Groups	Parameters					
	SOD activity, c.u.	Catalase activity, nkat/g of tissue	Basic $O_2^{\bullet-}$ production, nmol/s per g of tissue	Production of $O_2^{\bullet-}$ from mithochondrial ETC, nmol/s per g of tissue	Production of $O_2^{\bullet-}$ from microsonal ETC, nmol/s per g of tissue	Free MDA, μmol/g of tissue
Control	1.87 ±0.11	182 ±17	0.26 ±0.01	7.84 ±0.13	9.55 ±0.19	6.64 ±1.44
Experimental	2.35 ±0.25*	253 ±20	3.87 ±0.08*	42.08 ±1.62*	36.53 ±0.42*	18.25 ±0.89*

Note:* - indicates that the difference is statistically significant when compared to the control group ($p<0.05$).

Against the background of the described morphological changes, an increase in SOD activity by 25.67% is observed without statistically significant changes in catalase activity (tab. 1). Basic production of $O_2^{\bullet-}$ increased 14.88 times, production of $O_2^{\bullet-}$ from mitochondrial ETC was elevated by 5.37 times and from microsomal ETC – by 3.83 times. The concentration of free MDA increased by 2.75 times. Thus, it can be noted that the development of oxidative stress is observed in the testes.

Table 2

Nitric oxide cycle function during 90-day central testosterone synthesis deprivation (M±m)

Groups	Parameters				
	gNOS activity, μmol/min per g of protein	iNOS activity, μmol/min per g of protein	cNOS activity, μmol/min per g of protein	Arginase activity, μmol/min per g of protein	NO^{2-} concentration, nmol/L
Control	0.54 ±0.04	0.13 ±0.02	0.41 ±0.03	2.48 ±0.05	3.83 ±0.25
Experimental	1.38 ±0.18*	1.23 ±0.17*	0.15 ±0.02*	0.24 ±0.03*	28.45 ±0.46*

Note:* - indicates that the difference is statistically significant when compared to the control group ($p<0.05$).

The total production of NO under these conditions increased 2.56 times (tab. 2). The activity of iNOS increased by 9.46 times, while cNOS activity decreased by 63.41%. Arginase activity dropped by

10.33 times. The concentration of nitrites increased by 7.43 times. Therefore we can state, that the functioning of the nitric oxide cycle shifts toward the predominance of NOS-dependent cleavage of L-arginine.

NO hyperproduction's effect on testicular function significantly depends on the source of NO production. If the source of its production is endothelial NO-synthase, then NO improves testicular function and spermatogenesis [8]. However, in case of iNOS as its main producer, excessive NO has damaging effects on the testicular function [13]. Decrease of arginase activity also worsens the testicular function since polyphenols produced in arginase pathway are necessary for testicular cell division and differentiation [6, 7].

Dilated vascular lumens in the testes are the result of nitric oxide overproduction. An increase in iNOS activity, margination of leukocytes in the testes vessels, and decrease in the activity of arginases may indicate a change in the polarization of macrophages in the testes from anti-inflammatory (M2) to pro-inflammatory (M1) phenotype. Whereas under physiological conditions, the testes macrophages must have immunosuppressive function and the M2 phenotype [10]. Zhao Y. et al. showed, that NF-κB → COX2 signal pathway contributes greatly to testosterone reduction [15]. Activation of NF-κB during testosterone deficiency caused by central deprivation may be one of the reasons of macrophage M1 polarization. Role of NF-κB activation during the prolonged testosterone synthesis deprivation and its mechanisms demand further studies.

Destructive disorders in the ultrastructural organization of the plate cytoplasmic Golgi complex in intestinal endocrinocytes are explained by the increased production of $O_2^{\bullet-}$ by microsomal ETC.

Changes in the mitochondria of sustentocytes and spermatocytes correlate with the increased production of $O_2^{\bullet-}$ by mitochondrial ETC. Therefore, interstitial endocrinocytes increase production of $O_2^{\bullet-}$ at the expense of microsomal ETC, and sustentocytes and spermatocytes due to mitochondrial ETC under the conditions of testosterone deficiency.

Analyzing the dynamics of changes in biochemical parameters when compared to the results of the previous work, it should be noted that there is a compensatory increase in the activity of antioxidant enzymes, which, however, does not prevent further exacerbation of oxidative stress [12].

With a 30-day deprivation of testosterone synthesis, a change in the source of nitric oxide production was observed without increase of its production amount. Continuation of testosterone synthesis deprivation for up to 90 days increases nitric oxide production while maintaining a leading role of iNOS in its production. [12].

An increase in the concentration of nitrites in the testes can lead to the development of nitritive stress, which is accompanied by nitration of the thiol groups of proteins with the formation of modified cysteine.

Conclusion

On the 90th day of the experiment including central deprivation of testosterone synthesis in animals, we found that most of the cells in the sustentocytes population had destructive changes in mitochondria. An opposite tendency was revealed in the interstitial endocrinocyte population. They had structural signs of functional stress aimed at supporting the secretory function of the testes.

Central deprivation of testosterone synthesis for 90 days leads to the development of oxidative stress due to overproduction of reactive oxygen species and the accumulation of nitrites in the testes tissues due to the increased activity of inducible NO synthase.

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Реферати

МОРФОФУНКЦІОНАЛЬНІ ОСОБЛИВОСТІ ІНТЕРСТИЦІЙНИХ ЕНДОКРИНОЦИТІВ ТА СУСТЕНТОЦИТІВ ЯЄЧКА ЩУРІВ ПРИ ЦЕНТРАЛЬНІЙ ДЕПРИВАЦІЇ СИНТЕЗУ ТЕСТОСТЕРОНА ПРОТЯГОМ 90 ДІБ

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На сьогоднішній день в світі спостерігається тенденція до зміни ставлення до сім'ї та сімейних цінностей. У розвинених європейських країнах спостерігається тенденція до високої сексуальної активності у чоловіків літнього віку і пізнього створення сім'ї з дітьми, що має певні труднощі у зв'язку зі зниженням вироблення тестостерону в літньому віці. Метою дослідження було встановити мікроскопічну організацію інтерстиціальних ендокріноцітов і сустентоцітов щурів, визначити джерела продукції оксиду азоту і інтенсивність окисного стресу в яєчках з експериментальної центральної депривації синтезу тестостерону з диферелін на 90-ту добу експерименту. Експеримент був проведений на 20 зрілих білих щурах-самцях. Щури були розділені на 2 групи: контрольна група (10), експериментальна група (10), яким підшкірно вводили диферелін (трипторелін ембонат) в дозі 0,3 мг / кг активної речовини протягом 90 днів. Тривала центральна депривація синтезу тестостерону у тварин призводить до появи структурних ознак функціонального стресу в популяції сустентоцітов і інтерстиціальних ендокріноцітов, які спрямовані на підтримку секреції яєчка. Центральна депривація синтезу тестостерону протягом 90 днів викликає розвиток окисного стресу за рахунок гіперпродукції активних форм кисню і накопичення нітритів в тканини яєчка через підвищену індуцібельной активності NO-синтази.

Ключові слова: сім'яники, інтерстиційні ендокриноцити, сустентоцити, NO- синтаза, iNOS, cNOS, L- аргінін, супероксиддисмутаза, мітохондріальна ЕТЛ, М1, М2, щури.

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МОРФОФУНКЦИОНАЛЬНЫЕ ОСОБЕННОСТИ ИНТЕРСТИЦИАЛЬНЫХ ЭНДОКРИНОЦИТОВ И СУСТЕНТОЦИТОВ ЯИЧКА КРЫС ПРИ ЦЕНТРАЛЬНОЙ ДЕПРИВАЦИИ СИНТЕЗА ТЕСТОСТЕРОНА В ТЕЧЕНИИ 90 ДНЕЙ

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По мере развития социума наблюдается тенденция к изменению отношения к семье и семейным ценностям. В развитых европейских странах наблюдается тенденция к высокой сексуальной активности у пожилых мужчин и позднему созданию семьи с детьми, что имеет определенные трудности в связи со снижением выработки тестостерона в пожилом возрасте. Целью исследования было установить микроскопическую организацию интерстициальных эндокриноцитов и сустентоцитов крыс, определить источники продукции оксида азота и интенсивность окислительного стресса в яичках с экспериментальной центральной депривацией синтеза тестостерона с диферелином на 90-е сутки. эксперимент. Эксперименты проводились на 20 зрелых белых крысах-самцах линии Вистар. Крысы были разделены на 2 группы: контрольная группа (10), экспериментальная группа (10), которым подкожно вводили диферелин (трипторелин эмбонат) в дозе 0,3 мг / кг активного вещества в течение 90 дней. Длительная центральная депривация синтеза тестостерона у животных приводит к появлению структурных признаков функционального стресса в популяции сустентоцитов и интерстициальных эндокриноцитов, которые направлены на поддержку секреции яичка. Центральная депривация синтеза тестостерона в течение 90 дней вызывает развитие окислительного стресса за счет гиперпродукции активных форм кислорода и накопления нитритов в ткани яичка из-за повышенной индуцибельной активности NO-синтазы.

Ключевые слова: семенники, интерстициальные эндокриноциты, сустентоциты, NO-синтаза, iNOS, cNOS, L-аргинин, супероксиддисмутаза, митохондриальная ЭТЦ, М1, М2, крысы.

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A MEASURE OF THE EFFECT OF COMPLEX FOOD ADDITIVES ON RATS' ADAPTIVE RESPONSES

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In the paper was the investigation of the effect of consumed complex food additives on the rats' adaptive response. 88 outbred mature male rats, housed in the common conditions, were involved into the study. Control rats consumed drinking water and received saline per os. The rats of the experimental group were given ad libitum access to water and, supplementary, consumed sodium nitrite solution. Sodium glutamate was administered at a dose of 20 mg/kg, Ponceau 4R at a dose of 5 mg/kg once daily per os. Doses of food additives were half less the allowable normal rate in food. After being exposed to open field test the rats were killed within 1, 4, 8, 12 and 16 weeks under thiopentone anesthesia overdose. Consumption of complex food additives at acceptable doses affects the behavioral responses of experimental animals. It has been established that just from the first week of observation, rats experienced increased anxiety, fear, blunting of adaptive responses, decreased activity and disturbance of the emotional state, which were intensified up to week 16 of the experiment.

Key words: open field test, sodium nitrite solution, sodium glutamate, Ponceau 4R, adaptive-locomotor behavior of rats.

The study is a fragment of the research project "Morphogenesis patterns of organs, tissues and neurovascular formations in normal condition, pathology and under the influence of exogenous factors", state registration No. 0118U004457.

The widespread use of food additives for various purposes in the production, processing, packaging and storage of products that are associated with, sometimes, quite wide limits of acceptable dosage, leads to cases of allergic reactions and disorders of respiratory, digestive, endocrine and nervous systems [12, 15].

Current publications highlight the outcomes of the effects of various exogenous factors on organs and systems [2], including the use of separate food additives [5, 10, 13]; however, little data on the effect of several chemical agents, consumed simultaneously, on the body have been found to date.

Monosodium Glutamate (E 621) is used as a flavor enhancer for many foods and as a salt substitute. It has been reported that E 621 can cause headache and dyspeptic events known as Chinese restaurant syndrome [14].

Sodium Nitrite (E 250) is a preservative and color retainer. Its negative impact on the digestive and respiratory systems has been proved [3].

Ponceau 4r (food colorant) can cause mental disorders in children; it can be also associated with attention deficit hyperactivity disorder and asthma-like attacks [11]. The etiology and pathogenesis of attention deficit hyperactivity disorder are poorly understood to date; consequently, such risk factors as hereditary predisposition, adverse course of the perinatal period, psychosocial and environmental factors are more commonly discussed. Moreover, more than 10 years ago, the factor of use of food additives was added to the above risk factors. It has been established that disorders in morphogenesis and functional genesis, namely, dysfunction of neurotransmitter systems of the brain and delayed neurodevelopment are the major causes in pathogenesis of attention deficit hyperactivity disorder [9].

The purpose of the paper was to study the effect of consumed complex food additives on the rats' adaptive response.

Materials and methods. The total of 88 outbred mature male rats, housed in the common conditions, were involved into the study. The rodents were divided into two groups (the control and the experimental ones). The control rats consumed drinking water and received saline per os. The experimental group rats were given access to water ad libitum and supplementary consumed 10% sodium nitrite solution [6]. Sodium glutamate was administered at a dose of 20 mg / kg in 0.5 ml of distilled water [8], Ponceau 4r at a dose of 5 mg / kg in 0.5 ml of distilled water [3] once daily per os. Doses of food additives were half less the allowable normal rate in food.

After being exposed to open field test the rats were killed within 1, 4, 8, 12 and 16 weeks under thiopentone anesthesia overdose [7].

To evaluate adaptive behavior, the rat was placed into the corner of the box and its spontaneous locomotor behavior was recorded for 60 seconds. Parameters of motor and exploratory behavior of animals (number of outer edge square crossings and number of central square crossings), vertical activity (number of rearings), and vegetative activity (number of urinations/defecations) were measured.

The resulting data have been processed quantitatively by the variance statistics using Student's t-test and *Excel* software.

The experimental part of the research has been carried out in compliance with the requirements of the international principles of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1986) and Resolution of the First National Congress on Bioethics (Kyiv, 2007) [6].

Results of the study and their discussion. The measure of numbers of outer edge square crossings showed 7.54 ± 0.35 crossings made by the animals of control group, indicating no anxiety and fear. During the observation, the parameter ranged from 7.61 ± 0.29 times within 1 week to 7.31 ± 0.29 times on week 16, with insignificant difference (Table 1).

With the increase in the period of consuming the complex food additives, the number of outer edge square crossings was tending to increase relative to the control group. The average number of outer edge square crossings in the experimental group was 12.46 ± 1.78 times, that was by 1.67 times more often compared to controls.

After 1 week of consuming the complex food additives the animals walked by 1.31 times more often on the outer edge, after 4 weeks by 1.51 times, after 8 weeks by 1.72 times, after 12 weeks by 1.88 times, after 16 weeks by 1.94 times, which indicated the presence of anxiety and fear, and thus, the increase in their manifestations in proportion to the period of consuming the complex food additives (table 1).

Table 1

Orientation and exploratory behavior of the rats on the outer edge squares

	Control group	Experimental group
Control	7.54±0.35	-
Week 1	7.61±0.29	10±0.23**
Week 4	7.46±0.35	11.3±0.37*. **
Week 8	7.46±0.31	12.9±0.24 *. **
Week 12	7.38±0.31	13.9±0.28 *. **
Week 16	7.31±0.29	14.2±0.29 **

Notes: hereinafter *p<0,05, compared to the previous time period of observation; ** p<0,05, compared to control group of animals.

The number of the central square crossings in the rodents of the control group, regardless of the time period, had no significant changes, accounting on the average of 2.46 ± 0.11 times, indicating no disorder of adaptive responses (table 2).

In the experimental group, there was a tendency to drastic reduce in the number of central square crossings during the observation. Rats who consumed the complex food additives for 1 week showed the parameter by 1.68 times lower than in the control group, and after 4 weeks it was by 4.62 times lower. Groups of animals that consumed additives for 8 weeks, 12 weeks, and 16 weeks avoided walking in the open field (table 2).

On the average, the animals of the experimental group crossed the central squares 0.39 ± 0.63 times, which is by 6.3 times less than in the control group, which showed the development of anxiety and blunting of the adaptive responses in rats, with increasing manifestations proportional to the duration of the consuming of food additives.

Table 2

Orientation and exploratory behavior of the rats on the central squares

	Control group	Experimental group
Control	2.38±0.24	-
Week 1	2.46±0.24	1.46±0.21**
Week 4	2.31±0.24	0.5±0.17*. **
Week 8	2.46±0.22	0**
Week 12	2.54±0.18	0**
Week 16	2.62±0.14	0**

Vertical activity of the animals, regardless of time period, had no significant changes, accounted on the average of 2.07 ± 0.07 times in the control group (table 3), indicating that the animals had no disturbance of activity and manifestations of fear.

In rats of the experimental group, we observed a tendency to decrease the number of erected postures with an average parameter of 0.85 ± 0.8 times. In animals who consumed food additives for 1 week it was by 1.27 times lower than in the control group of rats, for 4 weeks by 1.54 times lower, for 8 weeks by 1.74 times lower, and at 12 and 16 weeks the parameter was zero (table 3).

On the average, animals of the experimental group performed erected postures by 2.4 times less frequently, indicating activity disorder and appearance of fear with worsening of the health state that correlated with the duration of consuming the complex food additives.

Table 3

Vertical activity of the animals

	Control group	Experimental group
Control	2,08±0,24	-
Week 1	2,15±0,22	1,69±0,13**
Week 4	2,15±0,19	1,4±0,16**
Week 8	2±0,23	1,15±0,15**
Week 12	2,08±0,18	0*, **
Week 16	2±0,16	0*, **

Increased number of defecations and urinations indicated changes in the emotional state of animals. The rats of the control group had insignificant differences in the number of boluses depending on the observation period; the average value was 1.64 ± 0.08 times, which indicated an adequate emotional background.

Animals who consumed food additives tended to increase the number of boluses depending on the time period and their average number was 2.87 ± 0.5 times, which was by 1.75 times more than in the control group. Within a week of taking food additives animals had by 1.18 times more boluses than in the control group, after 4 weeks by 1.79 times, after 8 weeks by 1.72 times, after 12 weeks by 2.08 times, after 16 weeks by 2.1 times, which indicated changes and disorders of emotional state (table 4).

Table 4

Vegetative activity of the animals

	Control group	Experimental group
Control	1,69±0,24	-
Week 1	1,77±0,23	2,08±0,18**
Week 4	1,62±0,24	2,9±0,18*, **
Week 8	1,61±0,18	2,97±0,20**
Week 12	1,54±0,14	3,2±0,25**
Week 16	1,62±0,14	3,4±0,22*, **

The study findings have established a direct correlation between the changes in the parameters of the open field test and the duration of consuming the complex food additives, which is consistent with the data of other researchers [7] regarding the influence of ethanol and tincture of canuper on the central nervous system and emotional state of rats.

The average number of outer edge square crossings in animals who consumed food additives for 16 weeks was by 1.92 times greater than in the control group; the number of central square crossings was zero in the experimental group and 2.62 ± 0.14 times in the controls; the vertical activity of animals in the experimental group also was zero at 16 weeks, and in the controls it was 2 ± 0,16. Similar behavioral changes have been described by other authors in chronic alcohol intoxication in rats. [1]

Conclusion

Consumption of complex food additives at acceptable doses affects the behavioral responses of experimental animals. It has been established that just from the first week of observation, rats experienced increased anxiety, fear, blunting of adaptive responses, decreased activity and disturbance of the emotional state, which were intensified up to week 16 of the experiment.

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Реферати

ВИЗНАЧЕННЯ ВПЛИВУ КОМПЛЕКСУ ХАРЧОВИХ ДОБАВОК НА АДАПТИВНІ РЕАКЦІЇ ЩУРІВ

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В статті вивчений вплив вживання комплексу харчових добавок на адаптивні реакції щурів. Дослідження проведено на 88 статевозрілих безпорідних щурах-самцях. Щурам експериментальної групи, за умов безперешкодного доступу до рідини, давали пити розчин нітриту натрію. Глутамат натрію вводили в дозі 20 мг/кг, Понсо 4R – в дозі 5 мг/кг 1 раз на добу перорально. Дози харчових добавок вдвічі були меншими за допустиму норму у харчових продуктах. Тварин виводили з експерименту через 1, 4, 8 та 16 тижнів шляхом передозування тіопенталового наркозу. Перед цим проводили тест «відкрите поле». Встановлено, що вживання комплексу харчових добавок у допустимих дозах впливає на поведінкові реакції експериментальних тварин. З першого тижня спостереження у щурів посилюється тривога, страх, спостерігається притуплення адаптивних реакцій, зниження активності та порушення емоційного стану, які посилюються до 16 тижня експерименту.

Ключові слова. тест «відкрите поле», глутамат натрію, нітрит натрію, понсо 4R, адаптивно-дослідницька поведінка щурів.

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ОПРЕДЕЛЕНИЕ ВЛИЯНИЯ КОМПЛЕКСА ПИЩЕВЫХ ДОБАВОК НА АДАПТИВНЫЕ РЕАКЦИИ КРЫС

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В статье изучено влияние употребления комплекса пищевых добавок на адаптивные реакции крыс. Исследование проведено на 88 половозрелых беспородных крысах-самцах. Крысам экспериментальной группы, в условиях беспрепятственного доступа к жидкости, давали пить раствор нитрита натрия. Глутамат натрия вводили в дозе 20 мг/кг, Понсо 4R - в дозе 5 мг/кг 1 раз в сутки перорально. Дозы пищевых добавок вдвое были меньше допустимой нормы в пищевых продуктах. Животных выводили из эксперимента через 1, 4, 8 и 16 недель путем передозировки тиопенталового наркоза. Перед этим проводили тест «открытое поле». Установлено, что применение комплекса пищевых добавок в допустимых дозах влияет на поведенческие реакции экспериментальных животных. С первой недели наблюдения у крыс усиливается тревога, страх, наблюдается притупление адаптивных реакций, снижение активности и нарушение эмоционального состояния, которые усиливаются до 16 недели эксперимента.

Ключевые слова: тест «открытое поле», глутамат натрия, нитрит натрия, понсо 4R, адаптивно-исследовательское поведение крыс.

Рецензент Старченко І.І.

ШАНОВНІ КОЛЕГИ!

Матеріали для опублікування приймаються від спеціалістів у галузі теоретичної, профілактичної, клінічної медицини, суміжних дисциплін, а також досліджень в галузі біологічних наук (Наказ МОН України № 612 від 07.05.2019 р.). Мова публікацій – українська, англійська, російська.

Публікація повинна відбивати сучасний стан розробки досліджуваної проблеми, містити нові результати на основі проведеного дослідження, **перспективи подальших розробок у даному напрямку**. Висновки мають бути аргументованими відповідним ілюстративним матеріалом.

До друку приймаються наукові статті, які містять такі необхідні елементи: шифр УДК; назва статті; ініціали авторів та прізвища (кількість авторів однієї статті не повинна перевищувати п'яти осіб); назва установи та місто; дані про **зв'язок публікації з плановими науково-дослідними роботами** (з наведенням номеру держреєстрації)

Вступ: постановка проблеми у загальному вигляді; аналіз останніх (за останні 10 років) досліджень та публікацій, в яких започатковано розв'язання даної проблеми і на які спирається автор; визначення невирішених раніше частин загальної проблеми;

Мету

Матеріал та методи дослідження

Результати дослідження та їх обговорення

Висновки або підсумки

Перспективи подальших розробок у даному напрямку

Список літератури за Ванкуверським стилем спочатку кирилицею, потім – латиницею.

Реферати російською, українською і англійською мовами обсягом не більше 0,5 стор. У випадку наведення статті українською, або російською мовами додаткове резюме англійською мовою – 1,5-2 сторінки англійською мовою, англійською мовою – розширене резюме українською мовою.

Таблиці – **не більше 4**. Графіки (**не більше 4**) повинні мати чіткі калібрування по осям. Якщо наводяться декілька кривих, безпосередньо на рисунку необхідно вказати їх порядкові номера. Рисунки, крім діаграм, в електронному варіанті бажано надавати в розширенні PCX, фото (**не більше 4**) – в JPEG.

Список літератури оформлюється без скорочень. Автори подаються за абеткою, спочатку кирилицею, потім латиницею. Посилання в тексті зазначаються цифрами у квадратних дужках.

Статті редагуються і рецензуються членами редакційної ради – провідними фахівцями з відповідних галузей біології та медицини.

Текст набирається через 1,5 інтервал **без переносів**, розмір шрифту 14 у Times New Roman в редакторі MICROSOFT WORD. **Відступ абзацу – 1,25 см знаком табуляції.** Поля з усіх боків по 25 мм. Матеріал потрібно надавати на електронну пошту – **womab.ed@gmail.com**.

Автори несуть персональну відповідальність за правильність наведеної інформації.

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Реквізити для оплати буде надіслано авторам додатково, після отримання статті та її рецензування.

За додатковою інформацією звертайтеся до відповідального секретаря – професора Єрошенко Галини Анатоліївни.

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