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ELECTRONIC MICROSCOPIC RESEARCH OF TOOTH ENAMEL SURFACE AFTER USAGE OF DIFFERENT METHODS OF HOME BLEACHIG

Abstract. *Teeth colour plays an important role in the perception of a person, shaping his image and self-assessment. Thus, it has a significant influence on quality of life, due to its dental health. Nowadays world dental practice is increasingly focused on developing of more saving methods that provide the aesthetic needs of the patient. Aim. To study the influence of different bleaching agents on the ultrastructure of enamel by means of scanning electronic microscopy. Materials and methods. Investigation is undertaken on a 25 permanent teeth that were extracted for orthodontic indications in patients 20-30 years. For revealing of enamel surface structure changes after the action of bleaching facilities scanning electronic microscopy research method was used. Results. Electronic microscopic investigation showed that brushing with abrasive toothpaste with RDA=200 characterized by mechanical damage as a result of highly abrasive elements of toothpaste. Brushing with bleaching toothpaste RDA=120 led to less significant changes in enamel surface, indicated a less damaging effect of the paste on the surface of the enamel. Cleansing of the teeth with a paste with low abrasiveness (RDA of 75) caused minor damage to the enamel surface, indicated a slight abrasive effect of toothpaste. Bleaching with peroxide containing bleaching systems resulted in smooth enamel surface, which indicated that they to some extent dissolved the surface layer of enamel. Conclusions. Electronic microscopic studies confirmed the need of a differentiation of bleaching facilities, depending on the patient's teeth status. This will achieve an aesthetic effect with minimum damaging effects on hard tooth tissues. To prevent complications that arise as a result of bleaching, it is necessary to prescribe local remineralization therapy with hydroxyapatite- and fluoride containing facilities of individual or professional oral hygiene.*

Keywords: *discoloration, dental hard tissues, bleaching facilities, individual oral hygiene, ultrastructure of enamel, scanning electronic microscopy.*

Introduction. Changes of the teeth colour (discoloration, discoloritis) are common pathologic lesions of dental hard tissues among people of all ages. Teeth colour and its colour characteristics play an important role in the perception of a person, shaping his image and self-assessment. Thus, they have a significant influence on quality of life, due to its dental health [6, 8].

Nowadays world dental practice is increasingly focused on developing of more saving methods that provide the aesthetic needs of the patient. Today the most common procedure for improvement of teeth crowns colour is bleaching [12]. The demand of aesthetic dentistry services is relevant due to the high prevalence of dental diseases and bad habits that lead to hard tooth tissues discoloration (A. Watts, 2001). There are a quite a number of different bleaching facilities [15]. However, it should be noted that most of these facilities contain significant concentrations of peroxides that can damage hard tooth tissues [21, 20].

Thus, the results of clinical studies in recent years indicated the need for differentiation of bleaching facilities depending on patient's teeth status [2, 14]. This will ensure the most stable aesthetic and therapeutic result; reduce the level of teeth crowns preparation and therefore damage of the pulp and hard tooth tissues. Therefore, development of more effective and safe methods simultaneously correcting colour changes of hard tooth tissues is an actual problem of therapeutic dentistry.

As known, the action of the various bleaching systems and methods is in discoloration of organic matrix of interprismatic substances, with the insignificant dissolution of enamel surface, causing expansion of superficial and deep layers of enamel pores [12].

Objective. The aim of the investigation is to study the influence of different bleaching agents on the ultrastructure of enamel by means of scanning electronic microscopy.

Materials and methods of research. The object of the investigation – 25 permanent teeth that were extracted for orthodontic indications in patients 20-30 years (extracted incisors, canines, premolars upper and lower jaws).

The research method is scanning electronic microscopy – for revealing of enamel surface structure changes after the action of bleaching facilities.

Extracted teeth had been thoroughly washed from the blood in running water, cleaned from remains of soft tissues using brush at low revs. Each sample tooth previously prepared as follows. Tooth conventionally divided vertically into two parts. On one half of the crown applied liquid Opal-Dam (Ultradent Products Inc.) to isolate this part of the tooth and cured with polymerization lamp for 15 seconds, after which the samples were subjected to further investigation.

All teeth were divided into 2 groups: the first group – extracted teeth that had been brushed with abrasive bleaching toothpaste of varying abrasiveness index (15 samples); second – extracted teeth on enamel surface of which were applied peroxide containing facilities (10 samples).

Samples of the teeth of the first group were divided into 3 subgroups. The first subgroup (A-1) – enamel surface was brushed with toothpaste RDA=200 using a brush and micromotor at low rpm for 15 minutes. Then the sample tooth washed with running water and kept in sterile containers of isotonic solution (NaCl) to re-processing . This procedure is performed every day for 3 days, after which the sample was subjected to a scanning electronic microscopic research.

Second subgroup samples (A-2) were brushed with toothpaste RDA=100 for the same scheme for 3 days and subsequently performed scanning electronic microscopic research. Experimentally, it meets specified by the manufacturer using the method – brushing 1 per day at least 3 minutes for 2 weeks.

Third subgroup samples brushed by the foregoing scheme with toothpaste RDA=75 of 15 minutes a day every day for 6 days. Experimentally – is brushing twice a day at least 3 minutes for 2 weeks.

Samples of the teeth of the second group (B) were prepared for electronic microscopic examination as follows. On enamel surface of samples of B-1 were applied peroxide containing bleaching system Opalescence (Ultradent Products Inc.) with a concentration of active substances – 45% carbamide peroxide once, exposure time – 30 minutes. The samples of B-2 were applied bleaching system Yotuel 7 Hours (Biocosmetics laboratories) the concentration of active substance – 10% carbamide peroxide for 1 hour. Then the sample tooth washed with running water and kept in sterile containers of isotonic solution (NaCl) to re-processing. The procedure is performed daily for 7 days (equivalent recommended by the manufacturer of the term). Then the gel is washed from the sample under running water and stored in saline for further study.

Electronic microscopic study conducted by the method of F.M. Mammadov and other [9, 10, 11], by scanning electronic microscopy in the laboratory department of Institute of Materials Photoelectronics name after Frantsevich NAS of Ukraine (Head. Laboratory, Dr. A. Samiryuk). The study was conducted in several stages: preparation and teeth preparation, applying of different bleaching facilities, thin teeth sections preparation. To study the samples in a scanning electronic microscope from each sample tooth microsection of 0.5-0.7 mm, which had two surfaces, one of which was treated with bleaching agent (bleaching paste or system), the second – served as a control.

After teeth microsection preparation they were polished with fine-grained elastic discs «Soft-Lex» («3M»). Grinding and polishing teeth microsection surfaces performed to obtain a mirror surface. Just before electronic microscopic study teeth microsection surfaces were cleaned with petroleum ether. Teeth microsections were

fixed on brass pedestals using conductive carbon glue. They were placed in a vacuum chamber, where they spent spraying the surface of the gold thin sections (99,99%AU) to the formation of these films 150A thick pure gold. Such a top film thickness sufficient to further electronic microscopic study of samples in X-ray microanalyzer "Superprobe-733" (JEOL, Japan) (Petrov V.I.). After spraying pedestals with samples of thin sections were studied by X-ray microanalyzer "Superprobe-733" (JEOL, Japan). Absolution in the image of secondary electrons (SEI, Secondary Electron Image) 7 nM, working vacuum: 1x10-5A. The study was conducted at an accelerated voltage of 25 kV and beam current of 1x10-10A. The results were photographed with the built- in digital camera microscope, which is connected to a computer (hereinafter microphotographs of computer onto a CD-ROM).

The results recorded on electronic digital media with an increase in 1000. In micrographs obtained visually conducted comparing the objects.

All laboratory methods of research conducted at least five samples. The results were treated statistically [4, 23].

Results of the research. The areas of teeth enamel samples of all groups that are not subjected to pre-treatment of bleaching agents served as a control. In these areas typical enamel homogeneous structure was revealed. Clearly visible outlines of enamel prisms and natural furrows were present. On the surface of the enamel there were also areas without clear prisms outlines, uniform spaces between them filled with mineral crystals: the so-called aprismatic enamel. In general, the surface characteristic of the enamel was undergoing its usual pressures and the influence of hard food particles (Fig.1, 2, 3).

In the teeth microsection surfaces study, which were previously subjected to cleaning with abrasive toothpaste RDA=200 according to the scheme, revealed the following. The surface of enamel lost its distinctive topography of enamel prisms shape and structure – the so-called "smoothed enamel". On the enamel surface there were a lot of different depths scratches. These changes were the result of toothpaste highly abrasive elements action (Fig. 4, 5).

After brushing with bleaching toothpaste with abrasive index of 120 were found less significant changes in enamel surface compared with the results of A-1 group. In particular, more pronounced prismatic structure of enamel, areas of smooth enamel less pronounced. Almost no scratches and cracks on the surface of the enamel. Revealed changes suggest less damaging effect of the paste on the surface of the enamel (Fig. 6, 7).

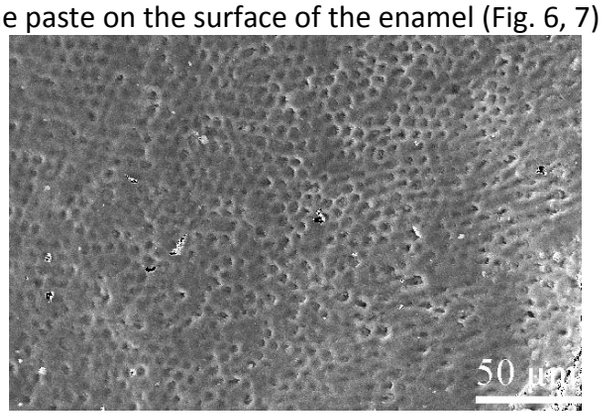

Fig. 1. Sound tooth enamel surface. Clearly visible prismatic structure of enamel surface with areas of aprismatic enamel. Scanning electron micrograph, x300

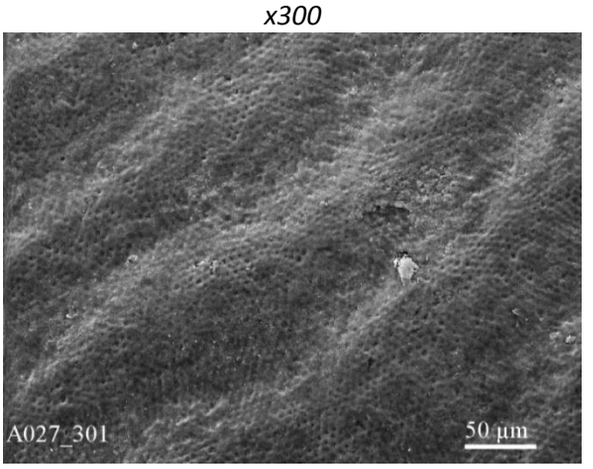

Fig. 2. Sound tooth enamel surface. Clearly visible prismatic structure of enamel surface with areas of aprismatic enamel and perikimata. Scanning electron micrograph, x300

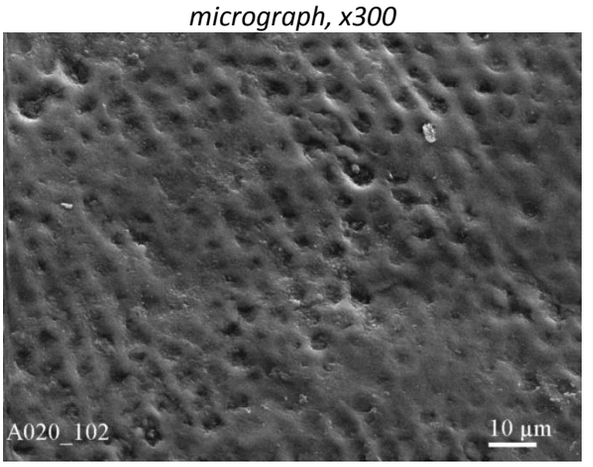

Fig. 3. Sound tooth enamel surface. Clearly visible prismatic structure of enamel surface with areas of aprismatic enamel. Scanning electron micrograph, x 1000

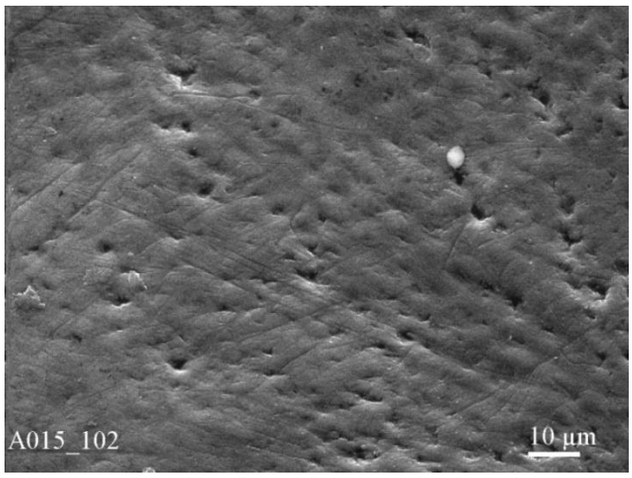

Fig. 4. Enamel surface of the tooth after cleansing with abrasive toothpaste with RDA=200. Smooth prismatic structure of enamel surface. Big number of different depths scratches on the enamel surface. Scanning electron micrograph, x 1000

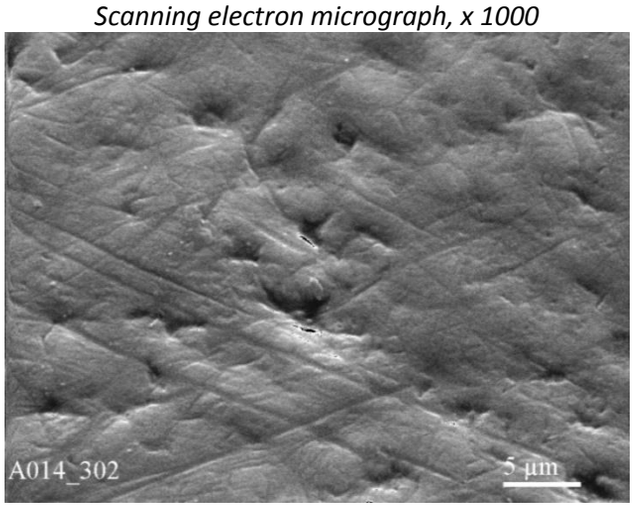

Fig. 5. Enamel surface of the tooth after cleansing with abrasive toothpaste with RDA=200. The enamel surface with almost lost enamel prisms. Large number of different depths scratches on the enamel surface. Scanning electron micrograph, x 2000

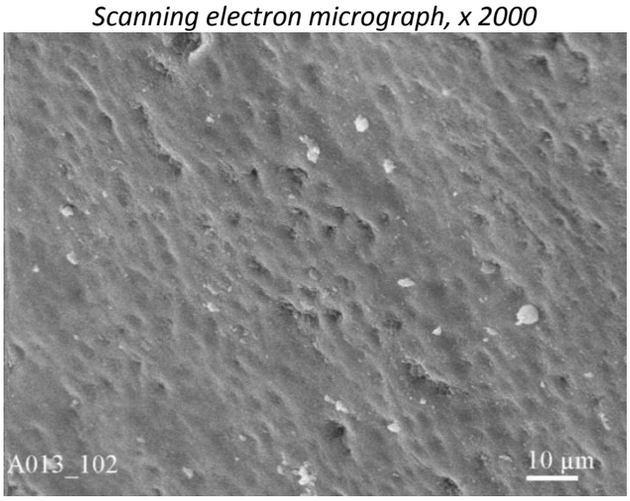

Fig. 6. Enamel surface of the tooth after cleansing with abrasive toothpaste with RDA=120. There are less noticeable enamel prisms without scratches on the enamel surface. Scanning electron micrograph, x 1000

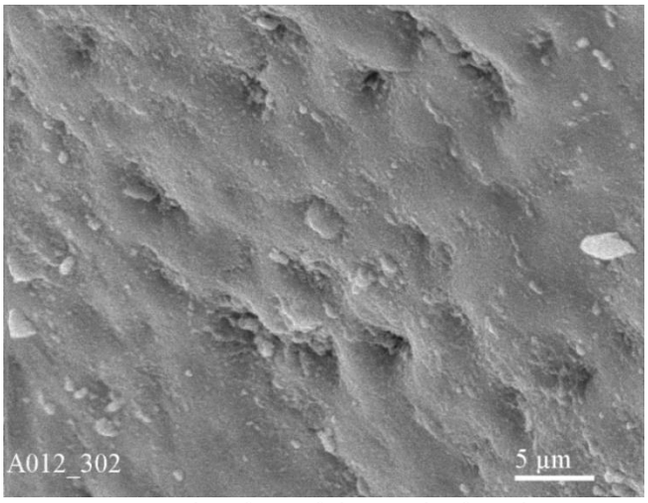

Fig. 7. Enamel surface of the tooth after cleansing with abrasive toothpaste with RDA=120. There are less visible outlines of the enamel prisms without scratches on the enamel surface. Scanning electron micrograph, x 2000

The analysis of teeth samples after brushing with a toothpaste with small abrasion (RDA=75) was revealed following. There were almost no changes in ultrastructure of the enamel – there were outlines of the enamel prisms. There is absence of smooth enamel areas. This indicates at slight abrasive effect of these toothpastes (Fig. 8, 9).

After usage of peroxide containing bleaching system Opalescence 45 % (Ultradent Products Inc.) was revealed the following. Enamel prisms outlines were practically lost. On the enamel surface were visible microscopic cracks, scratches, furrows, areas of demineralization of enamel crystals (Fig. 10, 11). Overall, this indicated that this bleaching system had less abrasive action.

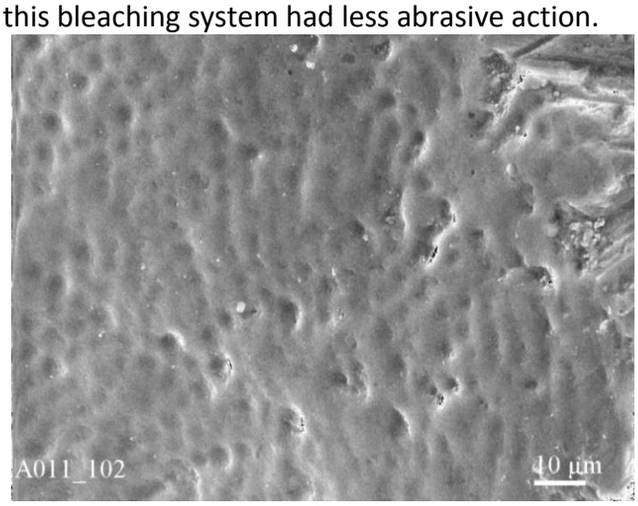

Fig. 8. Enamel surface of the tooth after cleansing with abrasive toothpaste with RDA= 75. Clearly visible outlines enamel prisms. Scanning electron micrograph, x 1000

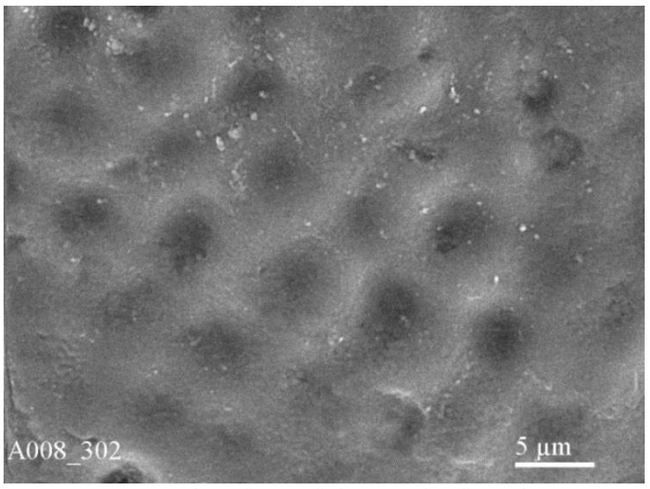

Fig. 9. Enamel surface of the tooth after cleansing with abrasive toothpaste with RDA= 75. Clearly visible outlines enamel prisms. Scanning electron micrograph, x 2000

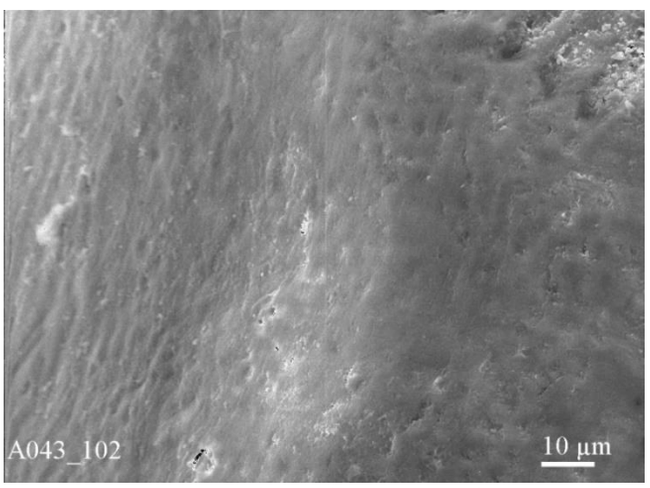

Fig. 10. Enamel surface of the tooth after usage of bleaching system Opalescence 45%. There are areas of smooth enamel and demineralization of enamel crystals. Scanning electron micrograph, x 1000

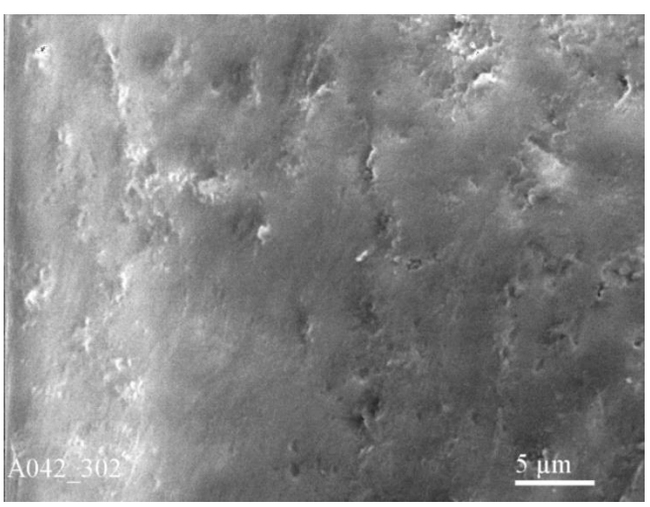

Fig. 11. Enamel surface of the tooth after usage of bleaching system Opalescence 45%. There are areas of smooth enamel and demineralization of enamel crystals. Scanning electron micrograph, x 2000

However, it greatly smoothed the surface of the enamel, which may indicate that this bleaching system to some extent dissolved the enamel surface layer.

After usage of professional bleaching system Yotuel 7 Hours (10% carbamide peroxide) destructive areas of enamel surface with "typical" ultramicroscopic structure were founded. Also, there were visible scratches on the enamel surface (Fig. 12, 13). Revealed changes suggest that this bleaching system dissolved the enamel surface and had relatively little abrasive effect.

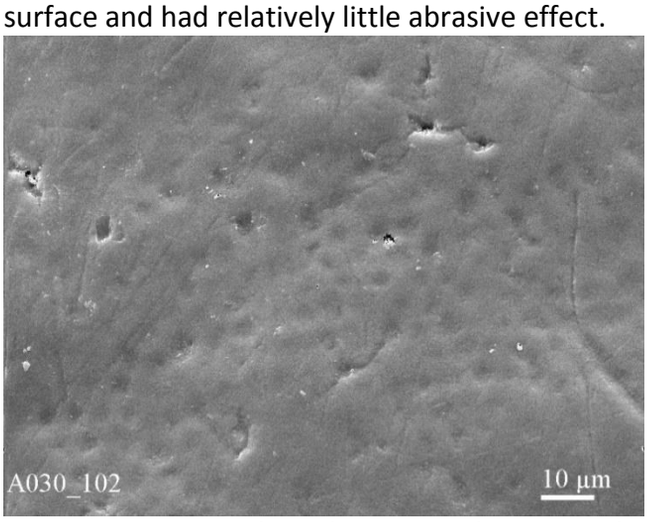

Fig. 12. Enamel surface of the tooth after usage of bleaching system Yotuel 7 Hours. Clearly visible destructive areas of enamel surface with "typical" ultramicroscopic structure. Scanning electron micrograph, x 1000

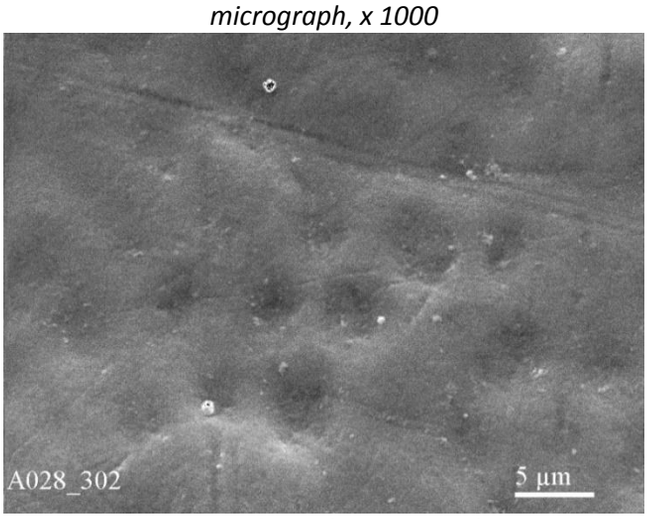

Fig. 13. Enamel surface of the tooth after usage of bleaching system Yotuel 7 Hours. Clearly visible destructive areas of enamel surface with "typical" ultramicroscopic structure. Scanning electron micrograph, x 2000

Discussion. An electronic microscopic investigation has shown that toothbrushing with a RDA 200 abrasive toothpaste causes a characteristic mechanical damage to the enamel

surface of the teeth due to the effect of the high abrasive elements of the toothpaste. Toothbrushing with whitening toothpaste with a RDA 120 abrasive index leads to less significant changes in the enamel surface, which indicates a lesser damaging effect of the paste on the enamel surface. Toothbrushing with toothpaste with low abrasive elements RDA 75 causes slight damage to the enamel surface, which indicates a slight abrasive effect of the toothpaste.

Bleaching of the teeth surfaces with a peroxide-containing whitening system Opalescence 45% (Ultradent Products Inc.) with less abrasive action results in smoothing of the enamel surface, indicating that this whitening system dissolves to a certain extent the enamel surface. The use of professional bleaching with the use of the Yotuel 7 Hours system results in the formation on the surface of enamel of areas of destruction of enamel with a "characteristic" ultramicroscopic structure. This indicates that this bleaching system dissolves the surface of the enamel although it has a relatively small abrasive effect.

The obtained data on the composition of bleaching toothpastes, their influence on the microflora and on the surface of the enamel of teeth provided the basis for a differential choice of personal hygiene products for use in the complex treatment of tooth discoloration in patients with periodontal disease.

Conclusions. The electronic microscopic investigation to some extent consistent with findings of a number of works which marked bleaching effectiveness of various facilities [18, 19, 13, 1, 16], their impact on enamel morphology [5, 17]. To prevent complications that arise as a result of bleaching, it is necessary to prescribe local remineralization therapy with hydroxyapatite- and fluoride containing facilities of individual or professional oral hygiene [7, 22, 3].

Electronic microscopic studies confirmed the need of a differentiation of bleaching facilities, depending on the patient's teeth status. This will achieve an aesthetic effect with minimum damaging effects on hard tooth tissues.

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STUDY OF THE STATE OF COMPENSATORY-ADAPTIVE MECHANISMS IN PREGNANT WOMEN WITH ADENOMATOUS GOITER

Abstract. *One of the most important functions of the thyroid gland is maintenance of a normal course of pregnancy and development of different organs and systems of the fetus. Any changes in the thyroid functions associated with metabolic disorders, disturbances of neuron-endocrine regulation can result in disorders of compensatory-adaptive mechanisms of the maternal organism and fetus. The state of lipid peroxide oxidation processes and efficacy of blood antioxidant defense in pregnant women with adenomatous goiter was studied depending on the degree of severity of the pathology. Pregnant women with I degree adenomatous goiter were found to have insufficiency of the protective antioxidant system (AOS) and exertion of the body compensatory-adaptive mechanisms. Pregnant women with II degree adenomatous goiter were found to have exhaustion of AOS components in response to considerable activation of lipid peroxide oxidation, which is indicative of exhaustion of the body compensatory-adaptive mechanisms before labor.*
Key words: *pregnancy, adenomatous goiter, lipid peroxide oxidation, protective antioxidant system.*

Thyroid diseases are one of the most frequent endocrine pathologies. They are found 10-15 times more frequently among women than in men. They are manifested during young reproductive age [3, 5]

The thyroid gland of the mother and fetus is considered to be regulated independently. At the same time, the hormones of the maternal thyroid gland are partially transmitted through the placenta. The hormones of the maternal thyroid gland play an important role during the whole gestational period. They effect the growth and differentiation of tissues, ossification processes, and formation of the central nervous system of the fetus [3, 5, 6].

On the level of target tissues thyroid hormones stimulate protein synthesis, regulate thermogenesis and energy balance, effect sexual development, menstrual function, and different metabolic processes. The most important function of the thyroid hormones is providing development of other organs and systems during the whole period of embryogenesis beginning from the first weeks of pregnancy. Due to this fact any changes in the thyroid function, even inconsiderable ones, provoke an increased risk of disorders in the development of the nervous and other systems of the body. Association with other disorders from the side of the neuron-endocrine regulation, hormonal balance, metabolic processes can result in disturbances of the compensatory-adaptive mechanisms of the maternal organism and fetus [3, 5, 6]

Investigation of clinical issues from the position of examination of membranous disorders is considered to be perspective [4, 7]. Lipid peroxide oxidation (LPO) is known to be one of the causes provoking disorders in the structure and function of cellular membranes. Toxic radicals formed in the process of lipid peroxidation produce harmful action on the proteins of the cellular membranes promoting disorders of enzymatic and hormonal functions of the body [1, 7, 8]. LPO processes within the norm are maintained on the physiological level due to the protection system existing in the cells of living organisms, and which is called antioxidant system (AOS) [2, 4, 7].

Metabolic processes in pregnant women suffering from adenomatous goiter have not been studied substantially. Lipid peroxide oxidation processes and antioxidant defense in pregnant women depending on the degree of adenomatous goiter have not been studied adequately either. These data are essential for identifying the mechanisms of adaptive response under stressful situation during labor, which is important for improvement of tactics of management of pregnancy and labor.

Objective: to study the state of lipid peroxide oxidation and efficacy of antioxidant blood defense in pregnant women suffering from adenomatous goiter depending on the degree of the pathology.

Materials and methods. The indices of LPO and AOS of the blood were studied during 22-24 and 34-36 weeks of pregnancy in 20 healthy women (control group) and 54 patients suffering from adenomatous goiter including 34 pregnant women with I degree adenomatous goiter (I group) and 20 individuals with II degree of adenomatous goiter (II group).

The content of LPO products in erythrocytes was determined by the level of lipid hydroperoxides and Malone dialdehyde. The state of AOS was assessed according to the content of reduced glutathione in erythrocytes and activity of glutathione peroxidase enzyme.

The data obtained were statistically processed by means of Student t-criterion. Changes were considered to be statistically significant with $p < 0,05$. Statistical calculations were performed by means of the electron table Exel for Microsoft Office.

Results and discussion. The age of the examined women varied from 20 to 34 years, and its was on an average 24,51±2,71 years in the main group and 25,12±2,21 – in the control one ($p>0,05$).

The structure of extragenital pathology mostly included increased anemia during pregnancy among the women from the main group in comparison with the control one (64,8% against 15%, $p<0,001$), bacteriuria (31,48% against 5%, $p<0,001$), gestational pyelonephritis (11,7% against 5%, $p<0,005$), hypotension (20,37% against 5%, $p<0,005$).

The course of pregnancy among the women from the main group was often complicated by preeclampsia: mild preeclampsia was found in 15 (27,78%) cases, moderate in 6 (11,7%), severe in 2 (3,7%). In the control group of women mild preeclampsia was found in 1 (5%) case. Threat of miscarriage was determined in 27 (50%) women from the main group and 2 (10%) – from the control group, $p<0,001$. Retardation of the intrauterine fetal development was diagnosed in 4 (7,4%) cases from the main group, and it was not diagnosed in the control group. A high rate of colpitis of various etiology should be noted here among the women from the main group (66,7%). Fungal infection caused by Candida albicans was registered in 27 (50%) pregnant women. These results correlate with those found in scientific literature [3, 5].

LPO processes were found to be activated even among healthy women. Thus, in 22-24 weeks of pregnancy the content of lipid hydroperoxides was 1,29±0,02 micromole/ml of erythrocytes, and in 34-36 weeks – 1,34±0,01 micromole/ml of erythrocytes ($p< 0,05$). The amount of Malone dialdehyde increased at the same time. In 22-24 weeks of pregnancy its content was 110,3±3,4 micromole/ml of erythrocytes, and in 34-36 weeks – 122,6±4,2 micromole/ml of erythrocytes, ($p< 0,05$). In response to increased content of LPO products healthy pregnant women developed activation of AOS of the blood. The content of glutathione in 22-24 weeks of pregnancy was 30,6±1,2 micromole/ml of erythrocytes, and in 34-36 weeks – 34,8±1,1 micromole/ml of erythrocytes, ($p< 0,05$). The content of glutathione peroxidase in 22-24 weeks was 23,4±1,1 micromole/ml of erythrocytes, and in 34-36 weeks – 27,6±1,2 micromole/ml of erythrocytes, ($p< 0,05$). Therefore, in healthy pregnant women LPO processes are intensified parallel to AOS activation, which is a compensatory-adaptive response of the body to prevent a harmful action of free radical lipid peroxidation products on different organs and tissues.

Higher intensification of LPO processes was found among women suffering from adenomatous goiter. Women with I degree adenomatous goiter developed increased content of lipid hydroperoxides (1,47±0,04 micromole/ml of erythrocytes in 22-24 weeks of gestation and 1,55±0,06 micromole/ml of erythrocytes in 34-36 weeks, ($p< 0,05$) and Malone dialdehyde (128,6±4,2 micromole/ml of erythrocytes and 135,8±3,5 micromole/ml of erythrocytes in 22-24 and 34-36 weeks of pregnancy respectively). At the same time, the content of reduced glutathione did not raise (34,3±1,2 micromole/ml of erythrocytes), which is indicative of the signs of antioxidant insufficiency of the body.

More considerable disorders in LPO and AOS systems were found in women suffering from II

degree adenomatous goiter. At the end of pregnancy in response to considerable activation of LPO the content of glutathione decreased (34,3±1,2 micromole/ml of erythrocytes and 24,5±0,9 micromole/ml of erythrocytes in 22-24 and 34-36 weeks of gestation respectively (p< 0,001), as well as activity of glutathione peroxidase reduced (33,4±1,3 micromole/ml of erythrocytes in 22-24 weeks and 27,6±1,2 micromole/ml of erythrocytes in 34-36 weeks of gestation, p< 0,001). It is indicative of exhaustion of AOS defense and compensatory-adaptive mechanisms of the organism of pregnant women.

Among the examined women from the control group the outcome of pregnancy was physiological labor in 20 (100%) of cases. Premature rupture of amniotic fluid sac (PRAFS) was registered in 1 (5%) women. The following complications in labor were found among the patients from the main group: poor birth activity – in 12 (22,2%) cases, PRAFS – in 15 (27,75%), bleeding in labor and early postnatal period – in 5 (9,25%), severe preeclampsia – in 2 (3,7%), fetal distress – in 3 (5,55%). 48 (88,9%) women with goiter gave birth through the maternal passages (physiological labor). The rest of women – 6 (11,1%) underwent Cesarean section. Indications for surgery were the following: poor birth activity, premature exfoliation of normal placenta, and fetal distress. This percentage of complications and pathologic labor in women from the main group was likely associated with high frequency of complications during the gestational period.

An average score of newborns according to Apgar scale in the main group was 7,6±0,1 which is reliably lower than that of the control group – 8,8±0,1 (p<0,05). It should be noted that 6 (11,1%) newborns required consultations of allied professionals concerning different developmental defects.

Conclusions. 1. In healthy women in the dynamics of pregnancy AOS activation of the blood protection occurs in response to intensification of LPO processes.

2. Pregnant women with I degree adenomatous goiter experience insufficient OAS defense and exertion of the compensatory-adaptive mechanisms of the body.

3. Pregnant women with II degree adenomatous goiter experience exhaustion of AOS defense components in response to considerable activation of lipid peroxidation processes, which is indicative of exhaustion of the compensatory-adaptive mechanisms before labor.

Prospects of further studies. Improvement of a comprehensive method of preparation and management of labor in women with adenomatous goiter considering anti-stress protective mechanisms is an advanced study. It will promote decrease of maternal and perinatal pathology.

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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NEW FUNCTIONALLY SUBSTITUTED DIALKYL CARBOXYLATE CYCLOHEXANE DERIVATIVES

Abstract. *We report synthesis and antimicrobial activity of new functionally substituted dialkyl carboxylate cyclohexane derivatives. The new cascade carboxylation reaction involving multicomponent interaction of alkyl 2-cyanoacetate (ethyl, isopropyl and butyl) with benzaldehyde and acetylacetone resulted in formation of three new dialkyl 1,3-dician-2,6-diphenyl-5-acetyl-4-hydroxy-4-methylcyclo-hexane-1,3-dicarboxylate derivatives (1a-1c). Correct elemental analysis and spectral data (IR, 1H-NMR, 13C-NMRspectra and MS) were used to characterize and confirm the structure of newly synthesized compounds. Agar well diffusion assay was used to determine antimicrobial activity of derivatives against Gram-positive and Gram-negative bacteria, and fungi. The synthesized compounds showed variable antimicrobial activity and were found to be more active against Gram-negative bacteria as compared to gram-positive bacteria and fungi.*

Keywords: *antimicrobial activity, cyclohexane derivatives, alkyl 2-cyanoacetate, benzaldehyde, acetylacetone, agar well diffusion*

Introduction. Due to ever increasing antimicrobial resistance and shortage of new antimicrobial drugs, synthetic organic compounds are extensively synthesized and explored as probable antimicrobial agents. Functionally substituted alicyclic compounds are best available targets [1]. One of the developed trends of modern organic chemistry in recent years is related with the development of productive methods for the synthesis of complex carboxy-heterocyclic compounds. The effectiveness of these methods is provided through creation of synthesis schemes with minimal stages, total convergence and minimal consumption of reagents, solvents and other material resources. The trend of multicomponent reactions has rapidly increased in the synthetic arsenal of organic chemistry. Multicomponent reactions are carried out in a single reactor on the basis of interaction of at least three substances. All the added reagents simultaneously constitute the final product through consistently happening elementary transformations i.e. cascade or tandem reactions [2-5]. Methylene active nitriles (malononitrile, malonodinitrile, alkyl 2-cyanoace-tates etc.) are one of the bifunctional reagents that perform as basis of various multicomponent reactions, generating multi vectoral transformations [6-8]. The chemistry of these compounds has not yet fully expanded its synthetic potential. Therefore in present study, we report the new cascade carboxylation reaction involving multicomponent interactions for synthesis of new dialkyl 1,3-dician-2,6-diphenyl-5-acetyl-4-hydroxy-4-methylcyclo-hexane-1,3-dicarboxylate derivatives and evaluation of their antimicrobial potential.

Purpose of study. The aim of the current research focuses to determine the new directions of the interaction of benzaldehyde, alkyl 2-cyanoacetate and acetylacetone in multicomponent cascade environment. The reaction of these reagents usually results in formation of 2-aminopyrene compounds [9-14]. But here, with help of new cascade caboxylation system, we focus on synthesis and antimicrobial activity of novel dialkyl dicarboxylate cyclohexane derivatives.

Material and methods. Synthesis of functionally

substituted dialkyl dicarboxylate cyclohexane derivatives. Cascade reaction involving multicomponent interactions of alkyl 2-cyanoacetate (ethyl, isopropyl and butyl) with benzaldehyde and acetylacetone led to development of three new dialkyl 1,3-dician-2,6-diphenyl-5-acetyl-4-hydroxy-4-methylcyclo-hexane-1,3-dicarboxylate derivatives: Diethyl 1,3-dician-2,6-diphenyl-5-acetyl-4-hydroxy-4-methylcyclohexane-1,3 dicarboxylate(1a), Diisopropyl 1,3-dician-2,6-diphenyl-5-acetyl-4-hydroxy-4-methylcyclo-hexane-1,3-dicarboxylate(1b) and Dibutyl 1,3-dician-2,6-diphenyl-5-acetyl-4-hydroxy-4-methylcyclohexane-1,3-dicarboxylate(1c).

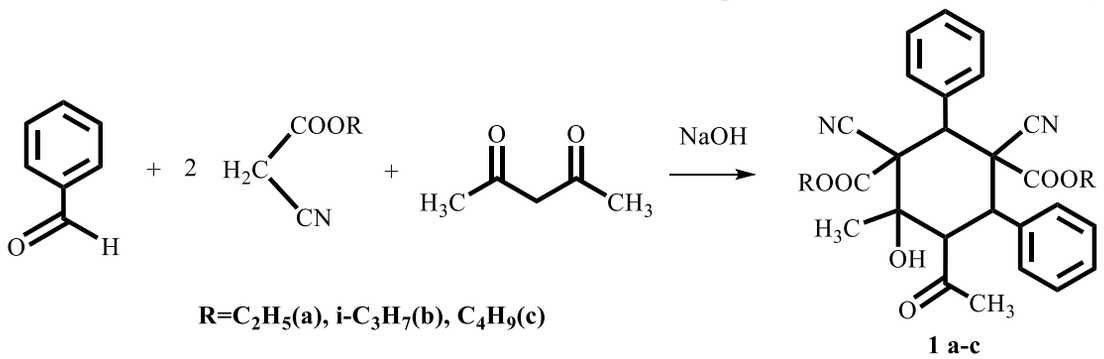
10 ml of ethanol, 0.53g of benzaldehyde (5 mmol) and 10 mmol of alkyl 2-cyanoacetates (ethyl for 1a, isopropyl for 1b and butyl for 1c) were placed in 50ml flat flask supplied with magnetic mixer. Afterwards, 3 ml of water solution of 0.1g of NaOH was added to the reaction medium in mixing condition. After half an hour, 0.5g of acetylacetone (5 mmol) and 0.53g of benzaldehyde (5 mmol) were added to the medium. The reaction medium was kept at room conditions for 48 hours after mixing for one more hour. The precipitated crystals were filtered and recrystallized in ethanol.

At the first stage, the intermediates of benzaldehyde and alkyl 2-cyanoacetates (A), and benzaldehyde and acetylacetone (B) are taken in the presence of NaOH as shown in scheme 2.

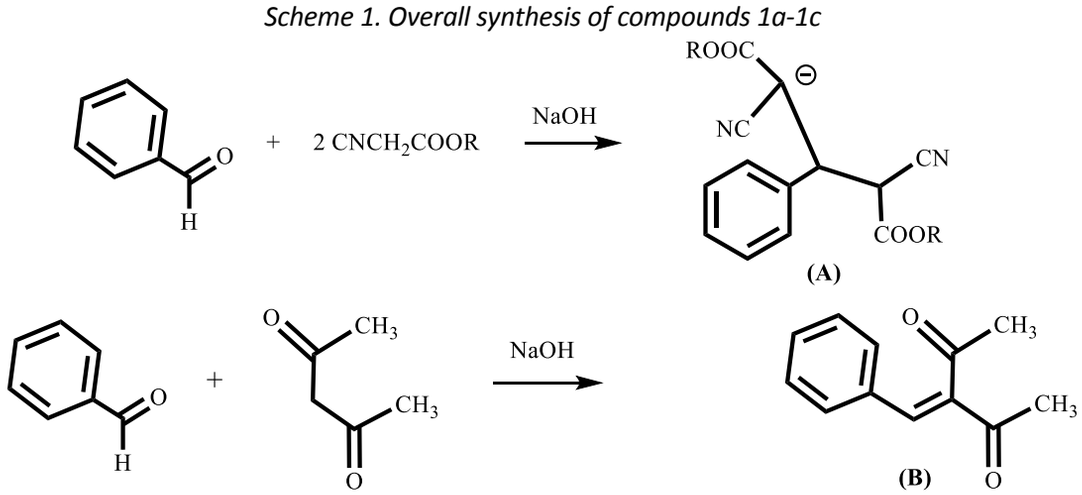
Subsequently, the phases of these intermediates are formed by the cascade carboxylation reaction as shown in the following scheme 3.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 instrument (300 MHz on ^{1}H and 75 MHz nuclei at ^{13}C cores) in a $(CD_3)_2SO$ solution, as residual signals of the solvent were used as the standard. The melting points were determined on a Kofler's table. TLC monitored the purity of the resulting compounds on *Silufol UV-254* plates, eluent acetone-hexane 1:1, developer-iodine vapor, UV detector. Carlo Erba 1106 analyzer was used to perform elemental analysis for C, H, and N.

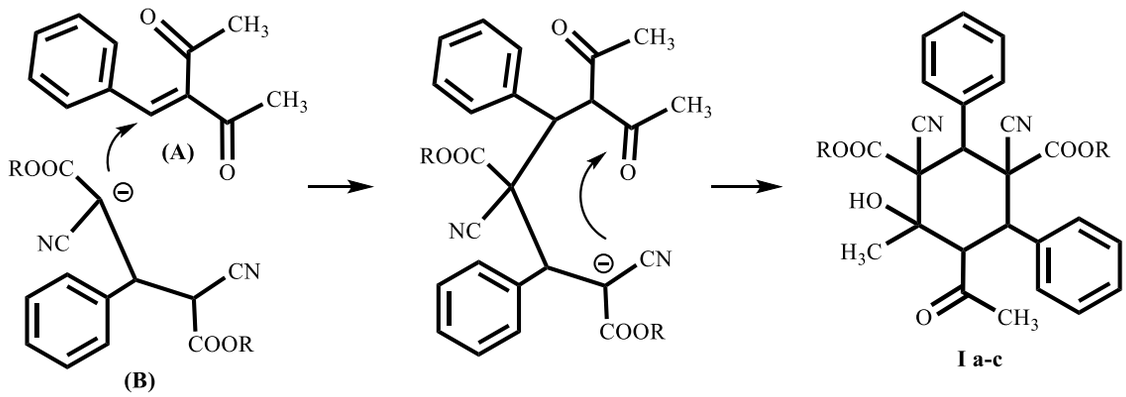
Determination of antimicrobial activity. Standard agar well diffusion assay [15] was used to determine antimicrobial properties of novel compounds. *In vitro* antibacterial properties were evaluated against *Escherichia coli BDU-12,*



Scheme 1. Overall synthesis of compounds 1a-1c



Scheme 2. Formation of intermediates A and B



Scheme 3. Interaction of intermediates A and B

Klebsiella pneumoniae BDU-44, Acinetobacter baumannii BDU-32, Pseudomonas aeruginosa BDU-49, Staphylococcus aureus BDU-23, Bacillus Subtilis BDU-50, Bacillus mesentericus BDU-51 and *Bacillus megaterium BDU-N20* using Mueller-Hinton agar and antifungal screening was performed against *Candida tropicalis BDU LK30, Candida pelliculosa BDU KT55* and *Candida pseudotropicalis BDU MA88* using sabouraud dextrose agar. All the test cultures were obtained from our own collection at Department of Microbiology, Baku State University. Three different concentrations of test compounds; 0.3% (3 mg of test compound per mL of DMSO), 0.1% (1 mg of test compound per mL of DMSO) and 0.05% (0.5 mg of test compound per mL of DMSO) were selected. DMSO was used as control and all the experiments were performed in triplicates.

Results. Diethyl 1,3-dician-2,6-diphenyl-5-acetyl-4-hydroxy-4-methylcyclohexane-1,3 dicarboxylate(1a). The synthesized compound is colorless solid in the yield of 67%. Melting point was found to be 163^{0}C. ^{1}H-NMRspectrum (300 MHz, $(CD_3)_2SO$), δ, ppm:1.00 (t, 3 H, $OCH_2C\underline{H}_3$); 1.07 (t, 3 H, $OCH_2C\underline{H}_3$); 1.10 (3H, s, $C\underline{H}_3$);2.1 (3H, s, $C\underline{H}_3$);2.65 (1H, d, C<u>H</u>); 3.55 (1H, d, C<u>H</u>); 3.90 (1H, s, C<u>H</u>); 4.04-4.10 (m, 4 H, 2 $OC\underline{H}_2CH_3$,); 4.90 (1H, s, O<u>H</u>); 7.39-7.41 (m, 6 H, Ph); 7.64-7.65 (m, 4 H, Ph). ^{13}C-NMRspectrum (75 MHz, $(CD_3)_2SO$), δC, ppm:13.46 ($OCH_2\underline{C}H_3$); 13.49 ($OCH_2\underline{C}H_3$); 19.32 ($\underline{C}H_3$); 31.17 ($\underline{C}H_3$); 40.52 (<u>C</u>H); 46.26 (<u>C</u>H); 50.33 (<u>C</u>H);63.86 ($O\underline{C}H_2CH_3$); 63.89 ($O\underline{C}H_2CH_3$); 69.59(<u>C</u>-OH);116.22 (C≡N); 117.37 (C≡N); 128.61(Ph); 129.63 (Ph); 130.66 (Ph); 131.79 (Ph); 163.41 ($\underline{C}O_2Et$); 165.13 ($\underline{C}O_2Et$); 207.20 (C=O). Found, %: C-69.40, H-6.10, N-5.60; $C_{29}H_{30}N_2O_6$, Calculated, %: C-69.31, H-6.02, N-5.57.

Diisopropyl 1,3-dician-2,6-diphenyl-5-acetyl-4-hydroxy-4-methylcyclo-hexane-1,3-

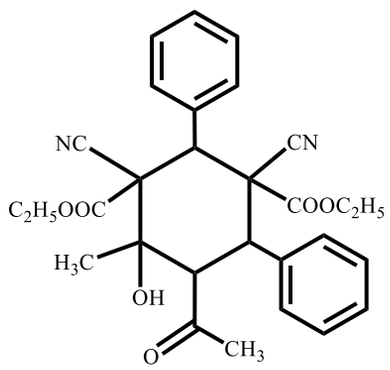


Fig.1. Structure of compound 1a

dicarboxylate(1b). The synthesized compound is colorless solid in the yield of 63%. Melting point was found to be 178^{0}C. ^{1}H-NMRspectrum (300 MHz, $(CD_3)_2SO$), δ, ppm: 1.17–1.33 m [12H, $CH(C\underline{H}_3)_2$], 1.10 (3H, s, $C\underline{H}_3$); 2,12 (3H, s, $C\underline{H}_3$); 2.74 (1H, d, C<u>H</u>); 3.55 (1H, d, C<u>H</u>); 3.85 (1H, s, C<u>H</u>);5.00–5.12 m [2H, $CH(CH_3)_2$];7.30- 7.57,(m, 10H, Ph). ^{13}C-NMRspectrum (75 MHz, $(CD_3)_2SO$), δC, ppm: 20.10 ($\underline{C}H_3$); 21.13 [$CH(\underline{C}H_3)_2$], 21.15 [$CH(\underline{C}H_3)_2$], 21.22 [$CH(\underline{C}H_3)_2$], 21.26 [$CH(\underline{C}H_3)_2$], 30.17 ($\underline{C}H_3$);40.56 (<u>C</u>H); 46.28 (<u>C</u>H); 50.39 (<u>C</u>H); 72.74 [<u>C</u>H(CH$_3$)$_2$]; 73.13[<u>C</u>H(CH$_3$)$_2$]; 115.22 (C≡N), 116.19 (C≡N), 128.60 (Ph); 129.63 (Ph); 130.61 (Ph); 131.87 (Ph); 163.15 (CO_2Pr-i); 164.92 (CO_2Pr-i), 206.13 (C=O). Found, %: C-70.25; H-6.52; N-5.32; $C_{31}H_{34}N_2O_6$, Calculated, %: C-70.17; H-6.46; N-5.28.

Dibutyl 1,3-dician-2,6-diphenyl-5-acetyl-4-hydroxy-4-methylcyclohexane-1,3-dicarboxylate(1c). The synthesized compound is colorless solid in the yield of 55%. Melting point was found to be 205^{0}C. ^{1}H-NMRspectrum (300 MHz, $(CD_3)_2SO$), δ, ppm: 0,98 (t, 4H, $OCH_2CH_2CH_2C\underline{H}_3$);1.00(t,3H, $OCH_2CH_2CH_2C\underline{H}_3$);1.10 (3H, s, $C\underline{H}_3$); 1,20-1,30 (8H, m,$C\underline{H}_2$); 2,17 (3H, s, $C\underline{H}_3$); 2.75 (1H, d, C<u>H</u>); 3.55 (1H, d, C<u>H</u>); 3.85(1H, s, C<u>H</u>); 3.95-4.10 (m, 4 H, 2$OC\underline{H}_2CH_2CH_2CH_3$); 5.06(1H, s, O<u>H</u>); 7.30-7.55 (m,10H, Ph). ^{13}C-NMRspectrum (75 MHz, $(CD_3)_2SO$), δC, ppm: 13.26 ($OCH_2CH_2CH_2\underline{C}H_3$); 13.50 ($OCH_2CH_2CH_2\underline{C}H_3$);

17.25($\underline{C}H_2$); 18.20($\underline{C}H_2$); 19.33($\underline{C}H_3$); 31.20 ($\underline{C}H_3$); 32.18($\underline{C}H_2$);33.37($\underline{C}H_2$);40.55 ($\underline{C}H$); 46.27 ($\underline{C}H$); 50.32 ($\underline{C}H$); 63.86 ($O\underline{C}H_2$); 63.89 ($O\underline{C}H_2$); 69.59 ($\underline{C}$-OH);116.17 (C≡N); 117.63 (C≡N); 128.21 (Ph); 129.43 (Ph); 131.23 (Ph); 132.37 (Ph); 164.44 ($\underline{C}O_2C_4H_9$); 165.71 ($\underline{C}O_2C_4H_9$); 208.80 (C=O). Found, %: C-71.05; H-7.04; N-5.11; $C_{33}H_{38}N_2O_6$, Calculated, %: C-70.95; H-6.96; N-5.01.

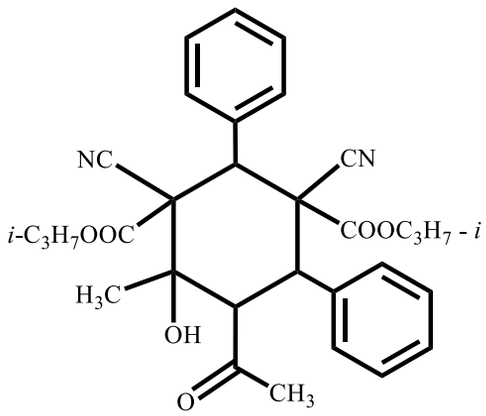


Fig.2. Structure of compound 1b

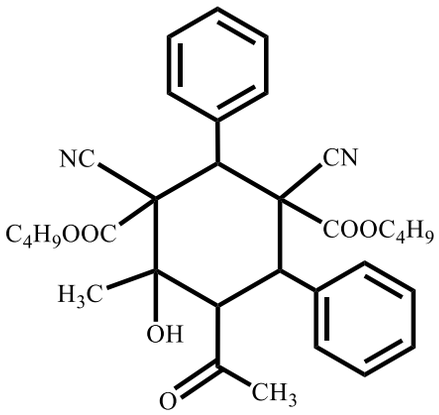


Fig.3. Structure of compound 1c

Antimicrobial activity. The antimicrobial activity of newly synthesized compounds (1a-1c) was tested against four Gram-negative bacteria, four Gram-positive bacteria and three yeast species. Tested compounds exhibited variable antimicrobial activity at concentration of 0.3% and 0.1%. DMSO was used as control and showed no activity against any of tested cultures. Overall results of antimicrobial activity are listed in table 1.

Table 1.

Average diameter of inhibition zone in mm

Test Culture	1a		1b		1c		DMSO
	0.3%	0.1%	0.3%	0.1%	0.3%	0.1%	
Escherichia coli	14.7±0.3	-	18±0.5	-	25±0.6	13±0.3	-
Klebsiella pneumoniae	-	-	-	-	-	-	-
Acinetobacter baumannii	17.3±0.9	14.7±0.7	19.3±1	16.3±0.3	23±0.1	-	-
Pseudomonas aeruginosa	12.3±1	-	15.3±0.9	-	-	-	-
Staphylococcus aureus	-	-	12.7±0.2	-	19.7±0.7	12±0.3	-
Bacillus Subtilis	14.7±0.3	-	-	-	-	-	-
Bacillus megaterium	-	-	11.7±0.6	-	11.7±0.7	-	-
Bacillus mesentericus	13.3±0.7	-	-	-	-	-	-
Candida tropicalis	-	-	-	-	-	-	-
Candida pelliculosa	-	-	-	-	-	-	-
Candida pseudotropicalis	-	-	-	-	-	-	-

(-)*: Inactivity*

Discussions. In the present study, it has been found that the use of benzaldehyde, alkyl 2-cyanoacetate and acetylacetone in a sequence of reactions and the use of sodium hydroxide as a catalyst by the acquisition of functional cyclohexane derivatives results in an original carboxylation reaction. Previously such multicomponent cascade reactions have been used for synthesis of 2-aminopyrene compounds [12-14]. The interaction of intermediates of benzaldehyde and alkyl 2-cyanoacetates (A) and benzaldehyde and acetylacetone (B) in the presence of sodium hydroxide is manifestation of new cascade carboxylation reaction.

All the synthesized compounds (1a-1c) are colorless solids with the yield between 67% and 55%. It is observed that with the increase in Carbon chain length of alkyl group, yield of the compound decreases and melting point increases. That's why minimum yield and maximum melting point was found for butyl derivative (1c) as compared to ethyl and isopropyl (1a and 1b, respectively) derivatives.

Compounds exhibited weak to moderate activity against different test cultures at 0.3% and 0.1% concentration. All the compounds were inactive at concentration of 0.05%. None of the

compound was found to be active against fungal strains. Generally, compounds showed better antimicrobial activity against Gram-positive bacteria as compared to Gram-negative bacteria. Benzofuran cyclohexane-5-carboxylate derivatives show more potent activity against Gram-positive bacteria as compared to Gram-negative bacteria [16]. These results contradict with our findings, which is due to presence of dialkyl group in our compounds. *Acinetobacter baumannii* and *Escherichia coli* were most sensitive test cultures. Compound 1c was found to be most active antibacterial compound, as zone of inhibition (25mm, 23 mm for *Escherichia coli* and *Acinetobacter baumannii,* respectively) was observed. Thus, increase in carbon chain length of alkyl group resulted in better antimicrobial activity of the synthesized compounds.

Conclusion. The novel cascade carboxylation system involving interactions of alkyl 2-cyanoacetate (ethyl, isopropyl and butyl) with benzaldehyde and acetylacetone led to formation of three new dialkyl 1,3-dician-2,6-diphenyl-5-acetyl-4-hydroxy-4-methylcyclo-hexane-1,3-dicarboxylate derivatives. New transformations i.e. cascade carbo-cyclation were determined during interaction of benzaldehyde, alkyl 2-cyanoacetates and acetylacetone. The structure of compounds was confirmed by elemental analysis and spectral data. These compounds exhibited moderate antibacterial activity against Gram-negative bacteria and weak activity against Gram-positive bacteria, and showed no activity against fungi.

Prospects for further research. Due to perpetual increasing antimicrobial resistance and dearth of new classes of antimicrobial drugs, cascade carboxylation system should be envisioned as productive method for synthesis of new compounds having better antimicrobial potential due to their unique mode of action.

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CLINICAL EVALUATION OF THE FIBER MATRIX APPLICATION EFFECTIVENESS DURING THE GUIDED BONE REGENERATION OF PERIODONTAL INTRAOSSEOUS JAW DEFECTS

Abstract. *Modifications of the surgical manipulation algorithms aimed at providing the mechanism of periodontal regeneration requires detailed study in the course of clinical research and appropriate examination on sufficient clinical samples of patients under conditions of direct and remote monitoring of relevant criteria changes for assessing the success of the treatment. Objective was to determine the level of efficacy and substantiate the reasonability of application of fibrous matrix of polylactic acid foams as an alternative approach to target bone regeneration in the process of reconstruction of the intraosseous periodontal defects of the jaws. The total study involves 56 patients with diagnosed intraosseous jaw defects associated with the pathology of marginal periodontitis, and without available contraindications for the procedure of target bone regeneration. Treatment of intraosseous periodontal defects among the patients of the experimental group was performed by filling the prevailing defect volume by the developed fibrous matrix followed by overlapping it with the minimum portion of bone graft (CeraBone, Botiss) and polymeric membrane (KLS Martin), modified individually according to the defect configuration by thermosetting compression method. During evaluation of bone defect volume reduction after 12 months of surgery using the data of Cone-beam Computed Tomography and the graphic principle of super-imposition, it was found that in the experimental group bone defect volume decreased by 31,19 ± 4,07 standard units (from 62,56±4,25 to 31,37±4,18 standard units), and in the comparison group by 29,18±1,39 standard units (from 59,74±3,91 to 30,56±2.,2 standard units). The computer analysis of the treatment of periodontal defects with the use of fibrous matrix and xenografts enables us to recommend the use of fibrous polylactic acid foams matrix as a modification of the classical approach of target bone regeneration during rehabilitation of patients with periodontal lesions.*
Key words: *periodontal surgery, regeneration, jaw defects, treatment.*

Introduction. The task of periodontal therapy is realization of the primary and secondary prevention of periodontal diseases by means of controlling the factors of infection and inflammation, maintenance and improvement of the condition and function of the gums, periodontal ligament, cement of the root and surrounding alveolar bone, which all together form the structure of the dental periodontium [1, 2, 3, 4]. Success of periodontal surgery depends on a number of local and patient-associated factors. It can be achieved only in case of complete elimination of an infectious focus and providing appropriate conditions for the following regeneration of the periodontal tissue [1, 2, 4].

Results of systematic examination conducted by Kao R.T. et al. (2015) determined that application of different biologically active agents with the purpose to improve the protocols of treatment of periodontal defects are characterized by the effect of the similar procedure to perform intraosseous damages by means of allografts or manipulation of target tissue regeneration [5]. At the same time all the above approaches provide achievement of better results of treatment in comparison with performing mechanical cleaning of the area of a defect only.

Although, even in spite of such conclusions of a systematic examination and considering variability of the existing surgical approaches to treatment of periodontal defects, while choosing the method of surgery and appropriate materials a doctor should consider effect of a number of local and general factors with the aim to predict success of surgery [2, 6]. Modification of the algorithms of surgical manipulations with the purpose to provide the mechanisms of periodontal regeneration require a detailed examination in the course of clinical studies and appropriate checking on sufficient clinical sampling of patients under conditions of a direct and remote monitoring by the changes of appropriate criteria of assessment of the

conducted treatment success.

Objective: to determine the level of efficacy and substantiate the reasonability of application of fibrous matrix of polylactic acid foams as an alternative approach to a target bone regeneration in the process of reconstruction of the intraosseous periodontal defects of the jaws.

Materials and methods. With the aim to realize a stated objective the process of investigation was divided into two interrelated stages. At the first stage the search and systematization of data were performed concerning the results of treatment of intraosseous periodontal defects of the jaws using various surgical algorithms and osseous agents of different origin in order to fill intraosseous lesions. Google Scholar (https://scholar.google.com.ua/) was used as the main search system, providing the process of search by the main key words. The publications selected for further work were processed by means of content-analysis method with formulation of appropriate categories of the study.

The second stage of the study expected treatment of intraosseous defects of the jaws among periodontal patients at the clinical base of Ivano-Frankivsk National Medical University applying two different surgical approaches. According to their peculiarity the group of comparison and the group of control were formed.

Formation of the generally examined number of patients included consideration of a number of clinical factors used as inclusion criteria: 1) periodontitis at the remission stage without pronounced inflammatory changes on the moment of performing surgery; 2) availability of three or two-walled intraosseous periodontal defects in the area of the afflicted teeth evidenced clinically and by X-ray; 3) the lack of performing surgery in the area of intraosseous defect during the previous 12 months; 4) rejection from antibiotics during the previous 3 months; 5) possibility to correct the degree of oral hygiene and maintenance of its appropriate level during a long period of time by means of teaching, motivation and controlling a patient; 6) a patient's written consent to perform a complex of diagnostic (conical-radiation computed examination, probing, instrumental diagnostics) and surgical manipulations with the aim to restore intraosseous defects of the jaws and controlling the results of treatment. The following exclusive criteria were included: 1) acute periodontitis or chronic periodontitis at the stage of exacerbation; 2) systemic somatic pathology available, that potentially could influence on the result of surgery; 3) one-wall periodontal defects available; 4) smoking as a patient's bad habit, pregnancy of breastfeeding.

The final amount of the total examined sampling included 56 patients with diagnosed intraosseous defects of the jaws associated with periodontal pathology and without contraindications available concerning the procedure of direct osseous regeneration. All the patients before realization of surgery underwent detailed periodontal examination and the procedure of Cone-beam Computed Tomography. Using the method of a randomized distribution the total number of examined patients was distributed into the experimental group (29 individuals – group I) and comparison group (27 individuals – group II). Surgery was performed with the aim of directed osseous regeneration of intraosseous periodontal defects in both groups by one and the same surgeon according to the following protocol: 1) infiltration anaesthesia; 2) intra-sulcate cuts from the buccal and lingual sides; 3) separation of the mucous-periosteal flap; 4) curettage and irrigation of osseous defect, mechanical cleaning of the root of an afflicted tooth; 5) filling the area of periodontal defect; 6) reposition of the mucous-periosteal flap; 7) suture.

Treatment of intraosseous periodontal defects of patients from the experimental group was conducted by means of filling of the prevailing amount of defects developed by the article's authors by means of the fibrous matrix followed by overlapping with a minimum portion of the osseous augment (CeraBone, Botiss) and polymeric membrane (KLS Martin), modified individually according to the peculiarities of the defect configuration by means of thermosetting compression method (Certificate for Invention of Ukraine № 114143). The fibrous matrix was made of polylactic acid polymeric foams Resorb X produced by KLS Martin, by means of polymer phase separation method followed by gamma sterilization. The applied fibrous matrix was on an average 30 mm thick, and the diameter of fibers – from 4 mcm to 10 mcm.

Osseous defects among the patients from the

comparison group were treated by mean of filling of the whole amount of the defect by bone-substitute material (CeraBone, Botiss) followed by its overlapping with a resorption membrane (Mucoderm, Botiss).

After defects were filled, the following stage of surgical manipulation included reposition of the mucous-periosteal flap to the level of the enamel-cement region with the aim to reduce apical migration of the gingival border. After the procedure of a directed osseous regeneration was over the wound was sutured completely by means of interrupted suture removed 10 days later.

Repeated periodontal examination of patients was conducted 6 months and 12 months later. Repeated procedure of the Cone-beam Computed Tomography with the purpose to analyze the amount of filling periodontal defects with the osseous tissue 12 months after primary surgery was made. A controlling tomographic examination a year later after primary surgery was proved by peculiarities of the osseous tissue visualization on the tomographic sections in the process of its formation and considering principles of radiological safety [7].

The outcome volume of osseous defects was determined in the software Materialise Mimics (Materialise NV) by means of their segmentation from the imported scans of computed tomography [8, 9, 10]. The similar procedure was performed with Cone-beam Computed Tomography (CBCT) – sections obtained a year later after surgery. Applying the principle of super-imposition the initial and residual sizes of intraosseous defects were compared determining the volume of filling the defect with the osseous tissue in standard units [11].

The depth of periodontal probing in the region of intraosseous defects was measured by means of a periodontal probe designed by the University of North Carolina marking a working part with the interval of 1 mm. The volume of the periodontal attachment loss was determined by means of summarizing the results of depth of periodontal pockets and assessment of apical migration of the gingival border [12, 13]. With the purpose of representation mean values in every group of patients, mean difference of the given parameters after 6 and 12 months of monitoring, the level of statistical significance of the obtained results and their difference were determined.

The results were statistically processed in the software Microsoft Excel 2016, included in the software packet of Microsoft Office 2016 (Microsoft).

Results. The total examined sampling involved 56 patients including 29 patients (51,79%) from the group I (experimental group) and 27 patients (48,21%) from the group II (comparison group). By gender signs the patients were distributed in the following way: 13 men (44,83%) and 16 women (55,17%). Statistically this distribution did not differ from that registered in the comparison group including 14 men (51,85%) and 13 females (48,15%). An average age of patients from the experimental group was 47,9±1,54 years, and the patients from the comparison group – 43,2±2,12 years.

On the moment of making periodontal examination before surgery an average parameter of the depth of periodontal probing in the region of defect in the experimental group was 5,72±1,34 mm, and in the comparison group - 5,04±1,28 mm; average parameters of the level of periodontal attachment loss were 6,88±1,34 mm and 6,51±1,28 mm in the experimental and comparison groups respectively. There was no statistical difference found between the initial parameters of the depth of periodontal probing and the level of periodontal attachment loss in the region of intraosseous defects between the two groups of the study ($p>0,05$). Therefore, they are eligible for further comparative analysis of clinical parameters at different stages of monitoring.

6 months after performed surgery the mean parameter of the depth of periodontal probing in the region of defects in the experimental group was 3,08±0,56 mm, and the average values of the periodontal attachment loss –4,24±0,59 mm. In the comparison group after the similar period of observation the mean parameter of the depth of periodontal probing in the region of defects decreased to 3,19±0,71 mm, and the level of periodontal attachment – to 4,32±0,39. 12 months later an average depth of periodontal probing in the region of defects in the experimental group where defects were filled with the use of fibrous matrix made of polylactic acid foams was 2,95±0,32 mm, and in the comparison group where osseous defects were filled with bone-substitute material – 3,01±0,57 mm. Statistical difference between the parameters of the probing depth in the region of periodontal defects marked in the experimental and comparison groups 12 months after treatment was not registered ($p>0,05$). It enables

to summarize that under the above conditions of the study both applied agents demonstrate similar clinical effect from the view of criteria changes of periodontal probing depth reduction. At the same time, in both groups the parameters of probing depth registered 12 months later after treatment were 2,77±1,02 mm and 2,03±0,71 mm ($p<0,05$) statistically smaller concerning the parameters registered before surgery respectively. A similar tendency was found during analysis of the parameter of periodontal attachment loss: 12 months after treatment an average parameter of it in the experimental group was 3,55±0,12 mm, and in comparison group – 3,22±0,41 mm (statistical difference between the groups was absent - $p>0,05$). At the same time an average level of reduction of periodontal attachment loss 12 months after surgery was 3,33±1,22 mm and 3,29±0,87 mm respectively in the group I and group II. The difference between the parameters registered before treatment and in 12 months of monitoring was statistically valuable ($p<0,05$).

While determining the reduction level of the volume of osseous defects 12 months after surgery applying the data of Cone-beam Computed Tomography and graphic principle of super-imposition it became possible to determine that in the experimental group the volume of osseous defect decreased by 31,19±4,07 standard units (from 62,56±4,25 to 31,37±4,18 standard units), and in the comparison group – by 29,18±1,39 standard units (from 59,74±3,91 to 30,56±2,52 standard units). The difference between the parameters registered before treatment and 12 months after surgery was statistically valuable ($p<0,05$).

The obtained results are indicative of the fact that application of the fibrous matrix from polylactic acid foams can serve as an effective alternative for filling of intraosseous periodontal defects of the jaws in the process of performing the procedure of target osseous regeneration. Statistical difference between the efficacy of application of the suggested fibrous matrix and bone xenograft from the view of assessment of parameters of periodontal probing depth reduction, decreased level of the periodontal attachment and filling defects with the osseous tissue after 12 months of observation under conditions of the above study was not registered ($p<0,05$). The advantages of the fibrous matrix and bone substitute of xenogenic origin consist of availability to actually unlimited volume of the material necessary for replacement of periodontal defect, exclusion of the necessity to take autogenic osseous tissue, decrease of discomfort for a patient during surgery and improvement of the algorithm of surgical manipulation directed to restoration of osseous tissue deficiency in the region of afflicted periodontal units of the dentition.

Discussion. Thus, on the basis of the conducted investigations approbation of the modified protocols of periodontal surgery was found to be reasonable with the aim to find the variants able to provide achievement of the most predicted result under certain clinical conditions. Due to this fact the use of the fibrous matrix made of polylactic acid and polymeric membranes can be considered as a relevant alternative to classical algorithms of target osseous regeneration in the process of reconstruction of intraosseous periodontal defects of the jaws requiring appropriate clinical reasoning.

Reynolds M.A. et al. (2015) in the result of conducted systematic examination came to the point that positive changes in the structure of the periodontal complex manifested in the form of increasing level of clinical attachment, reduction of the depth of periodontal pockets and radiological increase of the osseous tissue level are indirect criteria of success of the conducted periodontal treatment and the signs of realization of the mechanism of an effective regeneration of the periodontal tissue. At the same time, the authors admitted that though in the course of periodontal surgery the application of different by origin bone-substitution grafts is characterized by evidence-proved high level of efficacy, such approaches as target bone regeneration and application of biologically active agents are clinically promising in the course of rehabilitation of stomatological patients with various forms of periodontal tissue lesions [14]. While choosing an approach to treatment not only the doctor's experience and availability of different grafts should be considered, but specificity of the mechanisms of periodontal regeneration and a potential effect of different types of surgery and applied materials on them.

Conlusions. Realization of the procedure of target bone regeneration with the use of the fibrous matrix made of polylactic acid foams as the main material to fill intraosseous defects of

the jaws is an effective alternative to classical approaches of surgical treatment of two- and three-wall periodontal lesions. This approach is characterized by the advantages similar to xenografts as bone-substitutes with the analogical aim, excluding the need to remove autogenic osseous tissue, minimize discomfort during surgery and not restricting a doctor in access to the necessary volume of an applied agent. The conducted comparative analysis of the results of treatment of periodontal defects with the use of fibrous matrix and xenograft according to the parameters of reduction of the periodontal probing depth, decrease of the level of periodontal attachment loss and the volume of filling in the region of affliction with the osseous tissue as the assessment criteria, determined the lack of statistical difference between the examined parameters. In its turn, it enables to recommend application of the fibrous matrix made of polylactic acid foams as a modification of a classical approach of target bone regeneration in the course of rehabilitation of patients with periodontal lesions.

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PECULIARITIES OF ADHESION PROCESS PREVENTION FOLLOWING LAPAROSCOPIC OPERATIONS IN GYNECOLOGY

Abstract. *In order to minimize the risk of the adhesive process development in the abdominal and pelvic cavities after laparoscopic gynecological interventions, women who underwent laparoscopic intervention for therapeutic or diagnostic purposes, were administered Longidase in the postoperative period depending on the complication, duration of operation, and total blood loss during operation. The conducted researches and the results obtained dictate the necessity of prevention of the adhesion formation, since it contributes to the better postoperative period course, reduction of the temperature reaction, pain syndrome, restoration of the function of the organs of the abdominal and pelvic cavity.*
Key words: *adhesion process, laparoscopic intervention.*

The formation of intraperitoneal and pelvic adhesions is a principal clinical problem in the abdominal and pelvic surgery, associated with reparative processes after surgery [2,3,7]. Today, due to an increase in the number and traumatism of operations on the abdominal cavity organs, adhesive disease is observed more often following surgical treatment [1,4,5]. After surgical operations on abdominal organs, adhesive disease develops in 2-10% of cases, however, according to autopsies, the frequency of adhesion origin in the abdominal cavity is significantly higher [8, 11, 15].

The adhesions are the bands of the fibrous connective tissue (synechia, fusion) between the small pelvis organs affecting their mobility [10, 14]. The mechanism of the adhesion process development is complicated and insufficiently explored. With the least damage of cells at participation of various factors of the local and general action, except epithelization, the process of the fibrin formation, converting into collagen - the main component of adhesions, is in progress [9, 13]. Investigations of the pathogenesis of the adhesions' formation have shown that the main reason for their occurrence is a decrease in the level of plasminogen activator within the damaged peritoneum. The fibrin organization occurs until the end of the first three days after the traumatic agent action, and if plasminogene activity and local fibrinolysis are inhibited during this time, the formation of adhesions occurs. Ischemic tissue damage at surgical intervention or inflammatory peritoneal response is a powerful factor inhibiting tissue fibrinolysis [1, 12]. Thus, rough manipulations with the tissue, the blood presence, ischemia or tissue hypoxia, tissue drying during the operation, the presence of the foreign material elements (doctor's gloves, suturing material, tampon fibers, etc.) are considered to be the routine factors of the increased risk of the postoperative formation of adhesions.

Formation of the adhesion process in the postoperative period is of the particular importance in gynecology today, since the postoperative intraperitoneal adhesion takes the leading positions among the causes of the tubal-peritoneal infertility [2, 8, 11]. The frequency of adhesive complications in small-invasive gynecology according to the data of various authors is observed in 55-97% of patients after abdominal operations and is due to the volume, severity of surgical intervention, microflora increased resistance to antibiotics, changes in immunological reactivity of the organism, etc.

The adhesion process following the abdominal interventions can stipulate intestinal obstruction, infertility of the tubal-peritoneal genesis, chronic pelvic pain syndrome, impaired function of the small pelvis organs (dysuria, constipation), dyspareunia. During the repeated surgical interventions, especially with laparoscopic access,

the adhesive process in the abdominal cavity and the small pelvis, formed after the surgery, is a potential factor in the risk of the internal organs damage [4, 10].

The aim of the work was to minimize the risk of adhesive development in the abdominal and small pelvic cavity after laparoscopic gynecological interventions. Women who underwent laparoscopic intervention with a therapeutic or diagnostic purpose (n = 30), in the postoperative period, were administered Longidase intramuscularly at a dose of 3000 IU once every 3 days with a total course of 5-15 injections, depending on the complexity, duration of operation and total blood loss during it (Group I).

Longidase - a conjugate of hyaluronidase with the derivative of N-oxide of poly-1,4-ethylenepiperazine, which possesses an enzymatic proteolytic (hyaluronidase) activity of prolonged action, has immunomodulatory, chelate, antioxidant and anti-inflammatory properties. The prolongation of the enzyme action is achieved by its covalent bond with a physiologically active high molecular carrier (Polyoxidonium), which has its own pharmacological activity. In addition, Longidase has anti-fibrotic properties, weakens the course of the inflammation acute phase, regulates (increases or decreases depending on the initial level) the synthesis of mediators, increases the humoral immune response and the resistance of the organism to infection. The covalent bond in the preparation provides simultaneous local presence of the proteolytic enzyme and a carrier capable of binding the released inhibitors. Due to these properties, Longidase has not only the ability to depolymerize the matrix of the connective tissue in the fibrous granulomatous formations, but also to suppress the reverse (regulatory) reaction directed to the synthesis of the connective tissue components.

Analysis of the postoperative period course in women who underwent laparoscopic intervention for a curative and diagnostic purpose showed that complications were not observed in any patient who was recommended Longidase prior the traditional management according to the proposed scheme. The group of comparison consisted of 30 women after laparoscopy with the traditional post-operative period (group II, n = 30). The duration of the temperature reaction was on average 44.8 hours in group I, while in the main group it was 22.6 hours. The duration of the pain syndrome in women with traditional post-operative period was 51.6 hours, in women of group I - 39.4 hours. The quality of the postoperative period not to a small extent depends on the time to restore the function of the intestine. So, in women who received Longidase, the restoration of the bowel function occurred in 36.2 hours, while in women of Group II it was twelve hours longer. In the analysis of hemogram indices, it should be noted that normalization of the indices' levels of leukocytes, hemoglobin, ESR is more rapid (on average, for two days). In general, the duration of a patient's staying in the hospital was different. The average bed-day of patients with the traditional post-operative management period was 95.8 hours, while the patients who received Longidase additionally, were discharged from the hospital on an average after 76.8 hours.

Thus, Longidase use in combination with traditional approaches leads to a reduction of the adhesion process, promotes a better postoperative period course, reduces the duration of the temperature reaction, pain syndrome, restores the function of the organs of the abdominal and pelvic cavity, hemogram indices, and, consequently, reduction of the patients' staying in a hospital, that has a certain economic effect, and improvement of the life quality of women. The above-mentioned fact dictates the need to prevent the adhesion process during and after laparoscopic interventions, which minimizes the risk of the distant complications.

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INVESTIGATION OF HYPOGLYCEMIC ACTION OF THE EXTRACT MADE OF DANDELION (TARAXACUM OFFICINALE) ROOTS AND RHIZOMES

Abstract. *hypoglycemic action of the extract made of Taraxacum officinale roots and rhizomes is examined in the experiment on rats in the dose of 0,1 g/kg with a single use against the ground of glucose tolerance test. Taraxacum officinale extract on 60% extract agent is found to possess more pronounced hypoglycemic action both in comparison with other Taraxacum officinale extracts and the mixture "Arphasetin" registered and allowed for administration in Ukraine. It enables to study its pharmacological properties further with the purpose to be introduced in practical medicine as a sugar-reducing agent.*

Key words: *Taraxacum officinale, extract, glucose tolerance test, hypoglycemic (sugar-reducing) action.*

Introduction. In spite of a progressive development of medicine diabetes mellitus (DM) remains one of the social-medical issues both in Ukraine and in the majority of countries of the world. The pathology ranks third in the structure of mortality rate after cardiovascular and oncological ones with annual increase of sickness rate to 3 % [8].

During 13 years occurrence of the pathology in Ukraine 54,5 % has increased, and sickness rate — 82 % as much. The following 20 years the WHO will assess the number of DM patients to grow to 592 millions of people, that is, it will 55 % increase more[1, 4].

Oral sugar-reducing drugs are of a top priority for type 2 DM (insulin-independent) patients. They are mostly synthetic by their nature. All of these drugs possessing a good therapeutic effect have side effects and are expensive [5].

Therefore, the studies are directed to the search and finding of new oral drugs, which possessing a good therapeutic effect will have less side effects.

In recent years the scientific search of pharmacological agents of a plant origin, their investigation and introduction into the official medicine has increased in range. Advantages of pharmacological agents of a plant origin are their low toxicity, mild action, inability to be accumulated, administration for a long time in combination with other drugs of a plant origin and chemotherapy, possibility to be indicated for patients of any ages irrespective of the degree of DM severity, and lower costs in comparison with synthetic agents [2]. One of such plants is dandelion (*Taraxacum officinale*), its roots and rhizomes are used as medicinal raw material.

Objective. To study pharmacological properties of extracts made of *Taraxacum officinale* roots and rhizomes with the aim to determine possible hypoglycemic action under conditions of glucose tolerance test through the peritoneum with a single administration of the examined agents.

Materials and methods. The extracts made of the roots and rhizomes of *Taraxacum officinale* were used for the study. To obtain the extracts made of the roots and rhizomes of *Taraxacum officinale* the medicinal raw material was infused on 10%, 20%, 30%, 40%, 50%, 60%, 70, 80%, 90%, 96% ethyl alcohol.

A daily therapeutic dose of the extracts for people is 0,02 - 0,04 g/kg [3]. Applying specific sensitivity coefficients introduced by Yu.R. Rybolovlev and his method of calculation of a human dose for a rat: 0,02 g/kg / 0,45 =X

g/kg/1,89, a conventional therapeutic dose is determined to be 0,08 - 0,2 g/kg [7]. The dose of extracts chosen for the experiments was 0,1 g/kg.

The only pharmacological agent of a plant origin with evidenced sugar-reducing activity registered and allowed to be used in Ukraine, the mixture "Arphasetin" was chosen as a drug of comparison (produced by Ltd "Liktravy", Zhytomyr) in the form of extract in the dose of 24 ml/kg [9].

The amount of dose of the mixture "Arphasetin" for rats was determined as 24 ml/kg for extracts, and on the basis of the instruction for use specific sensitivity coefficients and methods of calculation of a human therapeutic dose for a rat were made according to Yu.R. Rybolovlev (a therapeutic dose of the extract for a man with an average body weight of 70 kg per day is 300–400 ml/70 kg=5,ml/kg, and further: 5,7/0,45=X/1,89=24 ml/kg) [7].

Determination of hypoglycemic action of *Taraxacum officinale* extracts in comparison with the extract of "Arphasetin" mixture with their single administration was made on the pattern of acute hyperglycemia in rats with the body weight of 180-220 g (7 animals in every group), caused by intraperitoneal introduction of glucose in the dose of 3 g/kg.

The experimental animals were distributed in the following way: 1 group of animals with simulated pathology, the following groups of animals received the examined *Taraxacum officinale* extracts: 2 group – on 10 % extract agent, 3 group - on 20 % extract agent, 4 group - on 30 % extract agent, 5 group - on 40 % extract agent, 6 group – on 50 % extract agent, 7 group – on 60 % extract agent, 8 group – on 70 % extract agent, 9 group – on 80 % extract agent, 10 group – on 90 % extract agent, 11 group – on 96 % extract agent, 12 group of animals received the drug of comparison (the extract of "Arphasetin" mixture).

In animals from all the groups blood was taken from the caudal vein to determine the initial glucose level. After that the experimental groups (from 2 to 11) were introduced to the examined extracts intraperitoneally on 1% starch paste in the dose of 0,1 g/kg, the extract of "Arphasetin" mixture (12 group) in the dose of 24 ml/kg, the control group of animals received an equivalent amount of drinking water intraperitoneally. 1 hour later glucose solution in the dose of 3 g/kg was introduced to all the rats. After that blood was taken from the caudal vein of all the animals in order to determine glucose level 15 minutes after its introduction. Glucose concentration in the blood was determined by means of glucose oxidase method with the help of the set of reagents produced by "Felicit-Diagnostics" firm [6].

Results and discussion. Intraperitoneal introduction of glucose in the dose of 3g/kg resulted in development of acute hyperglycemia manifested by a reliable increase of glucose level in all the groups of animals in comparison with the initial findings (Table).

Table

Effect of a single introduction of the extracts made of the roots and rhizomes of *Taraxacum officinale* on glucose level in the blood of rats with normal glucose level under conditions of glucose tolerance test

Groups of animals	Initial glucose level	15 minutes after pathology simulation	Hypoglycemic action
	C, mmol/L	C, mmol/L	**%**
Control (glucose)	4,40±0,12	10,01±0,37*	
10% extract + glucose	4,17±0,27	7,70±0,36*#	23,08
20% extract + glucose	4,34±0,16	7,04±0,58*#*	29,67
30% extract + glucose	4,33±0,28	6,90±0,32*#*	31,07
40% extract + glucose	3,94±0,14	6,94±0,25*#*	30,67
50% extract + glucose	4,57±0,28	7,57±0,37*#*	24,38
60% extract + glucose	3,79±0,24	5,63±0,51*#*	43,76
70% extract + glucose	3,11±0,14	6,06±0,24*#*	39,46
80% extract + glucose	3,53±0,26	6,26±0,55*#*	37,46
90% extract + glucose	4,30±0,24	8,0±0,49*#	20,08
96% extract + glucose	4,10±0,12	7,79±0,37*#	22,18
Mixture «Arphasetin» + glucose	4,14±0,27	8,56±0,36*#	14,49

Notes: * - p<0,05 in comparison with the initial data;

- p<0,05 in comparison with simulated pathology;

* - p<0,05 in comparison with the mixture «Arphasetin»

Thus, glucose level in the blood of animals receiving glucose load increased 2,28 times in the simulated pathology, in animals receiving the extracts on an average glucose level increased the initial data 1,7 times (thus, when the extract on 10% extract agent was introduced, glucose level in the blood increased 1,85 times, 20% - 1,62 times, 30% - 1,59 times, 40% - 1,76 times, 50% - 1,66 times, 60% - 1,49 times, 70% - 1,95 times, 80% - 1,77 times, 90% - 1,86 times, 96% - 1,9 times respectively). At the same time, the lowest difference was found in the groups of animals receiving *Taraxacum officinale* extracts made on 60% ethyl alcohol (1,49 times). When the drug of comparison "Arphasetin" was used glucose level was 2,07 times higher than that of the initial level.

Under effect of a single introduction of *Taraxacum officinale* extracts in the dose of 0,1 g/kg glucose level in the blood compared with the control pathology on an average 1,45 times decreased. The data were reliably similar with the use of all the concentrations of *Taraxacum officinale* extracts (thus, with introduction of the extract on 10% extract agent glucose level in the blood 1,3 times decreased, 20% - 1,42 times, 30% - 1,45 times, 40% - 1,44 times, 50% - 1,32 times, 60% - 1,78 times, 70% - 1,65 times, 80% - 1,6 times, 90% - 1,25 times, 96% - 1,28 times respectively). The best result was found with the introduction of *Taraxacum officinale* extract on 60% extract agent which decreased glucose level 1,78 times as much in comparison with that of pathology. When the drug of comparison "Arphasetin" (the drug of the study) was used glucose level 1,17 times decreased in comparison with the untreated animals.

It should be noted that sugar-reducing activity of the drug of comparison on the base of "Arphasetin" mixture (14,49 %) with a single introduction in the dose of 24 ml/kg is 5,59% less in comparison with the lowest index of the examined agent - *Taraxacum officinale* extract on 96 % extract agent (20,08 %).

According to the data of the experiment sugar-reducing activity after introduction of *Taraxacum officinale* extracts on 60% extract agent is 43,76 % 15 minutes after glucose introduction, which is 3,02 times more than that of the reference drug "Arphasetin".

A comparative analysis of sugar-reducing activity of the examined drugs enables to conclude that *Taraxacum officinale* extract possesses a considerable hypoglycemic action with a single introduction in the dose of 0,1 g/kg in comparison with the simulated pathology and reference mixture"Arphasetin".

It should be noted that according to the expression of sugar-reducing properties 60% extract of *Taraxacum officinale* has advantages over other extracts and the drug of comparison.

Conclusions: 1. A hypoglycemic action of alcohol extract of *Taraxacum officinale* with a single introduction is proved against the ground of glucose tolerance test.

2. Taraxacum officinale extract on 60 % extract agent possesses more pronounced hypoglycemic action in comparison with other *Taraxacum officinale* extracts and the mixture "Arphasetin" registered and allowed for administration in Ukraine.

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CHANGES OF STRUCTURAL COMPONENTS AND BLOOD VESSELS IN LYMPH NODES AT EXPERIMENTAL OBESITY

Abstract. *Obesity is a chronic heterogeneous disease. Has a tendency to recurrent leakage. The purpose of the work was to study changes of structural components and blood vessels of rat mesenteric lymph nodes through different terms of abolition of a high-calorie diet with the prior induction of experimental obesity. Materials and methods. We carried out the study on 66 white rats of reproductive age (5.0-7.0 months) weighing 220-240 g. Microanatomy of the mesenteric 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. With the aid of biochemical blood analysis, it has been investigated determine the glucose, ALT, AST, cholesterol and triglycerides. Results. The level of glucose in the blood of white male rats gradually increases within six weeks after the abolition of a high-calorie diet, but eight weeks after the abolition of a high-calorie diet returns to the level of intact animals. The level of glucose in the blood of white female rats fluctuates throughout the experiment and eight weeks after the abolition of a high-calorie diet by 13% exceeds the rate of intact animals. As a result of our study, we found that two weeks after the abolition of a high-calorie diet in both male and female rats, the number of secondary lymphoid nodules in the cortical substance of the lymph nodes of white rats increases, the hematological centers of which are enlarged, enlightened, arteries and veins are deformed, extended, full-blooded. Six weeks after the abolition of a high-calorie diet, the amount of adipose tissue in the thickness of the capsule and around the organ does not decrease, medullar and cortical lymph sinus remain enlarged and deformed. Conclusions. With the increase in the duration of abolition of a high calorie diet in both male and female rats, the number of secondary lymphoid nodules in the parenchyma of the mesenteric lymph nodes decreases somewhat, around the luminous center there is no clear mantle, medullar, cortical, and marginal lymph sinus are slightly less extensive.*
Key words*: obesity, experiment, lymphocytes, lymph nodes, arteries, veins.*

Introduction. Obesity is a chronic heterogeneous disease. Has a tendency to recurrent leakage [6, 16]. Obesity is part of a metabolic syndrome as a complex of humoral and metabolic disorders in the body [5, 7-10, 12-15]. It leads to a delay in water and sodium, which leads to hypervolemia, an increased amount of sodium in the vessel walls. It has a vasoconstrictor effect [2, 4]. An increase in the volume of circulating blood and peripheral vascular resistance adversely affects blood pressure, which is a risk factor for cardiovascular disease [1, 4, 11].

Influence of obesity as a concomitant disease on the structure of myocardium in patients with hypertension is studied. It has been found that with increasing body mass index, it increases systolic blood pressure, diastolic blood pressure and heart rate, the average value of the mass of the left ventricular myocardium, the absolute value of the thickness of the walls of the left ventricle, as well as the relative thickness of the walls [1]. The influence of obesity on the structure of the kidneys in patients with hypothyroidism has been analyzed. A decrease in the velocity of glomerular filtration was found [2].

The urgent task of modern medicine is to study the effect of obesity on the structure of the lymph nodes, which belong to the secondary lymphoid (immune) organs. They are biological "filters" in which antigens are neutralized, there is antigen-dependent proliferation and differentiation of T- and B-lymphocytes [13].

The purpose of the work was to study changes of structural components and blood vessels of rat mesenteric lymph nodes through different terms of abolition of a high-calorie diet with the prior induction of experimental obesity.

Materials and methods. We carried out the study on 66 white rats of reproductive age (5.0-

7.0 months) weighing 220-240 g.

Microanatomy of the mesenteric 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 eight week, whereupon by a two weeks fed a standard diet of vivarium instead of a high-calorie diet; the second group (10 animals), being fed a high-calorie diet for eight week, whereupon by a four weeks fed a standard diet of vivarium instead of a high-calorie diet; the third group (10 animals), being fed a high-calorie diet for eight week, whereupon by a six weeks fed a standard diet of vivarium instead of a high-calorie diet; the fourth group (10 animals), being fed a high-calorie diet for eight week, whereupon by a eight weeks fed a standard diet of vivarium instead of a high-calorie diet. 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, and fructose solution was added into water.

Control was provided by 16 white rats, fed a standard diet of vivarium instead of a high-calorie diet.

All experimental animals were kept under the vivarium 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.

Results. After 2 weeks of abolition of fed a high-calorie diet, both in male and in female rats the medullary lymph sinuses of the mesentery lymph nodes are enlarged, tortuous. The number of lymphocytes in medullary lymph sinuses gap to decrease, the number of the proportion of reticular and connective tissue to grow. B-lymphocytes, plasmacytes and macrophages are densely located in the medullary lymph cords. «Empty» blood capillaries have thickened walls. The number of postcapillaries venules with high endothelium in the paracortical region of the mesenteric lymph nodes grows both (fig. 1A).

The number of secondary lymphoid follicles in the cortical substance of the mesentery lymph nodes continues to grow both in male and in female rats, the germinal center is cleared, enlarged (fig. 1B). Arteries and veins are deformed, varicose, full-blooded, there are signs of adhesion and aggregation of platelets in the lumen. The amount of adipose tissue grows around the nodes and in capsule.

The level of glucose in the blood of white male rats gradually increases within six weeks after the abolition of a high-calorie diet, but after eight weeks after the abolition of a high-calorie diet returns to the level of the intact animals. The level of glucose in the blood of white female rats during the experiment it fluctuates, and eight weeks after the abolition of a high-calorie diet exceeds by 13.0% the intact animals' index (table 1). The ALT level in the blood of white male rats gradually decreases to its minimum after six weeks after the abolition of a high-calorie diet, it is by 29.5% less than that of intact animals. During the next two weeks of experiment, it increases somewhat and it is by 18.6% less than the rate of intact animals. The ALT level in the blood of white female rats during the experiment it fluctuates, and after eight weeks after the abolition of a high-calorie diet it is by 8.0% less the intact animals' index (table 2).

The AST level in the blood of white male and female rats during the experiment it fluctuates, and after eight weeks after the abolition of a high-calorie diet it is by 31.5% and 34.6% less than that of intact animals (table 2).

The level of cholesterol in the blood of white male rats grows to its maximum after two weeks after the abolition of a high-calorie diet, which is 2.7 times correspondingly higher than the rate of intact animals. Then it is gradually decreases and returns to the level of intact animals. The level of

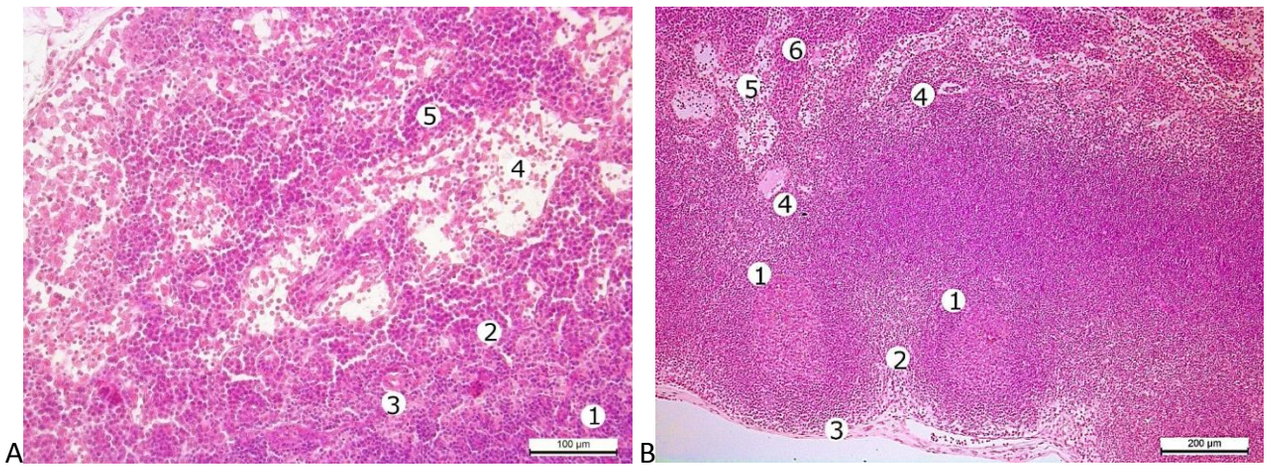


Fig. 1. A mesenteric lymph node of an intact white rat male (A) and white female rats' (B) after two weeks of abolition of fed a high-calorie diet. Stained with hematoxylin and eosin.
Magnif.: A. obj. × 20, ocul. × 10. Designations: 1 – cortical substance; 2 – paracortical region; 3 – venules in the paracortical region; 4 – medullary lymph sinus; 5 – medullary lymph cord.
Magnif.: B. obj. × 10, ocul. × 10. Designations: 1 – secondary lymphoid follicles with the cleared, enlarged germinal center; 2 – cortical lymph sinus; 3 – capsule; 4 – varicose and full-blooded venules with high endothelium in the paracortical region; 5 – medullary lymph sinus; 6 – medullary lymph cord.

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±0.07	6.0±0.08
Group I	8.41±0.09	7.57±0.1
Group II	7.72±0.1	8.09±0.11
Group III	7.96±0.07	8.22±0.06
Group IV	5.82±0.1	6.78±0.08

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	86.2±0.3	58.8±0.21	120.7±0.39	114.3±0.7
Group II	84.7±0.31	75.8±0.29	173.3±0.33	189.6±0.67
Group III	53.9±0.4	63.6±0.22	119.0±0.77	125.7±0.56
Group IV	62.3±0.08	47.1±0.09	120.4±0.45	109.8±0.44

cholesterol in the blood of white female rats grows to its maximum after six weeks after the abolition of a high-calorie diet, which is 4.5 times higher than the rate of intact animals. During the next two weeks, it decreases somewhat and is 2.2 times higher than the rate of intact animals (табл. 3).

The level of triglycerides in the blood of white male and female rats at the beginning of the experiment decreases, and after two weeks after the abolition of a high-calorie diet it is 44.8% and 17.9% correspondingly less than the rate of intact animals. By the end of the experiment, the level of triglycerides gradually increases and it is correspondingly lower by 5.8% та 19.4% than in the intact animals (table 3).

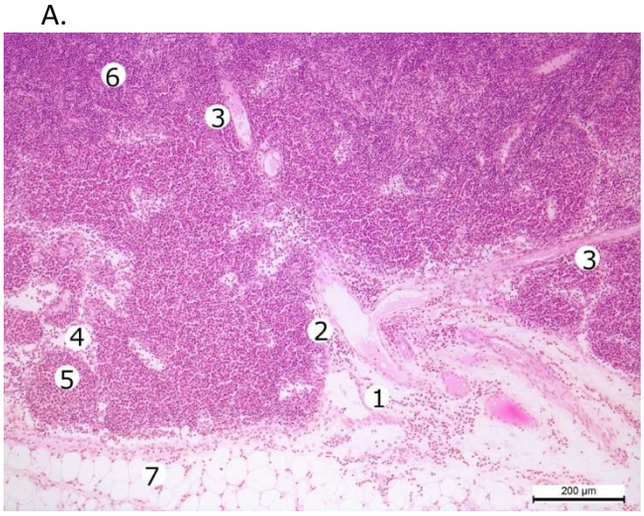
After 4 weeks of abolition of fed a high-calorie diet, both in male and in female rats the number of secondary lymphoid follicles in the cortical substance are not decrease. The medullary and cortical lymph sinuses are enlarged, tortuous. Arteries and veins are deformed, varicose and full-blooded in the hilum of mesenteric lymph nodes (fig. 2 A). The number of B-lymphocytes in B-dependent zones and in the lumen of the vessels grows (fig . 2 B).

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±.,02	0.69±0.009	0.67±0.01
Group I	2.45±0.011	0.93±0.011	0.37±0.006	0.55±0.01
Group II	1.29±0.013	1.34±0.01	0.51±0.09	0.6±0.011
Group III	1.86±0.01	3.92±0.013	0.59±0.008	0.67±0.009
Group IV	0.93±0.01	1.93±0.011	0.65±0.007	0.54±0.01

A.



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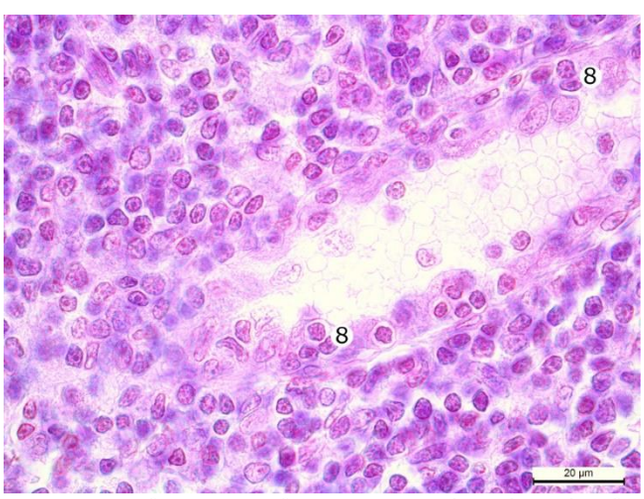

Fig. 2. A fragment of a mesenteric lymph node of a white male rat after four weeks of abolition of fed a high-calorie diet. Stained with hematoxylin and eosin. Magnif: A - obj. × 10, ocul. × 10 (A); B - obj. × 100, ocul. × 10 (B). Designation: 1 – hilum of a lymph node; 2 – varicose and full-blooded artery in the hilum; 3 – varicose artery in parenchyma; 4 – medullary lymph sinus; 5 – medullary lymph cord; 6 – paracortical region; 7 – adipose tissue around the nodes and in capsule; 8 – the output of lymphocytes through the wall of an enlarged venule.

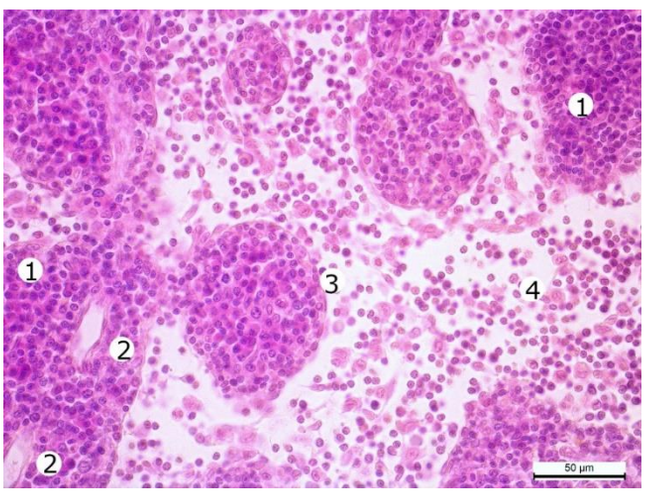

Fig. 3. A fragment of medullary substance of a mesenteric lymph node of a white female rat after six weeks of abolition of fed a high-calorie diet. Stained with hematoxylin and eosin. Magnif: obj. × 40, ocul. × 10. Designation: 1 – B-lymphocytes, plasmacytes and macrophages are densely located in the medullary lymph cords; 2 – varicose and deformed venule; 3 – reticuloendotheliocytes; 4 – varicose and deformed medullary lymph sinus.

After 6 weeks of abolition of fed a high-calorie diet, the amount of adipose tissue around the nodes and in capsule does not decrease, cortical and medullary lymph sinuses stay varicose and deformed (fig. 3). The inclusion of a yellow-brown color in the cortical substance observed, the vast majority of which are concentrated in the germinal center of secondary lymphoid follicles. The number of the plasmacytes and active macrophages grows (fig. 4).

After eight weeks of abolition of fed a high-calorie diet, the number of secondary lymphoid follicles in the cortical substance of the mesentery lymph nodes somewhat decreases, the enlightened germinal centeres without a clear mantle zone around him (fig. 5). The medullary, cortical and marginal lymph sinuses somewhat

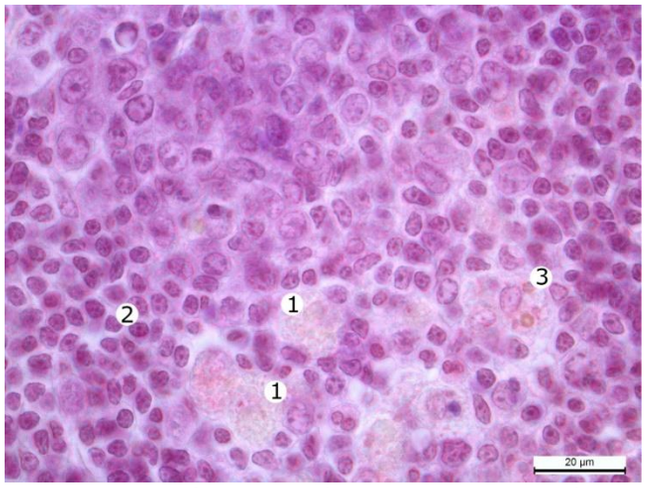

Fig. 4. A fragment of cortical substance of a mesenteric lymph node of a white female rat after six weeks of abolition of fed a high-calorie diet. Stained with hematoxylin and eosin. Magnif: obj. × 100, ocul. × 10. Designation: 1 – the inclusion of a yellow-brown color in the cortical substance; 2 – B-lymphocytes; 3 – macrophages.

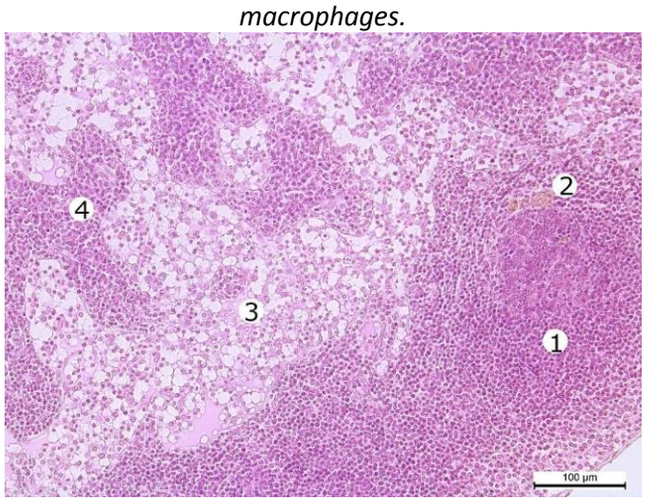

Fig. 5. A fragment of a mesenteric lymph node of a white female rat after eight weeks of abolition of fed a high-calorie diet. Stained with hematoxylin and eosin. Magnif: obj. × 20, ocul. × 10. Designation: 1 – the germinal center of secondary lymphoid follicles without a clear mantle zone around him; 2 – the inclusion; 3 – medullary lymph sinus; 4 – medullary lymph cords.

less advanced. Arteries with a thickened wall, dilated; veins and venules are dilated and full-blooded, mainly in hilum and in the medullary substance.

Discussion. 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 the weakening of the hematopoietic barrier, lymphedema and the progressive violation of the processes of recirculation of lymphoid and myeloid cells. In addition, obesity is accompanied by chronic inflammation of the white adipose tissue, which causes local and systemic inflammatory response from the immune system, associated with structural and functional changes in the lymphoid organs [10].

In lymph nodes there is development of both cellular and humoral immune response. However, due to microenvironmental features that promote the differentiation of T-lymphocytes in the direction of Tx1, the lymph nodes are more oriented towards the development of the cellular immune response. Investigated by the authors of the inguinal lymph nodes are regional organized lymphoid structures for antigen-expressing cells of the visceral adipose tissue and intestine. In female rats with obesity, there was a statistically insignificant increase in the relative weight of the inguinal lymph nodes with a simultaneous decrease in their cellularity compared with similar indices in intact animals, indicating the development of lymphedema. Also noted a significant individual variability of indicators in this group [3].

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.

Conclusions: As a result of the study performed on male and female rats, we found that:

1. After 2 weeks of abolition of fed a high-calorie diet, both in male and in female rats the number of secondary lymphoid follicles in the cortical substance of the mesentery lymph nodes grows, the germinal center is cleared, enlarged; arteries and veins are deformed, varicose, full-blooded.

2. With an increase of terms of abolition of fed a high-calorie diet, both in male and in female rats the number of secondary lymphoid follicles in the cortical substance of the mesentery lymph nodes somewhat decreases, the enlightened germinal centeres without a clear mantle zone around him. The medullary, cortical and marginal lymph sinuses somewhat less advanced.

Prospects for further research in this direction related to the further study of morphometric and

submicroscopic changes in the structural components of lymph nodes of rats through different terms of experimental obesity and in conditions of its correction.

Relationship with scientific programs, plans and themes. This study is a part of complex projects: “Features of the lymphoid organs and vascular bed structural organization in the normal ontogenesis and their alteration regularities under the effect of antigens, chemical and physical factors on the organism” - state registration number 0115U003903 and “Structure of organs and their bloodstream in the ontogenesis, under the influence of laser irradiation and pharmaceuticals, with blood supply disorders, reconstructive operations and diabetes mellitus”- state registration number 0110U001854.

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ANALYSIS OF PHARMACEUTICAL SUPPLY OF PATIENTS SUFFERING FROM GASTROESOPHAGEAL REFLUX DISEASE

Abstract *Gastroesophageal reflux disease is an urgent issue of current gastroenterology as it results in a number of complications. Therefore, the objective of the work was to improve the quality of pharmacotherapy of patients suffering from gastroesophageal reflux disease by means of making pharmacoeconomic analysis of the administration of proton pump inhibitors and propulsantes in order to improve the order of formation of a local card of therapeutic-preventive establishments. According to the results of the analysis the therapeutic regimen "Nolpaza+Itomed" from the group of "E" class was found to be the most economically available.*
Key words: *gastroesophageal reflux disease, pharmacoeconomic analysis, cost-benefits.*

Introduction. In the era of development of fast food people are note used to consider heartburn as a sign of some serious disease. Unpleasant sensations occurring in case of overeating or excessive intake of certain foods are eliminated by antacid means, and meals can be continued. Such a superficial attitude to heartburn is explained by its occurrence among practically healthy people. Though, chronic relapsing disease caused by disorders of the motor-evacuation function of the gastroesophageal area with spontaneous or regularly repeated reflux of the gastric or duodenal content into the esophagus leads to the damage of the esophageal mucosa. The World Organization of Gastroenterology recognized gastroesophageal reflux disease (GERD) as a disease of the XXI century involving from 20 to 50% of the population from different countries of the world. GERD is a leading cause of decreased quality of life, ability to work and development of various complications [1]. Such complications as peptic ulcers, esophageal strictures, Barrett esophagus, esophageal adenocarcinoma and others can develop [2, 3].

In Ukraine GERD became statistically registered since 2009 and now it constitutes 10 cases per 1000 of population [4]. According to the survey GERD occurrence among the organized adult population is on an average 30,0%, but the number of people suffering from heartburn increases both among men and women similarly. Occurrence of GERD increases with advancing age of the respondents resulting in changes of the structure in clinical manifestation of the disease and domination of extra-esophageal signs of the disease [3].

GERD is an important issue of current gastroenterology. Therefore investigation of the pharmaceutical market concerning supply of patients suffering from GERD with appropriate

medicines remains urgent.

Objective of the work was to make pharmacoeconomic analysis of pharmaceutical supply of GERD patients for further application of the obtained results in elaboration of organization-economic measures concerning increasing availability of medical and pharmaceutical aid given for a determined category of patients.

Materials and methods. Methodology of pharmacoeconomic analysis assumes mutual use of retrospective analyses by the findings of case histories: analysis of frequency of medical indications and their ranking according to the degree of their value (Vital-Essential-Non-essential-analysis – VEN-analysis).

The study was conducted on the basis of 120 medical cards of hospital patients and treatment indication sheets of a therapeutic institution in the town of Chernivtsi.

Results. For the selection of medicines and making pharmacoeconomic analysis concerning "cost-benefits" in the process of pharmaceutical supply of GERD patients we have made ABC-analysis of trade names of medicines using Pareto principle according to the amount of costs for their use.

By the results of the analyzed case histories 227 medical preparations were prescribed in 2018. General costs were 616478,25 hrn. (Fig. 1). The group A included 32 medicines, and a part of costs spent for them constituted 80,11% (493860,73 hrn.) of the total sum, the group B included 71 medicines constituting 15,02% (92595,03 hrn.), and the group C – 124 medicines – 4,84% (29837,55 hrn).

The analysis of a part of these groups from the total range of medicines indicated (Fig.1)

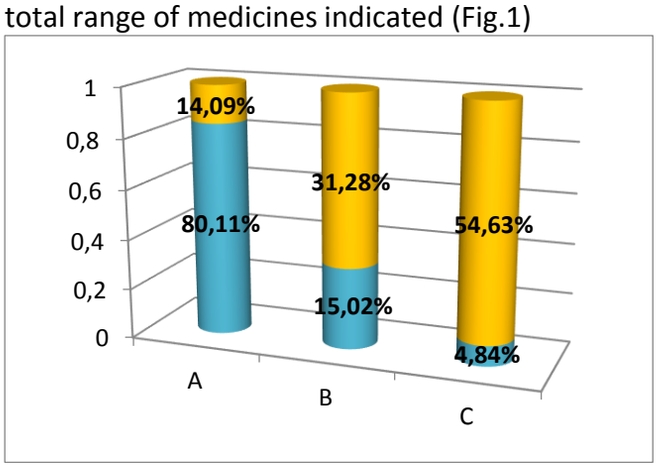

Fig. 1. ABC-rating of distribution of costs spent on medicines

determined the following: the group A constituted 14,09%, the group B – 31,28% and the group C – 54,63%.

For making VEN-analysis a comparison standard was the State Register of Medical Preparations of the 10th issue dated 10.05.2018. A numerical advantage of medicines from the category N (secondary) was found in the therapeutic regimens – 181 medicines. The group A included 3 vital («V») drugs (9,38%), while from the group B the medicines with V index were 6 in number (8,45%), and from the group C – 8 drugs (6,45%). The class «E» (essential) of medical preparations from the group A included 7 drugs (21,87%), and from the groups B and C – 9 (12,68%) and 13 (10,48%) respectively, that totally constituted 29 medicines. The class «N» of the secondary medicines from the group A included 22 medicines (68,75 %), 56 (78,87%) – group B and 103 medicines (83,07%) – group C.

The results of the conducted VEN-analysis found that the most numerous group was the one of class «E» including the medicines from the protocol of GERD treatment.

According to the protocol of GERD treatment such groups of medicines as proton pump inhibitors (PPI) and peristalsis stimulators are preferred mainly.

We have reviewed the pharmaceutical market of PPI and peristalsis stimulators in Ukraine in 2018 (Table 1). The State Register of Medical Preparations of Ukraine of the 10th issue recommends for the treatment of GERD 6 international generic names of PPI including 140 names of drugs: omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole and dexlansoprazole. On the IV quarter of 2018 the pharmaceutical market of Ukraine concerning PPI group was mostly formed at the expense of medicines produced abroad (86,43 %), and domestic production constituted only 13,57%.

A retail segment of the pharmaceutical market of the peristalsis stimulators is presented by 35 medicines included in 4 international generic names: metoclopramide, domperidone, itopride hydrochloride and mosapride. Among them a considerable part belongs to the medicines of domestic production (60%), India – 14,28%, European countries – 20,00%, Canada and Japan – 5,72% only.

Table 1

Pharmaceutical market of proton pump inhibitors and peristalsis stimulators in 2018

ATC-code	INN	Amount of names	Amount of producers	Ratio of domestic/import drugs
A02BC01	omeprazole	22	30	7/23
A02BC02	pantoprazole	27	63	5/58
A02BC03	lansoprazole	3	6	1/5
A02BC04	rabeprazole	9	15	3/12
A02BC05	esomeprazole	11	25	3/22
A02BC06	dexlansoprazole	1	1	-/1
A03FA01	metoclopramide	7	10	8/2
A03FA03	domperidone	13	21	13/8
A03FA07	itopride	1	1	-/1
A03FA09	mosapride	3	3	-/3

The pharmacoeconomic analysis "cost-benefits" was made in order to determine the most available combination of medicines from these groups. By the results of the analyzed treatment sheets concerning treatment of hospital patients we have chosen several schemes of pharmacotherapy of GERD patients, namely: «Esolong+Itomed», «Esolong+Motoricum», «Nolpasa+Itomed» and «Nolpasa+Motoricum». The data concerning the cost (minimal, mean and maximal) of blockers H^+/K^+-ATphase and peristalsis stimulators (in hryvnas) were taken from the pharmacies of different forms of property in the town of Chernivtsi.

Having compared single, daily, and course expenses spent on pharmacotherapy of GERD patients, we have noticed that their "cost-benefits" index in anti-reflux treatment of patients who received anti-secretory drug from the group of blockers of H+/K+-ATphase – Esolong or Nolpasa and peristalsis stimulator – Itomed or Motoricum (Table 2), was the most effective in the combinations Esolong+Itomed and Nolpasa+Itomed. At the same time, the cost of daily treatment by the drugs is practically similar, but the cost of a course treatment by the scheme «Esolong+Itomed» is more expensive than the cost of pharmacotherapy «Nolpasa+Itomed».

Table 2

Generalized indices of «cost-benefits» schemes of pharmacotherapy of GERD patients

Pharmacotherapy scheme	Cost of a dose, hrn.			Index of efficacy	«Cost-benefits» index
	single	daily	course		
Esolong+Itomed	18,25	33,75	472,51	0,88	305,91
Esolong+Motoricum	14,36	22,10	309,41	0,54	145,60
Nolpasa+Itomed	15,08	30,58	428,12	0,87	255,41
Nolpasa+Motoricum	11,19	18,93	265,02	0,57	128,40

Discussion. Therefore, according to the results of the conducted pharmacoeconomic analysis of "minimization of loss", the indication of Nolpasa+Itomed appeared to be more economically profitable.

Conclusions: 1. ABC-rating of medicines included into the pharmacotherapy schemes for GERD patients determined that the group A (expensive drugs) included 32 remedies constituting 14,09% out of the total amount of

drugs; the group B (an average price) – 71 medicines constituting 31,28%; the group C (of low cost) – 124 medicines constituting 54,63%.

2. According to the results of the conducted pharmacoeconomic analysis of “minimization of loss”, the indication of Nolpasa+Itomed appeared to be more economically profitable (the price of the course of treatment was 428,12 hrn.).

Prospects of further studies. The results of the study will enable to improve the order of formation of a local register at a therapeutic-preventive establishment as well as the quality of pharmacotherapy of patients suffering from gastroesophageal reflux disease.

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THE STUDY OF MORPHOMETRIC CHARACTERISTICS OF THE CAPILLARY NETWORK AT THE EARLY TERMS OF THE POROUS FIBROSE MATRIX SUBCUTANEOUS IMPLANTATION

Abstract. *From year to year medicine and bioengineering have become more and more interested in biopolymers. The materials applied in bioengineering to make biografts should possess a spectrum of special properties and provide engineering or microengineering constructions with characteristics peculiar for living tissues, that is: ability to self-reproduction, ability to change structure and properties in response to environmental factors. The study was conducted on 20 laboratory animals (rabbits) divided into two groups. The first group included 10 animals operated on with the formation of "pocket" in the subcutaneous tissue followed by applying stitches. The second group included 10 animals which underwent subcutaneous implantation of biopolymer matrix in the back area between the shoulder-blades. 9 segments were taken for examination: one located in the center and each 4 segments from the paracentral and peripheral areas. The results obtained are indicative of the lack of both acute and chronic response inflammatory infiltration, as well as acute or chronic graft rejection as a foreign substance in the implanted area of the animal. The fibrous matrix created by us due to its hygroscopicity and porosity creates a distinctive bridge for emergence and development of the capillary network.*
Key words: *biopolymer, biograft, capillary network.*

Introduction. Nowadays medicine and bioengineering have become more and more interested in biopolymers. The materials applied in bioengineering to make biografts should possess a spectrum of special properties and provide engineering or microengineering constructions with characteristics peculiar for living tissues, that is: ability to self-reproduction, ability to change structure and properties in response to environmental factors. [1]. The problem arising in front of tissue engineering is to optimize isolation, reproduction and differentiation of cells, to construct the frames (matrix) or systems of supply promoting maintenance, coordination of tissue regeneration in three dimensions [2, 3]. One of the important criteria that should be considered in matrix construction is its ability to maintain stable hemodynamics inside and around of the frame. Hemodynamic stability and, respectively, tissue vitality first of all will depend on the character of the capillary network development inside of the scaffold [4, 5].

Objective: to assess the character of the capillary network development at the early terms of subcutaneous implantation of biopolymer fibrous matrix in the experiment.

Materials and methods. We have developed fibrous matrix made of the granules of 100% pure polylactide. This matrix was applied in conducting the research. The matrix was developed by means of polymer phase division method. The fibrous matrix was on an average 30 mm thick. The diameter of its fibers was from 4 mcm to 10 mcm (Fig. 1, Fig. 2).

The above matrix was exposed to gamma sterilization. The scaffolds hermetically double

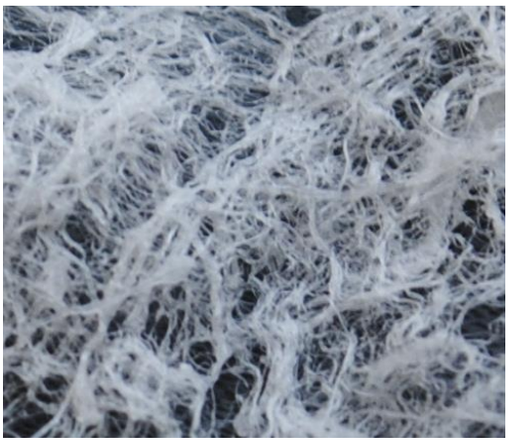

Fig. 1 Fibers of biopolymer matrix (macrograph).

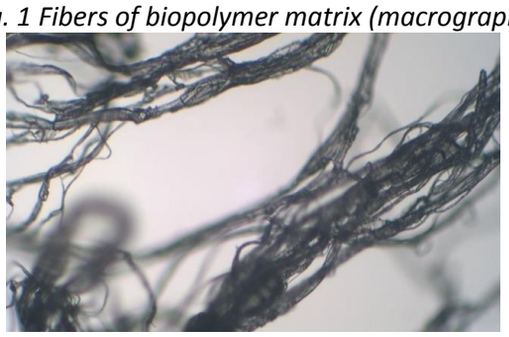

Fig. 2 Fibers of biopolymer matrix (micrograph, magnification: x100).

packed for sterilization were evenly distributed under electron beam with the energy of particles 4 mega electron volts (MeV) and duration of impulses 4,5 microseconds (mcs). Every package «Medicom» standardized EN 868-5, ISO 11140-1, ISO 11607-1, in which the polymer was packed was 0,6 mm thick. On radiation the number of impulses varied from 4 to 70.

Sterilization occurred by the following parameters: frequency of the accelerator work was 250 Hz, maximum energy of electrons was 5 MeV, maximum beam power was 5 kW, duration of impulses was 4,5 mcs, pulse current 1,5 A, suppressive radiation power at the distance of 1 m from the target was – 104 R/sec. The dose of radiation of the object was up to 50 Gy.kg on the basis of the volume and density of the material. According to the norm, the maximum tolerance dose of 50 Gy.kg was with maximum electron power of 5 MeV. Processing with the electrons with the power less than 10 MeV did not cause nuclear transmutations, that is it did not lead to the occurrence of radioactive isotopes and did not create residual radiation background of the object.

After sterilization biopolymer matrix was surgically implanted under the skin of a laboratory animal. The study was conducted on 20 laboratory animals (rabbits) divided into two groups. The first group included 10 animals operated on with the formation of “pocket” in the subcutaneous tissue followed by applying stitches. The second group included 10 animals which underwent subcutaneous implantation of biopolymer matrix in the back area between the shoulder-blades.

1 month later the matrix was surgically removed from the animal body together with adjacent tissues. To make general histological examination the matrix together with the adjacent tissues was dissected perpendicular in 25 similar segments. 9 segments were taken for examination: one located in the center and each 4 segments from the paracentral and peripheral areas. The obtained parts of the graft were fixed in 10% neutral formalin solution (Ph-7,0). The time of fixation was 24 hours. Then the pieces of the examined organs were placed into the ascending battery of alcohols for dehydration, followed by placement into chloroform, chloroform-paraffin mixture (1:1), paraffin (at the temperature of 37°C). After paraffin preparation the pieces were coated with paraffin. Series paraffin sections were made 4-6 mcm thick on the sliding microtome. The specimens were stained with hematoxylin and eosin [6].

Histological specimens were examined by means of the light microscope Leica DME under different magnifications of the lens and eyepiece. Morphometric parameters were determined by means of the system to obtain microscopic images of histological specimens (microscope Leica DME and digital camera "Nikon P5100") and the program of image analysis ImageTool 2.0 for Windows at the Department of Pathomorphology and Forensic Medicine, Ivano-Frankivsk National Medical University.

The results were statistically processed by means of the computer programs Microsoft Excel and Statistica 5.5 (MultipleRegression) applying the methods of variation statistics and correlation.

To examine blood vessels of the fibrous matrix the ether-chloroform mixture of French blue was used (10 g of the stain per 100 ml of the solvent consisting of ether and chloroform in the ratio 3:1). This mixture was injected into the thoracic region of the aorta. 3-4 hours after the blood vessels were filled in with the above mixture, and the graft together with the adjacent tissues was removed and fixed in 10 % neutral formalin solution during 14 days.

On a freezing microtome sections were made 30-50 mcm thick. They were dehydrated in the alcohols of an increasing concentration, clarified in salicylic acid methylene ether and placed in

polysterol. After that the sections were examined under the binocular microscope МПС-6 with different magnification.

Results. Pathomorphological examination of the peripheral graft areas of the 1-month term determined development of the connective tissue and capillaries in the space between matrix fibers. The vessels in the connective tissue are located unevenly (Fig. 3 exposition 1_025), on an average 49345,18±4,22 mcm^2 of the square per one vessel. An average gauge is 697,61±3,99 mcm^2, with the norm 597,24± 3,12 mcm^2. The vessels are mainly of a capillary type, with thin walls, an average thickness of 3,2±0,14 mcm, and clear basal membrane. Endotheliocytes with clear oval elongate nuclei line the space inside. The groups of erythrocytes are available in the vascular lumen.

Pathomorphological examination of the paracentral areas of grafts determined found thin vessels of a capillary type, arterioles, and venules in the connective tissue (Fig. 4 exposition 1_028). An average thickness of the walls of these vessels is 3,09±0,17mcm, the square of the transverse

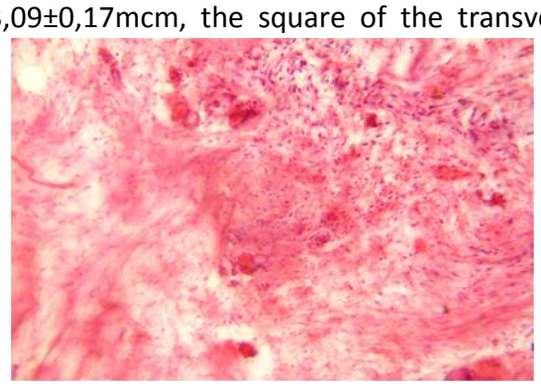

Fig. 3 Exposition 1_025 Staining: hematoxylin and eosin. (micrograph, magnification: x100).

section is 739,56±4,32 mcm^2, in comparison with 2,97±0,13mcm and 728,45±3,98 mcm^2 in the control group. According to the morphometric examination there is 37698,96 ±4,32 mcm^2 of the connective tissue matrix per one vascular section.

In certain areas on the borders with the graft fibers the groups of leukocytes are found in the connective tissue. The centers of angiomatosis in the form of transverse sections of vessels are found around the parts of matrix fibers in the connective tissues (Fig. 5 Exposition 1_020).

Pathomorphological examination of the central areas of grafts found that spaces between the graft fibers are filled with the connective tissue in which small blood vessels full of blood are found – an average square of the transverse vascular section is 1321,23±4,75 mcm^2, wall thickness – 2,65±0,16 mcm (Fig. 6 Exposition 1_004). In the intact animals these parameters are 934,23±4,05 mcm^2 and 2,44±0,14 mcm respectively. The amount of vessels per the unit of square is a little larger of the norm in cases of loose location of fibers constituting 20915,92 mcm^2 of the

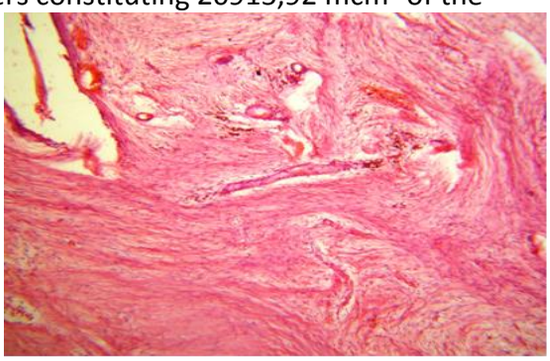

Fig. 4 exposition 1_028 Staining: hematoxylin and eosin. (micrograph, magnification: x100).

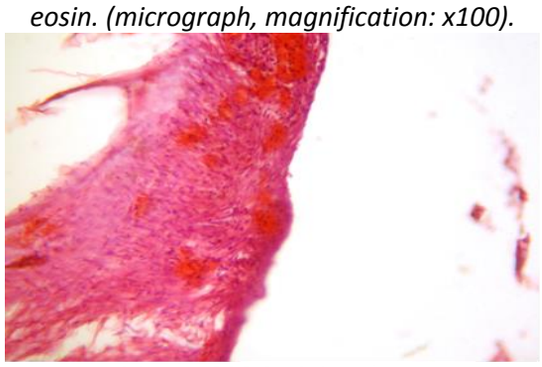

Fig. 5 Exposition 1_020 Staining: hematoxylin and eosin. (micrograph, magnification: x100).

connective tissue per one transverse section of the vessel. In other cases there is 24797,47±3,33 mcm^2 of the connective tissue per one transverse section of the vessels. By means of the morphometric and statistical analyses an increased density of the vascular bed in the areas around synthetic fibers was found (19872,94±4,32 mcm^2 of the connective tissue square per one vascular section) concerning the connective tissue deeper located, which is described in the loose and denser connective tissues.

The areas with slightly marked segmental leukocyte infiltration are determined around the part of the graft fibers.

Injection of vessels determined that the blood stream of the adjacent tissues to the matrix and inside of the polymer matrix consists of the links interrelated between themselves: arteries, arterioles, pre-capillary arterioles, hemocapillaries, extra-capillary venules, venules and veins (Fig. 7).

The arteriole (20-30 mcm in diameter) is divided dichotomically or extends 10-12 pre-capillary arterioles (10-20 mcm in diameter), mainly from its one side. Smaller in the diameter (10 mcm) extremity of the pre-capillary arteriole in certain areas empties into the venule, but more often the final part of the pre-capillary arteriole is

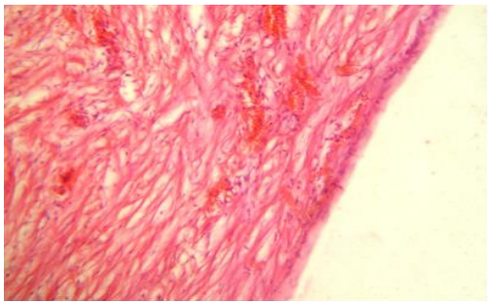

Fig. 6. Exposition 1_004 Staining: hematoxylin and eosin. (micrograph, magnification: x200)

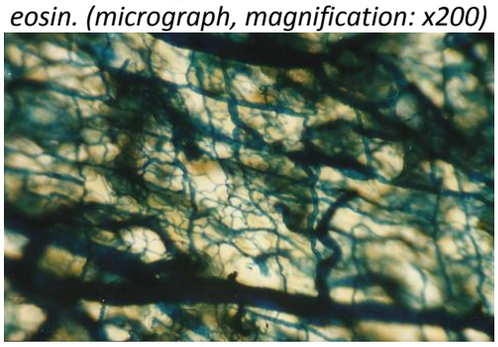

Fig. 7 Arteries, arterioles, pre-capillary arterioles, гемокапіляри, hemocapillaries, extra-capillary venules, venules and veins

divided dichotomically into the hemocapillaries or united into venules. Pre-capillary arterioles (10-20 mcm) in the majority of cases are dichotomically divided into hemocapillaries consisting of arterial (5-10 mcm) and venous parts (10-20 mcm). Hemocapillaries forming the blood stream in the form of network empty into the extra-capillary venules (15-25 mcm), which join together and form venules (25-40 mcm). Arterial branches and arterioles emerge from the arteries penetrating into the whole thickness of the subcutaneous tissue.

Results and discussion. Therefore, on the basis of the conducted research it was found that the state of the capillary network surrounding fibers of the biopolymer matrix does not differ from the animals in the control group, except a small amount of leukocytes available. Inconsiderable amount of leukocytes and macrophages available can be indicative of the process of material hydrolysis, which mechanism is associated with the activity of the enzymatic systems of cells. Availability of the blood vessels not only in the periphery of the matrix, but inside of it as well is indicative of a developed blood network providing not only supply of nutrients deep into the matrix, but active elimination of waste products, providing active development of biosynthetic processes in the tissue. Vascular plethora is indicative of it. It is evidence of thin wall capillaries available with slightly seen lumen and fibers located loosely, which is indicative of neoangiogenesis. The process of neoangiogenesis continues with development and maturation of the connective tissue.

Conclusions: 1. The lack of a great number of neutrophils, increased amount of macrophages and lymphocytes are indicative of the lack of both acute and chronic response to inflammatory infiltration, as well as acute and chronic response to graft rejection as a foreign substance in the implanted area of animals.

2. The fibrous matrix, developed by us, due to its hydroscopic and porous features, creates a specific bridge for the growth and development of the capillary network.

Prospects of further studies include the use of the porous fibrous material in the treatment of granulomas, cystogranulomas, cysts and assessment of clinical results, cytological and morphological changes in the area of implantation of the given material.

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ANALYSIS OF MEDICINAL PLANTS INCLUDED IN THE CONTENT OF EXTEMPORAL (MAGISTRAL) FORMULAS

Abstract. *The pharmaceutical market of extemporal (magistral) formulas containing medicinal raw material in was analyzed Chernivtsi pharmacies. Preparation of extemporal drugs using medicinal raw material was found to be topical and reasonable.*
Key words: *extemporal formulas, medicinal plants, medicinal raw material.*

Introduction. Nowadays great attention in the international pharmaceutical practical work is paid to the issues of producing drugs in the pharmacies. Manufacturing medicines in pharmacies has more than 400-year history. It is maintained in all the leading countries of the world with highly developed economy and pharmaceutical industry [2]. The world experience is indicative of the fact that the majority of the world countries prioritize maintenance and development of an individual approach to the needs of a patient. In our country many representatives of management begin to understand the hole importance in the development of "personal medical agents" conception. Under such conditions it is extemporal preparation of drugs that becomes of a new value, and today it is represented as manufacturing of medicines according to the needs of every patient individually [3].

The issues concerning development of the pharmacy unit in Ukraine becomes important in the context of European integration as well.

In spite of a wide range of officinal medicines in pharmacies, extemporal prescription remains rather timely and has a number of advantages: accurate dosage of active substances according to the age and body mass of a patient; possibility to choose the most reasonable ratio of ingredients; lack of stabilizers, preservatives, colouring agents, flavoring substances, which is especially important for infants and children, elderly persons, patients with chronic diseases complicated by allergy anamnesis etc.; taking into account genetic, age, gender peculiarities of the human organism; reasonable prices for the course of treatment; impossibility of falsification [2]. Meanwhile, the interest to use medicinal pants in the content of extemporal prescription is increasing. It is stipulated by the fact that in case of correct dosage they are practically non-toxic, harmless, relatively available, effective and in some cases without analogues due to their comprehensive action. Substantial resources, availability of medicinal raw material, possibility to cultivate make these medicines economically available.

Objective: to investigate the pharmaceutical market of extemporal formulas containing medicinal raw material and natural extracts.

Materials and methods. The need to prepare medicines according to extemporal formulas in the pharmacy really exists, and pharmaceutical industry does not produce such medicines. It especially refers to medicines used for the treatment of specific diseases, medicines with a limited shelf-life and multicomponent content, those with individual doses and in case

incompatible ingredients are available. A doctor prescribes a rational combination of substances different by their pharmacological action considering an individual approach to a patient providing decrease of unfavourable effect of certain ingredients. Extemporal medicines enable to provide an individual approach to the treatment of a patient and at the same time they have a reasonable price for the public at large [1].

In recent 8 years in Ukraine the number of pharmacies able to produce medicines has reduced (from 3724 in 2009 to 327 at the beginning of 2017) as well as the whole extemporal production (on an average 44% lower in the country in comparison with 2009) [2]. Though, in recent years the number of pharmacies able to produce medicines has begun to grow. Thus, today in Chernivtsi region there are 6 manufacturing pharmacies including 3 in the town of Chernivtsi and 3 more – in the regional districts.

The study was conducted on the basis of manufacturing pharmacies in the town of Chernivtsi, in particular, municipal pharmacy № 2, pharmacy № 5 «Under St. Igor Patronage» and educational-manufacturing pharmacy of Higher State Educational Establishment of Ukraine «Bukovinian State Medical University». Mixtures of medicinal plants indicated by the doctors from the Municipal Polyclinic №5 in Chernivtsi were analyzed as well.

Results and discussion. A wide range of medicinal plants, teas and mixtures is available at the pharmacies. Though, they are used after being prepared at home, which cannot guarantee their correct manufacturing and use resulting in reduced pharmacological effect.

In the course of the investigation we have found that the pharmacies prepare only 5 semi-solid forms of medications and 4 liquid forms. These forms contain only 4 kinds of medicinal raw material (chamomile flowers, rhizome and roots of valerian, leaves of peppermint, herb of nettle) out of 112 medicinal plants included in the State Pharmacopoeia of Ukraine. For example, ointment applied in case of inflammatory processes of the skin: Riboflavini 0,01; Retinoli acetatis 0,05; Lanolini, Vaselini ana 5,0; Decocti flores Chamomillae ex 1,0 – 10 ml.

Liquid forms of medications include a mixture with sedative action: Folium Menthae 4,0; Natrii bromidi 3,0; Amidopyrini 0,6; Coffeini-natrii benzoatis 0,4; Magnesia sulfatis 0,8; Aquae purificatae 200,0.

It is indicative of availability to use medicinal plants in manufacturing medicines in pharmacies.

There is a certain practice in the use medicinal teas that are selected in the best possible way, studied and effectively used by doctors in a comprehensive treatment and rehabilitation of patients with stomach pathology (9 teas), disorders of the intestine (6), liver (19), gallbladder (5) and pancreas (7). Thus, for example, with chronic enterocolitis associated with constipation the following medicinal tea appeared to be rather effective (100 g):

Herba Hyperici 20,0;
Herba Millefolii 20,0;
Flores Chamomillae 30,0;
Folia Menthae 10,0;
Rhizomata Calami 20,0.

Conclusion. Further development of such an area in Ukrainian pharmacy as manufacturing extemporal medicines using medicinal raw material is topical and reasonable.

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FORMATION OF COMMUNICATIVE COMPETENCE IN MEDICAL STUDENTS

Abstract. *The article presents ways of forming the communicative competence of medical students. Examples of innovative technologies that promote the formation and improvement of professional communication skills and the development of clinical thinking of future physicians are given.*
Key words: *medical education, communicative competence.*

Objective. In recent years increases interest of scientists in the fields of organization of training medical specialists; content and management of medical education quality; problem of professionalism development in medical specialists; professional communication skills of future physicians.

Discussion. In today's society it is an important ability for a medical specialist to quickly perceive any form of communication, to acquire necessary information, to reproduce it in dialogue interaction and to manage system of speech communications within its competence. The proficiency, image and success of future specialist depend on the wealth of one's vocabulary, level of communicative culture and language technology.

Kuzmina N. defines professionalism as a measure of mastering modern means of solving professional problems by a person, productive ways of its implementation, and identifies three common features of this phenomenon: 1) possession of special knowledge of the purpose, content, object and means of labor; 2) possession of special skills at the preparatory, executive and final stages of activity; 3) mastering special skills that allow to carry out the activity itself and to obtain desired results [4].

Professionalism of the clinician, in addition to the professional competence, implies a high level of general competencies possession, in particular communicative.

The communicative competence of doctor involves formation of communicative skills and also skills that are necessary for medical interaction and the construction of a therapeutic diagnosis with patient, as well as the presence of certain professional qualities, and first of all, tolerance.

The results of many studies show an inadequate level of communicative competence of future physicians (emotional barriers, emotional instability).

Simulation training significantly brings medical education closer to the real conditions of practical medical activity, promotes the mastery of the system of skills of successful implementation of specific types of professional medical activities and improving the quality of medical care.

However, unfortunately, even with the help of auxiliary materials and phantoms it is impossible to fully reproduce all clinical conditions of doctor's work; no "mannequin" is able to convey emotions of alive person. That is why there are problems in communication between doctor and patient.

In order to develop communication skills for interaction with patients, one of three options of imitation technologies is possible: first is the involvement of a patient-actor ("standardized patient"). The negative side of this technology is the need for additional financing. Second method – to involve volunteer students as statists. This technique, compared with the traditional model of a "standardized patient" does not require any material costs, but the use of volunteer students may not be on a permanent basis, because they need to prepare for classes in other departments. Third option – conducting practical classes by using

interactive techniques, such as business games. Such classes are conducted when students have studied most of the diseases.

Already from the third year of studies, medical students need to develop professional linguistic communicative competence, which aims to form professional communication skills in real situations "patient-doctor".

At the Department of Propaedeutic of Internal Diseases, one of the methods of innovative technologies – educational simulation game, or "role-playing game", is used. The role-playing game is conducted during a practical class. The teacher distributes roles between students and they get a specific task. One student acts as a patient, the other one – in the role of a doctor; third student (reviewer) – conducts an analysis of actions of both the patient and the doctor, indicating their inaccuracies and errors. Teacher conducts an analysis of actions of each participant, comments on answers, and acts as a consultant. In the process of a role-playing action, they represent real situations that await them in the future career: the provision of urgent aid in urgent situations, simulation of conditions for some diseases and choosing best treatment tactics for patient [1].

Applying innovative technologies in educational process, namely, the role-play game, allows to master professional communication skills of medical students, which can include the following: skills of effective transfer of professional information adequately to the situation and psychological characteristics of the patient (skills of accurate, short and specific information transmission, rephrasing information using a variety of speech styles, understanding the meaning of patient statements, etc.) and possessing convincing language skills (skills of effective expressin of their point of view, effective reasoning of their language, communication skills for proving the benefits of new technologies and materials for treatment; skills of flexible response to the objections of patient, etc.).

Conclusions. As a result, the formation of communicative competence during all stages of studying at a medical university should be a dominant, system-forming component of the professional training of future specialists in the system of Health Care. New approaches to the development of communicative competence will increase the effectiveness of the process of forming psychological competence of doctors during studying at higher medical establishments. Communicative training should rely not on the transfer of formal knowledge, but on the formation of professional communication experience and its effective use during medical practice [2, 3].

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THE PROGNOSTIC VALUE OF HEMODYNAMICS INDICES AND BIOMARKERS I-FABP AND L-FABP IN ABDOMINAL COMPARTMENT SYNDROME IN CHILDREN WITH ACUTE NEUROINFECTIONS

Abstract. *Introduction. Infectious diseases in children may be associated with risk factors of developing of intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS). Material and methods. We conducted a retrospective study of cases of ACS in children with infection diseases. Parameters of central and peripheral hemodynamic assessed by echocardiography and doppler ultrasound, and biochemical markers (I-FABP, L-FABP, ALT, bilirubin, creatinine, BUN) were evaluated. Results. Seven cases of ACS and IAH were investigated. Increased abdominal pressure and ACS were associated with significant elevation of serum creatinine (81,37±35,92 mcmol/l amid elevated IAP and 57,14±19,63 in normal IAP, p<0,05), intestinal serum biomarker I-FABP (13,44±4,58 ng/ml amid elevated IAP and 2,65±1,25 amid normal IAP), higher cardiac output (6,0±0,57 l/min/m2 vs 4,3±0,34 l/min/m2 in normal IAP, p<0,05), decreased diastolic blood flow velocity in renal and superior mesenteric arteries (3,4±1,08 cm/s vs 18,7±1,58 cm/s in renal arteries, 5,1±0,87 cm/s vs 17,5±3,90 cm/s in superior mesenteric artery, p<0,05), and elevated peripheral resistance index (RI) in the renal artery (0,92±0,02 vs 0,70±0,02, p<0,05). Conclusion. Assessment of biochemical tests and hemodynamic parameters may be used as additional diagnostic tool for children with ACS.*
Keywords: *abdominal compartment syndrome, FABP, hemodynamic, children.*

Introduction. Abdominal compartment syndrome (ACS) is a rarely diagnosed serious condition that can complicate the course of different diseases. It is believed that among children who receive therapy in intensive care units, the frequency of ACS fluctuates at the level of 0.6-4.7%, while the mortality rate reaches 40-60%[1]. Currently, diseases with a high risk of intra-abdominal hypertension (IAH) and abdominal compartment include trauma, intestinal obstruction, necrotic enterocolitis, abdominal wall defects, diaphragmatic hernia and septic shock with massive intravenous infusion[2]. In cases of acute infectious of the central nervous system (CNS) in children, the frequency of IAH and ACS has not yet been studied.

Purpose of the study. Estimate prognostic value of biochemical markers and hemodynamic indices in the diagnosis of abdominal compartment syndrome in children with acute CNS infections.

Material and methods. Retrospective chart review of children with abdominal compartment syndrome who were treated in the intensive care unit of the municipal children's infectious diseases hospital in 2015-2017 due to acute neuroinfections. Cases of a documented increase in abdominal pressure and symptoms of abdominal compartment were selected for further analysis. ACS in patients was determined according to the criteria of the World Association for Abdominal Compartment Syndrome (2013). Intra-abdominal pressure (IAP) was determined in the presence of risk factors for the development of IAH and ACS. Patients' intra-abdominal pressure was measured using a standard bladder catheter. Increased pressure was considered to be more than 10 mm Hg[2]. ACS was diagnosed in cases of steady increase in abdominal pressure of more than 10 mm Hg and the appearance of organ

dysfunctions. The presence of organ dysfunction was determined according to the criteria described in the International pediatric sepsis consensus conference (2005) and the logistic scale of organ dysfunction PELOD (1999). To determine the intensity of injury of organs of the gastrointestinal tract, the level of biomarkers I-FABP and L-FABP was investigated[3]. As part of an additional examination, according to local protocols, the intensive care unit also conducted a study of central and peripheral hemodynamics using echocardiography and Doppler ultrasound (DUS). The ultrasound machine Siemens Sienna with convex sensors 5-7.5 MHz and 3.5-5 MHz and a linear sensor 7.5 MHz. An echocardiographic study was performed transthoracically with the calculation of the end-diastolic and end-systolic volumes of the left ventricle with the subsequent calculation of the stroke volume (SV) according to Teichholz (1976), the systolic index (SI) and the ejection fraction (EF). Preloading of the left ventricle was assessed by the end-diastolic diameter (EDD) of the left ventricle. DUS was carried out according to a standard method with the determination of systolic (V max) and diastolic (V min) blood flow rates, the index of peripheral resistance RI (RI = (Vmax-Vmin)/Vmax) was calculated. The characteristics of blood flow in the abdominal aorta, renal arteries, superior mesenteric artery, celiac trunk, and posterior tibial artery were studied.

Results. We analyzed 53 case histories of children in the intensive care unit with a diagnosis of acute neuroinfection. Among them, there were 42 patients with bacterial meningitis, 10 patients with encephalitis and 1 patient with viral meningitis. We selected 6 cases from this group that met the criteria of abdominal compartment syndrome in the form of a registered increase in abdominal pressure with the concomitant appearance of organ and system dysfunction. The maximum registered value of abdominal pressure is 26 mm Hg. The age of patients was from 1 month to 10 years. Boys - 4 (57.1%), girls - 3 (42.9%). 3 children were diagnosed with unspecified bacterial meningitis, 2 children were diagnosed with generalized meningococcal infection (meningitis and coccemia), 1 child was diagnosed with viral encephalitis (unspecified ethiology). In 2 children, increased intra-abdominal pressure and clinical manifestations of abdominal compartment were observed during hospitalization; these symptoms have been developed in 3 children within two to three days, in another one - after the 10th day of stay in the intensive care unit. The duration of the period of increased intra-abdominal pressure ranged from 3 to 6 days (median - 4 days). The development of ACS in all 6 patients was accompanied by the development of acute renal dysfunction, in 4 patients - with neurological disorders (depression of consciousness), in 2 patients - with associated respiratory dysfunction, in 3 patients - with coagulation hemostasis, in all 6 patients - with inhibition of intestinal peristaltic activity with a significant amount of gastric stasis. An ultrasound examination revealed free fluid in the abdominal cavity in all 6 patients, in addition in the pleural cavity – in 3 patients and in the pericardial cavity in 3 patients. In all patients, conservative tactics (nasogastric and rectal drainage, early enteral feeding, adequate sedation, correction of infusion therapy and providing negative fluid balance) were used in the treatment of intra-abdominal hypertension. In all the studied patients, a positive trend was observed during treatment, there were no fatal cases.

Laboratory and instrumental studies were conducted in all patients over time and covered both the period of intra-abdominal hypertension and after normalization of abdominal pressure during therapy. Further, we compared the indices obtained in the days when IAP was increased, with the same indices obtained after the normalization of IAP. The results of biochemical studies in patients at different periods of the disease are shown in Table 1.

Table 1.

Biochemical markers (M ± SD) in the period of normal and increased IAP

Index	High IAP	Normal IAP
pH	7,40±0,07	7,37±0,08
BE, mmol/L	-2.31±6,06	-1,47±5,97
Creatinine, µmol/l	81,37±35,92*	57,14±19,63*
Urea, mmol/L	13,07±11,48	6,47±2,81
ALT, U/l	76,21±47,14	66,30±70,57
Bilirubin, µmol/l	14,66±4,24	16,18±0,93
I-FABP, ng/ml	13,44±9,16*	2,65±2,49*
L-FABP, ng/ml	355,03±325,86	156,16±82,11

** - significant difference between groups (p <0.05 according to the Mann-Whitney criterion)*

The average pH level in observed patients varied between 7.22–7.54. Episodes of decompensated acidosis were reported in 5 of 7 patients, and two children had an increase in pH above 7.45. There were no significant differences in pH between episodes on the background of increased and normal abdominal pressure. The deficit of bases for BE varied widely (from -14.40 to 10.10 mmol/l). The average BE indexes on the background of increased and normal IAP did not differ significantly. The creatinine index was recorded in the range of 35 - 158 µmol/l. An increase in creatinine above the age norm was observed in 6 out of 7 patients. A higher average creatinine level was recorded in children during the period of increased IAP, lower creatinine level was recorded at normal IAP level (p=0.04363, according to Mann-Whitney criterion). The average urea level was also slightly higher during the period of IAP increase, but the difference in comparison with the urea level at the normal IAP value was insignificant (p>0.05). ALT levels in patients ranged from 12.0 U/l to 280.0 U/l. A significant increase in ALT (more than 2 norms) was observed in three children, including one patient was diagnosed with bacterial meningitis and two patients - with encephalitis. There was no significant difference between ALT levels at increased and normal IAP levels (p>0.05, according to Mann-Whitney criterion). Total bilirubin in our patients ranged from 9.8 to 229.9 µmol/l. There was no significant difference between the indicators at increased and normal IAP (p>0.05). Among the study group of patients, an increase in bilirubin level above the normal level was observed only in a patient with viral encephalitis. I-FABP level, when measured during increased IAP, averaged 13.44 (from 3.91 to 25.54 ng/ml), and 2.65 against the background of normal IAP (from 0.1 to 5.8 ng/ml) (p = 0.03662, according to Mann-Whitney criterion). L-FABP was also higher in patients with increased IAP (355.03, 145.93 to 914.53 ng/ml) than in patients after IAP normalization (156.16 ng/ml, 37.16 to 251.02 ng/ml) (p>0.05).

The average values of central hemodynamics obtained against the background of normal and increased intra-abdominal pressure are presented in table 2.

The systolic blood pressure in patients against the background of increased IAP and the development of ACS did not change significantly and did not go beyond the age norm. Diastolic pressure during increased IAP tended to decrease in all patients, but these changes were statistically insignificant (p>0.05 according to Mann-Whitney criterion). The index of contractile function of the left ventricle (EF) during the development of ACS did not change significantly. In all patients with increased IAP and development of ACS, an increase in cardiac output was observed. The average systolic index was significantly higher compared with the determination during the period of normal IAP (p = 0.028 according to Mann-Whitney criterion).

Indicators of arterial blood flow in peripheral vessels, obtained in the period of increased and normal IAP, are shown in table 3.

Table 2.

Central hemodynamic indices (M±SD) in the period of normal and increased IAP levels

Index	High IAP	Normal IAP
sBP, mm Hg	96,2±13,47	105,5±23,13
dBP, mm Hg	52,6±13,70	62,2±21,76
SI, l/min/sq	6,0±2,13*	4,3±1,97*
EF, %	68,0±10,56	66,6±10,38

sBP - systolic blood pressure, dBP - diastolic blood pressure, SI - systolic index, EF - ejection fraction.

Table 3.

Peripheral hemodynamic indices (M±SD) at normal and increased IAP levels

Vessel/index	High IAP	Normal IAP
Abdominal aorta		
V max, m/s	145,6±68,1	142,9±52,6
V min, m/s	6,3±6,5	11,7±7,5
Renal artery		
V max, m/s	54,1±33,9	66,5±28,8
V min, m/s	3,4±4,0*	18,7±7,9*
Celiac trunk		
V max, m/s	115,7±40,2	124,3±58,2
V min, m/s	22,1±16,2	33,7±14,9
Superior mesenteric artery		
V max, m/s	148,8±112,2	162,7±74,8
V min, m/s	5,1±2,5*	17,5±16,1*
Posterior tibial artery		
V max, m/s	34,6±18,7	30,9±14,5
V min, m/s	2,4±5,2	2,4±3,1

** - significant difference between groups (p <0.05 according to the Mann-Whitney criterion).*

The mean systolic velocity (V max) in the abdominal aorta did not differ significantly during increased and normal abdominal pressure. The diastolic velocity (V min) with an increased IAP tended to decrease, however, the difference in the average indices was unreliable (p> 0.05). In the renal and superior mesenteric arteries, systolic and diastolic blood flow velocity decreased against the background of abdominal hypertension. Most of the changes were related to diastolic velocity, and the difference between the mean values of V min was significant (p<0.001, according to Mann-Whitney criterion). In addition, the peripheral resistance index (RI) in the renal artery on the background of IAH significantly increased to 0.92±0.086, compared with the level at normal IAP - 0.70±0.112 (p<0.00001 according to Mann-Whitney criterion). In the celiac trunk, there was a tendency to a decrease in both systolic and diastolic velocities, but there was no significant difference between the averages. The average values of V max and V min in the posterior tibial artery practically did not differ from the results obtained at normal abdominal pressure (p> 0.05).

Discussion. The frequency of abdominal compartment syndrome in the intensive care unit among children with acute infectious lesions of the central nervous system was 13.2%, which is comparable to the frequency of this syndrome in non-infectious patients[1]. In this paper, we investigated which laboratory and instrumental studies indicators are more closely related to abdominal hypertension and abdominal compartment syndrome. Among the biochemical markers, we identified a correlation between the increase in IAP with an increase in the level of biomarkers I-FABP and L-FABP[4]. At the same time, we observed high levels of these indices in three patients even before the onset of symptoms of increased abdominal pressure. This confirms the view that the starting factor of abdominal hypertension, as a rule, are disorders of the gastrointestinal organs[2].

In the pathogenesis of abdominal compartment, an increase in the peripheral resistance of the abdominal vessels with a subsequent drop in cardiac output and a decrease in blood pressure also plays an important role[5]. However, against the background of abdominal hypertension, we noted in our patients only statistically insignificant multidirectional changes in blood pressure. The absence of correlation of blood pressure with IAH is noted by the authors of other studies[6]. High abdominal pressure and a decrease in venous return theoretically should lead to a drop in cardiac output. However, an increase in abdominal pressure in our patients was associated with a significant increase in cardiac output. In our opinion, this may be due to the fact that septic diseases are more often associated with normal or increased cardiac output due to tachycardia, reduced afterload and the use of intensive infusion therapy[7]. It is also possible that an increase in IAP among our patients did not reach a certain “critical” level, after which cardiac output should decrease.

Changes in the regional blood flow, in particular in the renal and superior mesenteric arteries, with an increase in abdominal pressure were unidirectional. According to the literature, the blood flow in the renal arteries responds rather early to an increase in IAP. Among the indicators of blood flow, the resistance index (RI) in the renal arteries demonstrates a large correlation. According to the results of its observations, Umgelter A et al reports a significant increase in RI in the renal arteries with an increase in abdominal pressure up to 20 mm Hg[8]. Experimental data published in the literature also indicate that an increase in intra-abdominal pressure leads to a decrease in diastolic velocity in the mesenteric artery, which coincides with our results[9].

Conclusions. The development of acute renal failure and accumulation of free fluid in the abdominal cavity are characteristic of the abdominal compartment syndrome in children with acute neuroinfections. ACS is characterized by an increase in the level of creatinine from biochemical blood markers, as well as biomarkers I-FABP and L-FABP. Among the hemodynamic indices, a decrease in diastolic linear velocity and an increase in peripheral resistance index (RI) in the renal and superior mesenteric arteries has a higher prognostic value for the diagnosis of intra-abdominal hypertension and abdominal compartment syndrome, as well as an increase in cardiac output.

Prospects for further research. The main limitations of our study are small sample cohort and single-centre design. Future multicenter trials

with large number of patients can determine precision values of hemodynamic and biomarkers parameters that may be used for early diagnosis of abdominal compartment syndrome in children with acute CNS infection.

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