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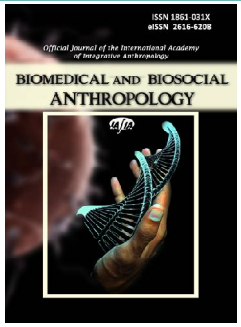

Forms of infectious complications after use of metal foreign bodies of the auricle and determination of the ability of detected microorganisms to biofilm formation

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Ear or nose are quite vulnerable to foreign bodies. Foreign bodies cause various side effects in the body. A special ategory consists of foreign bodies that are introduced for aesthetic purposes, in particular piercing products. Decoration implanted in the tissues of the ear or nose is a foreign body and is a field of increased contamination and reproduction of pathogenic and opportunistic microorganisms. The aim of the study was to determine the infectious forms of complications that occurred after prolonged use of metal foreign bodies and to study the ability of biofilms by microorganisms isolated from the pathological contents of the foreign body of the auricle. 93 patients who applied to the ENT department of Kharkiv Regional Hospital for complications after implantation of metal foreign bodies and 10 people, control group, which had no foreign bodies, and were randomly selected from healthy individuals, were examined, to determine the qualitative composition of the microbiocenosis of the auricle skin. The material for the study was pathological discharge from a foreign body of the auricle. The microbiological study was performed using MICRO-LA-TEST identification kits. Studies of the formation of biofilms were studied by determining the ability of bacterial strains to adhere to the surface of polystyrene. The obtained cultures were washed with suspension media individual for each family of bacteria. The optical density of bacterial suspensions was measured using a microplate reader "MultiskanEX" (type 355). Statistical analysis of the obtained data was performed using MSExcel, Statisica 10 software. As a result of the conducted researches the dependence between the development of infectious complications of the auricle in the presence of metal foreign bodies and the microbiocenosis of the pathological focus was revealed. The study allowed to establish the structure of the microbial landscape of the skin of the auricle in the area of the metal foreign body, to determine the dominant forms of complications of infectious origin, after prolonged use of metal foreign bodies and to study the ability to form biofilms by microorganisms from different metals. The ability of various types of microorganisms to form biofilms when using products from different types of metals has been studied. It is established that the use of metal foreign bodies made of silver and gold reduces the risk of purulent-inflammatory process. It is proved that the optical density of biofilms of most microorganisms isolated from the pathological contents of the area of foreign bodies made of silver and gold is significantly lower than when using steel and titanium products.

Keywords: *microbiocenosis, microorganisms, purulent-inflammatory process, auricle, complications, foreign bodies, biofilms.*

Introduction

The microbial landscape of the skin of the auricle under the influence of external factors has changed over time. If previously the leading causative agent of purulent-inflammatory complications of implantation of metal foreign bodies was considered Staphylococcus aureus, recently the role of Pseudomonas aeruginosa has increased to an average of 78 % of cases [29]. In some cases, bacterial or bacterial-fungal associations act as an etiotropic factor. The ratio of different types of microorganisms that are part of the microflora of the skin of the auricle can serve as an

indicator of the functional value of the mechanisms of protection of the microorganism. The microflora of the skin is the result of a set of complex relationships of micro- and macroorganisms, taking into account the influence of many aggressive environmental factors, including the puncture of the auricle [14]. It is known that most bacteria in the environment exist in the form of biofilms attached to substrates, the formation of which is a complex and regulated biological process [1, 27]. The formation of biofilms by microorganisms is one of the mechanisms of bacterial survival in the environment [5, 17].

From the studied features of skin microbiocenosis in pathological conditions, namely in the occurrence of purulent-inflammatory process, the existence of the phenomenon of mutual enhancement of pathogenicity in associations of fungi of the genus Candida and bacteria has been proved [23]. In this case, fungi cause sensitization of the body, suppress the functional activity of cellular immunity and neutrophil phagocytosis, contribute to the development of allergodermatoses and the spread of microbial infection [2].

Under stressful conditions for the body, which includes the implantation of metal foreign bodies, there is a selection of opportunistic pathogens that acquire the properties of pathogenicity and persistence [4, 8]. As a result, the translocation of microbes and toxins into the bloodstream and infection of lymphoid tissue occurs and is maintained, so opportunistic pathogens can become etiological agents of infectious diseases of the skin. Today, most microbiologists recognize that a significant number of microorganisms in natural and artificial environments exist in the form of structured, attached to the surface of groups - biofilms, which show a change in phenotype, expressed by changes in growth parameters and expression of specific genes [9, 15, 19]. The film usually includes 15-20 % of the bacterial mass, which is firmly attached to a surface, and 80-85 % of the protective matrix, which reduces the effect of antibiotics and antiseptics on target microcultures by tens, hundreds and even thousands of times [20, 28]. Biofilms are continuously changing heterogeneous groups that may consist of a single species of bacteria or fungi or, more often, may be polymicrobial. It is known that the formation and development of microbial communities is coordinated by the system "quorum sensing" (QS), the main function of which is the production of signaling molecules and the ability of bacteria to perceive these signals [7]. The QS system controls the cell density of the bacterial population, the production of many extracellular pathogenic factors, which provides bacteria with the opportunity to overcome the protective mechanisms of the macroorganism during infection [21]. In the case of QS inhibition, the production of bacterial virulence factors is reduced and the formation of the biofilm is disrupted [12, 28].

The purpose of the study is to determine the infectious forms of complications that occurred after prolonged use of metal foreign bodies and to study the ability to form biofilms by microorganisms isolated from the pathological contents of the foreign body of the auricle.

Materials and methods

The work was performed on the basis of the ENT clinic of Kharkiv National Medical University. We examined 93 patients who applied to the ENT department of the Kharkiv Regional Hospital for complications after implantation of metal foreign bodies and 10 people, control group, to determine the quality of the microbiocenosis of the skin of the auricle, who had no foreign bodies, and were randomly selected from healthy persons.

The obtained material from the area of the foreign body of the auricle was taken and delivered to the laboratory in accordance with the requirements of collection and delivery of material for microbiological laboratories proposed by the Shupyk National Medical Academy of Postgraduate Education (Kyiv). The material for the study was pathological discharge from a foreign body of the auricle.

The study was conducted in compliance with the basic bioethical provisions of the Council of Europe Convention on Human Rights and Biomedicine (04.04.1997), the Helsinki Declaration of the World Medical Association on the ethical principles of scientific medical research with human participation (1964-2008), and the order of Ministry of Health of Ukraine № 690 dated 23.09.2009. The conclusion of the Commission on Ethics and Bioethics of Kharkiv National Medical University confirms that the study was conducted in compliance with human rights, in accordance with current legislation in Ukraine, meets international ethical requirements and does not violate ethical standards in science and standards of biomedical research.

The microbiological study was performed using MICRO-LA-TEST identification kits, which are designed for standard identification using micromethods and allow the identification of most clinically important microorganisms in a short time. The following nutrient media were used for primary seeding: 5 % blood agar, Chistovich's yellow-salt agar, Endo medium, Hottinger's medium, Tarozzi's semi-liquid medium, Saburo's medium.

When determining the concentration of microbial cells, the percentage of viable cells is determined, which is determined by the number of living cells per unit volume of suspension (number of colony-forming units in ml - CFU/ml). Standardization of the microbial suspension was performed using the McFarland turbidity standard (McF - McFarland) using a device "Densi-La-Meter". Studies of the formation of biofilms were studied by determining the ability of bacterial strains to adhere to the surface of polystyrene in 96-well plates for enzyme-linked immunosorbent assay [17, 20, 26]. Cultures were grown according to generally accepted methods in microbiology on the suspension media recommended for each family of bacteria. The obtained cultures were washed with suspension media individual for each family of bacteria. The optical density of the initial

bacterial suspension was measured on a "Densi-La-Meter" and adjusted to the appropriate McFarland concentration using a suspension medium. The optical density was measured using a microplate reader "MultiskanEX" (type 355), which is a photometer with replaceable filters and is able to perform standard photometric measurements.

Statistical analysis of the obtained data was performed using MSExcel software, Statisica 10 [3, 30]. These programs have a complete set of proven statistical procedures, with an in-depth understanding of the relationships between data and the structure of forecasts [30]. The results of the mean values of the indicators between the groups were compared using parametric (Student's test) and non-parametric criteria (U Mann-Whitney, χ^2 Pearson) [13, 22].

The probability of intergroup differences of particles is calculated using Fisher's exact criterion φ. We used the method of correlation analysis as well as methods of descriptive statistics. The difference between the indicators was considered probable at $p<0.05$.

Results

The total number of the group was 93 people, with an absolute predominance of women (94.6 %), which corresponds to a gender ratio of 1:18. The structure of complications found in patients of the clinical group was dominated by perichondritis of the auricle and secondary infection; the category of "other" complications included atheroma formation, rupture and defects of the earlobe, etc.

In total, 26 cases of secondary soft tissue infection, 18 cases of auricle defects, 15 cases of perichondritis, 7 cases of contact dermatitis, 7 cases of keloid scars, and 20 other complications were registered in the structure of complications, incl. atheroma and ruptures of the earlobe.

When comparing the frequency of complications, it was found that people who use silver, gold or composite jewelry, the chances of developing different types of pathology are almost the same (Table 1).

Exclusion criteria were the presence of traumatic brain injury, generalized infectious, somatic and genetic diseases.

Table 2 shows the results of comparing the frequency of complications in patients with metal foreign bodies of the clinical group.

The structure of the microbiocenosis of the skin of the auricle of the control group was represented by the following microorganisms: *Peptostreptococcus spp.* - $(2.2\pm0.2)x10^2$ CFU/ml; *Staphylococcus aureus* - (1.5±0.5)x102 CFU/ml; *Micrococcus spp.* - $(1.4\pm0.3)x10^1$ CFU/ml; *Enterococcus spp.* - $(2.1\pm0.2)x10^1$ CFU/ml; *Candida spp.* - $(2.4\pm0.3)x10^2$ CFU/ml; *Actinomyces spp.* - $(1.6\pm0.2)x10^1$ CFU/ml; *Staphylococcus epidermidis* - $(1.4\pm0.2)x10^2$ CFU/ml; Enterobacter spp. -$(2.2\pm0.4)x10^1$ CFU/ml; *E. coli* - $(1.4\pm0.1)x10^1$ CFU/ml; *Staphylococcus pyogenes* - $(1.1\pm0.1)x10^1$ CFU/ml.

As a result of the study, it was found that out of 93 people, complications occurred in 21 people (22.6 %) who used silver products (group I). In the microbiological analysis of patients in the area of a foreign body in patients with atheroma, the degree of contamination of *Staphylococcus aureus* $(5.8\pm0.4)x10^4$, *S. pyogenes* $(7.4\pm0.8)x10^3$, *Staphylococcus epidermidis* $(5.4\pm0.6)x10^3$, *Candida spp.* $(4.1\pm0.8)x10^2$ was 2 times higher than in the control group. However, their number is acceptable values for a normal microbial landscape ($n=x10^{1-4}$). The analysis of the condition of the microflora of the skin of the auricle of patients with contact dermatitis showed that the number of opportunistic pathogens did not exceed normal values and corresponded to the control group. Among the complications after prolonged wearing of silverware, was a secondary infection, which is localized in the area of the foreign body. As a result of the study it was found that the degree of contamination of the foreign body area was quite high, in the area of secondary infection were isolated: *Staphylococcus aureus* $(9.6\pm0.8)x10^8$ CFU/ml; *Staphylococcus epidermidis* $(6.3\pm0.2)x10^6$ CFU/ml; *Candida spp.* $(3.4\pm0.4)x10^6$ CFU/ml, which were the

Table 1. Comparison of the frequency of complications of metal foreign bodies depending on the chemical composition of jewelry.

	Silver	Gold	Alloy	Titanium
Silver		2=0.950 p=0.333	2=0.522 p=0.471	X2=7.547 p=0.011 φ2=0.041
Gold			2=3.563 p=0.058	X2=13.424 p=0.000 φ2=0.041
Alloy				X2=7,042 p=0.012 φ2=0.041

Table 2. Stratification characteristics of complications in individuals of clinical groups of the contingent of the prospective stage of the study.

Number of examined	Material of products	Complications	Number of complications	
			absolute	%
Clinical group (persons with implants in the auricles), n=93				
I group (n=21)	silver	atheroma	12	12.9
		contact dermatitis	5	5.4
		secondary infection	4	4.3
II group (n=25)	gold	perichondritis	7	7.5
		secondary infection	11	11.8
		keloid scars	7	7.5
III group (n=37)	alloy	rupture of the earlobe	6	6.5
		auricles defect	13	14.0
		contact dermatitis	2	2.2
		perichondritis	8	8.6
		secondary infection	8	8.6
IV group (n=10)	titanium	rupture of the earlobe	2	2.2
		auricles defect	5	5.4
		secondary infection	3	3.2

etiological factors of secondary infection in the area of the metal foreign body. Pathogenic properties of microbial contamination were manifested due to the reproduction of microorganisms and their penetration from the surface into the wound tissue.

Further studies were performed to determine the ability of microorganisms sown from the pathological contents of a foreign body to form biofilms. According to the results of the study, it was found that all isolates formed dense diurnal biofilms: *Peptostreptococcus spp.* - (1.942±0.083) OD; *Staphylococcus aureus* - (2.959±0.091) OD; *Micrococcus spp.* - (1.683±0.042) OD; *Enterococcus spp.* - (2.214±0.071) OD; Candida spp. - (3.622±0.091) OD.; *Actinomyces spp.* - (3.462±0.083) OD; *Staphylococcus epidermidis* - (2.791±0.060) OD; *Enterobacter spp.* - (2.382±0.080) OD; *E. coli* - (1.640±0.041) OD; *Staphylococcus pyogenes* - (2.732±0.091) OD.

Among 93 people, 25 (26.9 %), who wore gold products, had complications in the form of perichondritis and keloid scars by 7 and 11 - secondary infections of the metal foreign body, group II. Microbiological examination of patients with perichondritis revealed that the microbial landscape of the skin of the auricle of the experimental group of patients differed from the control group in content, *Staphylococcus aureus* $(8.4\pm0.9)x10^4$, *Staphylococcus pyogenes* $(6.3\pm0.5)x10^3$, *Candida spp.* $(6.2\pm0.6)x10^3$ та *E. coli* $(1.4\pm0.2)x10^4$, which exceeded the contamination of the foreign body area of the control group by 2 - 3 degrees. However, their number corresponded to the values of the normal microflora of the skin of the auricle. Among the complications of wearing gold products is the occurrence of secondary infection. As a result of the study, as in the use of silver products, etiological agents found that the degree of contamination of the foreign body was an order of magnitude higher than in the group of patients who used silver products and 3 - 7 orders of magnitude higher than in the control group. From the area of secondary infection were identified: *Staphylococcus aureus* $(4.6\pm0.4)x10^9$ CFU/ml; *Staphylococcus epidermidis* $(3.7\pm0.3)x10^7$ CFU/ml; *E. coli* $(4.8\pm0.4)x10^7$ CFU/ml; *Enterobacter* $(8.6\pm0.8)x10^7$ CFU/ml; *Candida spp.* $(9.8\pm0.3)x10^6$ CFU/ml; *Actinomyces spp.* $(7.8\pm0.8)x10^5$. It was found that the microorganisms isolated from the pathological content formed dense biofilms: *Peptostreptococcus spp.* - (1.986±0.082) OD; *Staphylococcus aureus* - (2.312±0.093) OD; *Micrococcus spp.* - (1.342±0.041) OD; *Enterococcus spp.* - (2.420±0.073) OD; *Candida spp.* - (3.761±0.080) OD; *Actinomyces spp.* - (3.521±0.062) OD; *Staphylococcus epidermidis* - (1.573±0.060) OD; *Enterobacter spp.* - (2.640±0.082) OD; *E. coli* - (1.462±0.044) OD; *Staphylococcus pyogenes* - (2.191±0.090) OD.

Among the identified complications in patients wearing gold products, keloid scars were observed in 7.0 %. When determining the structure of the microbiocenosis of the skin of the auricle of patients with keloid scars, after using gold products, it was found that there was no significant difference between the composition of microorganisms in the normoflora of the control group and the experimental.

It was found that among the persons who sought help 37 (11.5 %) used alloy products, group III. Of these, 6 - cases of rupture of the earlobe, 13 - ear defects, 8 cases of perichondritis and secondary infection and 2 - contact dermatitis.

Microbiological examination showed that the degree of contamination of the skin of the auricle of patients with rupture of the earlobe when using surgical alloy products was higher by 2 - 3 orders of magnitude than in the control group. The microflora was presented: *Staphylococcus aureus* $(5.8\pm0.4)x10^6$ CFU/ml; *Peptostreptococcus spp.* $(8.2\pm0.6)x10^6$ CFU/ml; *E. coli* $(2.9\pm0.8)x10^6$ CFU/ml; *Staphylococcus epidermidis* $(5.4\pm0.6)x10^6$ CFU/ml; *Enterobacter spp.* $(7.2\pm0.9)x10^6$ CFU/ml; *Candida spp.* $(4.1\pm0.8)x10^6$ CFU/ml. A complication after prolonged wearing of surgical alloy products was the occurrence of contact dermatitis in the area of a foreign body. The analysis of the condition of the microflora of the skin of the auricle showed that the degree of microbial contamination corresponded to the control group. Of all cases of complications after wearing alloy products, perichondritis of the auricle was detected in 21.6 %. The structure of the microbiocenosis was presented by: *E. coli* $(6.8\pm0.3)x10^6$ CFU/ml; *Staphylococcus epidermidis* $(2.4\pm0.7)x10^6$ CFU/ml; *Enterobacter spp.* $(6.7\pm0.8)x10^6$ CFU/ml та *Actinomyces spp.* $(4.2\pm0.3)x10^5$ CFU/ml.

After a microbiological study, it was found that the degree of contamination in the area of foreign bodies in secondary infection was quite high, and we identified: *Staphylococcus aureus* $(6.8\pm0.6)x10^9$ CFU/ml; *Staphylococcus epidermidis* $(3.8\pm0.4)x10^9$ CFU/ml; *Candida spp.* $(8.4\pm0.8)x10^6$ CFU/ml; *E. coli* $(5.4\pm0.6)x10^8$ CFU/ml; *Enterobacter spp.* $(4.2\pm0.5)x10^8$ CFU/ml, which were the etiological factors of secondary infection in the area of foreign bodies. A particularly favorable moment for the development of infection was the presence of damaged tissues and hemorrhages in the wound, which contributed to the development of microorganisms. The main form of bacterial existence is biofilms, not individual planktonic cells. Being in this phenotypic form for a long time, microorganisms produce extracellular polysaccharides and become more tolerant to biocides, namely antibiotics, antiseptics and disinfectants and recover quickly after mechanical destruction, and again form dense biofilms within 24 hours. Therefore, according to the results of the study, it was found that all isolates formed dense daily biofilms: *Peptostreptococcus spp.* - (2.159±0.040) OD; *Staphylococcus aureus* - (2.942±0.082) OD; *Micrococcus spp.* - (1.931±0.070) OD; *Enterococcus spp.* - (2.672±0.044) OD; *Candida spp.* - (3.984±0.062) OD; *Actinomyces spp.* - (3.841±0.083) OD; *Staphylococcus epidermidis* - (2.283±0.092) OD; *Enterobacter spp.* - (2.958±0.081) OD; *E. coli* - (2.194±0.060) OD; *Staphylococcus pyogenes* - (2.681±0.044) OD.

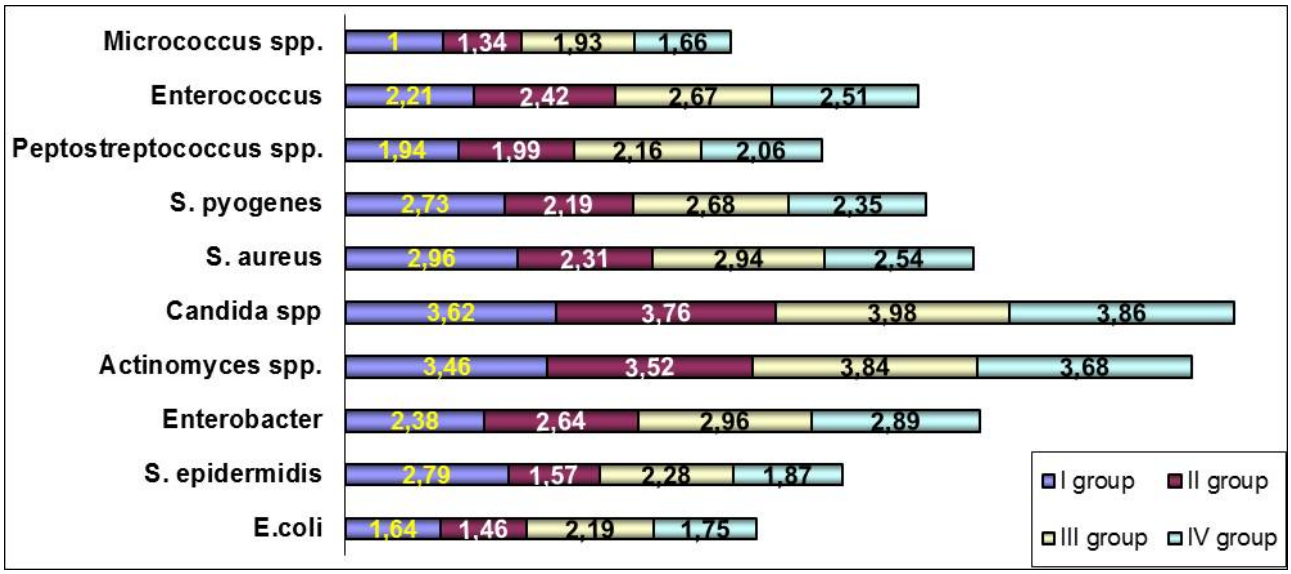

Fig. 1. Optical density of biofilms formed by microorganisms isolated from the zone of metal foreign bodies.

In the study of the group of patients who used titanium products - 10 (10.8%), group IV. The structure of complications was represented by: ruptures of the earlobe when wearing tunnels in 2 patients, in 5 - ear defects and in 3 - secondary infection of metal foreign bodies.

The microbiological study found that the degree of contamination of the skin of the auricle of patients with rupture of the earlobe after using titanium products was higher than in the control group, the microflora was represented by: *Staphylococcus aureus* $4x10^7$ CFU/ml; *Peptostreptococcus spp.* $9x10^5$ CFU/ml; *E. coli* $8x10^6$ CFU/ml; *Staphylococcus epidermidis* $8x10^7$ CFU/ml; *Enterobacter spp.* $4x10^6$ CFU/ml; *Candida spp*. $7x10^4$ CFU/ml мл; *Staphylococcus pyogenes* $9x10^5$ CFU/ml; *Micrococcus spp.* $8x10^5$ CFU/ml, the number of which exceeded normal values of skin colonization by these microorganisms.

In the study of the area of secondary infection were identified: *E. coli* $(3.6\pm0.3)x10^7$ CFU/ml, *Staphylococcus aureus* $(8.4\pm0.8)x10^8$ CFU/ml; *Staphylococcus epidermidis* $(6.5\pm0.6)x10^8$ CFU/ml; *Candida spp*. $(4.2\pm0.4)x10^5$ CFU/ml, *Enterobacter* $(3.9\pm0.4)x10^7$ CFU/ml; *Enterococcus* $(4.6\pm0.4)x10^6$ CFU/ml, which were the etiological agents of secondary infection. Further research was conducted to determine the ability of microorganisms sown from the pathological contents of the foreign body zone to form biofilms. It is proved that when using titanium products, from pathological secretions microorganisms had the ability to form dense biofilms, forming an association of microbes: Candida albicans, E. coli, Staphylococcus aureus та Staphylococcus epidermidis. The optical density of biofilms of microorganisms isolated from the pathological contents of the area of the foreign bodies of the auricle using titanium products were significantly higher than those used when using silver or gold products: *Peptostreptococcus spp.* - (2.061±0.042) OD; *Staphylococcus aureus* - (2.540±0.073) OD; *Micrococcus spp.* - (1.661±0.041) OD; *Enterococcus spp.* - (2.512±0.032) OD; *Candida spp.* - (3.864±0.040) OD; *Actinomyces spp.* - (3.683±0.043) OD; *Staphylococcus epidermidis* - (1.872±0.061) OD; *Enterobacter spp.* - (2.893±0.060) OD; *E. coli* - (1.753±0.040) OD; *Staphylococcus pyogenes* - (2.531±0.042) OD.

Discussion

Analyzing the data obtained, it can be argued that the number of microorganisms that colonize the skin of the auricles increases in the presence of foreign bodies of alloys and titanium. Prolonged use of metal foreign bodies made of silver and gold reduces the possibility of purulent-inflammatory process and prevents the formation of dense biofilms, as one of the main factors of pathogenicity and resistance of microorganisms to antimicrobial drugs.

The formation of biofilms is one of the main strategies that increases the survival of bacteria in the environment, including in the host organism [6]. The ability of microorganisms to exist in biofilms creates great difficulties for medical practice [10, 29], as it significantly increases the resistance of bacteria to antibacterial drugs [16, 21], as well as to the effects of disinfectants [18], adverse environmental factors such as low or high pH levels, high osmotic power and the body's immune defenses [11]. The formation of bacterial biofilms on implants and equipment, catheters, artificial heart valves, lenses, venflons is the cause of a number of purulent-inflammatory processes with severe course [16]. Despite its great popularity and prevalence, the implantation of metal foreign bodies in the auricles has certain problems related to human health. The implantation of metal foreign bodies is associated with perforation of the skin, mucous membranes, muscles,

cartilage, with the subsequent implantation in them of various products made of surgical steel, titanium, noble and polymeric materials [3, 24]. Then there may be complications: violation of the microbiocenosis of the skin, purulent-inflammatory processes of the ear or nose, the formation of keloid and hypertrophic scars, bleeding, defects of the auricles, allergic reaction to foreign body material [9, 25]. In case of insufficient observance of the rules of asepsis, namely: use of non-sterile instruments, insufficient treatment of the implantation site, violation of care techniques after implantation, use of low-quality products, the wound is infected with pathogenic microorganisms [24].

This study showed that the predominant forms of complications of infectious origin, after prolonged use of metal foreign bodies, are perichondritis of the auricle 16.1 % and secondary infection 27.9 %. Since one of the main factors of non-specific protection of the body from environmental microorganisms is the skin, those microorganisms that are opportunistic pathogens and contaminate our skin, when this mechanical barrier is damaged, due to the emergence of a favorable environment (blood, serum in place of damage), begin to show their pathogenic factors. Among them, toxins, pathogenic enzymes and the ability to form biofilms, which cause specific inflammation, which is manifested by infectious-inflammatory processes. It was proved that microorganisms that are isolated from the area of the metal foreign body had the ability to form dense biofilms. The formation of biofilms by isolated microorganisms is one of the mechanisms of the existence of bacteria in the environment [21]. Biofilms are highly organized, mobile, heterogeneous biological systems, which consist of actively functioning cells and cells at rest, enclosed in an exopolymer matrix [6]. They may consist of one or more species of microorganisms [7]. It was previously thought that microorganisms form biofilms on medical devices, such as catheters, endotracheal tubes, IUDs, contact lenses [8]. Currently, it is shown that biofilms of microorganisms are detected in more than 90 % of cases of purulent-inflammatory diseases [9]. Under natural conditions, organisms exist and show their activity, usually in associations, which can change under the influence of new objects introduced into the biosphere, which did not exist before, for example, synthetic polymeric materials and products from them [14].

Studies have shown that the optical density of biofilms of the detected microorganisms was quite different and depended on the type of metal and the type of microorganism (Fig. 1).

Microscopic examination of mixed biofilms revealed that the use of metal foreign bodies made of steel and titanium produces dense biofilms, compared with biofilms formed by microorganisms when using silver and gold products.

Conclusions

1. The predominant forms of complications of infectious origin, after long-term use of metal foreign bodies, are perichondritis of the auricle 16.1 % and secondary infection 27.9 %.

2. Studies have shown that the use of silver and gold products prevents the formation of dense biofilms, as one of the factors of pathogenicity and resistance of microorganisms, as well as reduces the possibility of purulent-inflammatory processes of the auricle.

References

[1] Afinogenova, A. G., & Darovskaia, E. N. (2011). Микробные биопленки ран: состояние вопроса [Microbial biofilms injuries: state of the question]. *Травматология и ортопедия России - Traumatology and Orthopedics of Russia,* 3(61), 119-125.

[2] Alekseeva, N. V., Stepanova, T. V., Tolordava, E. R., & Romanova, Iu. M. (2010). Разработка средств борьбы с биопленками: влияние препарата "Лапрот" (на основе человеческого лактоферрина) и антибиотика ципрофлоксацина на рост и процесс образования биопленок бактериями Pseudomonas aeruginosa in vitro [Development of means of combating biofilms: the effect of the drug "Laprot" (based on human lactoferrin) and the antibiotic ciprofloxacin on the growth and formation of biofilms by the bacteria Pseudomonas aeruginosa in vitro]. *Медицинский алфавит - Medical alphabet*, 3(15), 6-11.

[3] Bashkatov, B., & Surinov, A. (2019). *Международная статистика. Учебник для бакалавриата и магистратуры [International statistics. Textbook for undergraduate and graduate programs].* М.: Юрайт - M.: Yuright.

[4] Beloborodova, N. V., & Bairamov, I. T. (2010). Влияние комбинации кларитромицина с имипенемом на формирование микробной биопленки Pseudomonas aeruginosa [Effect of the combination of clarithromycin with imipenem on the formation of the microbial biofilm of Pseudomonas aeruginosa]. *Инфекции в хирургии - Infections in surgery,* 8(2), 71-74.

[5] Fadeev, S. B., Nemtseva, N. V., Perunova, N. B., Tarasenko, V. S., & Bukharin, O. V. (2010). Формирование биопленок возбудителями раневой инфекции и флегмон мягких тканей [Formation of biofilms by causative agents of wound infections and phlegmons of soft tissues]. *Хирург - Surgeon,* (1), 11-18.

[6] Flemming, H. C., & Wingender, J. (2010). The biofilm matrix. *Nature reviews microbiology,* 8(9), 623-633. doi: 10.1038/nrmicro2415

[7] Galimzianov, Kh. M., Bashkina, O. A., Dosmukhanova, E. G., Abdrakhmanova, R. O., Demina, Iu. Z., Daudova, A. D., ... & Rubalskii, E. O. (2018). Клиническое значение биопленкообразования у бактерий [Clinical significance of biofilm formation in bacteria]. *Астраханский медицинский журнал - Astrakhan Medical Journal,* 13(4), 32-42. doi: 10.17021/2018.13.4.32.42

[8] Gefen, O., Chekol, B., Strahilevitz, J., & Balaban, N. Q. (2017). TDtest: easy detection of bacterial tolerance and persistence in clinical isolates by a modified disk-diffusion assay. *Scientific reports,* 7(1), 1-9. doi: 10.1038/srep41284

[9] James, G. A., Swogger, E., Wolcott, R., Pulcini, E. D., Secor, P., Sestrich, J., ... & Stewart, P. S. (2008). Biofilms in chronic wounds. *Wound Repair and regeneration,* 16(1), 37-44. doi:

10.1111/j.1524-475X.2007.00321.x

[10] Khmel, I. A. (2018). *Биопленки бактерий и связанные с ними трудности медицинской практики [Bacterial biofilms and associated medical practice difficulties].* Access mode: https://img.ras.ru/files/center/biofilms.doc

[11] Khrenov, P. A., & Chestnova, T. V. (2013). Обзор методов борьбы с микробными биоплёнками при воспалительных заболеваниях [Review of methods of combating microbial biofilms in inflammatory diseases]. Вестник новых медицинских технологий. *Электронное издание - Bulletin of new medical technologies. Electronic edition*, (1), 48.

[12] Kremenchutskyi, H. M., Stepanskyi, D. O., Yurhel, L. H., & Koshova, I. P. (2010). Інформаційні комунікації мікроорганізмів [Information communications of microorganisms]. Вісник Дніпропетровського університету. Біологія. *Медицина - Bulletin of Dnipropetrovsk University. Biology. Medicine,* 1(1), 66-70.

[13] Leng, T. A., & Sesik, M. (2011). *Как описывать статистику в медицине [How to describe statistics in medicine].* M. Практическая медицина - M. Practical medicine.

[14] Liao, J., Schurr, M. J., & Sauer, K. (2013). The MerR-like regulator BrlR confers biofilm tolerance by activating multidrug efflux pumps in Pseudomonas aeruginosa biofilms. *Journal of bacteriology,* 195(15), 3352-3363. doi: 10.1128/JB.00318-13

[15] Linski, A. R., Mikucka, A., Szmytkowski, J., & Gospodarek, E. (2009). In vivo biofilm on the surface of a surgical mesh implant. *Polskie Towarzystwo Mikrobiologow Polish Society of Microbiologists*, 58(4), 367-369. PMID: 20380148

[16] Lyamin, A. V., Botkin, E. A., & Zhestkov, A. V. (2012). Problems in medicine related to bacterial films. *Clinical Microbiology and Antimicrobial Chemotherapy,* 14(4), 268-275.

[17] Moons, P., Michiels, C. W., & Aertsen, A. (2009). Bacterial interactions in biofilms. *Critical reviews in microbiology,* 35(3), 157-168. doi: 10.1080/10408410902809431

[18] Morozova, N. S., & Marievskii, V. F. (2009). Дезинфектологические аспекты проблемы борьбы с биопленкой [Disinfectological aspects of the problem of combating biofilm]. *Профілактична медицина (епідеміологія, мікробіологія, вірусологія, паразитологія, інфекційні хвороби) - Preventive medicine (epidemiology, microbiology, virology, parasitology, infectious diseases)*, (2), 3-7.

[19] Ovnanian, K. O., & Trchunian, A. A. (2009). Ультраструктурная архитектоника межклеточных контактов в биопленках бактерий in vitro и in vivo [Ultrastructural architectonics of intercellular contacts in bacterial biofilms in vitro and in vivo]. *Национальная академия Армении - National Academy of Armenia,* 109(1), 78-85.

[20] Parshikov, V. V., Chebotar, I. V., Khodak, V. A., & Samsonov, A. A. (2012). Исследование in vitro микробной биопленки на поверхности синтетических макропористых эндопротезов для пластики брюшной стенки [In vitro study of microbial biofilm on the surface of synthetic macroporous endoprostheses for abdominal wall repair]. *Современные технологии в медицине - Modern technologies in medicine,* (1), 15-20.

[21] Popat, R., Crusz, S. A., Messina, M., Williams, P., West, S. A., & Diggle, S. P. (2012). Quorum-sensing and cheating in bacterial biofilms. *Proceedings of the Royal Society B: Biological Sciences,* 279(1748), 4765-4771. doi: 10.1098/rspb.2012.1976

[22] Rebrova, O. Iu. (2006). *Статистический анализ медицинских данных. Применение пакета прикладных программ Statistica [Statistical analysis of medical data. Application of the Statistica software package].* M., Медисфера - M., Medisphere.

[23] Shirobokov, V. P., Iankovskii, D. S., & Dyment, G. S. (2010). *Микробная экология человека с цветным атласом. Учебное пособие [Human microbial ecology with color atlas. Tutorial].* К.: ООО "Червона Рута-Турс - К.: ООО "Chervona Ruta-Turs.

[24] Struev, I. V., Semeniuk, V. M., Naumkina, E. V., & Odinokii, A. I. (2008). Микрофлора раневого канала при пирсинге языка, верхней и нижней губы и ее чувствительность к антибактериальным препаратам [Microflora of the wound channel with piercing of the tongue, upper and lower lip and its sensitivity to antibacterial drugs]. *Институт стоматологии - Institute of Dentistry,* 1(38), 94-95.

[25] Suleman, L. (2016). Extracellular bacterial proteases in chronic wounds: a potential therapeutic target?. *Advances in wound care*, 5(10), 455-463. doi: 10.1089/wound.2015.0673

[26] Tsyhanenko, A. Ia., Mishina, M. M., & Kurbanov, R. A. (2010). Спосіб відтворення біоплівок мікроорганізмів in vitro [The method of reproduction of biofilms of microorganisms in vitro]. Патент № 47944 UA МПК G09B 23/00 - Patent № 47944 UA МПК G09B 23/00.

[27] Vinnik, Iu. S., Serova, E. V., Andreev, R. I., Perianova, O. V., Rukosueva, T. V., Leiman, A. V., & Michurov, E. I. (2013). Особенности формирования микробных биоплёнок на различных субстратах. Возможность изучения биоплёнок на желчных конкрементах [Features of the formation of microbial biofilms on various substrates. Possibility of studying biofilms on gallstones]. *Современные проблемы науки и образования - Modern problems of science and education,* (5), 323-323.

[28] Vorobey, E. S., Voronkova, O. S., & Vinnikov, A. I. (2012). Бактеріальні біоплівки. Quorum sensing - "відчуття кворуму" у бактерій в біоплівках [Bacterial biofilms. Quorum sensing - "quorum feeling" in bacteria in biofilms]. *Biosystems Diversity,* 20(1), 13-22.

[29] Weigel, L. M., Donlan, R. M., Shin, D. H., Jensen, B., Clark, N. C., McDougal, L. K., ... & Patel, J. B. (2007). High-level vancomycin-resistant Staphylococcus aureus isolates associated with a polymicrobial biofilm. *Antimicrobial agents and chemotherapy,* 51(1), 231-238. doi: 10.1128/AAC.00576-06

[30] Zubov, N. N., Kuvakin, V. I., & Umarov, S. Z. (2020). *Статистика в биомедицине, фармации и фармацевтике [Statistics in biomedicine, pharmacy and pharmaceuticals].* ООО ДиректМедиа - OOO DirectMedia.

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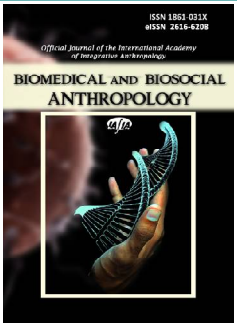

Morphological changes in the tissues of the knee joints of rats in carrageenan-induced experimental arthritis

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Every fifth inhabitant of the earth has been diagnosed with osteoarthritis of various etiologies. Morphological studies of arthritis provide a theoretical basis for creating optimal treatments for this pathology. Given the polyetiological nature of the disease, the choice of the optimal experimental model, which would be as close as possible to the real conditions of inflammatory process reproduction, is the topical issue. The purpose of the study was to confirm the pathological reaction of the joint tissues of laboratory animals in response to intraperitoneal administration of ?-carrageenan. The study was performed on 50 white Wistar rats males aged 12 weeks, weighing 130-150 g. The animals were euthanized by an overdose of anaesthesia according to the terms of the study (1 - 30 days). Fragments of the distal metaepiphyses of the femur and proximal metaepiphyses of the tibia were used for histological examination. Staining of sections obtained on the microtome was performed with haematoxylin, eosin, and Van Gieson`s stain. From the first day of the experimental study, a corresponding reaction of the joint tissues was being observed. Particularly pronounced were the changes in the synovial membrane in the form of oedema of the villi accompanied by an increased filling of blood vessels with foci of thrombosis. Gradually, up to 5 days in the synovial membrane, proliferative changes took place with a clear definition of the multilineage of the integumentary layer, vascular reaction with a tendency to thrombosis, in some places necrosis of synoviocytes was observed, but relative integrity of the morphological structure was still provided by protective barriers of bone and cartilage. On the 7th day pronounced resorption of both bone and cartilage tissue occurred, tissue structure became disorganized and functional layer became thin, accompanied by massive intracellular lysis. The process of synoviocytes necrobiosis with fatty degeneration spread. The histological picture of 10 days is characterized by generalized destruction of bone beams; the destroyed cartilage was replaced by granulation tissue with the presence of cavities. Massive foci of lymphocytic infiltration were observed in the synovial membrane. On the 14th day, a fragmentation of cartilage happened, most of the bone beams (trabeculae) were destroyed. After 3 weeks the morphological picture of cartilage tissue was determined by the appearance in the lacunae of viable cells, the number of which was close to normal. Bone beams were restored, although they remained thin. In a synovial membrane, the hyperplasia of apical departments of villi, leukocytes infiltration, disorganization of connective tissue, and separate vascular disturbances remained. 30 days of the experiment were characterized by a relative recovery of structural relationships to normal. The obtained data confirm the feasibility of using carrageenan in experimental studies of osteoarthritis.

Keywords: *osteoarthritis, knee joint, rats, carrageenan.*

Introduction

The reasons for the development of inflammatory and, as a consequence, degenerative-dystrophic changes of the joints are various, and therefore, scientists who perform experimental research, have a difficult choice of experimental techniques to obtain the most reliable data based on the objectives.

The available literature allows us to conclude that most studies are devoted to the study of the peculiarities of rheumatoid arthritis [4, 16, 19]. A large number of works are devoted to post-traumatic arthritis [6, 8, 21].

Nevertheless, in the general structure of diseases according to Alekseeva L. I. [1], a significant amount of cases are nonspecific idiopathic arthritis or arthritis caused by degenerative-dystrophic changes of the joint, as an exacerbation of a chronic process.

All these conditions have different etiopathogenesis, although a similar clinical picture, so the choice of adequate effective treatment is a topical problem.

Almost all drugs undergo preclinical studies in the context of creating appropriate biological experiments. Currently, the study of drug action in intact laboratory animals and experimental pathology is carried out following international standards, according to GLP (Good laboratory practice). The conditions of experimental research should meet state regulations on bioethics. Of course, these norms are humane and reflect the position of mankind concerning the ecology of the planet, but from the standpoint of scientific requirements, they significantly limit the informativeness of experimental sources.

However, to create a model of post-traumatic osteoarthritis, a large number of techniques have been proposed, which are based either on direct mechanical damage of the articular cartilage (or a complex of articular elements) or on creating joint instability with subsequent development of pathological changes. An overview of these techniques is covered in detail in the articles of Gromyko M. V. and Gritsuk A. I. [9] and Mc Coy A. M. [14]. The main feature of these experimental studies is the mandatory presence of significant energy applied to the joint or repeated (chronic) joint injury, which occurs in human society with a probability of only 12 % [2].

To date, a large number of issues regarding metabolic osteoarthritis remain unresolved. The lack of understanding of the nature of the inflammatory process affecting the joint tissues, the polyvalence of pathological processes, the presence of a significant number of classifications of arthrological diseases make certain demands on experimental models of certain pathologies. The choice of the optimal model depends on many research-related factors, which are based on the capabilities of research centres, urgency, efforts of obtaining the desired results, increasing the reliability of data due to quantity, and taking into account situational features of immediate research tasks, etc [17, 22].

The most common model of experimental arthritis is an attempt to initiate rheumatoid arthritis by various methods. By definition, it is a systemic connective tissue disease with a predominant lesion of small joints with an erosive-destructive component of unknown aetiology with complex autoimmune pathogenesis. This state is achieved by the following methods: 1) the introduction of oil solutions (adjuvant induction); 2) introduction of autogenous solutions (collagen induction); 3) infectious induction. Often these techniques are combined. This model when used in the experiment on small animals provides a picture of chronic inflammation of the joints accompanied by the systemic response of the organism.

Each of these techniques has its advantages and disadvantages over each other. Complex procedure for antigen preparation, multicomponent administration of antigen, duration of the experiment due to the slow process of clinical manifestations of the disease (collagen-induced arthritis); the expressed bacteria-specific answer with development of acute inflammatory process (adjuvant-induced arthritis) does not always allow to receive the model corresponding for the experiment [7, 9].

The purpose of the study was to confirm the pathological reaction of the joint tissues of laboratory animals in response to the intraperitoneal administration of -carrageenan, followed by the use of experimental data to determine the therapeutic effect of biologically active substances.

Material and methods

This paper presents a fragment of an experimental study performed on 50 white Wistar rats males aged 12 weeks, weighing 130-150 g, according to the current legislation, including the "Rules for the use of laboratory experimental animals", 1984 and the Helsinki Declaration of Humane attitude to animals.

There were 10 animals in the intact group, which, given the purity of the line of test samples, and, accordingly to the requirements for statistical reliability of the data were considered quite sufficient.

The experimental group consisted of 40 animals, which were simulated aseptic inflammation by intraperitoneal administration of 5 mg of -carrageenan ("Sigma" USA) dissolved in 1 ml of isotonic sodium chloride solution.

Animals were euthanized by an overdose of anaesthesia according to the terms of the study (1 - 30 days).

Histological material - fragments of the distal metaepiphyses of the femur and proximal metaepiphyses of the tibia - were fixed with 10 % neutral formalin, after decalcification of bone tissue they were dehydrated in alcohols of increasing concentrations and immersed in paraffin. Staining of sections obtained on the microtome staining was performed with haematoxylin, eosin, and Van Gieson stains, followed by the study of the material using a microscope Biorex-3 BM-500T with a digital photomultiplier DCM 900 with programs adapted for these studies.

Results

From the first day of the experimental study, a corresponding reaction was observed in the joint tissues of the knee joints of rats. Changes in the synovial membrane in the form of inflammatory phenomena of the synovial membrane were especially pronounced. Significant oedema of the villi accompanied by increased filling of blood vessels with foci of thrombosis, mostly parietal, indicated the presence of an acute inflammatory process. Fragmentary defibering of collagen fiber groups in comparison with the intact group was also observed

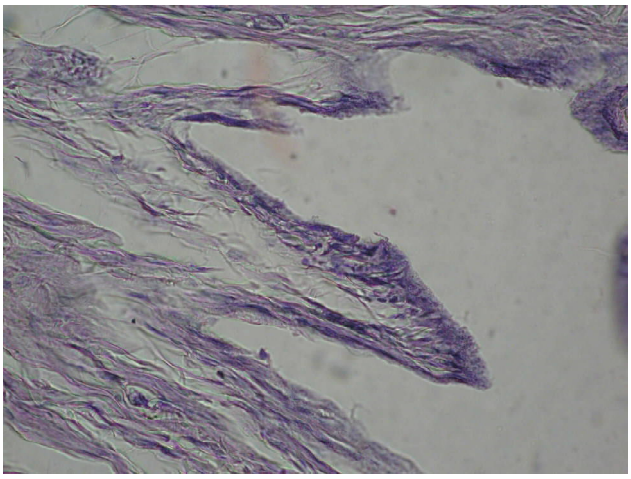

Fig. 1. Swelling of the villi of the synovial membrane. Hematoxylin-eosin. x400.

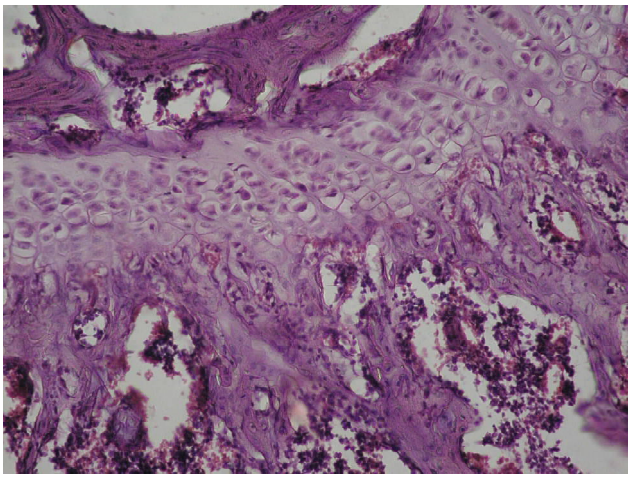

Fig. 2. Elements of chondrocyte pycnosis. Hematoxylin-eosin. x400.

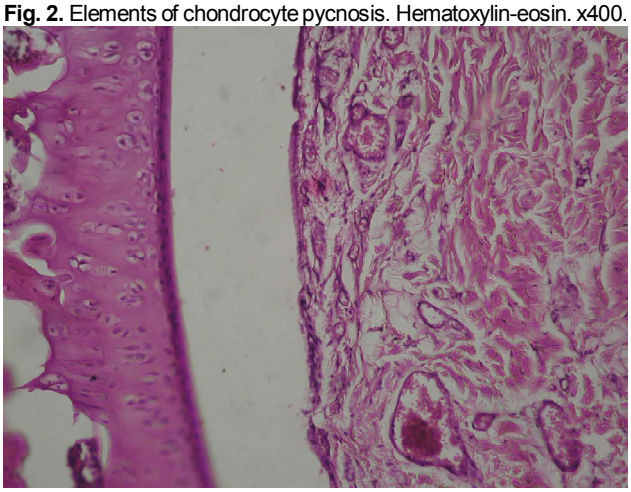

Fig. 3. Fragmentation of the integumentary layer of the synovial membrane. 5th day. Hematoxylin-eosin. x400.

(Fig. 1).

The histological picture of bone tissue did not differ from the norm, although the filling of blood vessels, especially the venous component, corresponded to the process of activation of anti-inflammatory mechanisms.

Articular cartilage retained a columnar structure, but near the subchondral bone were found elements of chondrocytes pyknosis with the formation of gaps (Fig. 2)

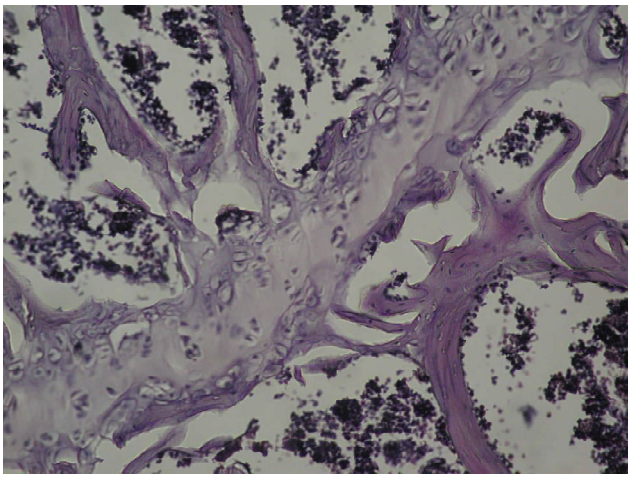

Fig. 4. Resorption of bone beams. 7th day. Hematoxylin-eosin. x400.

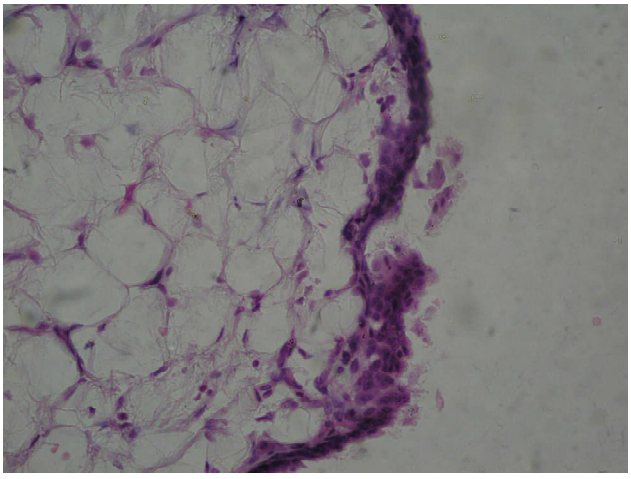

Fig. 5. Necrobiosis of synoviocytes. 7th day. Hematoxylin-eosin. x400.

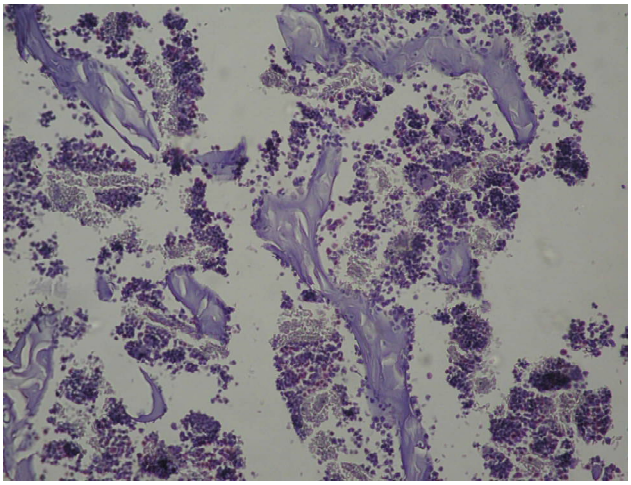

Fig. 6. Generalized destruction of bone tissue. 10th day. Hematoxylin-eosin. x400.

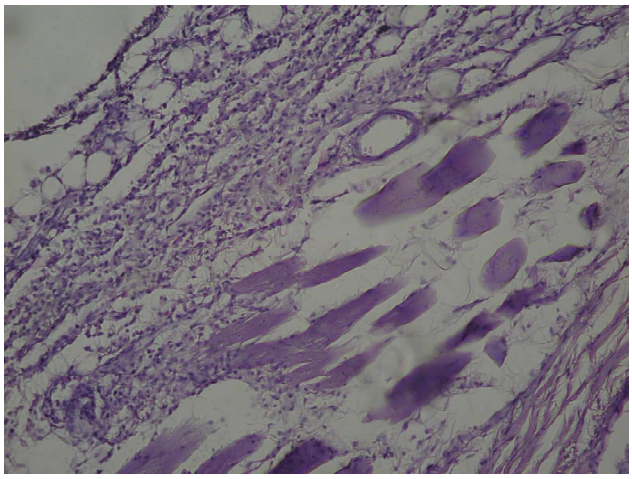

Fig. 7. Lymphocytic infiltration of the synovial membrane. 7th day. Hematoxylin-eosin. x400.

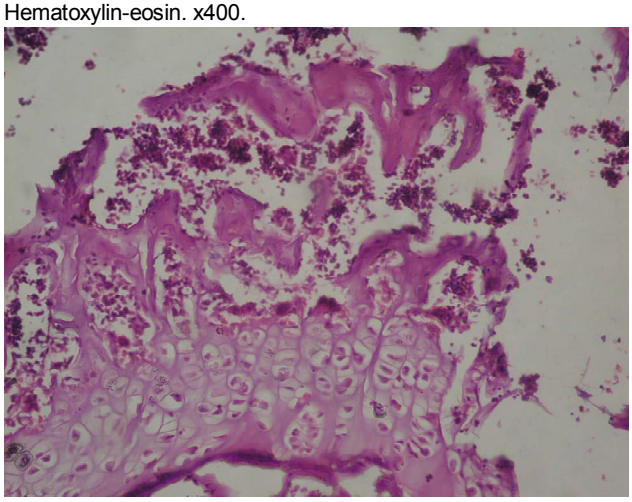

Fig. 8. Fragmentation of cartilage tissue. 14th day. Hematoxylin-eosin. x400.

Gradually, up to 5 days in the synovial membrane, proliferative changes take place with a clear definition of the multilineage of the integumentary layer, vascular reaction with a tendency to thrombosis. In some place's necrosis of synoviocytes is observed, but relative integrity of the morphological structure is still provided by protective barriers of bone and cartilage (Fig.3).

Protective barriers of bone and cartilage also ensure the relative integrity of the morphological structure.

On the 7th day, there is pronounced resorption of both bone and cartilage tissue, the structure became disorganized, the thinning of the functional layer, and massive intracellular lysis occurred.

The process of necrobiosis of synoviocytes spreads, as evidenced by the foci of intracellular lysis with fatty degeneration (Fig. 4, 5).

The histological picture after 10 days is characterized by generalized destruction of bone trabeculae; the destroyed cartilage is replaced by granulation tissue with the presence of cavities.

Massive foci of lymphocytic infiltration are determined in the synovial membrane (Fig. 6, 7).

On the 14th day, there is a fragmentation of cartilage, most of the bone beams are destroyed. Massive pyknosis and karyolysis of chondrocytes are characteristic of this period.

In the synovial tissue the microcirculatory tract is dominated by the venous component, the vascular wall of the arterioles is thickened; there is lacunarity around the vessels, fragmentation of collagen fibers. The cover layer is thinned or absent in some places (Fig. 8).

After 3 weeks, the morphological picture of cartilage tissue is determined by the appearance in the lacunae of viable cells, the number of which is close to normal. Bone beams are restored, although they remain thin. From a synovial membrane the hyperplasia of apical departments of villi, infiltration by leukocytes, disorganization of connecting fabric, separate vascular disturbances remain.

On the 30 day of the experiment, a relative return of structural relationships to normal was observed.

Discussion

Another place in the reproduction of experimental osteoarthritis is occupied by chemically induced models, the advantages of which are the absence of the need for surgery, which denies the influence of the external infectious component of inflammation; ease of manipulation; the short time of obtaining results, which is of particular importance when performing short-term research. The special significance of these minimally invasive techniques lies in the approximation to the real conditions of development of the inflammatory process of the joint in humans and, most importantly, the possibility of using this model for purely therapeutic intervention [12].

It should be noted that the chemicals that are mostly used for the reproduction of experimental arthritis (talc, turpentine, formalin, etc.) do not reflect the real picture of the disease due to the impossibility of them penetrating the joint under real conditions. In this regard, substances with a probable effect on joint tissues met in everyday life or during treatment are of great interest to scientists whose work is focused on practical experience [11, 17]

A special place in these conditions is occupied by experimental studies of participation in the homeostasis of ƛ-carrageenan - a substance that in a certain concentration is found in high demand foods, used in industry as a preservative, and registered as a food additive E 407. As stabilizer carrageenan, is also used in the production of household chemicals (toothpaste, hair-gels, and air fresheners). Most experimental studies of the biological activity of carrageenan are devoted to its participation in the development of pathological changes in the gastrointestinal tract; however, there is a large amount of work that indicates a significant effect of carrageenan on the functioning of other systems and organs. The presence of inflammatory processes in the experiment was found in laboratory animals also in the liver, salivary glands, joint

tissues [15].

The study of the last localization was first reliably confirmed in the works of Levy L. [13]. Reproduction of experimental arthritis was performed by intraplantar administration of 1 % carrageenan solution. Sugishita E. in 1981 described the acute phase of mouse paw oedema using a 3 % solution of carrageenan. Subsequent studies of scientific heirs have proven the existence of a sequence of development of two phases of the acute inflammatory process in paraarticular tissues [10, 20, 23].

Intraplantar administration of carrageenan is used to create conditions for the study of inflammatory processes of the extremities at the present stage [5, 18].

The effect of carrageenan on the functional components of the joint due to changes in the general condition of the body is isolated. Most scientists consider the reaction of the joint tissues as a reproduction of the model of rheumatoid arthritis, which causes a reason for discussion. Violation of homeostasis, caused by the introduction of an active substance of a certain concentration, is naturally reflected in the form of functional changes in highly sensitive tissues, which certainly include tissues that form the elements of the musculoskeletal system, especially the most mobile [3].

These data served as a basis for choosing the use of ƛ-carrageenan to reproduce a model of experimental nonspecific knee arthritis.

Our experimental study showed that intraperitoneal administration of certain concentrations of carrageenan causes pathological changes of an inflammatory nature in the joint tissues. Manifestations of nonspecific arthritis gradually increase up to 14 days, followed by restoration of morphological structure up to 30 days. Early manifestations of inflammation, as well as residual changes, are most characteristic of the synovial tissue of the joint.

Conclusions

The obtained data confirm the expediency of intraperitoneal administration of ƛ-carrageenan in experimental studies to reproduce a model of nonspecific arthritis of the knee joints.

References

[1] Alekseeva, L. I., Taskina, E. A., & Kashevarova, N. G. (2019). Osteoarthritis: epidemiology, classification, risk factors, and progression, clinical presentation, diagnosis, and treatment. *Modern Rheumatology Journal,* 13(2), 9-21. doi: 10.14412/1996-7012-2019-2-9-21

[2] Bailey, K. N., Furman, B. D., Zeitlin, J., Kimmerling, K. A., Wu, C. L., Guilak, F., & Olson S. A. (2020). Intra-articular depletion of macrophages increases acute synovitis and alters macrophage polarity in the injured mouse knee. *Osteoarthritis and cartilage*, 28(5), 626-638. doi: 10.1016/j.joca.2020.01.015

[3] Bittencourt, J. A., Neto, M. F., Lacerda, P. S., Bittencourt, R. C., Silva, R. C., Lobato, C. C., … Santos, C. B. (2019). In Silico Evaluation of Ibuprofen and Two Benzoylpropionic Acid Derivatives with Potential Anti-Inflammatory Activity. *Molecules,* 24(8), 1476. doi: 10.3390/molecules24081476

[4] Buch, M. H, Eyre, S., & McGonagle D. (2021). Persistent inflammatory and non-inflammatory mechanisms in refractory rheumatoid arthritis. *Nat Rev Rheumatol,* 17(1), 17-33. doi: 10.1038/s41584-020-00541-7

[5] Cordeiro, M. S., Simas, D. L., Perez-Sabino, J. F., Merida-Reyes, M. S., Munoz-Wug, M. A., Oliva-Hernandez, B. E., ... Giorno, T. (2020). Characterization of the Antinociceptive Activity from Stevia serrata. *Cav. Biomedicines,* 8(4), 79. doi: 10.3390/biomedicines8040079

[6] Delco, M. L., Kennedy, J. G., Bonassar, L. J., & Fortier, L. A. (2017). Post-traumatic osteoarthritis of the ankle: A distinct clinical entity requiring new research approaches. *J Orthop Res*, 35(3), 440-453. doi: 10.1002/jor.23462

[7] Gaynetdinova, A. N., Zalyalyutdinova, L. N., Abdulganieva, D. I., Imanaeva, A. Ya., & Gayfullin, A. N. (2015). Экспериментальное обоснование применения тиоктовой кислоты с метотрексатом в комбинированной терапии ревматоидного артрита на модели адъювантного артрита [Experimental basis of thioctic acid addicton to methotrexate in combined therapy of rheumatoid arthritis by adjuvant arthritis model]. *Инновационные технологии в медицине - Innovative technologies in medicine*, 4(89), 19-23.

[8] Golovach, I. Y., & Yehudina, Y. D. (2019). Posttraumatic osteoarthritis: contemporary views of development, progression and therapeutic approaches. *Политравма - Polytrauma*, (1), 82-89.

[9] Gromyko, M. V., & Gritsuk A. I. (2012). Экспериментальные модели ревматоидного артрита [Experimental models of rheumatoid arthritis]. *Проблемы здоровья и экологии - Health and Ecology Issues,* 2(32), 115-118.

[10] Henriques, M. G., Silva, P. M., Martins, M. A., Flores, C. A., Cunha, F. Q., Assreuy-Filho, J., & Cordeiro, R. S. (1987). Mouse paw oedema. A new model for inflammation?. *Braz. J. Med. Biol. Res.*, 20(2), 243-249. PMID: 3690058

[11] Hladkykh, F. V., Student, V. O., Stepaniuk, N. H., & Vernyhorodskyi, S. V. (2017). Патоморфологическое и компьютерное томографическое исследование влияния ибупрофена и его комбинации с 2-фенил-3-карбетокси-4-диметиламино-метил-5-оксибензофурана гидрохлоридом (винбороном) на состояние суставов нижних конечностей крыс с экспериментальным ревматоидным артритом [Pathomorphological and computerized tomography study of ibuprofen and combination with 2-phenyl-3-carbethoxy-4-dimethylaminomethyl-5-oksibenzofuran hydrochloride (vinboron) influence on the joints of lower extremities of rats with experimental rheumatoid arthritis]. *Фармация и фармакология - Pharmacy & Pharmacology,* 5(5), 457-486. doi: 10.19163/2307-9266-2017-5-5-457-486

[12] Kuyinu, E. L., Narayanan, G., Nair, L. S., & Laurencin, C. T. (2016). Animal models of osteoarthritis: classification, update, and measurement of outcomes. *J Orthopaedic Surg Res*, (11), 19. doi: 10.1186/s13018-016-0346-5

[13] Levy, L. (1969). Carrageenan paw edema in the mouse. Life Sci, 8(11), 601-606. doi: 10.1016/0024-3205(69)90021-6

[14] McCoy, A. M. (2015). Animal Models of Osteoarthritis: Comparisons and Key Considerations. *Vet. Pathol,* 52(5), 803-818. doi: 10.1177/0300985815588611

[15] Muzhikyan, A. A., Shekunova, E. V., Kashkin, V. A., Makarova, M. N., & Makarov, V. G. (2018). Histological evaluation of joint pathology in various models of chronic arthritis in rats. *Laboratory Animals for Science,* 1, 32-45. doi: 10.29926/

2618723X-2018-01-04
[16] Nasonov, E. L. (2017). Фармакотерапия ревматоидного артрита: новая стратегия, новые мишени [Pharmacotherapy for rheumatoid arthritis: new strategy, new targets]. *Научно-практическая ревматология - Rheumatology Science and Practice,* 55(4), 409-419. doi: 10.14412/1995-4484-2017-409-419
[17] Nosivets, D. S. (2019). Экспериментальные модели патологии хрящевой ткани [Experimental models of cartilage tissue pathology]. *Запорожский медицинский журнал - Zaporozhye medical journal*, 21(4), 554-560. doi: 10.14739/2310-1210.2019.4.173362.
[18] Pelypenko, A. V., Shepitko, V. I., & Pelypenko, L. B. (2019). Morphofunctional characteristics of a microcirculatory beds subchondral bone at the introduction of cryo-conversed placenta on the background of aseptic inflammation in the rat. *World of medicine and biology,* 2(68), 187-191. doi: 10.26724/2079-8334-2019-2-68-187-191
[19] Ponyk, R. M., & Korytko, Z. I. (2019). Захворюваність та особливості реабілітації хворих на ревматоїдний артрит в умовах сьогодення [Disease and peculiarities of rehabilitation of patients with rheumatoid arthritis in the present time]. *Здобутки клінічної і експериментальної медицини - Achievements of Clinical and Experimental Medicine,* (3), 183-187. doi: 10.11603/1811-2471.2019.v.i3.10504
[20] Posadas, I., Bucci, M., Roviezzo, F., Rossi, A., Parente, L., Sautebin, L., & Cirino, G. (2004). Carrageenan induced mouse paw oedema is biphasic, age weight dependent and displays differential nitric oxide cyclooxygenase 2 expression. *British Journal of Pharmacology,* 142(2), 331-338. doi: 10.1038/sj.bjp.0705650
[21] Punzi, L., Galozzi, P., Luisetto, R., Favero, M., Ramonda, R., Oliviero, F., & Scanu, A. (2016). Post-traumatic arthritis: overview on pathogenic mechanisms and role of inflammation. *RMD Open,* 2(2), e000279. doi: 10.1136/rmdopen-2016-000279
[22] Shepitko, V. I., & Pelypenko, O. V. (2015). Сучасні погляди на структурну організацію суглобових тканин [Current concepts of the structural organization of joint tissues]. *Світ медицини та біології - World of medicine and biology*, 3(52), 175-183.
[23] Sugishita, E., Amagaya, S., & Ogihara, Y. (1981). Anti-inflammatory testing methods: comparative evaluation of mice and rats. *J. Pharmacobiodyn,* 4(8), 565-575. doi: 10.1248/bpb1978.4.565

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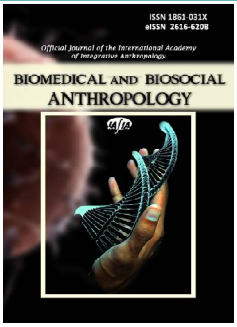

Peculiarities of relationships of characteristics of adaptation capabilities of the organism and indicators of motor activity of students

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The health of student youth is largely determined by the level of functional capabilities of the organism, which depends on the level of motor activity, that is the total number of movements that a person performs in a given period of time. The purpose of the work is to establish the features of the relationship between the characteristics of adaptive capacity, functional status and level of development of psychophysiological functions and criteria for motor activity of students. The research was conducted on the basis of National Pirogov Memorial Medical University, where 385 students (200 young girls and 185 young boys) were supervised, who, taking into account the peculiarities of the distribution of different levels of motor activity, were divided into 3 comparison groups - with potentially low, medium and potentially high levels of motor activity. The values of daily energy consumption, number of locomotions and duration of the dynamic component in the daily budget were used as the leading criteria of hygienic assessment of students' motor activity. Functional features and adaptive capabilities of the organism were determined using conventional methods. The analysis of the obtained results involved the use of a standard application package of multidimensional statistical analysis "Statistica 6.1 for Windows". The results of studies conducted on the basis of correlation analysis procedures indicate the fact that the largest number of correlations between the characteristics of psychophysiological functions and the leading characteristics of health and indicators of academic performance in professionally oriented disciplines studied are recorded in girls, and boys who belonged to the group with an average level of physical activity (daily energy expenditure of 9000-11000 kJ in young girls and 11000-13500 kJ in young boys). The use of cluster analysis procedures during the prognostic assessment of indicators of health and academic performance in professionally-oriented disciplines, made it possible to identify 3 clusters of the studied characteristics of the functional state of students, which have the most pronounced effect on their values: visual-motor speed cluster (indicators of the latent period of simple and differentiated visual-motor response), visual-sensory cluster (indicators of critical fusion of light flickers and efficiency of work performed) and integrative-coordination cluster (a number of indicators that reflect the properties of major nervous processes, characteristics coordination of movements, indicators of attention functions, etc.). Using factor analysis procedures, it determined that both young girls and young boys have the most positive impact on academic performance in vocational disciplines such factors as "functional state of the visual sensory system", "functional state of coordination" and "functional state of higher nervous activity".

Key words: *students, motor activity, functional state of organism, adaptation capabilities, peculiarities of relationships.*

Introduction

The issues of preserving the health of student youth, improving the adaptive and functional capabilities of girls and boys who study are among the most pressing issues of theoretical and preventive medicine that need to be addressed [13, 15, 20].

In this context, it should be noted that the processes of

gradual deterioration in the performance of students of modern higher education institutions, which are registered, raise these issues to one of the key places in the structure of unresolved issues and determine the comprehensive development of such areas of hygiene for children, adolescents and young people as university medicine in general and university hygiene in particular [3, 8, 13].

Numerous recent scientific studies have shown that the health of student youth is largely determined by the level of functional capabilities of the body, which, in turn, depends on the level of motor activity, ie the total number of movements that a person performs for a single time interval (minute, hour, day, week). Therefore, the criterion indicators of motor activity of children, adolescents and youth are motor activity during educational and work activities, motor activity in the process of physical education, motor activity in free time, etc. [5, 6, 14, 17, 18].

However, it should be noted that in contrast to the physiological and hygienic regulation of motor activity of student youth, which have been the subject of a number of scientific studies conducted in recent decades, the physiological and hygienic regulation of motor activity of student youth is almost not studied, although and the conditional classification of the factors influencing processes of formation of habitual motor activity is defined. As favorable factors determine a healthy lifestyle, optimal alternation of work and rest, physical and mental work, a rational daily routine, a variety of means of physical education and more. Instead, among the unfavorable factors include educational overload, neglect of physical culture, unfavorable psychological climate, the presence of bad habits [1, 4, 7, 14, 17, 22, 23].

However, so far not fully formed idea of the basics of students' health on the basis of physiological and hygienic features of motor activity, not studied features of normal motor activity of modern students studying in higher medical education, not studied features of psychophysiological functions of the body and processes of formation of characteristics of mental and physical working capacity of students which differ in features of the organization of motor activity, etc.

The purpose of the work is to establish the features of the relationship between the characteristics of adaptive capacity, functional status and level of development of psychophysiological functions and criteria for motor activity of students.

Materials and methods

Comprehensive research was conducted on the basis of National Pirogov Memorial Medical University, Vinnytsya. 385 students (including 200 young girls and 185 young boys) were supervised in the dynamics of the 6-year period, which, taking into account the peculiarities of the distribution of different levels of motor activity, were divided into 3 comparison groups - respectively into groups with potentially low (1 group of motor activity - values of daily energy consumption up to 9000 kJ in young girls and up to 11000 kJ in young boys), average (2 group of physical activity - values of daily energy consumption from 9000 to 11000 kJ in young girls and 11000 to 13500 kJ in young boys) and potentially high (3 group of motor activity - values of daily energy expenditure over 11000 kJ in young girls and over 13500 kJ in young boys) levels of motor activity.

The values of daily energy consumption, number of locomotions and duration of the dynamic component in the daily budget of time were used as the leading criteria of hygienic assessment of students' motor activity. The values of daily energy consumption (kJ) were calculated by applying the time-table method. The number of locomotions in the daily cycle (steps) was determined based on the use of standard digital pedometers SIGETA PMT-01, I-PDM 2002 new та Pedometr G014. The duration of the dynamic component in the daily budget of time (minutes) was estimated by timing the main types of daily educational and extracurricular activities [15, 17].

Functional features of higher nervous activity were evaluated on the basis of determining the values of latent periods of simple and differentiated visual-motor response, indicators of mobility and balance of nervous processes using chronoreflexometry, functional characteristics of the visual sensory system and somatosensory analyzer were investigated by estimating the values of the critical frequency of light flicker on the basis of the technique "Svitlotest" and coordination of movements by tremometry, stability of attention and mental performance were studied using Schulte tables and based on the use of proofreading [9, 14, 16, 17, 19].

Indicators of morbidity with temporary disability and chronic morbidity and the results of subjective assessment of students' own health were used as criterion indicators of the state of health and adaptive capacity of the organism. At the same time, academic performance indicators were determined on the basis of copying data on annual and intermediate student performance, as well as in accordance with the results of final tests in individual disciplines with their subsequent analysis [9, 14, 16, 19].

The obtained data were subjected to statistical processing using the application package of multidimensional statistical analysis "Statistica 6.1" (licensed № BXXR901E245722FA) based on the application of procedures of descriptive statistics, correlation, cluster and factor analysis.

Results

Analyzing the results obtained during the application of correlation analysis procedures, it should be noted that the indicators of health and adaptive capacity of the body, typical for young girls of the 1st group of motor activity (daily energy consumption up to 9000 kJ), were determined to have a close correlation with the characteristics of the level of development of such psychophysiological functions as the magnitude of the latent period of a simple visual-motor

reaction (r=0.34, p<0.05), mental endurance (r=0.35, p<0.05), the critical frequency of light flicker (r=-0.28, p<0.05) and the integrated indicator of coordination of movements (r=0.27, p<0.05), however, indicators of the level of academic success in professionally-oriented disciplines to be determined were marked by the presence of close correlations with the latent period of differentiated visual-motor reaction (r=0.37, p<0.05), mental endurance (r=0.39, p<0.05), critical frequency of light flicker (r=-0.54, p<0.01) and bones of touch during tremometry (r=0.27, p<0.05).

At the same time, the indicators of health and adaptive capacity of the body, inherent in young boys of group 1 motor activity (daily energy expenditure up to 11000 kJ), which were determined, had a close correlation with the characteristics of the level of development of psychophysiological functions such as balance nervous processes (r=0.39 p<0.05), the degree of involvement in the activities performed (r=0.37, p<0.05), and mental endurance (r=0.34, p<0.05), at the same time, indicators of the level of academic performance in professionally-oriented disciplines to be determined, were characterized by strong correlations with the critical frequency of light fusion flicker (r=-0.43, p<0.05) and the integral indicator of coordination of movements during tremometry (r=0.32, p<0.05).

During the assessment of the relationship between health indicators and adaptive capacity of the body, inherent in girls 2 groups of motor activity (daily energy expenditure from 9000 to 11000 kJ), a close correlation was established between the studied values and the characteristics of the level of development such psychophysiological functions as the magnitude of the latent period of a simple visual-motor reaction (r=0.44, p<0.01) and differentiated visual-motor reaction (r=0.33, p<0.05), balance (r=0.41, p<0.001) and mobility (r=0.31, p<0.05) of nervous processes and the number of touches during tremometry (r=0.28, p<0.05), at the same time, indicators of the level of academic success in professionally oriented disciplines, which were determined, were characterized by strong correlations with the values of the latent period of simple visual-motor reaction (r=0.53, p<0.001) and differentiated visual-motor reaction (r=0.49, p<0.001), (r=0.38, p<0.01) and mobility (r=0.29, p<0.05) nervous processes, the critical frequency of light flicker (r=-0.41, p<0.05) and the number of touches during tremometry (r=0.30, p<0.05).

However, indicators of health and adaptive capacity of the body, inherent to young people of 2 group of motor activity (daily energy expenditure from 11000 kJ to 13500 kJ), which were determined, had a close correlation with the characteristics of the level of development of psychophysiological functions such as the magnitude of the latent simple visual-motor reaction (r=0.68, p<0.001) and differentiated visual-motor reaction (r=0.46, p<0.001), balance (r=0.42, p<0.001) and mobility (r=0.36, p<0.05) of nervous processes, the critical frequency of light flicker (r=-0.36, p<0.05) and the number of touches during tremometry (r=0.38, p<0.01), at the same time, indicators of the level of academic success in professionally-oriented disciplines to be determined were characterized by the presence of strong correlations with the values of the latent period of simple visual-motor reaction (r=0.47, p<0.001) and differentiated visual-motor reaction (r=0.46, p<0.001), balance (r=0.38, p<0.01) and mobility (r=0.29, p<0.05) of nervous processes and the number of touches during tremometry (r=0.32, p<0.05), ie a much larger number was registered there are correlations than in the previous case.

Finally, during the research it should be noted that the indicators of health and adaptive capacity of the body, inherent in girls 3 groups of physical activity (daily energy expenditure above 11000 kJ), which were determined, were closely correlated with the characteristics of the level of development such psychophysiological functions as the values of the latent period of differentiated visual-motor response (r=0.34, p<0.05) and data on the number of touches (r=0.31, p<0.05) and the values of the integrated index of coordination of movements (r=0.35, p<0.05) during tremometry, however, indicators of academic performance in professionally oriented disciplines were subject to determination, were characterized by the presence of strong correlations with the balance of nervous processes (r=0.37, p<0,05), as well as indicators of the number of touches (r=0.34, p<0.05) and the values of the integrated index of coordination of movements during tremometry (r=0.29, p<0.05).

At the same time, the indicators of health and adaptive capacity of the body, inherent in young men of the 3rd group of motor activity (daily energy expenditure over 11000 kJ), which were determined, had a close correlation with the data of the correlates of psychophysiological functions both for the number of touches (r=0.30, p<0.05) and the values of the integrated indicator of coordination of movements (r=0.32, p<0.05) during tremometry, at the same time, indicators of the level of academic success in professionally oriented disciplines were characterized by strong correlations with the values of critical fusion (r=-0.35, p<0.05) and integrated coordination of movements during tremometry (r=0.35, p<0.05). Thus, it was among the representatives of this group of students that the lowest number of correlations was observed between such important from the adaptively significant point of view indicators as leading characteristics of health status and indicators of academic success in professionally oriented disciplines and a number of subjects' indicators of psychophysiological functions.

During the use of cluster analysis procedures for both young girls and young boys group 1 of physical activity (daily energy consumption up to 9000 kJ in young girls and up to 11000 kJ in young boys) and in the case of determining the leading characteristics of health, and in the case of prognostic assessment of the level of academic performance in professionally-oriented disciplines, the presence of 3 leading clusters of psychophysiological

functions should be considered inherent, namely: visual-motor speed cluster (cluster № 1), visual-sensory cluster (cluster № 2) and integrative-coordination cluster (cluster № 3). The visual-motor speed cluster should include indicators of the latent period of simple and differentiated visual-motor response, the visual-sensory cluster - indicators of the critical frequency of light flicker fusion and the efficiency of work performed, the integrative-coordination cluster - a number of indicators that reflect as properties of the main nervous processes, accurate in their content characteristics of coordination of movements, especially the number of touches during tremometry and an integrated indicator of coordination of movements, as well as a number of characteristics of attention functions such as degree of involvement in mental activity and mental endurance, and the last cluster was the closest to the characteristics of health and academic performance, which were studied in the multidimensional space of the measured indicators.

The situation was similar for both students of the 2nd group of physical activity (the level of daily energy expenditure from 9000 to 11000 kJ for young girls and from 11000 kJ to 13500 kJ for young boys). During the research, both during the determination of the leading characteristics of health and during the prognostic assessment of academic performance in professionally-oriented disciplines, the following clusters of psychophysiological functions should also be considered a priority: visual-motor speed cluster (cluster № 1), visual-sensory cluster (cluster № 2), integrative-coordination cluster (cluster № 3). These included indicators of the latent period of simple and differentiated visual-motor response (cluster № 1), indicators of critical fusion of light flicker and efficiency of work performed (cluster № 2), a number of indicators that reflect the properties of the main nervous processes, accurate in terms of content characteristics of coordination of movements, especially the number of touches during tremometry and an integral indicator of coordination of movements, as well as a number of characteristics of attention functions, such as the degree of involvement in activities and mental endurance (cluster № 3) and as in the previous case, the last cluster was the closest to the characteristics of health and academic performance in the multidimensional space of indicators measured.

Finally, the relationship between the leading characteristics of health status and the characteristics of the level of academic performance in professionally oriented disciplines and psychophysiological functions of students of the 3rd group of motor activity (daily energy expenditure over 11000 kJ in young girls and over13500 kJ in young boys) was quite similar to the previous two cases. And in this case the most significant should be considered visual-motor speed cluster (cluster № 1), visual-sensory cluster (cluster № 2), integrative-coordination cluster (cluster № 3). The visual-motor speed cluster included indicators of the latent period of simple and differentiated visual-motor response, the visual-sensory cluster included indicators of the critical frequency of light flicker fusion and the efficiency of work performed, the integrative coordination cluster included a number of indicators. reflecting as properties of the main nervous processes, accurate in their content characteristics of coordination of movements, especially the number of touches during tremometry and an integral indicator of coordination of movements, as well as a number of characteristics of attention functions such as degree of involvement and mental endurance. The latter cluster, in this case as well, was closest to the characteristics of health and academic performance that were studied in the multidimensional space of the measured indicators.

According to the data of factor analysis procedures among students belonging to 1 group of motor activity, features of interdependence of characteristics of level of educational success on professionally-oriented disciplines (y) and indicators of development of psychophysiological functions of young girls and young boys should be defined and formalized in the form relationships (1-2):

in young girls of 1 group of motor activity:

$$y = 0.391f_1 + 0.135f_2 + 0.438f_3; \quad (1)$$

where the factor f_1 - should be defined as the "functional state of the visual sensory system" (the share of variance - 32.68 %) and is associated with the critical frequency of fusion of light flickers of female students; factor f_2 - should be defined as a "functional state of coordination of movements" (the share of variance - 21.71 %) and, above all, includes in its structure indicators that provide information about the features of such leading characteristics of coordination abilities of the studied girls as indicators of the number of touches tremometry and the value of the integrated indicator of coordination of movements; factor f_3 - should be defined as a "functional state of higher nervous activity" (the share of variance - 22.38 %) and, above all, combines in its structure indicators of the latent period of differentiated visual-motor response and balance of nervous processes in young girls;

in young boys of 1 group of motor activity:

$$y = 0.3121f_1 + 0.194f_2 + 0.505f_3; \quad (2)$$

where the factor f_1 - should be defined as the "functional state of the visual sensory system" (the share of variance - 33.59 %) and is associated with the critical frequency of fusion of light flickers of students; factor f_2 - should be defined as the "functional state of coordination of movements" (the proportion of variance - 26.95 %) and combines in its structure the characteristics of the body's coordination abilities, namely: indicators of the number of touches during tremometry, test speed and magnitude integrated indicator of coordination of movements; factor f_3 - should be defined as a "functional state of higher nervous activity" (the proportion of variance - 24.50 %) and, above all, includes in its structure indicators of the latent period of simple and differentiated visual-motor response of young boys.

Peculiarities of interdependence between the characteristics of the level of academic success in professionally-oriented disciplines (y) and indicators of development of psychophysiological functions of the body among students belonging to 2 groups of motor activity, it was necessary to present and formalize in the form of relationships (3-4):

in young girls of 2 group of motor activity:

$y = 0.324f_1 + 0.212f_2 + 0.428f_3$; (3)

where the factor f_1 - should be defined as a "functional state of higher nervous activity" (the share of variance - 32.20 %) and, above all, combines in its structure indicators of the latent period of simple and differentiated visual-motor response of girls; factor f_2 - should be defined as the "functional state of the visual sensory system" (the share of variance - 25.87 %) and is associated with the critical frequency of fusion of light flickers of female students; factor f_3 - should be defined as "functional state of coordination of movements" (dispersion share - 22.89 %) and, first of all, includes in its structure indicators that provide information about the features of such leading characteristics of coordination abilities of the studied young girls as indicators of the number of touches tremometry and the value of the integrated indicator of coordination of movements;

in young boys of 2 group of motor activity:

$y = 0,388f_1 + 0,395f_2 + 0,237f_3$; (4)

where the factor f_1 - should be defined as "functional state of higher nervous activity" (the share of variance - 31.83 %) and, above all, includes in its structure indicators of the latent period of simple and differentiated visual-motor response of adolescents, factor f_2 - should be defined as functional the state of the visual sensory system "(share of variance - 23.87 %) and is related to the indicators of the critical frequency of merging of light flickers of students; factor f_3 - should be defined as the "functional state of coordination of movements" (the share of variance - 27.02 %) and combines in its structure the characteristics of coordination abilities, namely: indicators of the number of touches during tremometry, test speed and the value of the integral movement coordination indicator;

Peculiarities of the interdependence between the characteristics of the level of academic success in professionally-oriented disciplines (y) and indicators of development of psychophysiological functions of the body among students belonging to 3 groups of motor activity, had to be defined and formalized in the form of relationships (5-6):

in young girls of 3 group of motor activity:

$y_2 = 0.190f_1 + 0.352f_2 + 0.348f_3$; (5)

where the factor f_1 - should be defined as the "functional state of coordination of movements" (the share of variance - 28.08 %) and, above all, includes in its structure indicators that provide information about the characteristics of such leading characteristics of coordination abilities of the studied young girls, as indicators of the number of touches during tremometry and the value of the integrated indicator of coordination of movements; factor f_2 - should be defined as "functional state of the visual sensory system" (dispersion share - 27.49 %) and is related to the critical frequency of fusion of light flickers of female students; factor f_3 - should be defined as a "functional state of higher nervous activity" (the share of variance - 22.01 %) and, above all, combines in its structure indicators of the latent period of simple and differentiated visual-motor response of young girls;

in young boys of 3 group of motor activity:

$y = 0.373f_1 + 0.240f_2 + 0.338f_3$; (6)

where the factor f_1 - should be defined as the "functional state of coordination of movements" (the proportion of variance - 31.00 %), which is determined by the values of the number of touches during the tremometry; factor f_2 - should be defined as the "functional state of the visual sensory system" (the share of variance - 28.67 %) and is related to the critical frequency of fusion of light flickers of students; factor f_3 - should be defined as a "functional state of higher nervous activity" (the share of variance - 21.59 %) and, above all, includes in its structure indicators of the latent period of simple and differentiated visual-motor response of young boys.

Discussion

The initial component of prognostic research in any field of preventive medicine should be considered the use of correlation analysis procedures, the main content of which is to establish the relationship of the studied indicators both among themselves and with a number of criteria that have a certain interpretation of phenomena, which are observed and analyzed according to the values of the correlation coefficient and the characteristics of the degree of its significance [2, 8, 10, 11, 12, 14, 16, 19, 21].

The use of correlation analysis procedures in the studies showed that the largest number of correlations between the characteristics of psychophysiological functions and the leading characteristics of health and indicators of academic performance in vocational disciplines studied were recorded in girls and in boys who belonged to 2 groups of physical activity (level of daily energy expenditure from 9000 to 11000 kJ in young girls and from 11000 kJ to 13500 kJ in young boys), which according to existing ideas confirms the most pronounced positive impact on the processes of their development and formation of such organization of motor activity. The lowest number of correlations was characteristic of students of the 3rd group of physical activity (daily energy expenditure level over 11000 kJ in young girls and more than 13500 kJ in young boys), indicators of students belonging to the 1st motor activity group (daily energy consumption level up to 9000 kJ in young girls and up to 11000 kJ in young boys), occupied an intermediate position.

The application of agglomeration-hierarchical methods of cluster analysis, the main purpose of which is to

determine the patterns of grouping of individual objects of study taking into account their leading features by combining into separate local sets, ie into separate clusters in the multidimensional space of the studied features, provided an opportunity to (based on finding the minimum distance between the individual indicators that are closest and combining them into a single cluster and giving it a common index, as well as calculating the distances from the formed clusters to other units of homogeneous groups) identify 3 leading clusters that have a positive impact on processes of formation of both criterion characteristics of the state of health, and indicators of the level of academic success in professionally-oriented disciplines [2, 8, 11, 14, 16, 19, 21].

Adequately, based on the subject and objectives of the study, the use of cluster analysis procedures both in the prognostic assessment of leading indicators of health and in determining the level of academic success in professionally-oriented disciplines, provided an opportunity to identify 3 leading clusters of functional characteristics the body of students who had the most pronounced effect on their values, namely: visual-motor speed cluster (indicators of the latent period of simple and differentiated visual-motor response), visual-sensory cluster (indicators of the critical frequency of light flicker and work efficiency) and integrative-coordination cluster (a number of indicators that reflect both the properties of the main nervous processes, accurate in their content characteristics of coordination of movements, especially the number of touches during tremometry and the value of the integrated indicator of coordination of movements, and a number of characteristics tic of attention functions, such as the degree of involvement in the activity performed and mental endurance), which was actually the closest to the characteristics of health and academic performance in the multidimensional space of the measured indicators.

Another method of establishing the interdependence of indicators that determine the functional state and adaptive capacity of the body of young girls and young boys, which are characterized by different approaches to the organization of motor activity and, consequently, different values of motor activity in the context of their impact on the state of the studied indicators. is a factor analysis, the main procedures of which provide an opportunity to perform a quantitative analysis of directly non-measurable indicators that can be assessed by studying certain features, and, therefore, allow a correct description of multidimensional objects with redundant output characteristics based on deep, system-forming in their content, the processes of formation of their indicators [2, 8, 11, 14, 16, 19].

Using factor analysis procedures, it was determined that both young girls and young boys have the most positive impact on academic performance in vocational disciplines such factors as "functional state of the visual sensory system", "functional state of coordination" and "functional state of higher nervous activity". However, the share of their variance in the overall structure of factor loads differs significantly: among students whose daily energy consumption does not exceed 9000 kJ (young girls) and 11000 kJ (young boys), the most significant contribution is inherent in such a factor as the "functional state of the visual sensory system", which is primarily related to the critical frequency of light flashes fusion of students (young girls have a share of dispersion of 32.68 %, young boys - respectively 33.59 %), among students whose daily energy consumption ranges from 9000 to 11000 kJ (young girls) and from 11000 to 13500 kJ (young boys), - for such a factor as "functional state of higher nervous activity" (young girls have a share of variance of 32.20 %, young boys - respectively 31.83 %), among students whose daily energy expenditure exceeds 11000 kJ (young girls) and 13500 kJ (young boys), - for such a factor as "functional state of coordination of movements" (in young girls the share of variance is 32.20 %, respectively, in young boys - respectively 31.83 %).

Given the peculiarities of the processes of professional development of future medical professionals associated with the need to assimilate large amounts of theoretically and practically significant information, this situation indicates in favor of clear signs of positive effects of motor mode, characteristic of students, the value of daily energy expenditure range from 9000 to 11000 kJ and from 11000 to 13500 kJ, respectively, which contributes to the predominant development of the leading functional characteristics of higher nervous activity of studying young girls and young boys.

Conclusions

1. The results of research conducted on the basis of correlation analysis procedures show the fact that the largest number of correlations between the characteristics of psychophysiological functions and the leading characteristics of health and indicators of academic performance in professionally oriented disciplines studied, is registered in both young girls and young boys, who belong to the 2nd group of physical activity (the level of daily energy expenditure from 9000 to 11000 kJ in young girls and from 11000 kJ to 13500 kJ in young boys).

2. The use of cluster analysis procedures both during the prognostic assessment of leading indicators of health, and when determining the level of academic success in professionally-oriented disciplines, provides an opportunity to identify 3 leading clusters of studied characteristics of the functional state of students who perform the most pronounced influence on their values, namely: visual-motor speed cluster (indicators of latent period of simple and differentiated visual-motor reaction), visual-sensory cluster (indicators of critical frequency of flickering of light and efficiency of work performed) and integrative-coordination cluster (a number of indicators that reflected as properties of the main nervous processes, characteristics of coordination of movements, indicators of attention functions, etc.), which is closest to the characteristics of health and

academic performance.

3. When using factor analysis procedures, it was determined that among both young girls and young boys the most positive impact on academic performance in professional-oriented disciplines are factors such as "functional state of the visual sensory system", "functional state of coordination" and "functional state of higher nervous activity".

4. Given the peculiarities of the processes of professional development of future medical professionals, which is associated with the need to assimilate large amounts of theoretically and practically significant information, the data indicate in favor of clear signs of positive influence of motor mode inherent in students, the value daily energy consumption ranges from 9000 to 11000 kJ and from 11000 to 13500 kJ, respectively, which contributes to the predominant development of the leading functional characteristics of higher nervous activity of young girls and young boys and requires further consideration and analysis from the standpoint of determining its structural and dynamic characteristics in weekly, monthly and annual cycles.

References

[1] Ahn, S., & Fedewa, A. L. (2011). A meta-analysis of the relationship between children's physical activity and mental health. *Journal of Pediatric Psychology,* 36(4), 385-397. doi: 10.1093/jpepsy/jsq107

[2] Antomonov, M. Iu. (2017) *Математическая обработка и анализ медико-биологических данных [Mathematical processing and analysis of biomedical data].* Киев: МИЦ "Мединформ" - Kiev: MIC " Medinform ".

[3] Bailey, R. (2006). Physical education and sport in schools: A review of benefits and outcomes. *Journal of School Health,* 76(8), 397-401. doi: 10.1111/j.1746-1561.2006.00132.x

[4] Biddle, S. J., & Asare, M. (2011). Physical activity and mental health in children and adolescents: A review of reviews. *British Journal of Sports Medicine,* 45(11), 886-895. doi: 10.1136/bjsports-2011-090185

[5] de la Haye, K., Robins, G., Mohr, P., & Wilson, C. (2011). How physical activity shapes, and is shaped by, adolescent friendships. *Social Science and Medicine*, 73(5), 719-728. doi: 10.1016/j.socscimed.2011.06.023

[6] Ferrer-Caja, E., & Weiss, M. R. (2000). Predictors of intrinsic motivation among adolescent students in physical education. *Research Quarterly for Exercise and Sport,* 71(3), 267-279. doi: 10.1080/02701367.2000.10608907

[7] Houwen, S., Hartman, E., & Visscher, C. (2009). Physical activity and motor skills in children with and without visual impairments. *Medicine and Science in Sports and Exercise*, 41(1), 103. doi: 10.1249/MSS.0b013e318183389d

[8] Moroz, V. M., Makarov, S. Yu., Serebrennikova, O. A., & Serheta, I. V. (2020). *Навчальний стрес та психофізіологічні критерії оцінки адаптаційних можливостей організму студентів закладів вищої медичної освіти [Educational stress and psychophysiological criteria for assessing the adaptive capacity of the body of students of higher medical education].* Вінниця : ТОВ "ТВОРИ" - Vinnytsya: TOV "TVORY".

[9] Raigorodskii, D. Ya. (2011). *Практическая психодиагностика. Методики и тесты [Practical psychodiagnostics. Techniques and tests].* Самара: Издательский дом "Бахрах-М" - Samara: Publishing house "Bakhrakh-M".

[10] Raudsepp, L., & P?ll, P. (2006). The relationship between fundamental motor skills and outside-school physical activity of elementary school children. *Pediatric Exercise Science,* 18(4), 426-435. doi: 10.1123/pes.18.4.426

[11] Rebrova, O. Yu. (2006). *Статистический анализ медицинских данных. Применение пакета прикладных программ Statistica [Statistical analysis of medical data. Application of the Statistica software package].* Москва: МедиаСфера - Moscow: MediaSphere.

[12] Reed, J., Metzker, A., & Phillips, D. (2004). Relationships between physical activity and motor skills in middle school children. *Perceptual and Motor Skills,* 99(2), 483. doi: 10.2466/pms.99.2.483-494

[13] Serdiuk, A. M., Polka, N. S., & Serheta, I. V. (2012). *Психогигиена детей и подростков, страдающих хроническими соматическими заболеваниями [Psychohygiene of children and adolescents suffering from chronic somatic diseases].* Вінниця: Нова книга - Vinnytsya: Nova knyha.

[14] Serheta, I. V., Bardov, V. H., Drezhenkova, I. L., & Panchuk, O. Yu., (2020). *Гігієнічні нормативи рухової активності студентів закладів вищої медичної освіти та шляхи її оптимізації [Hygienic standards of motor activity of students of higher medical education institutions and ways of its optimization].* Вінниця : ТОВ "ТВОРИ" - Vinnytsya: TOV "TVORY".

[15] Serheta, I. V., Panchuk, O. Yu., Stoian, N. V., Drezhenkova, I. L., & Makarov, S. Yu. (2016). Університетська гігієна у контексті імплементації "Закону про вищу освіту": фізіолого-гігієнічні основи, реалії та шляхи розвитку [University hygiene in the context of the implementation of the "Law on Higher Education": physiological and hygienic foundations, realities and ways of development]. *Довкілля та здоров'я - Environment and health,* 4(80), 46-52.

[16] Serheta, I. V., Panchuk, O. Yu., & Yavorovskyi, O. P. (2020). *Гігієнічна діагностика професійної придатності студентів закладів медичної освіти (на прикладі стоматологічних спеціальностей) [Hygienic diagnostics of professional suitability of students of medical education institutions (on the example of dental specialties)].* Вінниця : ТОВ "ТВОРИ" - Vinnytsya: TOV "TVORY".

[17] Sukharev, A. G. (1991). *Здоровье и физическое воспитание детей и подростков [Health and physical education of children and adolescents].* Москва: Медицина - Moscow: Medicine.

[18] Thomas, N., & Williams, D. (2008). Inflammatory factors, physical activity, and physical fitness in young people. *Scandinavian Journal of Medicine & Science in Sports,* 18(5), 543-556. doi: 10.1111/j.1600-0838.2008.00824.x

[19] Tymoshchuk, O. V., Polka, N. S., & Serheta, I. V. (2020). *Наукові основи комплексної гігієнічної оцінки якості життя та адаптаційних можливостей сучасної учнівської і студентської молоді [Scientific bases of complex hygienic assessment of quality of life and adaptive possibilities of modern pupil and student youth].* Вінниця : ТОВ "ТВОРИ" - Vinnytsya: TOV "TVORY".

[20] World Health Organization. (2013). Young people's health - a challenge for society. Report of a study group on young people and health for all by the year 2000. World Health Organization.

[21] Wrotniak, B. H., Epstein, L. H., Dorn, J. M., Jones, K. E., & Kondilis, V. A. (2006). The relationship between motor

proficiency and physical activity in children. *Pediatrics,* 118(6), 1758-1765. doi: 10.1542/peds.2006-0742

[22] Zeng, Q., Dong, S. Y., Sun, X. N., Xie, J., & Cui, Y. (2012). Percent body fat is a better predictor of cardiovascular risk factors than body mass index. *Brazilian Journal of Medical and Biological Research,* 45(7), 591-600. doi: 10.1590/S0100-879X2012007500059

[23] Ziviani, J., Poulsen, A., & Hansen, C. (2009). Movement skills proficiency and physical activity: A case for Engaging and Coaching for Health (EACH)-child. *Australian Occupational Therapy Journal*, 56(4), 259-265. doi: 10.1111/j.1440-1630.2008.00758.x

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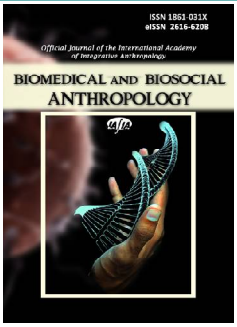

Cognitive disorders in patients after cardiac surgery

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The occurrence of cognitive disorders is a common problem after surgery. The degree of worsening of cognitive functions after surgery and anesthesia has a significant impact on the patient's health and is significantly associated with prolonged recovery in the hospital, increased morbidity and delayed functional recovery. The aim of the study was to increase the effectiveness of the diagnosis of moderate cognitive impairment and to determine its gender and age characteristics in patients before and after cardiac surgery in the early postoperative period (3 and 7 days). We examined 56 patients who underwent cardiac surgery for coronary heart disease in 37 (66.1 %) and valvular heart defects in 19 (33.9 %) patients. Assessment of cognitive functions was performed before surgery, on the 3rd and 7th day of the postoperative period. Testing was performed using the Montreal Cognitive Test. Statistical processing of the obtained data was performed on a personal computer using the statistical software package SPSS 12.0 for Windows using parametric and non-parametric methods. It was found that presence of cognitive disorders before surgery was registered in 37 (66.1 %) patients, mostly among the age of group of 60-74 years and had no gender difference. It was found that in the early postoperative period there is a significant worsening of cognitive functions in patients after cardiac surgery on 3rd day - in 45 (80.4 %), on 7th day - in 44 (78.6 %) patients, respectively.

Keywords: *cognitive disorders, Montreal cognitive test, cardiovascular diseases, cardiac surgery, coronary heart disease.*

Introduction

Despite the improvement of surgical techniques and the implementation of effective brain protection strategies, the incidence of moderate cognitive impairment (CD) after cardiac surgery has remained relatively stable for many years. It is established that the frequency of CD in 1-3 months after cardiac surgery is from 10-16 % to 40 % [6, 12, 17]. Most studies show a decrease in its severity over time from 3 months to 1 year after surgery [6, 14].

The occurrence of postoperative cognitive dysfunction is associated with a combination of factors often associated with artificial circulation: embolism, hypoperfusion and inflammatory response [2]. However, not only these factors and their potential brain effects can lead to CD. It is known that such disorders occur in patients who underwent heart surgery without artificial circulation, as well as those who underwent transcatheter interventions. There is evidence that vascular risk factors play an important role in the development of both early and late postoperative cognitive dysfunction [4]. According to A. C. Sauer et al. [22] delirium after cardiac surgery is independently associated with decreased cognitive function 1 month after surgery, but cognitive performance is usually restored within 1 year. Patients with a predisposition to CD can be identified before surgery due to worse results in the task of checking attention.

It should be noted that postoperative cognitive changes in adults are superimposed on normal age-related neurophysiological changes [26]. Thus, it is important to compare postoperative cognitive changes with those observed before surgery, according to risk factors for decreased cognitive function. It was found that the thickness of the intima-media complex of the internal carotid artery, but not the intima-media of the common carotid artery, was associated with a higher prevalence of silent cerebral infarctions, large hyperintensive areas of white matter, lower total brain volume and lower verbal memory productivity and nonverbal memory performance [19].

Cognitive dysfunction is relatively common in patients with chronic heart failure (CHF), the deficiency is most pronounced in the areas of executive function, memory, speech and mental speed. It was found that 25 % of patients with CHF had cognitive deficits, compared with 15 % of patients with cardiovascular disease (CVD) uncomplicated CHF and 4 % of healthy individuals. Independent risk factors for CD in patients with CHF are intelligence, functional class (FC) of CHF and the presence of apolipoprotein (Apo) E allele ε4 [25]. One study assessed cognitive function depending on the severity of CHF. Severe cognitive impairment was present in 9.2 % of patients, but only 20 % of them had dementia. Cognitive dysfunction was more common in patients with FC IV than with FC II CHF. Changes in the severity of CHF were not associated with changes in the severity of cognitive disorders [9].

A number of authors report the association of cognitive impairment with chronic kidney disease. U. E. Williams et al. [27] found that the majority of patients (53.2 %) with stage 3-5 CKD have moderate cognitive impairment compared to the control group.

A recent study [20] suggests that pre-existing coronary heart disease (CHD) is associated with an accelerated decline in cognitive function. The study included 7888 patients who underwent cognitive assessment at the beginning of follow-up (2002 - 2003) and again in one of the periods (2004 - 2005) or (2016 - 2017) and did not have a history of coronary heart disease. The coronary heart disease incident was identified as a diagnosis of myocardial infarction (MI) and/or angina pectoris during follow-up. The results showed that coronary heart disease is associated with an accelerated decline in cognitive function during the median follow-up of 12 years. The annual progression of CD does not differ between groups with verified coronary heart disease and individuals without coronary heart disease. There was no short-term decrease in cognitive function immediately after the MI incident. Over the years since the diagnosis of coronary heart disease, global cognition, verbal memory, and temporal orientation have declined significantly faster than before the MI/angina incident.

Many researchers have used pre- and postoperative neuropsychological testing to assess cognitive dysfunction after cardiovascular surgery. It is known that for most people, performance improves with retesting at short intervals. Several methods can explain this learning effect and the internal variability of retesting [3]. Some tests have "floor" or "ceiling" effects that reduce the sensitivity to detect cognitive changes in patients with high or low baseline cognitive function. For example, the Trail Making Test (Part B) has a high sensitivity to detecting cognitive impairment in patients with high levels of cognitive function, but has a reduced sensitivity to detecting disorders in patients with severe preoperative cognitive impairment [18]. In contrast, the Mini Mental Status Examination has a "ceiling" effect in cognitively healthy people, but is sensitive to cognitive changes in patients with mild cognitive dysfunction [8]. It is also important to consider the timing of pre- and postoperative testing. Cognitive dysfunction in the early postoperative period is likely to be affected by postoperative pain, the use of narcotic analgesics and acute postoperative recovery [7].

It is important for clinical practice to use simple and reliable tools to help clinicians assess the risk of cognitive change and identify individuals who need closer monitoring, prevention, and possibly additional treatment.

The aim of the work is to increase the efficiency of diagnosis of moderate cognitive impairment and to determine its sex and age characteristics in patients before and after cardiac surgery in the early postoperative period (3 and 7 days).

Materials and methods

56 patients were examined, including 19 (33.9 %) men and 37 (66.1 %) women (p=0.02). The age of patients ranged from 31 to 79 years, with an average of 60.86±8.87 years. The gradation by age showed that the group younger than 45 years included 2 (3.2 %), 45-59 years - 20 (32.3 %), 60-74 years - 31 (50.0 %), 75-90 years - 3 (4.8 %) patient accordingly.

Cardiac surgery was performed for coronary heart disease in 37 (66.1 %) and valvular heart defects in 19 (33.9 %) patients (p=0.02). The duration of the operation ranged from 240 to 600 minutes, averaging 371.9±102.0 minutes. In 25 (44.6 %) cases, operations were performed in the conditions of artificial circulation (AC) - bypass, the average duration of which did not differ from operations without AC (389.4±116.9 vs. 355.5±86.2, p=0.34).

The most common comorbidity in the examined patients was hypertension (HT), it was diagnosed in 45 (80.4 %) people, including 15 (33.3 %) women and 30 (66.7 %) men (χ^2=0.036, p=0.84).

Analyzing the severity of HT, it was found that 5 (8.9 %) patients had stage 1, 16 (28.6 %) had stage 2, 24 (42.9 %) had stage 3, and 7 (12.5 %) had stage 1, 14 (25.0 %) - 2 degree, in 24 (42.9 %) - 3 degree of HT respectively. The average duration of HT was 7.91±7.35 years. The course of HT in 17 (37.7 %) patients was uncontrolled, in 28 (62.3 %) - controlled, respectively (χ^2=2.928, p=0.09). Analyzing sex features, the controlled course of HT was in 6 (31.6 %) women and 10 (27.0 %) men, respectively (χ^2=0.572, p=0.449). The risk of cardiovascular complications in 1 (1.8 %) - low, 7 (12.5 %) - moderate, in 20 (35.7 %) - high and in 28 (50.0 %) patients - very high.

Thyroid diseases were observed in - 9 (16.1 %), oncological diseases - 3 (5.4 %), diseases of the gastrointestinal tract (GI tract) - 31 (55.4 %), gout - 3 (5.4 %), diabetes mellitus (DM) - 7 (12.5 %), diseases of the musculoskeletal system - 3 (5.4 %), chronic obstructive pulmonary disease/bronchial asthma - 7 (12.5 %) patients, respectively. CHF I FC were observed in 4 (7.1 %), II FC - in 13 (23.2 %), III FC - in 38 (67.9 %), IV FC - in 1 (1.8 %)

Table 1. Analysis of the distribution of probable risk factors for cognitive impairment.

Factors	Proportion of patients (n, %)
Signs of structural remodeling of the carotid arteries	44 (78.6 %)
Dyslipidemia	23 (41.1 %)
Acute cerebrovascular accident (ACA) in the anamnesis	3 (5.4 %)
MI in the anamnesis	20 (35.7 %)
Atrial fibrillation	17 (30.4 %)
Glomerular filtration rate < 60 ml/min/1.72m^2	22 (39.3 %)

patients, respectively. According to echocardiographic examination, 40 (71.4 %) patients had preserved left ventricular systolic function (ejection fraction (EF) >50 %), 9 (16.1 %) had intermediate EF (40-50 %), and 7 (12.5%) - reduced EF (<40 %). Obesity - in 15 (26.8 %) patients, among them in 11 (19.6 %) - stage 1, in 3 (5.4 %) - stage 2, in 1 (1.8 %) - stage 3 obesity, respectively.

According to coronary angiography in 5 (8.9 %) patients revealed lesions of 1 coronary artery (CA), in 5 (8.9 %) - 2 branches of CA, in 27 (48.2 %) - 3 branches of CA, in 19 (33.9 %) - vascular lesions was not detected.

We also analyzed the probable causes of cognitive impairment in patients who underwent cardiac surgery (Table 1).

It should be noted that 44 (78.6 %) patients already had signs of structural remodeling of the carotid arteries (in the case of atherosclerotic plaques in the carotid arteries and/or intima-media thickness (IMT) >0.9 mm and/or blood flow rate >1.2 m/s), 20 (35.7 %) patients had a history of MI, 3 (5.4 %) - ACA, respectively. Signs of dyslipidemia were observed in 23 (41.1 %) patients. Decreased glomerular filtration rate (GFR) less than 60 ml/min/1.72m^2 was observed in 22 (39.3 %) patients. The average GFR (according to the formula CKD-EPI) was 60.71±15.09 ml/min/1.72m^2.

Atrial fibrillation (AF) is present in 17 (30.4%) patients, among them - in 5 (8.9 %) paroxysmal, in 6 (10.7 %) - persistent and in 6 (10.7 %) - permanent form of AF. The average score on the scale CHA2DS2VASc was 2.410±0.870.

Analyzing the sex and age characteristics of patients (Table 2) who underwent cardiac surgery, it was found that women were older than men (65.84 vs. 58.30, p=0.002), more often had thyroid disease (31.6 % vs. 8.1 %, p=0.02), there is a history of acute cerebrovascular accident (ACA) - stroke (15.7 % vs. 0 %, p=0.01). In turn, more than half of men had diseases of the gastrointestinal tract (64.9 % vs. 36.8 %, p=0.04).

Assessment of cognitive functions was performed before surgery, on the 3rd and 7th day of the postoperative period. Testing was performed using the Montreal Cognitive Test (MOCA). The MOCA test is a quick tool for screening for cognitive deficits [https://www.mocatest.org]. It is highly sensitive (90 %) and specific (87 %) for detecting people with cognitive disorders [11]. This test is recommended for use in people aged 55-85 years.

The test was performed by a cardiologist who had previously been trained in the methodology, evaluation and interpretation of the MOCA test (online) and received a certificate, which is mandatory for the use of this questionnaire. The time of the MOCA test is short (approximately 10 minutes), which did not cause discomfort or a negative attitude of the patient. Testing includes 12 stages, which allows you to assess the various cognitive functions of the patient: attention, concentration, executive functions, memory, language, visual and constructive skills, abstract thinking, arithmetic and orientation. The maximum possible result is 30 points. A score of 26 or higher is considered normal, 18-25 is mild, 10-17 is moderate, and less than 10 is severe cognitive impairment. To the total score, add 1 point if the education is less than 12 years and 2 points if the patient's education is less than 10 years [https://www.mocatest.org].

Statistical processing of the obtained data was performed on a personal computer using the statistical software package SPSS 12.0 for Windows. Quantitative data (with normal distribution of characteristics) are presented in the form (M±σ), where M is the average value of the sample, and σ is the standard deviation. The reliability of the difference in quantitative values was calculated according to Student's criterion, the percentage - χ^2, the dynamics of indicators was estimated by χ^2 by the method of McNemar.

Table 2. Sex and age characteristics of the examined patients.

Parameters	Men (1) (n=37)	Women (2) (n=19)	Total (n=56)	p_{1-2}
Average age, years	58.30±8.29	65.84±7.93	60.86 ±8.86	=0.002
Hypertensive disease	30 (81.0 %)	15 (78.9 %)	45 (80.3 %)	=0.84
Uncontrolled course of hypertensive disease	7 (18.9 %)	10 (52.6 %)	40 (64.5 %)	=0.45
Type II diabetes	4 (10.8 %)	3 (15.7 %)	7 (12.5 %)	=0.59
Atrial fibrillation	9 (24.3 %)	8 (42.1 %)	17 (30.4 %)	=0.17
Average score on the scale CHA_2DS_2VASc	2.330±0.866	2.500±0.926	2.410±0.870	=0.7
Obesity	8 (21.6 %)	7 (36.8 %)	15 (26.7 %)	=0.22
Diseases of the thyroid gland	3 (8.1 %)	6 (31.6 %)	9 (16.1 %)	=0.02
ACA	0	3 (15.7 %)	3 (5.35 %)	=0.01
MI	14 (37.8 %)	6 (31.5 %)	16 (25.8 %)	=0.64
Gastrointestinal diseases	24 (64.9 %)	7 (36.8 %)	31 (55.4 %)	=0.04

Notes: in this and subsequent tables, the reliability of the difference in quantitative values is calculated by the Student's criterion, the percentage - by the criterion χ^2.

Results

Analysis of MOCA test results showed that the mean total score before surgery was 23.25±3.16 and did not differ between men and women (23.73 vs. 22.32, p=0.12).

Analysis of the sex and age characteristics of CD showed that the number of patients with CD before surgery was the same among both women and men. There was also no sex difference in the severity structure of the CD (Table 3).

The mean age of the group of patients with pre-operative CD was 62.05±7.91 and did not differ from the mean age of patients without CD (62.05 vs. 58.53, p=0.16). The distribution of patients according to age gradations (Fig. 1) showed that the largest number of patients with CD was observed among the age group 60-74 years (42.9 % vs. 12.5 %, p<0.05).

It was found that the average test score on the 3rd day after surgery was 22.34±4.78. There was a tendency to a significant decrease compared to the result before surgery (23.25 vs. 22.34, p=0.08). There was no sex difference in the results of the cognitive function questionnaire on day 3 of the postoperative period (22.70 vs. 21.63, p=0.43).

Analysis of the distribution of the severity of CD on day 3 of the postoperative period (Table 4) depending on the article showed that there was no difference between men and women.

The mean age of the group of patients with CD on day 3 after surgery was 61.51±9.42 and did not differ from the mean age of patients without CD (61.51 vs. 58.18, p=0.26). The distribution of patients according to age gradations (Fig. 2) showed that 2 (4.4 %) patients were under 45 years of age, 14 (31.1 %), and 60-74 years of age were 26 (57.8 %)

Table 3. Gender and age characteristics of patients with existing CD before operation.

Parameters	Men (n=37)	Women (n=19)	p
CD available (n=37)	24 (64.9 %)	13 (68.4 %)	=0.79
Mild CR (n=33)	21 (56.8 %)	12 (63.2 %)	=0.85
Moderate CD (n=4)	3 (8.1 %)	1 (5.3 %)	=0.85

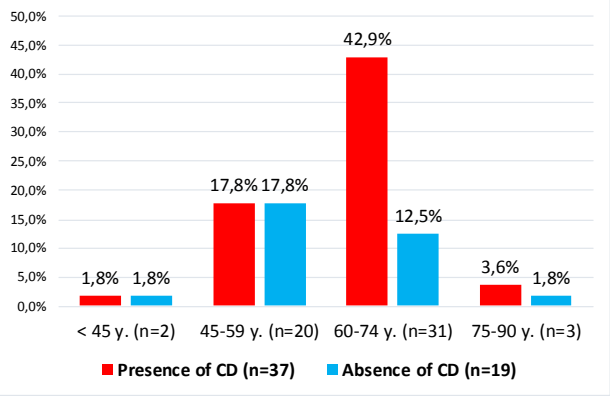

Fig. 1. Distribution of CD among patients of different ages before surgery.

Table 4. Sex and age characteristics of patients with CD on day 3 of the postoperative period.

Parameters	Men (n=37)	Women (n=19)	p
CD available (n=45)	28 (75.7 %)	17 (89.5 %)	=0.21
Mild CR (n=42)	27 (72.9 %)	15 (79.0 %)	=0.26
Moderate CD (n=3)	1 (2.7 %)	2 (10.5 %)	=0.26

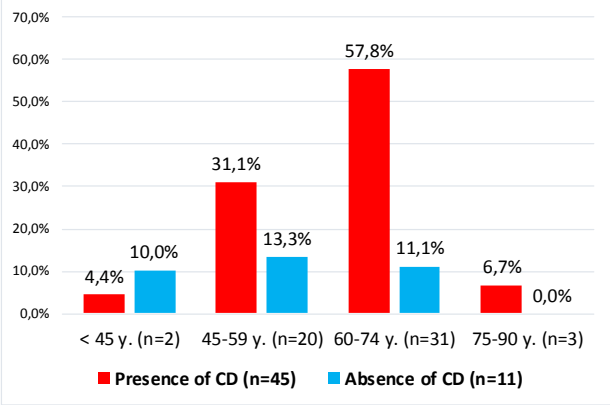

Fig. 2. Distribution of CD among patients of different ages on day 3 of the postoperative period.

Table 5. Sex and age characteristics of patients with CD on day 7 of the postoperative period.

Parameters	Men (n=37)	Women (n=19)	p
CD available (n=44)	27 (73.0 %)	17 (89.5 %)	=0.21
Mild CR (n=41)	25 (67.6 %)	16 (84.2 %)	=0.42
Moderate CD (n=1)	1 (2.7 %)	0 (0 %)	=0.42
Severe CD (n=2)	1 (2.7 %)	1 (5.3 %)	=0.42

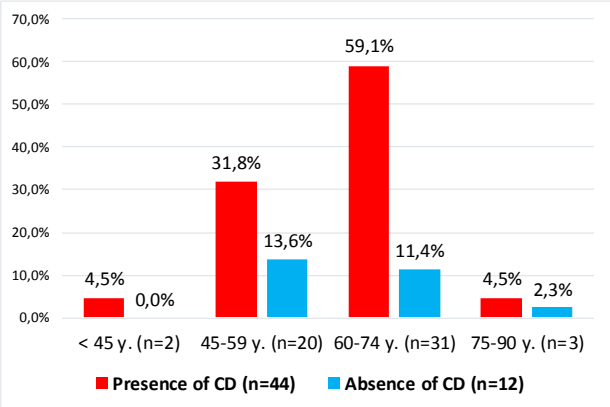

Fig. 3. Distribution of CD among patients of different ages on day 7 of the postoperative period.

and 75-90 years -3 (6.7 %) patients, respectively.

In turn, on the 7th day after surgery, the mean score on the MOCA scale was 23.05±4.68 and was higher than the result of the third day of the postoperative period (23.05 vs. 22.34, p=0.01), but did not differ statistically from the result before surgery (23.05 vs. 23.34, p=0.73). There was no difference in the test between men and women on day 7

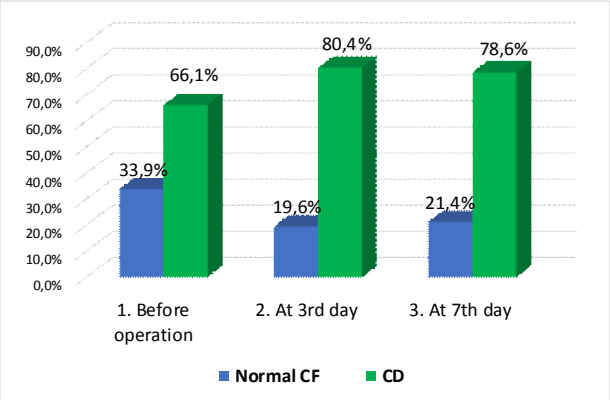

Fig. 4. Frequency of persons who had cognitive impairments during the questionnaire (before surgery, for 3 days, 7 days).

(23.16 vs. 22.84, p=0.81).

Analysis of the distribution of the severity of CD on day 7 of the postoperative period (Table 5) depending on the sex showed that there was no difference between men and women.

The mean age of the group of patients with CD on day 7 after surgery was 60.82±9.10 and did not differ from the average age of patients without CD (60.82 vs. 61.00, p=0.95). The distribution of patients according to age gradations (Fig. 3) showed that CD among the age group younger than 45 years were in 2 (4.5 %) patients, 45-59 years - in 14 (31.8 %), 60-74 years - in 26 (59.1 %) and 75-90 years - in 2 (4.5 %) patients, respectively.

Analyzing the dynamics of cognitive disorders in the early postoperative period (Fig. 4), it was found that the proportion of patients who already had CD before surgery was 37 (66.1 %). On the 3rd day after surgery, there was a significant increase in the proportion of patients with CD (80.4 % vs. 66.1%, p=0.04). In turn, on the 7th day of the postoperative period, the share of patients with CD was 44 (78.6 %), which tended to be reliable compared to the data before surgery (78.6 % vs. 66.1 %, p=0.07).

Discussion

A large amount of evidence demonstrates the relationship between the impact of surgical interventions on the course of neurocognitive functions. There are conflicting data on the effect of anesthesia on the development of long-term CD in a population of patients with normal preoperative cognitive function. However, it is known that pre-operative cognitive impairment can lead to susceptibility to CD progression [1] and is of scientific interest in drug selection, potential drug interactions, communication difficulties during testing, and ways to prevent and treat CD.

According to the literature, a week after cardiac surgery, cognitive decline is observed from 50 to 70 % of patients [15].

One study found that coronary artery bypass grafting (CABG) using artificial circulation was complicated by short-term and long-term neurocognitive dysfunction (96 and 55 % of cases, respectively). Also, in the early period after CABG in 68 % of patients revealed a decrease in regional cerebral blood flow, and in the dynamics after 6 months - in 55 % of cases [5].

L. Evered et al. [6] found that the incidence of CD on 7 day in patients after hip joint replacement surgery was 17 %, and after CABG - 43 % (p<0.01). However, after 3 months, the incidence of CD in all groups was about 17 % (p=0.13) and did not depend on the nature, type of surgery or anesthetic. Risk factors for cardiovascular disease did not predict the occurrence of CD after any of the procedures.

One prospective study showed that late cognitive decline (1 to 6 years) decreased in patients who underwent CABG surgery, but the degree of this reduction did not differ from that observed in patients of the same age with coronary heart disease who were treated only with medication [23].

Q. Nguyen et al. [16] examined 197 patients who underwent CABG or valve replacement surgery, and 44 (22 %) developed postoperative delirium. The results of the study showed that postoperative delirium was associated with increased anxiety and depression at 6-9 months after undergoing cardiac surgery.

A. Itagaki and others [10] found that 34.8 % of patients who underwent cardiac surgery developed postoperative delirium. A multivariate analysis, adjusted for baseline characteristics, showed that only in the group of patients who already had cognitive impairment and general weakness before surgery, there was a risk of delirium after surgery (odds ratio 7.494; 95 % confidence interval 1.539-36.49).

As might be expected, the timing of cognitive function testing may have an important impact on results. It is known that preoperative testing should be done before the day of surgery, as the patient is unlikely to be able to focus on cognitive tests immediately before entering the operating room. In turn, the timing of testing after surgery is contradictory. Unfortunately, there is little data on cognitive recovery after anesthesia. Clinical trials have reported testing from the actual day of surgery, a few days to weeks after surgery, and months after surgery. Postoperative CD are limited in time, so the timing of testing is an important issue and makes comparing the results somewhat difficult [24].

Perhaps the most controversial aspect of the definition of CD is the degree of change, which is considered statistically or clinically significant. Several authors have criticized the high variability of this aspect. The meta-analysis showed that the available research in the field of cardiac surgery is characterized by a wide range of variability due to existing factors related to the patient (age, education, comorbidity), factors of cardiovascular surgery (hypothermia, artificial circulation, aortic compression, bleeding), physiological factors (inflammation, microembolization), intraoperative factors (anesthesia, cerebral oxygenation, hypotension), perioperative factors (drugs, sleep, complications) and postoperative factors

(rehabilitation, depression, social support). It becomes more difficult to identify postoperative CD in patients when variable measurement of cognitive function is used using various neuropsychological tests and numerous analytical criteria. In addition, it is known that re-testing at short intervals can cause a learning effect, because repeated repetition of tests increases the knowledge of the test structure, and thus the results tend to increase [21].

It was found that increasing of age, level of education (patients without higher education), the need for further surgery, postoperative infections and respiratory complications were associated with early postoperative CD. T. G. Monk et al. [13] found that independent risk factors for CD 3 months after surgery were increased age, lower level of education, a history of acute cerebrovascular accident and the presence of CD at discharge. Patients with CD at discharge from the hospital were more likely to die in the first 3 months after surgery (p=0.02).

Thus, when faced with CD studies with different results, it is difficult to know whether the differences are significant or simply related to when and how cognitive function was determined after cardiac surgery.

Conclusions

1. It was found that the existing cognitive disorders before surgery were registered in 66.1% of patients, mostly among the age group 60-74 years and had no sex difference.

2. It is established that in the early postoperative period there is a significant deterioration of cognitive functions in patients after cardiac surgery (on the 3rd day - in 80.4 %, on the 7th day - in 78.6 % of patients, respectively).

References

[1] Belrose, J. C., & Noppens, R. R. (2019). Anesthesiology and cognitive impairment: a narrative review of current clinical literature. *BMC anesthesiology,* 19(1), 1-12. doi: 10.1186/s12871-019-0903-7

[2] Berger, M., Terrando, N., Smith, S. K., Browndyke, J. N., Newman, M. F., & Mathew, J. P. (2018). Neurocognitive function after cardiac surgery: from phenotypes to mechanisms. *Anesthesiology,* 129(4), 829-851. doi: 10.1097/ALN.0000000000002194

[3] Berger, M., Nadler, J. W., Browndyke, J., Terrando, N., Ponnusamy, V., Cohen, H. J., ... & Mathew, J. P. (2015). Postoperative cognitive dysfunction: minding the gaps in our knowledge of a common postoperative complication in the elderly. *Anesthesiology clinics,* 33(3), 517-550. doi: 10.1016/j.anclin.2015.05.008

[4] Bruggemans, E. F. (2013). Cognitive dysfunction after cardiac surgery: Pathophysiological mechanisms and preventive strategies. *Netherlands Heart Journal,* 21(2), 70-73. doi: 10.1007/s12471-012-0347-x

[5] Chernov, V. I., Efimova, N. Y., Efimova, I. Y., Akhmedov, S. D., & Lishmanov, Y. B. (2006). Short-term and long-term cognitive function and cerebral perfusion in off-pump and on-pump coronary artery bypass patients. *European Journal of Cardio-thoracic Surgery,* 29(1), 74-81. doi: 10.1016/j.ejcts.2005.10.001

[6] Evered, L., Scott, D. A., Silbert, B., & Maruff, P. (2011). Postoperative cognitive dysfunction is independent of type of surgery and anesthetic. *Anesthesia & Analgesia*, 112(5), 1179-1185. doi: 10.1213/ANE.0b013e318215217e

[7] Evered, L., Silbert, B., Knopman, D. S., Scott, D. A., DeKosky, S. T., Rasmussen, L. S., ... & Nomenclature Consensus Working Group. (2018). Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018. *Anesthesiology,* 129(5), 872-879. doi: 10.1016/j.bja.2017.11.087

[8] Galvin, J. E., & Sadowsky, C. H. (2012). Practical guidelines for the recognition and diagnosis of dementia. *The Journal of the American Board of Family Medicine,* 25(3), 367-382. doi: 10.3122/jabfm.2012.03.100181

[9] Huijts, M., Van Oostenbrugge, R. J., Duits, A., Burkard, T., Muzzarelli, S., Maeder, M. T., ... & Brunner-La Rocca, H. P. (2013). Cognitive impairment in heart failure: results from the trial of intensified versus standard medical therapy in elderly patients with congestive heart failure (TIME-CHF) randomized trial. *European journal of heart failure*, 15(6), 699-707. doi: 10.1093/eurjhf/hft020

[10] Itagaki, A., Sakurada, K., Matsuhama, M., Yajima, J., Yamashita, T., & Kohzuki, M. (2020). Impact of frailty and mild cognitive impairment on delirium after cardiac surgery in older patients. *Journal of cardiology,* 76(2), 147-153. doi: 10.1016/j.jjcc.2020.02.007

[11] Julayanont, P., Brousseau, M., Chertkow, H., Phillips, N., & Nasreddine, Z. S. (2014). Montreal Cognitive Assessment Memory Index Score (MoCA-MIS) as a Predictor of Conversion from Mild Cognitive Impairment to Alzheimer's Disease. *Journal of the American Geriatrics Society,* 62(4), 679-684. doi: 10.1111/jgs.12742

[12] Knipp, S. C., Matatko, N., Wilhelm, H., Schlamann, M., Thielmann, M., Losch, C., ... & Jakob, H. (2008). Cognitive outcomes three years after coronary artery bypass surgery: relation to diffusion-weighted magnetic resonance imaging. *The Annals of thoracic surgery,* 85(3), 872-879. doi: 10.1016/j.athoracsur.2007.10.083

[13] Monk, T. G., Weldon, B. C., Garvan, C. W., Dede, D. E., Van Der Aa, M. T., Heilman, K. M., & Gravenstein, J. S. (2008). Predictors of cognitive dysfunction after major noncardiac surgery. *The Journal of the American Society of Anesthesiologists,* 108(1), 18-30. doi: 10.1097/01.anes.0000296071.19434.1e

[14] Newman, M. F., Kirchner, J. L., Phillips-Bute, B., Gaver, V., Grocott, H., Jones, R. H., ... & Blumenthal, J. A. (2001). Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. *New England Journal of Medicine,* 344(6), 395-402. doi: 10.1056/NEJM200102083440601

[15] Newman, M. F., Mathew, J. P., Grocott, H. P., Mackensen, G. B., Monk, T., Welsh-Bohmer, K. A., ... & Mark, D. B. (2006). Central nervous system injury associated with cardiac surgery. *The Lancet,* 368(9536), 694-703. doi: 10.1016/S0140-6736(06)69254-4

[16] Nguyen, Q., Uminski, K., Hiebert, B. M., Tangri, N., & Arora, R. C. (2018). Midterm outcomes after postoperative delirium on cognition and mood in patients after cardiac surgery. *The Journal of thoracic and cardiovascular surgery,* 155(2), 660-667. doi: 10.1016/j.jtcvs.2017.09.131

[17] Ottens, T. H., Dieleman, J. M., Sau?r, A. M. C., Peelen, L. M., Nierich, A. P., de Groot, W. J., ... & DExamethasone for Cardiac Surgery (DECS) Study Group. (2014). Effects of

dexamethasone on cognitive decline after cardiac surgery: a randomized clinical trial. *Anesthesiology,* 121(3), 492-500. doi: 10.1097/ALN.0000000000000336

[18] Rasmussen, L. S., Larsen, K., Houx, P., Skovgaard, L. T., Hanning, C. D., Moller, J. T., & ISPOCD group. (2001). The assessment of postoperative cognitive function. *Acta Anaesthesiologica Scandinavica*, 45(3), 275-289. doi: 10.1034/j.1399-6576.2001.045003275.x

[19] Romero, J. R., Beiser, A., Seshadri, S., Benjamin, E. J., Polak, J. F., Vasan, R. S., ... & Wolf, P. A. (2009). Carotid artery atherosclerosis, MRI indices of brain ischemia, aging, and cognitive impairment: the Framingham study. *Stroke,* 40(5), 1590-1596. doi: 10.1161/STROKEAHA.108.535245

[20] Rovio, S. P., Pahkala, K., & Raitakari, O. T. (2019). Cognitive Decline Before and After Incident Coronary Heart Disease: Opportunity to Intervene Cognitive Function Trajectories. *Journal of the American College of Cardiology,* 73(24), 3051-3053. doi: 10.1016/j.jacc.2019.04.020

[21] Rudolph, J. L., Schreiber, K. A., Culley, D. J., McGlinchey, R. E., Crosby, G., Levitsky, S., & Marcantonio, E. R. (2010). Measurement of post-operative cognitive dysfunction after cardiac surgery: a systematic review. *Acta Anaesthesiologica Scandinavica,* 54(6), 663-677. doi: 10.1111/j.1399-6576.2010.02236.x

[22] Sauer, A. C., Veldhuijzen, D. S., Ottens, T. H., Slooter, A. J. C., Kalkman, C. J., & Van Dijk, D. (2017). Association between delirium and cognitive change after cardiac surgery. *BJA: British Journal of Anaesthesia*, 119(2), 308-315. doi: 10.1093/bja/aex053

[23] Selnes, O. A., Grega, M. A., Bailey, M. M., Pham, L. D., Zeger, S. L., Baumgartner, W. A., & McKhann, G. M. (2008). Cognition 6 years after surgical or medical therapy for coronary artery disease. *Annals of neurology,* 63(5), 581-590. doi: 10.1002/ana.21382

[24] Silverstein, J. H. (2014). Cognition, anesthesia, and surgery. *International anesthesiology clinics,* 52(4), 42-57. doi: 10.1097/AIA.0000000000000032

[25] Vogels, R. L., Oosterman, J. M., Van Harten, B., Scheltens, P., Van Der Flier, W. M., Schroeder-Tanka, J. M., & Weinstein, H. C. (2007). Profile of cognitive impairment in chronic heart failure. *Journal of the American Geriatrics Society,* 55(11), 1764-1770. doi: 10.1111/j.1532-5415.2007.01395.x

[26] Wang, W. C., Dew, I. T., & Cabeza, R. (2015). Age-related differences in medial temporal lobe involvement during conceptual fluency. *Brain research,* 1612, 48-58. doi: 10.1016/j.brainres.2014.09.061

[27] Williams, U. E., Owolabi, M. O., Ogunniyi, A., & Ezunu, E. O. (2013). Prevalence and pattern of neurocognitive impairment in Nigerians with stages 3 to 5 chronic kidney disease. *International Scholarly Research Notices*, 2013. doi: 10.1155/2013/374890

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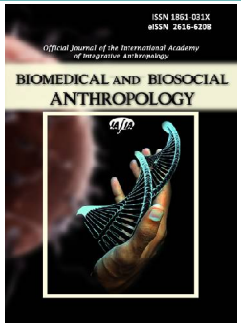

Antimicrobial activity of antiseptics in the prevention of postoperative infectious complications

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Recently, among hospital strains of microorganisms, an increase in the number of antiseptic-resistant strains of opportunistic pathogens has been registered, which significantly affects the effectiveness of these drugs. It is important to study their antimicrobial efficacy to justify rational use. The aim is to conduct a comparative study of the antimicrobial efficacy of antiseptics of decamethoxine, chlorhexidine, polyhexanide. During study we examined the antimicrobial activity against 186 clinical strains of microorganisms (Acinetobacter baumannii, Staphylococcus aureus, Pseudomonas aeruginosa, Enterococcus spp., Enterobacter spp.) isolated from patients with infectious complications in the postoperative period. The minimum inhibitory (MIC) and bactericidal concentrations (MBC) of 0.02 % and 0.1 % decamethoxine, 0.05 % chlorhexidine bigluconate, 0.1 % polyhexanide were determined; antimicrobial efficacy of drugs was evaluated by the index of antiseptic activity by conventional methods. The study found high antimicrobial properties of decamethoxine, chlorhexidine, which had a high bactericidal effect on clinical strains of S. aureus, Enterococcus spp., Enterobacter spp. Proved the benefits of antimicrobial activity of the drug based on decamethoxine ($p<0.001$). The polyhexanide has pronounced antimicrobial properties against A. baumannii, bacteria of the family Enterobactericae, P. aeruginosa. Thus, the leading gram-positive (Staphylococcus aureus, enterococci) and gram-negative pathogens (enterobacteria, acinetobacteria, pseudomonads) are sensitive to polyhexanide, chlorhexidine and the domestic drug decamethoxin, with a probable advantage of the antimicrobial properties of the latter over all gram-positive and most gram-negative microorganisms.
Keywords: *antiseptics, decamethoxin, chlorhexidine, polyhexanide.*

Introduction

Prevention of postoperative infectious complications has been and remains one of the most pressing problems of surgery, both in our country and abroad [20]. In modern conditions, infectious complications in the postoperative patient in most cases occur due to opportunistic pathogens that have become resistant to a wide range of antimicrobials [20]. The ability to develop resistance to antimicrobials is one of the leading properties of infectious complications. The high adaptability of pathogens to survival in the context of widespread use of antibiotics has led to a decrease in the effectiveness of antibiotic therapy, which significantly narrowed the possibilities in the fight against resistant isolates of microorganisms [2, 7, 10, 11]. The selective action of antiseptic drugs also leads to the elimination of sensitive cells of the microbial population and the spread of antiseptic-resistant strains [13, 18].

In such conditions, the use of antiseptics with a wide range of antimicrobial action is considered a priority. Among the known list of antiseptic drugs registered in Ukraine, 0.02 % decamethoxine and 0.05 % chlorhexidine bigliuconate are actively used in the prevention and treatment of infectious complications of the respiratory system [3]. For the purpose of perioperative prophylaxis, antiseptic treatment of means for respiratory and oxygen support of severe surgical patients is performed. Polyhexanide is known among the arsenal of modern antiseptics [12].

Nowadays, despite the proven high antimicrobial efficacy of antiseptics, there are more and more reports of a decrease in their effectiveness as a result of the formation of resistance to opportunistic pathogens. In view of the above, the study of antimicrobial activity of antiseptics

against the leading pathogens remains relevant, which can be a scientific justification for the choice of rational antiseptic prophylaxis and antiseptic therapy in clinical practice [4, 21].

The aim is to conduct a comparative study of the antimicrobial efficacy of antiseptic drugs decamethoxine, chlorhexidine, polyhexanide.

Materials and methods

On clinical strains of opportunistic pathogens isolated from patients with infectious complications in the postoperative period, who were treated in burns for severe burns, were studied antimicrobial efficacy of antiseptics based on polyhexanide, decamethoxine, chlorhexidine. Identification of microorganisms was performed in accordance with conventional methods for morphological, tinctorial, cultural, biochemical properties. A total of 186 clinical strains of opportunistic pathogens were used in the study. The structure of the studied pathogens of infectious complications was represented by isolates of S. aureus (n=56), P. aeruginosa (n=44), A. baumannii (n=43), Enterobacter spp. (n=23), Enterococcus spp. (n=22).

The antimicrobial properties of antiseptics based on 0.02 % and 0.1 % decamethoxine, 0.05 % chlorhexidine bigluconate, 0.1 % polyhexanide were investigated. The study evaluated the antimicrobial action of antiseptics, determining their minimum inhibitory (bacteriostatic) and bactericidal concentrations (MIC and MBC, respectively) on isolates of opportunistic pathogens by the standard method of double serial dilutions, guided by guidelines for determining the sensitivity of Health of Ukraine № 167 from 05.04.2007 [9].

The research was conducted in accordance with the Helsinki Declaration of the World Medical Association on the Ethical Principles of Human-Based Medical Research. Patients' written consent was required to participate in a clinical trial [17].

Comparative characterization of the clinical efficacy of the studied antiseptic drugs against clinical strains of opportunistic pathogens was performed using a quantitative indicator - the index of antiseptic activity (IAA) according to A. P. Krasilnikov, which was calculated according to the method. IAA is the ratio of the working concentration of the drug to the MIC of the antiseptic relative to a particular type of pathogen or MIC+2σ in the study of several strains of one type of pathogen [6, 15].

Results

The study revealed significant advantages of bactericidal properties of decamethoxine compared with chlorhexidine over clinical strains of Staphylococcus aureus and enterococci ($p<0.05$). The data obtained showed that bactericidal concentrations of decamethoxine against S. aureus and Enterococcus spp. were lower than chlorhexidine by 3.5 and 10.5 times, respectively (Table 1).

Polyhexanide MBC was determined for staphylococci (16.51±1.75 μg/ml). Polyhexanide showed similar bactericidal properties against enterobacteria and staphylococci. It was found that the bactericidal effect of decamethoxine on clinical A. baumannii was manifested in the presence of MBC, which was 3.1 times less than those of polyhexanide and 2 times less than chlorhexidine. Chlorhexidine had a bactericidal effect on Enterobacter spp. in the presence of 19.90±1.66 μg/ml.

Table 1. Quantitative characteristics of bacteriostatic, bactericidal action of antiseptics.

Clinical strains of microorganisms (number)	Decamethoxin	Chlorhexidine	Polyhexanide
	MBC *(μg/ml)		
S. aureus (n=56)	1.554±0.173	5.422±0.748**	16.51±1.75
Enterococcus spp. (n=22)	6.743±0.611	25.28±1.39**	4.080±0.392
Enterobacter spp. (n=23)	18.75±1.36	19.90±1.66**	14.83±2.20
A.baumannii (n=43)	51.13±7.40	70.54±16.55**	161.9±16.9
P. aeruginosa (n=44)	106.8±5.9	85.93± 6.30**	203.1±16.9

Notes: *MBC - minimum bactericidal concentration (in μg/ml); ** - $p<0.05$ compared with decamethoxine.

It was found that the antimicrobial properties of polyhexanide against Pseudomonas aeruginosa were twelve times weaker than against Staphylococcus aureus. Thus, isolates of Enterobacter spp. died in the presence of 14.83±2.20 μg/ml of polyhexanide, which were 10 times smaller than in the case of A. baumannii ($p<0.001$).

High bactericidal properties of decasan against S. aureus isolates, which were sensitive to 1.554±0.173 μg/ml of the drug, were proved. The bactericidal properties of chlorhexidine against A. baumannii were determined using a 2-fold higher concentration of antiseptic, which indicated a weaker activity against this type of microorganism. Clinical strains of A. baumannii were found to have a similar high sensitivity to polyhexanide as Enterobacter spp. ($p>0.05$).

Clinical strains of P. aeruginosa were endowed with high resistance properties. The vast majority of Pseudomonas aeruginosa isolates (85.4 %) were sensitive to decamethoxine (MBC 99.78±4.35 μg/ml). However, bactericidal properties against 14 (14.6 %) clinical strains of P. aeruginosa were not determined in 0.02 % decamethoxine solution, because the MBC of the drug exceeded 200 μg/ml. The obtained data showed the advantages of bactericidal properties of decane over sensitive strains of P. aeruginosa in comparison with polyhexanide in 2 times ($p<0.001$). Polyhexanide showed bactericidal antipseudomonad properties in the presence of high concentrations, which reached 203.1±16.9 μg/ml.

Given the significant differences in the quantitative content of the main active substances in the finished dosage forms of the studied antiseptics, it was considered insufficient to assess their antimicrobial efficacy only on the basis of MBC. A more detailed analysis of the antimicrobial efficacy of antiseptic drugs based on decamethoxine, chlorhexidine and polyhexanide was performed by calculating

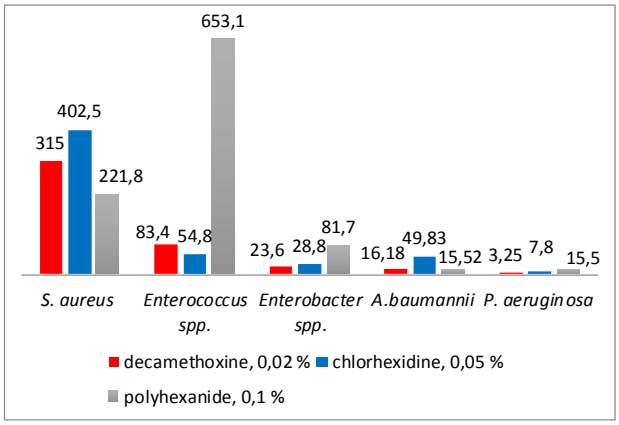

Fig. 1. Characteristics of antimicrobial efficacy of antiseptic drugs against clinical strains of gram-positive, gram-negative microorganisms.

the IAA (Fig. 1). Thus, IAA of the official forms of 0.02 % decamethoxine, 0.05 % chlorhexidine and 0.1 % polyhexanide was determined. As a result of the analysis of IAA indicators, the high antimicrobial efficacy of decamethoxin against gram-positive and gram-negative opportunistic pathogens was established. Significant advantages of antimicrobial efficacy of this antiseptic against S. aureus in comparison with 0.05 % chlorhexidine and 0.1 % polyhexanide were proved 3.5 and 10.5 times, respectively ($p<0.05$).

In terms of antimicrobial efficacy against enterococci, 0.1 % polyhexanide and 0.05 % chlorhexidine were superior to IAA 0.02 % decamethoxine (6.2 and 3.7 times, respectively; $p<0.001$). It was found that the application of polyhexanide was not effective against S. aureus, Enterococcus spp., because the IAA in both cases was much lower than the maximum allowable level of this indicator, which must be at least "4".

It was shown that the IAA of polyhexanide relative to Enterobacter spp. and A. baumannii significantly exceeded the corresponding index of 0.02 % decamethoxine (3.4 and 0.95 times, respectively; $p<0.001$) and chlorhexidine (2.8 and 0.3 times, respectively; $p<0.001$). No significant differences in the antimicrobial activity of 0.02 % decamethoxine, 0.05 % chlorhexidine and 0.1 % polyhexanide against acinetobacter and enterobacteria were found, as IAA values did not differ significantly and exceeded the maximum allowable threshold, indicating their high efficiency against these species.

The advantages of antimicrobial efficacy of polyhexanide in the concentrations of the finished dosage form in relation to clinical strains of P. aeruginosa have been established. 0.02 % decamethoxine and 0.05 % chlorhexidine showed 5-2 times less pronounced antipseudomonad activity than polyhexanide ($p<0.001$).

Discussion

With the rapid formation and spread of antibiotic resistance among the causative agents of infectious complications, scientists around the world have focused significant efforts on finding ways to overcome this problem. Among the alternative ways to control antibiotic-resistant pathogens, the active use of antiseptics, which have different mechanisms of action on microorganisms than antibiotics, is considered effective and promising [14]. Scientists have proven that microorganisms are much slower to form resistance to antiseptics [8, 12, 13, 16, 19, 20].

The use of antiseptics is recommended and regulated by the international scientific community in a set of measures for the prevention and treatment of infectious complications in the postoperative period in intensive care units and surgery caused by opportunistic pathogens [1, 4, 21]. Microbiological substantiation of the use of surfactant antiseptics based on decamethoxine, chlorhexidine is based on their proven high efficiency against a wide range of gram-positive, gram-negative microorganisms, which are problematic pathogens of infectious complications [1, 5, 12, 14]. Thus, as a result of the conducted researches the high bactericidal action of decasan against clinical strains of S.aureus, Enterococcus spp. was proved, which significantly exceeded the bactericidal properties of chlorhexidine by 3.3 and 3.7 times, respectively. The advantages of antimicrobial efficacy against these gram-positive bacteria in the antiseptic on the basis of decamethoxine in comparison with polyhexanide ($p<0.001$) were established.

The obtained data correlate with the data of the literature in which the high antimicrobial effect of decamethoxine on gram-positive opportunistic pathogens was shown and the reduction of antimicrobial properties of polyhexanide against pathogens of infectious complications was proved [3, 13, 14].

Studies have proven the high antimicrobial properties of polyhexanide against a number of gram-negative microorganisms (Enterobacter spp., A. baumannii, P. aeruginosa). At the same time, a significant decrease in the effectiveness of this antiseptic against clinical isolates of S. aureus.

The antimicrobial efficacy of decamethoxine and chlorhexidine against acinetobacteria has been proven, as evidenced by the IAA of these antiseptics, which did not differ significantly. However, according to a number of researchers and according to the study, a higher bactericidal effect on A.baumannii by decamethoxine was found, compared with chlorhexidine (3.7 times; $p<0.05$).

Non-fermenting gram-negative bacteria P.aeruginosa, which have high resistance to antimicrobials, including antiseptics, were sensitive to decamethoxine, chlorhexidine and polyhexanide. Antiseptics containing decamethoxine (0.02 %) and chlorhexidine (0.05 %) were characterized by sufficient antimicrobial efficacy against this type of pathogen.

Conclusions

1. Surface-active antiseptics decamethoxine, chlorhexidine, polyhexanide have high bactericidal properties against clinical strains of gram-positive and

gram-negative opportunistic pathogens, with pronounced advantages of antimicrobial efficacy of the drug based on decamethoxine against S.aureus (3.5 and 3.7 times; $p<0.05$), Enterococcus spp. (3.7 times; $p<0.001$) and Enterobacter spp. (1.3 times; $p<0.001$).

2. Polyhexanide exhibits high antimicrobial properties against a wide range of opportunistic pathogens, including enterococci, Staphylococcus aureus, enterobacteria.

3. High sensitivity of leading gram-positive pathogens (Staphylococcus aureus, enterococci), gram-negative pathogens (enterobacteria, acinetobacteria, pseudomonads) to domestic antiseptic drug based on decamethoxine justifies its high effectiveness in the treatment of its antimicrobial treatment.

4. Given the high risk of infection with opportunistic pathogens after surgery, the risk of antibiotic resistance, and pronounced antimicrobial properties of local antiseptics, the use of the latter is appropriate in the perioperative period for the prevention of infectious complications.

References

[1] Allegranzi, B., Bischoff, P., de Jonge, S., Kubilay, N. Z., Zayed, B., Gomes, S. M., ... & Group, W. G. D. (2016). New WHO recommendations on preoperative measures for surgical site infection prevention: an evidence-based global perspective. *The Lancet Infectious Diseases,* 16(12), e276-e287. doi: 10.1016/S1473-3099(16)30398-X

[2] Ayisi, L. A., & Adu-Sarkodie, Y. (2015). Extended-Spectrum-Beta-Lactamase (ESBL) production among Escherichia coli and Klebsiella species in Kumasi, Ghana. *Journal of Natural Sciences Research,* 5(8), 81-86.

[3] Compendium. (2019). *Компендіум - лікарські препарати [Compendium - drugs].* К.: МОРІОН - K.: MORION.

[4] European Centre for Disease Prevention and Control. (2013). Surveillance of surgical site infections in Europe 2010-2011. Eur. Cent. Dis Prev. Control.

[5] Gerba, C. P. (2015). Quaternary ammonium biocides: efficacy in application. *Applied and environmental microbiology*, 81(2), 464-469. doi: 10.1128/AEM.02633-14

[6] Krasil'nikov, A. P. (1995). *Справочник по антисептике [Antiseptic Handbook].* Минск: Вышейшая школа - Minsk: Higher School.

[7] Magiorakos, A. P., Srinivasan, A., Carey, R. T., Carmeli, Y., Falagas, M. T., Giske, C. T., ... & Monnet, D. T. (2012). Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clinical microbiology and infection,* 18(3), 268-281. doi: 10.1111/j.1469-0691.2011.03570.x

[8] Mama, M., Abdissa, A., & Sewunet, T. (2014). Antimicrobial susceptibility pattern of bacterial isolates from wound infection and their sensitivity to alternative topical agents at Jimma University Specialized Hospital, South-West Ethiopia. *Annals of clinical microbiology and antimicrobials,* 13(1), 1-10. doi: 10.1186/1476-0711-13-14

[9] Ministry of Health of Ukraine. (2007). Про затвердження методичних вказівок "Визначення чутливості мікроорганізмів до антибактеріальних препаратів" [About the statement of methodical instructions "Determination of sensitivity of microorganisms to antibacterial drugs"]. Нормативно-директивні документи МОЗ України. Наказ № 167 від 05.04.2007 - Regulatory documents of the Ministry of Health of Ukraine. Order № 167 from 05.04.2007.

[10] Nazarchuk, O. A. (2017). Microbiological and molecular research of the resistance in gram-negative pathogens of infectious complications to carbapenem antibiotics, approaches to its combating. *Moldovan Journal of Health Sciences*, 13(3), 22-32.

[11] Osolodchenko, T. P., Andreeva, I. D., Zavada, N. P., Lukyanenko, T. V., Batrak, O. A., & Ryabova, I. S. (2015). Чутливість до антибактеріальних препаратів збудників позалікарняних інфекцій [Sensitivity to antibacterial drugs of nosocomial infections]. *Аннали Мечниковського інституту - Annals of Mechnikov Institute*, (1), 29-38.

[12] Palii, G. K., Koval'chuk, V. P., & Fomina, N. S. (2014). Характеристика сучасного арсеналу дезінфекційних засобів та проблеми дезінфектології [Characteristics of the modern arsenal of disinfectants and problems of disinfection]. *Biomedical and biosocial anthropology,* (22), 82-85.

[13] Palii, G. K., Nazarchuk, O. A., Honchar, O. O., Nazarchuk, G. G., Oliynyk, D. P., & Bereza, B. M. (2013). Формування резистентності у штамів стафілококів до лікарських антисептичних препаратів [Formation of resistance in staphylococcal strains to antiseptic drugs]. *Вісник морфології - Reports of Morphology,* 19(2), 286-289.

[14] Palii, G. K., Pavliuk, S. V., Palii, D. V., Nazarchuk, O. A., Agafonov, K. V., & Dudar, A. O. (2018). Обґрунтування застосування антисептичних препаратів у системі профілактичних і лікувальних заходів (огляд літератури) [Rationale for the use of antiseptic drugs in the system of preventive and curative measures (literature review)]. *Буковинський медичний вісник - Bukovynian Medical Bulletin*, 22(4 (88)), 138-146. doi: 10.24061/2413-0737.XXII.4.88.2018.98

[15] Potapov, V. Yu., Vakulenko, E. N., & Protasenko, Ya. D. (2016). Выбор оптимальных антисептических средств для обработки костной полости в процессе хирургического лечения нагноившихся радикулярных кист [The choice of optimal antiseptic agents for the treatment of the bone cavity in the process of surgical treatment of suppurating radicular cysts]. *Український стоматологічний альманах - Ukrainian Dental Almanac,* (4), 40-42.

[16] Saperkin, N., Kovalishena, O., & Blagonravova, A. (2013). P089: Surveillance of bacterial resistance to disinfectants. *Antimicrobial Resistance and Infection Control,* 2(1), 1. doi: 10.1186/2047-2994-2-S1-P89

[17] Ukraine, Законодавство. (2008). Гельсінська декларація Всесвітньої медичної асоціації "Етичні принципи медичних досліджень за участю людини у якості об'єкта дослідження" [Helsinki Declaration of the World Medical Association "Ethical principles of medical research with human participation as an object of study"]. Гельсінкі: Прийнята - Helsinki: Accepted. http://zakon5.rada.gov.ua/laws/show/990_005

[18] Wisplinghoff, H., Schmitt, R., Wohrmann, A., Stefanik, D., & Seifert, H. (2007). Resistance to disinfectants in epidemiologically defined clinical isolates of Acinetobacter baumannii. *Journal of hospital infection,* 66(2), 174-181. doi: 10.1016/j.jhin.2007.02.016

[19] World Health Organization. (2001). WHO global strategy for containment of antimicrobial resistance (No. WHO/CDS/CSR/DRS/2001.2). World Health Organization.

[20] World Health Organization. (2014). Antimicrobial resistance: global report on surveillance. World Health Organization.

[21] World Health Organization. (2016). Global guidelines for the prevention of surgical site infection. World Health Organization.

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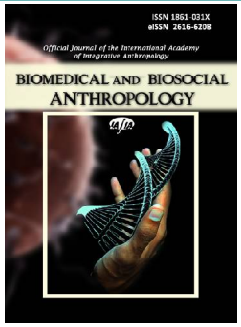

Strategic directions of implementing a system of psychophysiological support of professional activity of military pilots

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To date, the state aviation of Ukraine has an urgent problem of improving the existing system of medical support for flights by introducing measures of psychophysiological support for improving the professional health of military pilots, increasing the duration of their professional longevity and ensuring the safety of flights. That is why, the purpose of our research was to offer a list of strategic directions of scientific substantiation and development of a conceptual model of a system of measures for psychophysiological support of professional activities of military pilots based on an analysis of the problems of its implementation in the state aviation of Ukraine. For this, the methods of analysis and synthesis, generalization, induction and deduction, complex and system analysis were used. As a result of the research, it was found that the strategy for introducing a system of measures for psychophysiological support of the professional activities of military pilots should be perceived as a process of improving the existing system of medical support for flights of state aviation in Ukraine on the basis of defining qualitatively new goals and objectives of its functioning, harmonizing internal capabilities with the conditions of the professional environment, development of a set of measures to improve its reliability and efficiency in the long term. From these points of view, the systematic approach to determining the strategic directions of implementation of the said system should be based on the complex of organizational, regulatory, information-analytical, personnel and technological problems. To solve them, it is necessary to conduct research on health assessment of different categories of military pilots, hygienic assessment of conditions and features of their professional activity, selection of a set of informative psychophysiological characteristics and methods of their evaluation, development of mechanisms and criteria for access to flights, regulatory, legal, personnel and organizational bases of functioning of system of measures of psychophysiological support of professional activity of military pilots.

Keywords: *system of measures of psychophysiological support, strategic directions of its implementation, military pilots.*

Introduction

Many generations of domestic scientists have dedicated their lives to solving extremely important problems of such occupational medicine as aviation medicine - finding methods and ways to save lives and health, prolong professional longevity, ensure high efficiency, efficiency, reliability of aviation personnel and flight safety. The results of their titanic work to study the conditions and nature of flight work, study the mechanisms and consequences of negative, and often pathological, the impact of occupational factors and labor process on the body of military pilots, formed the basis of scientific substantiation, development and implementation of domestic health care system flights of aviation operating in Ukraine to date [23, 24]. This system is based on the principles of continuity, consistency, continuity and individuality of organizational, treatment and prevention, physiological and hygienic and rehabilitation measures during the commission and inter-commission periods.

As a result, the introduction in the 50-60s of the last century of measures of medical and psychological selection, normalized 45-day regular leave in sanatoriums, standardized 4 meals a day in flight canteens, regulatory regular and extraordinary medical examinations, as well as annual conducting medical and flight examination in the framework of the concept of occupational health, for 30 years has led to a decrease in aviation events due to deteriorating health and reduced efficiency of flight crew members in flight to the level of 0.3-0.8 % [25].

However, the current situation regarding aviation accidents and catastrophes [2, 7, 19, 26, 28], as well as the level of morbidity and disqualification of military pilots on medical grounds [13, 21, 25, 27], somewhat contradicts these data and shows about the lack of effectiveness of the presented approaches. In particular, according to some data [3] in the 80's the level of disqualification for the health of this contingent in the Armed Forces of the USSR was already 44 % and was constantly growing. Later, in the 90s of last century in the aviation of the Armed Forces of the Russian Federation, it was already 85 %. In Ukraine, the level of disqualification of flight crew for health reasons during 2001-2007 was 7.3-11.8 % [12]. Negative results of medical and psychophysiological prognosis on the human factor, social, humanitarian and economic consequences of low flight safety in general are impressive in their scale and do not inspire much optimism [28].

The main reason for the emergence and development of this situation, in our opinion, given the current conditions of technological progress, widespread use of new information technologies and modernization of technical systems, features of aviation in the area of anti-terrorist and peacekeeping operations, aggressive influence of social, demographic, environmental factors , today there is a low level and limited capabilities of the body of military pilots, as the weakest link in the aviation system "pilot-aircraft-environment". First of all, this "weakness" according to the literature [3, 19, 28, 29, 30] is due to the inconsistency of professionally determined requirements to the psychophysiological characteristics of this contingent.

That is why today in the state aviation of Ukraine there is an urgent problem of improving the existing system of medical flight support by introducing psychophysiological technologies to improve the professional health of military pilots, increase their professional longevity and overall life, flight safety and more. Analysis of literature sources on the current state of psychophysiological support of professional activities of military pilots in Ukraine and abroad [14, 15, 18, 26, 31, 32] allows to identify a set of key problems not only scientific justification, but also examples of systematic implementation of psychophysiological technologies and measures psychophysiological support as such in the existing system of medical support of flights of the state aviation of Ukraine. Awareness of these problems has led to a gradual definition of place and role [17], establishing on this basis a list of basic terms, their definitions and basic principles of functioning of the system of measures of psychophysiological support of professional activities of military pilots [16]. This approach, in our opinion, allows us to offer a list of strategic directions and a set of necessary research, which in fact should determine the method of its scientific substantiation and further development of a holistic conceptual model.

The purpose of the work is to propose a list of strategic directions of scientific substantiation and development of its conceptual model on the basis of the analysis of problems of introduction in the state aviation of Ukraine of the system of measures of psychophysiological support of military pilots' professional activity.

Materials and methods

To highlight the problems of introduction in the state aviation of Ukraine of the system of measures of psychophysiological support of military pilots, development of the main strategic directions of their solution and formation of a set of necessary researches on further scientific substantiation and development of a conceptual model of the specified system methods of analysis and synthesis, generalization, induction and deduction, complex and system analysis are used.

Results

Before highlighting the problems of introducing a system of psychophysiological support for military pilots in the state aviation of Ukraine and developing the main strategic directions for their solution, it is necessary to dwell on the characteristics of the very concept of "strategy". A review of modern scientific publications on the characteristics of this term indicates the absence of a single generally accepted definition [1, 5, 20, 22]. In essence, these literature sources consider two approaches to the definition of the term "strategy" - "strategy as a process" and "strategy as a result". In the first case, the strategy is perceived as a process of determining the direction of action from the initial to the final (desired) state, with the allocation of means to achieve the goal, building a plan and establishing rules for decision-making. Otherwise, the strategy is associated with the establishment of specific benchmarks or results of strategic activities that ensure the improvement and high efficiency of a particular system or organization. In this context, the strategy is often compared with the existing situation for a particular activity, measures to change it and achieve the desired results. Such a strategy is a concretized, according to certain indicators, position on finding ways to effectively achieve the goal by making the necessary changes to the components and their combinations within existing or updated systems [1, 20, 22].

That is why, in our opinion, the strategy of introducing a system of psychophysiological support for professional activities of military pilots should be perceived as a process of forming strategic directions for improving the existing

system of medical support of Ukraine state aviation on the basis of qualitatively new goals and objectives, coordination of internal capabilities professional environment, the development of a set of measures that can ensure greater reliability and efficiency in the long run.

From these positions, a systematic approach to determining the strategic directions of the introduction of a system of psychophysiological support for the professional activities of military pilots should be based on organizational, regulatory, information-analytical, personnel and technological issues.

The organizational problems, first of all, include the absence in the state aviation of Ukraine of any concept and interdepartmental program of introduction of measures of psychophysiological support of professional activity of military pilots. In addition, to date, no single governing and coordinating body has been identified in this area. Therefore, the functions established by the current legislation on the implementation of certain components of psychophysiological support are distributed between different units of the aviation activities of the state aviation of Ukraine or are not implemented at all, or are implemented spontaneously and unsystematically.

The existing regulations governing the work of the medical service of the aviation activities of Ukraine state aviation on medical support of military pilots professional activities do not contain any data on the establishment of types, stages, sequence, methods and timing of psychophysiological support, and those provisions that require consideration of the results of assessment of the psychophysiological state during the implementation of measures of dynamic medical surveillance are only declarative in nature due to the lack of a real mechanism for their implementation.

Institutions and divisions of the medical service of the aviation activities of Ukraine state aviation do not provide for information and analytical work on the results of psychophysiological support of professional activities of military pilots, mainly due to lack of a full register with relevant databases.

There is a lack of sufficient positions of psychophysiologists in the institutions and divisions of the medical service of the aviation activities of Ukraine state aviation, and the Ukrainian Military Medical Academy has long stopped recruiting students for internships (master's degrees) in "Psychophysiology".

From the technological point of view, there is an urgent need to develop and approve the established standards, software and hardware requirements, a list of measures of psychophysiological support, reflecting their types, stages, sequence and timing. The criteria for evaluating the effectiveness of psychophysiological technologies have not been defined either.

The solution to these problems, in our opinion, lies in the implementation of the following strategic areas:

development of a conceptual model of the system of measures of psychophysiological support of military pilots' professional activity of Ukraine state aviation;

reorganization (modernization) of the existing forces and structural subdivisions of the medical service of the subjects of aviation activity of the state aviation of Ukraine to expand their functionality to medical and psychophysiological support;

creation of a scientific and practical coordination center for psychophysiological support of professional activity of military pilots of Ukraine state aviation;

opening of research work on development of the concept of system of measures of psychophysiological support of professional activity of military pilots of the state aviation of Ukraine, with reflection of types, stages, sequence, methods and terms of carrying out, criteria of estimation of efficiency of application, and also questions of normative-legal, informational, organizational, material-technical, scientific-methodical and personnel support;

making appropriate changes to existing ones, as well as developing and approving in the prescribed manner new regulations on the introduction of a system of measures of psychophysiological support, standards and criteria for evaluating the effectiveness of their application;

creation of a register with databases for the implementation of information and analytical work on the results of psychophysiological support of military pilots' professional activities of Ukraine state aviation;

introduction of positions of psychophysiologists in institutions and subdivisions of medical service of subjects of aviation activity of Ukraine state aviation;

restoration in the Ukrainian Military Medical Academy of all forms of postgraduate training (specialization and master's degree) in the specialty "Psychophysiology";

introduction in the Ukrainian Military Medical Academy cycles of thematic improvement of medical service medical personnel of aviation activity subjects of Ukraine state aviation concerning psychophysiological support of military pilots' professional activity.

The basis for scientific substantiation and development of a conceptual model of the system of measures of psychophysiological support of military pilots' professional activity of Ukraine state aviation should be researches concerning:

implementation of professional description and hygienic assessment of conditions and features of professional activity of different categories of military pilots;

health assessment of various categories of military pilots;

allocation of a complex of informative psychophysiological characteristics for carrying out of actions of psychophysiological support of professional activity of various categories of military pilots;

formation of a set of methods for assessing professionally important psychophysiological characteristics of different categories of military pilots at different stages of psychophysiological support of their

professional activities;

assessment of basic psychophysiological and psychological characteristics of different categories of military pilots;

development of mechanisms and criteria for admission and determination of the degree of suitability of various categories of military pilots to perform flights;

development of normative-legal, personnel and organizational bases of functioning of the system of measures of psychophysiological support of military pilots' professional activity;

development of a conceptual model of the system of measures of psychophysiological support of military pilots' professional activity.

Discussion

The presented results of scientific research on determining the strategic directions of introduction in the state aviation of Ukraine system of measures of psychophysiological support of professional activity of military pilots are considered for the first time. Of course, given the existence of a strong social and economic effect of the introduction of psychophysiological technologies [4, 6, 8, 9, 21, 29], in modern literature there are examples of scientific justification and introduction of certain elements of psychophysiological support of professional activities, including military pilots. However, some of them are aimed at the implementation of psychophysiological selection measures and related psychophysiological examination [4, 9, 10, 29, 30]. The purpose of these measures, by definition, is to establish the degree of professional suitability of professionals to perform certain professional duties, in order to select a profession and appoint persons whose psychophysiological characteristics meet its requirements. Others, aimed at ensuring the effectiveness of the professional activities of flight crew by increasing the efficiency [12] of this contingent or optimizing the adaptive capacity of man [11].

All the presented models on the one hand differ significantly from each other in organizational and substantive aspects due to the lack of a clear strategy of scientific substantiation, development and implementation, and on the other - they are united by spontaneity and unsystematic implementation, lack of functional links or separation from the existing system. medical support, which leads to reluctance and resistance to the introduction of psychophysiological technologies in medical practice by both doctors and workers, in relation to which these measures should be taken [18]. That is why the definition of clear and understandable strategic directions of introduction of the system of measures of psychophysiological support of professional activity of military pilots of state aviation of Ukraine will allow in the future to approach scientific substantiation and development of its integral and really effective conceptual model.

Conclusions

1. As a result of the conducted researches the characteristic of organizational, normative-legal, information-analytical, personnel and technological problems of introduction in the state aviation of Ukraine system of measures of psychophysiological support of professional activity of military pilots is allocated and given.

2. The list of the basic strategic directions and a complex of necessary researches concerning a scientific substantiation and development of conceptual model of measures system of psychophysiological support of military pilots state aviation of Ukraine professional activity is offered.

References

[1] Ansoff, I. (1989). *Стратегическое управление [Strategic management].* Москва: Экономика - Moskva: Ekonomika.

[2] Baker, S. P., Lamb, M. W., Grabowski, J. G., Rebok, G., & Li, G. (2001). Characteristics of general aviation crashes involving mature male and female pilots. *Aviation, Space, and Environmental Medicine,* 72(5), 447-452. PMID: 11346011

[3] Bodrov, V. A. (1989). *Медико-психологические вопросы восстановления профессиональной работоспособности летного состава [Medical and psychological issues of restoration of professional performance of flight personnel].* Профессиональное здоровье летчиков и летное долголетие - Professionalnoe zdorovye lotchikov i lotnoe dolholeniye. Москва: Военное издательство - Moskva: Voennoye izdatelstvo. 50-59.

[4] Bor, R., Eriksen, C., Hubbard, T., & King, R. (Eds.). (2019). *Pilot Selection: Psychological Principles and Practice.* CRC Press.

[5] Dubichynskiy, V. V. (2009). *Сучасний тлумачний словник української мови: 60000 слів [Modern Ukrainian Dictionary of Interpretation: 60000 words].* Харків: ВД "ШКОЛА" - Kharkiv: VD "SHKOLA".

[6] Eaglestone, J., & Steinhardt, G. (2020). Pilot Selection - Psychological Principles and Practice. *Aviation Psychology and Applied Human Factors,* 10, 36-38. doi: 10.1027/2192-0923/a000183

[7] Gillis, L.G., Li, G., & Baker, S.P. (2001). General aviations crashes involving military personal as pilots. *Aviat. Space Environ. Med,* 72(11), 1001-1005. PMID: 11718504

[8] Johannes, B., Rothe, S., Gens, A., Westphal, S., Birkenfeld, K., Mulder, E., ... & Ledderhos, C. (2017). Psychophysiological Assessment in Pilots Performing Challenging Simulated and Real Flight Maneuvers. *Aerospace medicine and human performance*, 88(9), 834-840. doi: 10.3357/AMHP.4782.2017

[9] Kalnish, V. V. (2015). Пути совершенствования профессионального психофизиологического отбора и мониторинга профессионально важных качеств специалистов, работающих в условиях с повышенной опасностью [Ways to improve professional psychophysiological selection and monitoring of professionally important qualities of specialists working in conditions with increased danger]. *Український журнал з проблем медицини праці - Ukraïnskij zhurnal z problem medycyny pratsi,* (4), 14-25.

[10] Kalnysh, V. V., & Yena, A. I. (2001). Принципи професійного психофізіологічного відбору [Principles of professional psychophysiological selection]. *Гигиена труда - Hyhyena*

truda, (32), 131-144.
[11] Kokun, O. M. (2004). *Оптимізація адаптаційних можливостей людини: психофізіологічний аспект забезпечення діяльності [Optimization of human adaptive capacity: psychophysiological aspect of activity support].* Київ: Міленіум - Kyiv: Milenium.
[12] Kompaniiets, O. A. (2008). Професійна працездатність льотного складу за показниками постурографії [Professional efficiency of the flight crew according to posturography indicators]. *Український журнал з проблем медицини праці - Ukraïnskij zhurnal z problem medycyny pratsi*, 4(16), 55-59.
[13] Kotuza A. S. (2001). Особливості й тенденції захворюваності та дискваліфікація льотного складу Військово-повітряних Сил України [Peculiarities and tendencies of morbidity and disqualification of the flight staff of the Air Force of Ukraine]. *Вісник соціальної гігієни та організації охорони здоров'я - Visnyk sotsialnoyi hihieny ta orhanizatsiyi okhorony zdorovya*, (4), 35-38.
[14] Kravchuk, V. V. (2017). Сучасні підходи до збереження здоров'я та тривалості професійного довголіття військових льотчиків [Current approaches to maintaining the health and longevity of military pilots]. Проблеми військової охорони здоров'я: зб. наук. пр. *Української військово-медичної академії - Problemy viyskovoi ohorony zdorovya: zbirnyk naukovyh prac Ukrainskoyi viyskovo-medychnoyi academyi,* (49), 351-360.
[15] Kravchuk, V. V. (2018). Сучасний стан психофізіологічного забезпечення діяльності військових льотчиків [The current state of psychophysiological support for the activity of military pilots]. *Військова медицина України - Viyskova medicina Ukrainy,* (2), 29-34.
[16] Kravchuk, V. V. (2019). Основні принципи розроблення системи заходів психофізіологічного супроводу професійної діяльності військових льотчиків [The main principles of development of the system of measures psychophysiological support of professional activity of military pilots]. *Військова медицина України - Viyskova medicina Ukrainy*, (3), 90-94. doi: 10.32751/2663-0761-2019-03-12
[17] Kravchuk, V. V. (2019). Сучасні підходи до визначення місця та ролі заходів психофізіологічного супроводу в системі медичного забезпечення польотів державної авіації України [Modern approaches to determining the place and role of measures of psychophysiological support in the system of medical support of flights of the state aviation of Ukraine]. *Військова медицина України - Viyskova medicina Ukrainy,* (1), 63-67. doi: 10.32751/2663-0761-2019-01-09
[18] Kravchuk, V. V. (2018). Організаційні та методичні аспекти проведення заходів психофізіологічного супроводу професійної діяльності військових льотчиків [Organizational and methodological aspects of conducting activities of psychophysiological support of professional activity of military pilots]. Проблеми військової охорони здоров'я: зб. наук. пр. *Української військово-медичної академії - Problemy viyskovoi ohorony zdorovya: zbirnyk naukovyh prac Ukrainskoyi viyskovo-medychnoyi academyi,* (50), 74-84. doi: 10.32751/2663-077X-50-08
[19] Li, G., Baker, S. P., Lamb, M. W., Grabowski, J. G., & Rebok, G. W. (2002). Human factors in aviation crashes involving older pilots. *Aviation, space, and environmental medicine*, 73(2), 134-138. PMID: 11846182
[20] Litvinov, O. I. (2013). Стратегічні напрями стабілізації та розвитку економічної діяльності торговельних підприємств [Strategic directions of stabilization and development of economic activity of trade enterprises]. *Ефективна економіка - Efektyvna ekonomika,* (10).
[21] McCrery, B. F., & Van Syoc, D. L. (2002). Permanent flying disqualifications of USAF pilots and navigators 1995-1999. Aviat. Space Environ Med, 73(11), 1117-1121. PMID: 12433238
[22] Mizyuk, B. M. (2009). *Основи стратегічного управління [Fundamentals of strategic management]*. Львів: Магнолія 2006 - Lviv: Mahnoliia 2006.
[23] Order of the Ministry of Defence Ukraine (2015). № 519/30.09.2015: Правила медичного забезпечення польотів державної авіації України [Rules of medical support of flights of the state aviation of Ukraine]. Київ, Україна: Міністерство оборони - Kyiv, Ukraine: Ministry of Defence.
[24] Order of the Ministry of Defence Ukraine (2017). № 602/20.11.2017: Положення про лікарсько-льотну експертизу в державній авіації України [Regulations on medical and flight examination in the state aviation of Ukraine]. Київ, Україна: Міністерство оборони - Kyiv, Ukraine: Ministry of Defence.
[25] Ponomarenko, V. A. (1997) Психофизиологические резервы профессионального здоровья человека [Psychophysiological reserves of human occupational health]. *Вестник Российской АМН - Vesnik Rosiyskoy AMN,* (4), 24-28.
[26] Pruneti, C. A. (2020). Aircraft Pilots and Psychophysical health and Safety. *Journal of Depression and Anxiety,* 9(1), 352. doi: 10.35248/2167-1044.20.9.352
[27] Stokes, A. F., & Kite, K. (2017). *Flight stress: Stress, fatigue and performance in aviation.* Routledge.
[28] Ushakov, I. B. (2004). Медико-биологические основы обеспечения безопасности человека в авиации [Biomedical fundamentals of ensuring human safety in aviation]. *Авиакосмическая и экологическая медицина - Aviakosmicheskaya i ekolohicheskaya meditsina,* 38(1), 28-35.
[29] Yena, A. I. (2001). Актуальні проблеми і організаційні засади психофізіологічного забезпечення Збройних Сил України [Actual problems and organizational principles of psychophysiological support of the Armed Forces of Ukraine]. *Військова медицина України - Viiskova medytsyna Ukrainy,* (1), 54-62.
[30] Yena, A. I. (2003). Методичні підходи до професійного психофізіологічного відбору як важливого чинника забезпечення ефективності професійної діяльності військовослужбовців [Methodical approaches to professional psychophysiological selection as an important factor in ensuring the effectiveness of professional activities of servicemen]. *Військова медицина України - Viiskova medytsyna Ukrainy*, (3-4), 27-37.
[31] Zheng, Y., Lu, Y., Jie ,Y., & Fu, S. (2017). Flight Crew Workload Evaluation Based on the Workload Function Distribution Method. *Aerospace Medicine and Human Performance,* 88(5), 481-486. doi: 10.3357/AMHP.4681.2017
[32] Zheng, Y., Lu, Y., Jie ,Y., & Fu, S. (2019). Predicting workload experienced in a flight test by measuring workload in a flight simulator. *Aerospace Medicine and Human Performance,* 90(7), 618-623. doi: 10.3357/amhp.5350.2019

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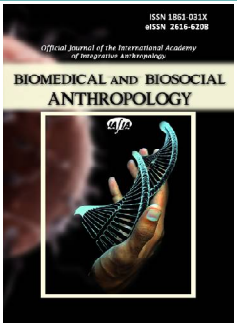

The prospects of finding new treatments for acne

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An important role in the development of acne is played by the activity of the skin microflora (namely the bacteria Propionibacterum acnes) and members of the genus Staphylococcus. In the schemes of complex treatment of patients with this disease, antibiotics from among macrolides or lincosamides are mainly used. It is of interest to study the current state of susceptibility of staphylococci and propionic bacteria to these drugs, as well as to other antimicrobial agents in order to determine the prospects for expanding the arsenal of methods for treating acne. The aim of the study was to study the susceptibility of microorganisms involved in the development of acne to antimicrobials and antagonistic effects of probiotic strains of lactobacilli. We conducted a bacteriological study of the content of rash elements in 60 patients with acne. The biological characteristics of 40 strains of Staphylococcus spp. and 15 strains of Propionibacterum acnes isolated and researched. The sensitivity of microorganisms to antibiotics and antiseptics was determined by the disco-diffusion method and the method of serial double dilutions of drugs in a liquid nutrient medium. Determination of the sensitivity of acne pathogens to the antagonistic effect of lactobacilli was performed by the method of two-layer agar by reducing the number of microorganisms. The results of the study made it possible to establish that the isolated strains of bacteria show a low level of sensitivity to antimicrobials, which in medical practice are most often used for topical therapy of acne. Only 17.5 % of isolated staphylococcal strains were sensitive to erythromycin, only 45.0 % of strains of this species were sensitive to clindamycin. Strains of Propionibacterum acnes showed a higher level of sensitivity to antibiotics than staphylococci. However, the established indicators do not allow to consider highly effective means for treatment of acne on their basis. At the same time, a high level of sensitivity of acne pathogens to antiseptic drugs decamethoxine and Aeroplysinin 1 and antagonistic effect of Lactobacillus acidophilus was established. Thus, the strains of Propionibacterum acnes and Staphylococcus spp., involved in the development of acne, are characterized by high levels of resistance to erythromycin, clindamycin, chloramphenicol, benzoyl peroxide, which are now the basis of the arsenal of topical therapy for patients with this disease. There is a need to find new effective drugs for the etiotropic therapy of acne.
Keywords: *skin microflora, acne, antibiotics, antiseptics.*

Introduction

In the context of the global spread of the phenomenon of polyresistance of microorganisms to antimicrobials, the urgency of finding treatments for diseases of microbial etiology is constantly growing. Despite the development of the latest medical technologies, the number of skin diseases of microbial origin is growing. One of the most common dermatoses that significantly impairs the quality of life of patients is acne. Acne (acne vulgaris, acne) affects more than 85 % of people aged 12 to 24 years, 8 % of people aged 25 to 34 years and 3 % of people aged 35 to 44 years. In 5-15 % of patients the disease has severe forms, which result in significant cosmetic defects in the form of hypo- and hypertrophic scars. Since acne is most often localized on exposed areas of the skin (face and upper torso), patients develop psycho-emotional disorders due to low self-esteem and peculiarities of perception in the social environment [3, 11, 21].

The pathogenesis of acne is complex and multifactorial, involving a number of exogenous and endogenous factors. The main pathogenetic factors that play an important role in the development of acne are follicular hyperkeratosis, microbial colonization of *Propionibacterium acnes*, sebum

hyperproduction and complex inflammatory mechanisms, including both innate and acquired immunity. It is believed that the starting point in the development of the disease is androgen-dependent hyperproduction of sebum with simultaneous acceleration of keratinization of the follicular epithelium, which create favorable conditions for the activation of autochthonous microflora. *Propionibacterium acnes* inhabit deep parts of follicles and closed comedones, hydrolyze sebum and block its protective function. Polymorphonuclear leukocytes, which absorb *Propionibacterium acnes*, release hydrolytic enzymes that destroy the epithelium, cause inflammatory processes, which destroy the structure of the dermis, and activate the complement system. Under these conditions, epidermal staphylococci, the products of which are a trigger of neutrophilic inflammation and the formation of pustules, are able to realize their pathogenic potential [2, 9, 16, 19]. The colonization density of *Propionibacterium acnes* skin changes with age, reaching a maximum in adolescence. The largest number of these bacteria is in seborrheic areas, as sebum is a nutrient medium for them. *Propionibacterium acnes* directly and indirectly involved in the occurrence of non-inflammatory (open, closed comedones) and inflammatory (papules, pustules, nodules) elements of the lesion. Bacteria secrete the exoenzyme lipase, which hydrolyzes sebum triglycerides to glycerol, and free fatty acids, which exhibit comedogenic properties [12, 20].

Given the important role of microorganisms in the etiopathogenesis of the disease, the main means of treating patients with mild acne and moderate disease are antimicrobial agents for topical use. In 2016, new guidelines for the treatment of acne patients were issued in Europe, America and Canada. For the treatment of acne requires an individual approach to the patient, taking into account the form and severity of the disease. Recommended methods must include topical therapy, antibiotics [1, 5, 15, 19]. Most commonly used dosage forms in which the main active ingredients are erythromycin, clindamycin, benzoyl peroxide, azelaic acid or combinations thereof. Sometimes used extemporaneously made forms according to ancient recipes using salicylic acid and chloramphenicol. In severe forms of the disease include systemic antibiotic therapy. Most often, the tetracycline antibiotic doxycycline is used for this purpose [6, 10, 17].

The effectiveness of such treatment regimens cannot be considered high, because the treatment is long-term and the appearance of patients' skin remains unattractive after treatment. At the current level of resistance of microorganisms to antibiotics, the low effectiveness of traditional acne treatment regimens may be due to this phenomenon. Data on the current state of susceptibility of microorganisms involved in the development of acne to antimicrobials are insufficient to make suggestions for the correction of treatment regimens. The sensitivity of acne pathogens to antiseptics from among the quaternary ammonium compounds, natural derivatives of bromothyrosine, remains unexplored. It is worth studying the prospects of using the antagonistic effect of probiotic strains of lactobacilli in the complex treatment of this disease.

The aim of the study was to study the sensitivity of microorganisms involved in the development of acne to antimicrobials and the antagonistic effect of probiotic strains of lactobacilli.

Materials and methods

The content of rash elements of 60 patients with papulopustular acne of moderate severity was studied by bacteriological method. The test material was plated on blood meat-peptone agar (MPA). GasPak EZ gas generating packages were used to create anaerobic conditions.

Identification of isolated microorganisms was performed taking into account morphological, tinctorial, cultural and biochemical properties. Biochemical properties of isolated staphylococcal strains were determined using test systems STAFItest 16.

The sensitivity of the isolated strains of microorganisms to oxacillin, cefazolin, ceftriaxone, chloramphenicol, doxycycline, cyprfloxacin, clindamycin was determined using the standard disco-diffusion method (DDM). Minimum bactericidal (MBC) concentrations of antibiotics most commonly used in the treatment of acne, antiseptic decamethoxine (1.10-decamethylene-bis-n, n-dimethylmen-tihoxycarbonylmethyl, ammonium dichloride) and 2-[(1S, 6R)3,5-Dibromo-1,6-dihydroxy-4-methoxycyclohexa-2,4-dien-1-yl] acetonitrile (Aeroplysinin 1) was determined by serial dilutions of antibiotics in a liquid nutrient medium [14].

The sensitivity of isolated strains of staphylococci and propionate bacteria to the antagonistic effect of culture of *Lactobacillus acidophilus* isolated from a serial sample of the drug Linex-forte (Sandos, Slovenia) was determined. Isolation of pure culture of lactobacilli was performed using a selective medium MRS-agar.

Determination of the level of antagonistic activity was performed by the method of two-layer agar. To do this, the suspension of the studied culture of lactobacilli in sterile isotonic sodium chloride solution based on the final concentration of 108 colony-forming units per 1 ml of nutrient medium (CFU/ml) was added to the molten meat-peptone agar and poured into Petri dishes. After cooling the agar, a second layer (10 ml) of molten agar was poured on its surface. In the lower layer, sown with lactobacilli, created optimal conditions for the cultivation of microaerophilic lactobacilli, eliminating the need to use anaerobic techniques. The plates were incubated for two hours at 37 °C.

Subsequently, a pure culture of bacteria isolated from acne patients (staphylococci or propiobacteria) was quantified on Gold cups prepared in this way. At the end of the daily incubation, the number of colonies grown on the

agar surface was counted. As a control, cups prepared in a similar manner, in the lower layer of the nutrient medium of which probiotic strains of microorganisms were not made. The antagonistic activity of the studied strains of lactobacilli was evaluated by the degree of reduction in the number of CFU of bacteria compared to the control.

Results

Gram-positive coccal microorganisms were isolated from 40 subjects (80.0 %) who tested positive. Of the isolated cocci, 87.5 % (35 strains) belonged to the species *S. epidermidis*. In one case, *S. aureus* was isolated, in two more - *S. hominis*, two strains of isolated coccal bacteria were assigned to the genus *Kocuria*. *Propionibacterum acnes* cultures were isolated in 15 patients (30.0 %). In particular, in 10.0 % of cases propiobacteria were sown in monoculture, and in other cases - in association with staphylococci. In 10 patients (16.7 %) from the material taken for bacteriological examination of microorganisms could not be isolated.

The level of sensitivity of the isolated strains of microorganisms to antibiotics, determined by the disco-diffusion method, is shown in Figure 1.

The data in Figure 1 show that the selected strains of bacteria showed low sensitivity to antibiotics, which are most often used in the topical therapy of acne patients in the form of soft or liquid dosage forms (clindamycin, erythromycin and chloramphenicol). At the same time propionobacteria show higher sensitivity, in comparison with staphylococci. Thus, about half of the isolated strains of propionobacteria were sensitive to erythromycin. Of the isolated strains of cocci, only 17.5 % were sensitive to this antibiotic. A relatively high level of sensitivity of isolated strains of propionate bacteria to chloramphenicol (80.0 %) was found, while in the coccal microflora this indicator was much lower (32.5 %). Only about half of the isolated strains of both types of bacteria were sensitive to clindamycin.

In severe forms of acne, doxycycline is used

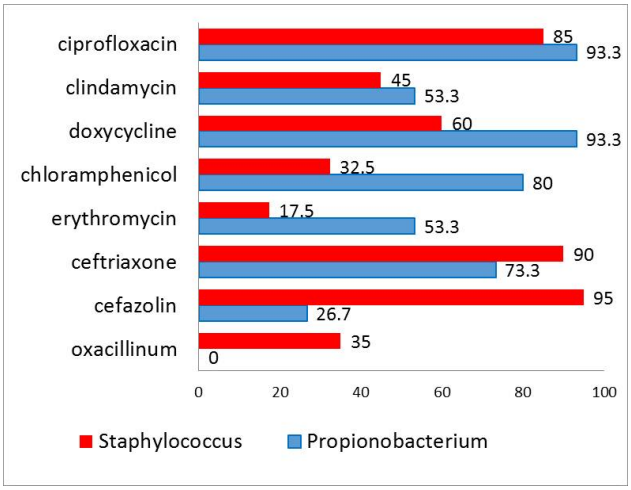

Fig.1. Sensitivity of isolated bacterial strains to antibiotics (% of susceptible strains).

Table 1. Sensitivity characteristics of selected strains of *Staphylococcus spp.* and *Propionibacterium spp.* to antibiotics and antiseptics.

Antimicrobial drug	Genus of microorganisms	
	Staphylococcus (n=40)	*Propionibacterium* (n=15)
	Minimum bactericidal concentration (M±m, μg/ml)	
Erythromycin	620.8±134.7	7.234±2.512
Clindamycin	504.7±122.5	39.28±9.61
Benzoyl peroxide	92.12±14.57	392.2±49.4
Salicylic acid	>1250	416.3±22.7
Aeroplysinin 1	24.53±3.21	12.45±1.72
Decamethoxine	2.928±0.718	1.475±0.431

systemically. According to our data, propionates have a high level of sensitivity to it (93.3 %). However, staphylococci, which support the inflammatory response in the lesions, are characterized by a much lower rate (60.0 %) of sensitivity to this antibiotic.

High levels of sensitivity of isolated strains of staphylococci were detected in relation to cephalosporins of I and III generations (95.0 % and 90.0 %, respectively). However, these antibiotics are used only systemically. The high level of sensitivity of the isolated strains of both types of bacteria to ciprofloxacin allows to predict the appropriate therapeutic efficacy in acne topical application of this drug, however, dosage forms based on it for the treatment of acne have not been developed to date.

The results of quantitative determination of the level of sensitivity of isolated strains of staphylococci and propionate bacteria to erythromycin, clindamycin, antiseptics benzoyl peroxide, salicylic acid, decamethoxine and the natural derivative of bromothyrosine Aeroplysinin 1 are summarized in Table 1.

The mean MBC values of erythromycin and clindamycin for staphylococci shown in Table 1 are not an objective reflection of the level of susceptibility of this genus, as for susceptible strains MBC ranged from 4-32 μg/ml. However, such strains were a significant minority. Stable strains of staphylococci remained viable in the presence of 4000 μg/ml antibiotics.

Against the background of the above average, a significantly higher level of vulnerability of propionate bacteria to the studied antibiotics is obvious, compared to staphylococci. After all, the MBC of ethithromycin and clindamycin for propionibacterium is 7.234 μg/ml and 39.28 μg/ml, respectively.

In contrast, an antiseptic with a peroxide mechanism of bactericidal action of benzoyl peroxide was more active against selected strains of staphylococci (MBC=92.12 μg/ml). However, the isolated strains of propionate bacteria were less sensitive to this drug (MBC=392.2 μg/ml).

Salicylic acid is part of anti-acne drugs, taking into account, mainly, its keratolytic effect. However, it is believed that this compound has an antiseptic effect. Listed in Table 1 average

Table 2. Quantitative characteristics of the growth inhibition of acne pathogens in the presence of lactobacilli.

Culture of microorganisms	Cultivation conditions	
	ordinary (control)	in the presence of *Lactobacillus acidophilus*
	quantitative characteristics (CFU/ml, M±m)	
Propionibacterium acnes	10^8±1.5x10^3	10^2±18.7
Staphylococcus spp.	10^8±2.3x10^3	10^5±3.7x10^2

MBC of salicylic acid for acne pathogens indicates a slight antimicrobial effect. Thus, staphylococci were insensitive to salicylic acid at the maximum concentration studied (1250 μg/ml). Propionate bacteria died in the presence of at least 400 μg/ml of this drug.

Aeroplysinin 1 was the first natural bromothyrosine isolated from the sponge *Aplysina aerophoba*. Since then, its antiviral, antibacterial, anti-inflammatory, antiangiogenic, action has been detected [4, 7, 8]. Due to a wide range of biological action, Aeroplysinin 1 is called a multitarget (multi-purpose) biologically active compound, aspects of medical use of which require detailed research [8]. The antimicrobial activity of this compound against pathogens of acne remained unexplored. We determined that *Propionibacterium* acnes and *Staphylococcus spp.* show a fairly high level of sensitivity to Aeroplysinin 1, the MBC of which for them is 12.45±1.72 μg/ml and 24.53±3.21 μg/ml, respectively.

Domestic antiseptic decamethoxine belongs to the quaternary ammonium compounds. The drug has a high level of antimicrobial activity, so it is widely used in purulent surgery, pulmonology, gynecology, ophthalmology and others. In terms of antimicrobial activity, decamethoxine has significant advantages over antibiotics and other domestic and foreign antiseptics of the same chemical series (benzalkonium chloride, cetylpyridinium chloride, miramistin). Thus, according to various authors, the MBC of decamethoxine for *Staphylococcus aureus* ranges from 1.5 μg/ml to 3.5 μg/ml, and for epidermal staphylococci is even lower [18, 22].

We determined that the average MBC of decamethoxine for isolated strains of staphylococci involved in the acne development was 2.928±0.718 μg/ml. All isolated strains of propionate bacteria also showed a high level of sensitivity to decamethoxine (MBC=1.475±0.431 μg/ml). These results suggest that decamethoxine may be an effective component of complex means of topical acne therapy.

Recent studies have shown that probiotic strains of lactobacilli are able to inhibit the biological activity of staphylococci isolated from the purulent elements of *acne vulgaris* [13]. We studied the sensitivity of isolated strains of staphylococci and propionates to the antagonistic effect of culture of *Lactobacillus acidophilus*, isolated from a serial sample of the drug Linex Forte (Sandos, Slovenia). Evaluation of antagonistic activity was performed on the growth rate of the tested strain of opportunistic bacteria on a normal nutrient medium and in the presence of lactobacilli in a two-layer medium. The results are illustrated in Table 2.

The results shown in table 2 indicate a high level of sensitivity of bacteria of etiological importance in the development of acne to the antagonistic effect of the probiotic strain of lactobacilli.

The number of colony-forming units of staphylococci on bilayer plates inoculated with lactobacilli was approximately 103 times less than in the control. The population of *Propionibacterium* acnes decreased in the presence of lactobacilli by 106 times. Obviously, it is worth exploring the possibility of using probiotic drugs in the acne complex treatment.

Discussion

Summarizing the above, it should be noted that the results of our bacteriological studies of the content of acne rash elements confirm the etiological role of *Propionibacterium* acnes and *Staphylococcus spp.* in the development of this disease. General threatening trends in the spread of the phenomenon of resistance of microorganisms to antimicrobials extend to the pathogens of acne. The level of resistance of bacteria involved in the acne development to the most commonly used in the acne treatment antimicrobials is quite high and can have a negative impact on the effectiveness of treatment of patients. Less than half of the isolated strains of staphylococci were sensitive to erythromycin, chloramphenicol, clindamycin. It is known that the activity of this type of bacteria contributes to the chronicity of pathological changes in the skin and the development of complicated forms of acne.

Of the two members of the microbial association involved in the acne development, propionate bacteria are more sensitive to the effects of antimicrobial drugs. However, draw attention to the opposites in the sensitivity of associates to different drugs: if strains of *Propionibacterium* acnes show high sensitivity to erythromycin, clindamycin and low sensitivity to benzoyl peroxide, staphylococci, by contrast, are resistant to these antibiotics and relatively sensitive. In the real existence of the microbial association in the lesion, such a phenomenon can increase the ability of microorganisms to survive and in the process of antimicrobial therapy to reduce its effectiveness. As a result, among the acne treatment, the advantage should obviously belong to the dosage forms of the combined multicomponent composition.

Given the long duration of the period when topical acne therapy is mainly drugs from the above list, and microorganisms accelerate the spread of mechanisms of resistance to antimicrobials, there is a need to study the effectiveness and implementation of new highly effective antimicrobials. The results of the study of the sensitivity of acne pathogens to the antimicrobial drugs decamethoxine and Aeroplysinin 1 in vitro indicate the prospects of creating

on their basis means of topical acne therapy. A high level of sensitivity of *Propionibacterium* acnes and *Staphylococcus spp.* to the antagonistic effect of *Lactobacillus acidophilus* opens the possibility of topical use of probiotics in the treatment of *acne vulgaris*.

Conclusions

1. Strains of *Propionibacterium* acnes and *Staphylococcus spp.*, which are currently involved in the development of acne, are characterized by a high level of resistance to erythromycin, clindamycin, chloramphenicol, benzoyl peroxide and other antimicrobials, which are currently used in the main list of anti-acne drugs as active substances.

2. The antimicrobial component of acne treatment regimens needs to be replenished with modern antimicrobials, to which propionibacterium and staphylococci remain highly sensitive.

3. It should be considered promising to upgrade the arsenal of topical acne therapy with drugs based on the quaternary ammonium compound decamethoxine, a derivative of bromothyrosine Aeroplysinin 1 and probiotic drugs containing lactobacilli strains with high antagonistic activity.

References

[1] Araviyskaya, E. R., & Sokolovsky, E. V. (2013). Системная антибиотикотерапия акне: некоторые дискуссионные вопросы [Systemic antibiotic therapy for acne: some controversial issues]. *Вестник дерматологии и венерологии - Vestnik dermatologii i venereologii,* 6 (90), 117-121.

[2] Bagmet, A. N., & Shapovalova, O. V. (2003). Коррекция нарушений микробиоценоза кожи при легкой форме угревой болезни [Correction of skin microbiocenosis disorders in mild acne]. *Дерматологія та венерологія - Dermatology and venereology*, 1(8), 44-46.

[3] Bhate, K., & Williams, H. C. (2013). Epidemiology of acne vulgaris. British Journal of Dermatoljgy, 3(168), 474-485. doi: 10.1111/bjd.12149

[4] Binnewerg, B., Schubert, M., Voronkina, A., Muzychka, L., Wysokowski, M., Petrenko, I., & Ehrlich, H. (2020). Marine biomaterials: Biomimetic and pharmacological potential of cultivated Aplysina aerophoba marine demosponge. *Material Science and Engineering: C*, (109), 110566. Access mode: doi :10.1016/j.msec.2019.110566

[5] Butareva, M. M., Znamenskaya, L. F., Kappusheva, I. A., Spiridonova, E. V., & Egorova, Yu. Yu. (2011). Принципы комбинированной терапии акне [Principles of combination therapy for acne]. *Вестник дерматологии и венерологии - Vestnik dermatologii i venereologii,* 6(87), 3-17.

[6] Del Rosso, J. Q., Thiboutot, D., Gallo, R., Webster G., Tanghetti, E., Eichenfield, L. F., … & Zaenglein A. (2013). Consensus recommendations from the American Acne & Rosacea Society on the management of rosacea, part 2: a status report on topical agents. *Cutis,* 92, 277-284. PMID: 24416742

[7] Fattorusso, E., & Minale, L. S. G. (1972). Aeroplysinin-1, an antibacterial bromo-compound from the sponge Verongia aerophoba. *Jornal of Chemical Society*, (1), 16-18. doi: 10.1039/p19720000016

[8] Garcia-Vilas, J. A., Martinez-Poveda, B., Quesada, A. R., & Medina, M. A. (2015). Aeroplysinin-1, a Sponge-Derived Multi-Targeted Bioactive Marine Drug. *Marine Drugs,* 14(1), 1. doi: 10.3390/md14010001

[9] Gollnick, H. P. (2015). From new findings in acne pathogenesis to new approaches in treatment. *Journal of the European Academy of Dermatology and Venereology*,5(29), 1-7. doi: 10.1111/jdv.13186

[10] Hoover, W. D., Davis, S. A., Fleischer, A. B., & Feldman, S. R. (2014). Topical antibiotic monotherapy prescribing practices in acne vulgaris. *Journal of Dermatological Treatment*, 2(25), 97-99. doi: 10.3109/09546634.2013.852297

[11] Kalyuzhna, L. D., & Petrenko, A. V. (2014). Тяжкі форми акне: можливості лікування [Severe forms of acne: treatment options]. *Український медичний часопис - Ukrainian Medical Journal,* 6(104), 1-3.

[12] Kutasevich, Ya. F., Mashtakova, I. A., Bagmet, A. N., & Shapovalova, O. V. (2003). Микробиоценоз кожи у больных угревой болезнью и пути его коррекции [Skin microbiocenosis in patients with acne and ways of its correction]. *Дерматологія та венерологія - Dermatology and venereology,* 1(8), 43-47.

[13] Lavryk, G. S, & Korniychuk, O. P. (2020). Антимікробна активність лактобацил відносно стафілококів, виділених з біоплівок хворих acne vulgaris [Antimicrobial activity of lactobacilli against staphylococci isolated from biofilms of patients with acne vulgaris]. *Мікробіологія і біотехнологія - Microbiology and biotechnology*, 1(48), 69-79. doi: 10.18524/2307-4663.2020.1(48).200905

[14] Methodical instructions MB 9.9.5-143-2007 (2007). *Визначення чутливості мікроорганізмів до антибактеріальних препаратів [Determination of sensitivity of microorganisms to antibacterial drugs].* Київ - Kyiv.

[15] Monakhov, S. A. (2016). Рациональная терапия акне [Rational therapy of acne]. *Український журнал дерматології, венерології, косметології - Ukrainian Journal of Dermatology, Venereology, Cosmetology*, 4(63), 70-78.

[16] Murillo N., & Raoult, D. (2013). Skin microbiota: overview and role in the skin diseases acne vulgaris and rosacea. *Futur Microbiology,* 2(8), 209-222. doi: 10.2217/fmb.12.141

[17] Naumova, L. O, & Sulik, Ya. O. (2016). Диференційована терапія вугрової хвороби у жінок молодого і зрілого віку з урахуванням гормональних порушень [Differentiated therapy of acne in young and mature women, taking into account hormonal disorders]. *Український журнал дерматології, венерології, косметології - Ukrainian Journal of Dermatology, Venereology, Cosmetology,* 11(60), 17-25.

[18] Paliy, G. K, Pavlyuk, S. V, Dudar, A. A, Paliy, D. V, & Kulyk, A. V. (2018). Характеристика резистентності мікроорганізмів до антимікробних препаратів [Characteristics of resistance of microorganisms to antimicrobial drugs]. *Вісник Вінницького національного медичного університету - Reports of Vinnytsia National Medical University*, 3(22), 417-421. doi: 10.31393/reports-vnmedical-2018-22(3)-04

[19] Savoskina, V. O. (2019). Акне. Новые возможности лечения (в соответствии с европейскими и американскими руководствами 2016 г. по лечению акне) [Acne. New treatment options (in line with the 2016 European and American guidelines for acne treatment)]. *Український журнал дерматології, венерології, косметології - Ukrainian Journal of Dermatology, Venereology, Cosmetology,* 4(75), 55-64. doi: 10.30978/UJDVK2019-4-55

[20] Svirid-Dzyadykevych, O. S. (2016). Вугрова хвороба: су-

часні погляди на патогенез і лікування та визначення перспективних напрямів підвищення ефективності терапії [Acne: modern views on the pathogenesis and treatment and identification of promising areas for improving the effectiveness of therapy]. *Український журнал дерматології, венерології, косметології - Ukrainian Journal of Dermatology, Venereology, Cosmetology,* 4(63), 41-49.

[21] Yaakubi Randa. (2017). Особливості мікробного пейзажу шкіри у хворих на вугрову хворобу [Peculiarities of microbial skin landscape in patients with acne]. *Дерматологія та венерологія - Dermatology and venerology*, 1(75), 30-33.

[22] Yurchyshyn, O. I. (2016) Вивчення протимікробної дії антисептиків відносно стафілококів - збудників піодермій з різними механізмами MLS-резистентності [Study of the antimicrobial effect of antiseptics on Staphylococci - causes of pyodermia with different mechanisms of MLS-resistance]. *Буковинський медичний вісник - Bukovinian Medical Herald,* 3(79), 197-201.

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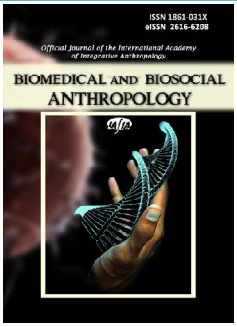

Skinfold thickness in men with mild and severe psoriasis without and taking into account the somatotype

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Significant prevalence and decline in quality of life caused by psoriasis in combination with the lack of etiotropic methods of its treatment, put this disease, in terms of relevance for modern medicine on a par with diabetes, hypertension, asthma etc. That is, there is a need to find easily accessible markers that would determine the susceptibility to this disease. The aim of the study was to establish the differences in the skinfold thickness between healthy and/or psoriatic Ukrainian men depending on the severity of the disease without and taking into account the somatotype. For 32 Ukrainian men of the first mature age, patients with mild psoriasis and 68 men with severe psoriasis (according to the PASI index) were determined skinfold thickness according to Bunak and determined the somatotype according to the Heath-Carter scheme. The control group consisted of 82 healthy men of similar age, selected from the database of the research center of National Pirogov Memorial Medical University, Vinnytsya. Statistical data processing was performed in the license package "Statistica 5.5" using non-parametric methods of evaluation of the obtained results. It was found that in patients with mild or severe psoriasis of men without division into somatotypes and in representatives of the mesomorphic somatotype compared to healthy men, the skinfold thickness is significantly higher at the lower angle of the scapula, abdomen and side, and significantly lower on the back and front of the shoulder, chest and thighs. When comparing the skinfold thickness between patients with mild or severe psoriasis of endo-mesomorphic somatotype with healthy men of similar somatotype, we found larger values of the skinfold thickness under the lower angle of the scapula (only with mild course), on the abdomen and side, and also smaller values of the skinfold thickness on the posterior surface of the shoulder and only in representatives with severe psoriasis - on the anterior surface of the shoulder, chest and thigh. Between patients with different degrees of severity of dermatosis both without distribution, and with distribution on various somatotypes of reliable or tendencies of differences of skinfold thickness are not revealed. Thus, there are pronounced differences in most indicators of the skinfold thickness between healthy and patients with mild or severe psoriasis of Ukrainian men of the first mature age, both without distribution and with the division into different somatotypes.

Keywords: *psoriasis, skinfold thickness, somatotype, men.*

Introduction

Psoriasis is a chronic immune-mediated inflammatory skin disease that has a chronic recurrent course that significantly affects the quality of life of patients. According to research, the leading triggers of the disease are stress (48.3 %), insolation (24.9 %) and infectious diseases (9.1 %) [18].

The prevalence of the disease is heterogeneous, but there is a peculiar trend when it is more prevalent in high-income countries. Thus, in the United Kingdom the prevalence is 2.2 %, in Norway 4.5 %, in the United States 2.2 %-3.15 %, and in Africa, Asia and Latin America the average is 0.5 % [18, 20]. In Israel, the average incidence rate is 2.69 % [24].

In the United States as of 2010, 7.2 million people suffered from psoriasis, and in 2013 this figure was already 7.4 million people. Although in general the authors of the study claim that since the early 2000s the number of patients with psoriasis in the country has stabilized [21].

In addition, it is known that psoriasis is often associated with various diseases of other body systems. Psoriatic arthritis occurs in 86 % of patients. Cardiovascular diseases, diabetes mellitus, sometimes rheumatoid arthritis, Crohn's disease, multiple sclerosis, etc. are often associated [2]. It should be noted that the complication of the cardiovascular system on the background of psoriasis is the most common cause of death in this group of patients, especially when it comes to psoriatic arthritis. According to the literature, the probability of death from the cardiovascular system in such patients increases by 50 % [4].

It is known that psoriasis is a multifactorial disease, ie it occurs both under the influence of genetic factors and environmental factors. Scientists are already well aware of which genes are associated with psoriasis (for example, the best known association with the HLA-Cw6 allele) [12]. Direct gene research is a complex and costly process. However, it can be successfully replaced by anthropometric research due to the fact that genes that encode certain phenotypic traits can be linked to certain genes associated with disease. This statement has been repeatedly proven in practice by various studies, in particular, for skin diseases [17].

One of the potential anthropometric indicators that can be successfully used for this purpose is the skinfold thickness. A group of researchers found that there is a correlation between the skinfold thickness on the leg and the risk of head and neck cancer [1].

M. R. Esco and co-authors [8] in the study found a relationship between heart rate variability, heart rate recovery and total skinfold thickness on the abdomen, chest and thighs ($p<0.01$).

Indicators of the skinfold thickness of the epigastric can be used to predict the occurrence of depression in the elderly [13].

In a study of 451 Hawaiians, a group of authors found that higher rates of skinfold thickness in the triceps were associated with a higher risk of Parkinson's disease. Similar results were achieved by a group of Swedish authors who found a correlation between the total skinfold thickness and the risk of Parkinson's disease [26].

The study of cardiovascular parameters and anthropometric parameters in groups of 100 people revealed a correlation between the rate of arterial stiffness and the skinfold thickness in the triceps ($r=0.377$, $p<0.001$), which was seen when performing regression analysis (arterial stiffness indicator = 6.41 + 0.072 x TST; $R^2=0.142$, $F_{(1-98)}=16.23$, $p<0.001$) [23].

J. Surendar and co-authors [25] in 2016 found an association between the total skinfold thickness, the peripheral skinfold thickness and the risk of diabetes.

Regarding the study of the skinfold thickness in people with psoriasis, the analysis of English-language scientometric databases revealed only one work in 1992 [22], where the author studied this indicator only among people with psoriasis of four "skin types". Thus, there is a need to conduct this study with the participation of both patients and healthy individuals and a modern assessment of the severity of psoriasis.

The aim of the study was to establish the differences in the skinfold thickness between healthy and/or psoriatic Ukrainian men depending on the severity of the disease without and taking into account the somatotype.

Materials and methods

The skinfold thickness (mm) was determined according to the scheme of Bunak V. V. [5] for 32 Ukrainian men of the first mature age (22-35 years) with mild psoriasis and 68 men with severe psoriasis. The Bioethics Committee of the National Pirogov Memorial Medical University, Vinnytsya (Minutes № 2 of 02.20.2020) found that the studies did not contradict the basic bioethical norms of the Declaration of Helsinki, the Council of Europe Convention on Human Rights and Biomedicine (1977), WHO regulations and Ukrainian laws.

Assessment of the severity and area of psoriatic lesions was performed using the total PASI index (Psoriasis Area and Severity Index) [9], according to which: mild severity - PASI value <10; moderate severity - PASI values from 10 to 20; severe - PASI value >20 [3].

The control group consisted of 82 healthy men of similar age group, whose anthropometric data were taken from the database of the research center National Pirogov Memorial Medical University, Vinnytsya.

Somatotype assessment was performed according to the Heath-Carter scheme [6]. The following distribution of somatotypes among men with mild and severe psoriasis was established: mesomorphs - 28 (87.5 %) and 55 (80.9 %), respectively; ectomorphs - 0 (0 %) and 2 (2.9 %), respectively; ecto-mesomorphs - 0 (0 %) and 2 (2.9 %), respectively; endomesomorphs - 4 (12.5 %) and 9 (13.2 %), respectively. Among healthy men, the distribution of somatotypes is as follows: endomorphs - 2 (2.4 %); mesomorphs - 39 (47.6 %); ectomorphs - 9 (11.0 %); ecto-mesomorphs - 13 (15.9 %); endomesomorphs - 13 (15.9 %); representatives of the middle intermediate somatotype - 6 (7.3 %).

Statistical processing of the obtained results was performed in the license package "Statistica 5.5" using non-parametric evaluation methods. The significance of the difference in values was determined using the Mann-Whitney U-test.

Results

When comparing the skinfold thickness between healthy and psoriatic men of mild and severe course without taking into account the somatotype, it was found (Table 1) significantly higher ($p<0.01$-0.001) values in healthy men of the skinfold thickness on the back and front of the shoulder, on chest and thighs; and significantly lower ($p<0.05$-0.001) values in healthy men of the skinfold

thickness under the lower angle of the scapula, abdomen and side. There were no significant or tendencies of differences in the skinfold thickness between men with mild and severe psoriasis without taking into account the somatotype (see Table 1).

Both between healthy and patients with mild psoriasis of mesomorphic and endomesomorphic somatotypes, significantly higher values of the skinfold thickness (p<0.01-0.001) were found in representatives of endomesomorphic somatotype (Table 2). Between healthy and patients with mild psoriasis of the mesomorphic somatotype, the picture of differences in the skinfold thickness is completely similar to the established differences without division into somatotypes (see Table 1, Table 2). Between healthy and mild psoriasis men of endo-mesomorphic somatotype, the picture of differences in the skinfold thickness is slightly different: in contrast to the established differences without division into somatotypes, there are no significant differences in the skinfold thickness on the front surface of the shoulder, chest and thighs (see Table 1, Table 2).

When comparing the skinfold thickness between patients with severe psoriasis course men of mesomorphic and endomesomorphic somatotypes, in latter found significantly higher values (p<0.05-0.01) of the skinfold thickness only on the back of the shoulder, forearm, abdomen, side and on the thigh (Table 3). Between healthy and severe psoriasis men of mesomorphic somatotype, the pattern of differences in the skinfold thickness is almost similar to the established differences in men without division into somatotypes (see Table 1) and between healthy and mild course of psoriasis mesomorphic men (see Table 2). Between healthy and severe course of psoriasis men of endo-mesomorphic somatotype, the picture of differences in the skinfold thickness differs from the established differences without division into somatotypes only in the absence of differences in the skinfold thickness at the lower angle of the scapula (see Table 3).

It should be noted that between patients with mild and severe psoriasis course in men of mesomorphic or endomesomorphic somatotypes, as well as without taking into account the somatotype, there are no significant or trends in differences in the skinfold thickness.

Table 1. Comparison of the skinfold thickness between healthy and psoriatic men without somatotype (M±σ).

Indicators	Healthy	Patients with psoriasis		$p_{h\text{-}mc}$	$p_{h\text{-}sc}$	$p_{mc\text{-}sc}$
		MC	SC			
GZPL	7.848± 2.914	4.938± 1.933	5.059± 1.819	**<0.001**	**<0.001**	>0.05
GPPL	5.592± 2.132	3.875± 1.792	3.868± 1.656	**<0.001**	**<0.001**	>0.05
GPR	4.173± 1.621	4.281± 1.727	4.177± 1.360	>0.05	>0.05	>0.05
GL	13.53± 3.92	17.31± 7.44	16.12± 6.63	**<0.01**	**<0.05**	>0.05
GGR	4.924± 1.729	3.938± 1.501	4.059± 1.761	**<0.01**	**<0.001**	>0.05
GG	12.33± 4.79	17.97± 8.68	17.63± 7.79	**<0.001**	**<0.001**	>0.05
GB	10.75± 4.41	20.28± 7.87	18.47± 7.17	**<0.001**	**<0.001**	>0.05
GBD	12.80± 3.85	8.906± 3.439	8.868± 3.425	**<0.001**	**<0.001**	>0.05
GGL	8.982± 2.691	10.25± 3.98	9.441± 3.431	>0.05	>0.05	>0.05

Notes: here and in the following tables, GZPL - the skinfold thickness on the back of the shoulder; GPPL - on the front surface of the shoulder; GPR - on the forearm; GL - under the lower angle of the scapula; GGR - on the chest; GG - on the abdomen; GB - on the side; GBD - on the thigh; GGL - on the shin; MC - mild course; SC - severe course; $p_{h\text{-}mc}$ - the reliability of the difference between the relevant indicators between healthy and patients with mild psoriasis; $p_{h\text{-}sc}$ - between healthy and patients with severe psoriasis; $p_{mc\text{-}sc}$ - between patients with mild and severe psoriasis.

Discussion

It is known from scientific literature sources that in various pathological processes the rate of genotype reaction clearly defines the limits of clinical variability and pathomorphosis of human diseases. At the phenotypic level, this reaction rate is registered by the macromorphological subsystem of the general constitution, namely its morphophenotype (somatic type, somatotype, body type) [19]. Therefore, the identification of phenotypic traits that are in close causal relationships with different links in the pathogenesis of multifactorial diseases is essential to justify the influence of hereditary or environmental factors on the predisposition or resistance of the population to psoriasis.

During the analysis of the skinfold thickness, in patients with mild or severe psoriasis men without division into somatotypes or representatives of the mesomorphic somatotype compared with healthy men of similar groups, we found: higher values of skinfold thickness - under the lower angle of the scapula, respectively by 27.9 % and 19.1 % and by 15.7 % and 23.5 %, on the abdomen respectively by 45.7 % and 43.0 % and by 30.3 % and 44.6 %, as well as on the side respectively by 88.7 % and 71.8 % and by 88.9 % and 86.7 %; lower values of skinfold thickness - on the back of the shoulder respectively by 37.1 % and 35.5 % and by 37.2 % and 30.7 %, on the front surface of the shoulder, respectively by 30.7 % and 30.8 % and by 31.3 % and 23.2 %, on the chest respectively by 20.0 % and 17.6 % and by 20.1 % and 8.2 %, as well as on the thigh, respectively by 30.4 % and 30.7 % and by 33.7 % and 29.6 %.

During the analysis of the skinfold thickness, in patients with mild or severe psoriasis course men of endo-mesomorphic somatotype compared with healthy men of similar somatotype, we found: higher values of skinfold thickness - under the lower angle of the scapula by 91.6 % (only with a mild course), on the abdomen respectively by

Table 2. Comparison of the skinfold thickness between healthy and patients with mild psoriasis men of mesomorphic and endomesomorphic somatotypes (M±σ).

Indicators	Healthy		p	MC of psoriasis		p	$p_{h/m\text{-}mc/m}$	$p_{h/em\text{-}mc/em}$
	mes.	en-mes.		mes.	en-mes.			
GZPL	7.108±2.344	11.09±2.18	**<0.001**	4.464±1.527	8.250±0.957	**<0.01**	**<0.001**	<0.05
GPPL	5.044±1.493	7.831±2.106	**<0.001**	3.464±1.427	6.750±1.500	**<0.01**	**<0.001**	>0.05
GPR	3.713±1.295	5.646±1.760	**<0.01**	3.893±1.423	7.000±1.155	**<0.01**	**>0.05**	>0.05
GL	13.09±3.51	16.96±3.02	**<0.01**	15.14±3.94	32.50±9.00	**<0.01**	**<0.05**	**<0.01**
GGR	4.515±1.147	6.254±1.926	**<0.01**	3.607±1.133	6.250±1.893	**<0.01**	**<0.01**	**>0.05**
GG	11.79±4.64	16.84±3.35	**<0.001**	15.36±4.25	36.25±10.31	**<0.01**	**<0.01**	**<0.01**
GB	9.721±3.502	15.72±3.58	**<0.001**	18.36±5.91	33.75±7.09	**<0.01**	**<0.001**	**<0.01**
GBD	12.22±3.50	16.05±3.99	**<0.01**	8.107±2.485	14.50±4.36	**<0.01**	**<0.001**	>0.05
GGL	8.741±2.720	11.50±2.32	**<0.001**	9.250±2.238	17.25±6.65	**<0.01**	>0.05	>0.05

Notes: here and the following tables, p is the significance of the difference between the corresponding indicators between the representatives of mesomorphic and endomesomorphic somatotypes; $p_{h/m\text{-}mc/m}$ - between healthy and patients with mild psoriasis and mesomorphic somatotype; $p_{h/em\text{-}mc/em}$ - between healthy and psoriasis patients with mild endomesomorphic somatotype.

Table 3. Comparison of the skinfold thickness between healthy and patients with severe psoriasis of mesomorphic and endomesomorphic somatotypes (M±σ).

Indicators	Healthy		p	MC of psoriasis		p	$p_{h/m\text{-}mc/m}$	$p_{h/em\text{-}mc/em}$
	mes.	en-mes.		mes.	en-mes.			
GZPL	7.108±2.344	11.09±2.18	**<0.001**	4.927±1.709	6.667±1.732	**<0.01**	**<0.001**	**<0.001**
GPPL	5.044±1.493	7.831±2.106	**<0.001**	3.873±1.504	4.778±2.108	>0.05	**<0.001**	**<0.01**
GPR	3.713±1.295	5.646±1.760	**<0.01**	4.073±1.120	5.667±1.581	**<0.01**	>0.05	>0.05
GL	13.09±3.51	16.96±3.02	**<0.01**	16.16±4.45	19.89±13.23	>0.05	**<0.001**	>0.05
GGR	4.515±1.147	6.254±1.926	**<0.01**	4.146±1.693	4.000±2.449	>0.05	=0.065	**<0.05**
GG	11.79±4.64	16.84±3.35	**<0.001**	17.05±5.83	26.11±11.50	**<0.05**	**<0.001**	**<0.05**
GB	9.721±3.502	15.72±3.58	**<0.001**	18.15±5.83	25.44±9.00	**<0.01**	**<0.001**	**<0.01**
GBD	12.22±3.50	16.05±3.99	**<0.01**	8.600±3.083	12.22±3.56	**<0.01**	**<0.001**	**<0.05**
GGL	8.741±2.720	11.50±2.32	**<0.001**	9.273±2.453	12.33±6.22	>0.05	>0.05	>0.05

Notes: $p_{h/m\text{-}sc/m}$ - between healthy and men with severe psoriasis and mesomorphic somatotype; $p_{h/em\text{-}sc/em}$ - between healthy and patients with severe psoriasis of endo-mesomorphic somatotype.

115.5 % and 55.0 % and on the side respectively by 114.7 % and 61.8 %; lower values of skinfold thickness - on the back of the shoulder respectively by 34.4 % and 66.3 %, on the front surface of the shoulder by 63.9 % (only with severe course), on the chest by 56.4 % (only with severe course) and on the thigh by 31.3 % (only with severe course).

S. V. Dmytrenko [7] in 2005-2006 in patients with limited psoriasis in men found significantly greater values of most skinfold thickness of the upper extremity and torso, as well as significantly greater values of the skinfold thickness in patients with advanced psoriasis men than in healthy men of the same age and place of residence (residents of the Podillia region of Ukraine).

In addition, the results of work on the study of the prevalence of somatotype and features of anthropometric parameters in patients with other skin diseases are widely presented. Thus, I. M. Makarchuk [14, 15] in 2014 examined 84 boys and 116 girls with acne and 150 healthy boys and 160 healthy girls (control group) in order to identify differences in transverse body sizes between the studied groups of persons, taking into account and without taking into account somatotype. Statistical processing of the obtained data showed that individuals with mesomorphic somatotype have the least pronounced homogeneity in anthropometric indicators.

In the works of I. V. Gunas and co-authors [10, 11] the peculiarities of somatotype distribution for both healthy and acne patients, residents of the Podillia region of Ukraine were found, namely - among boys suffering from acne there are more persons of mesomorphic and endomesomorphic somatotype, and among girls - mesomorphic somatotype.

The data identified during the study logically complement and agree with the findings of our previous work and the work of other teams of authors, thus increasing the effectiveness of future use of anthropometric indicators

to identify risk groups for psoriasis and its severity. This in turn will allow doctors to respond in a timely manner and modify the patient's lifestyle and improve his quality of life.

Conclusions

1. In men with mild and severe psoriasis course without division into somatotypes, as well as in patients of different disease course of mesomorphic somatotype, the skinfold thickness on the back and front of the shoulder, chest and thigh is smaller (p<0.01-0.001), and under lower angle of the scapula, on the abdomen and on the side - larger (p<0.05-0.001), compared with healthy men. In contrast to the established differences in skinfold thickness, in men of endomesomorphic somatotype patients with mild psoriasis course there are no significant differences in the skinfold thickness on the front surface of the shoulder, chest and thigh; and in representatives of severe psoriasis - only the skinfold thickness under the lower angle of the scapula.

2. The skinfold thickness is greater in men of endomesomorphic somatotype than in representatives of the mesomorphic somatotype when comparing healthy (p<0.01-0.001) or patients with mild course of psoriasis (p<0.01) men. In patients with severe course of psoriasis men of endomesomorphic somatotype, higher values (p<0.05-0.01) of the skinfold thickness were found only on the posterior surface of the shoulder, forearm, abdomen, side and thigh than in representatives of the mesomorphic somatotype.

3. There are no significant or trends in differences in the skinfold thickness between sick men with mild and severe psoriasis, both without and with somatotype.

References

[1] Achal, K. S., Farrell, C., Smith, A. B., Mucke, T., Mitchell, D. A., & Kanatas, A. N. (2011). Anterolateral thigh skinfold thickness and the European head and neck cancer patient: a prospective study. *Journal of Cranio-Maxillofacial Surgery*, 39(2), 111-112. doi: 10.1016/j.jcms.2010.05.007

[2] Armstrong, A. W., Schupp, C., & Bebo, B. (2012). Psoriasis comorbidities: results from the National Psoriasis Foundation surveys 2003 to 2011. *Dermatology,* 225(2), 121-126. doi: 10.1159/000342180

[3] Augustin, M., Kruger, K., Radtke, M. A., Schwippl, I., & Reich, K. (2008). Disease severity, quality of life and health care in plaque-type psoriasis: a multicenter cross-sectional study in Germany. *Dermatology,* 216(4), 366-372. doi: 10.1159/000119415

[4] Boehncke, W. H., & Boehncke, S. (2012). Cardiovascular mortality in psoriasis and psoriatic arthritis: epidemiology, pathomechanisms, therapeutic implications, and perspectives. *Current rheumatology reports,* 14(4), 343-348. doi: 10.1007/s11926-012-0260-8

[5] Bunak, V. V. (1941). *Антропометрия [Anthropometry].* M.: Наркомпрос РСФСР - M.: People's Commissariat of the RSFSR.

[6] Carter, J. (2003). *The Heath-Carter antropometric somatotype. Instruction manual.* Department of Exercise and Nutritional Sciences San Diego State University. CA. U.S.A.

[7] Dmytrenko, S. V. (2008). Особливості будови тіла мешканців Поділля, хворих на різні форми псоріазу [Peculiarities of the body structure of Podillya residents suffering from various forms of psoriasis]. *Вісник Вінницького національного медичного університету - Reports of Vinnytsia National Medical University,* 12(1), 75-79.

[8] Esco, M. R., Williford, H. N., & Olson, M. S. (2011). Skinfold thickness is related to cardiovascular autonomic control as assessed by heart rate variability and heart rate recovery. *The Journal of Strength & Conditioning Research*, 25(8), 2304-2310. doi: 10.1519/JSC.0b013e3181f90174

[9] Fredriksson, T., & Pettersson, U. (1978). Severe psoriasis - oral therapy with a new retinoid. *Dermatology,* 157(4), 238-244. doi: 10.1159/000250839

[10] Gunas, I., Majewski, O., & Makarchuk, I. (2016). Features of somatotype and body weight component composition in patients with acne: boys and girls of Podillya region of Ukraine. *Current Issues in Pharmacy and Medical Sciences,* 29(2), 97-100. doi: 10.1515/cipms-2016-0020

[11] Gunas, I. V., Maievskyi, O. Y., Dmitrenko, S. V., Makarchuk, I. M. Terekhovska, O. I., Cherepakha, O. L., & Ocheretna, O. L. (2017). Distribution variants of somatotype in healthy and patients with acne boys and girls from Podilsky region of Ukraine. *World of medicine and biology*, 4(62), 24-27. doi: 10.26724/2079-8334-2017-4-62-24-27

[12] Gupta, R., Debbaneh, M. G., & Liao, W. (2014). Genetic epidemiology of psoriasis. *Current dermatology reports,* 3(1), 61-78. doi: 10.1007/s13671-013-0066-6

[13] Kim, J. I., Yang, Y. M., Park, J. H., & Shin, H. J. (2015). Study on the relationship between skinfold thickness and geriatric depression in older adult woman. *Journal of Korean Biological Nursing Science,* 17(1), 44-49. doi: 10.7586/jkbns.2015.17.1.44

[14] Makarchuk, I. M. (2014). Comparison of transverse body sizes between healthy and acne patients boys and girls from Podillia, taking into account and without taking into account the somatotype. *Reports of Morphology,* 20(2), 482-488.

[15] Makarchuk, I. M. (2014). Differences between total and longitudinal body sizes between healthy and boys and girls with acne, taking into account and excluding the somatotype. *Biomedical and Biosocial anthropology,* 23, 44-48.

[16] Martin-Jimenez, C. A., Gaitan-Vaca, D. M., Echeverria, V., Gonzalez, J., & Barreto, G. E. (2017). Relationship between obesity, Alzheimer's disease, and Parkinson's disease: an astrocentric view. *Molecular neurobiology*, 54(9), 7096-7115. doi: 10.1007/s12035-016-0193-8

[17] Mateshuk-Vatseba, L. R., & Chaplyk-Chyzho, I. O. (2018). The most pronounced constitutional differences between healthy and sick with pyoderma in men or women in the western region of Ukraine. *Biomedical and Biosocial Anthropology*, (30), 20-26. doi: 10.31393/bba30-2018-03

[18] Mohd Affandi, A., Khan, I., & Ngah Saaya, N. (2018). Epidemiology and clinical features of adult patients with psoriasis in Malaysia: 10-year review from the Malaysian Psoriasis Registry (2007-2016). Dermatology research and practice, 2018. doi: 10.1155/2018/4371471

[19] Moroz, V. M., Gunas, I. V., & Serheta, I. V. (2003). Біомедична антропологія: проблеми, пошуки, перспективи (перше повідомлення) [Biomedical anthropology: problems, searches, prospects (first message)]. *Biomedical and biosocial anthropology*, (1), 2-5.

[20] Parisi, R., Iskandar, I. Y., Kontopantelis, E., Augustin, M., Griffiths, C. E., & Ashcroft, D. M. (2020). National, regional, and worldwide epidemiology of psoriasis: systematic analysis and

modelling study. *BMJ: British Medical Journal* (Online), 369. doi: 10.1136/bmj.m1590

[21] Rachakonda, T. D., Schupp, C. W., & Armstrong, A. W. (2014). Psoriasis prevalence among adults in the United States. *Journal of the American Academy of Dermatology*, 70(3), 512-516. doi: 10.1016/j.jaad.2013.11.013

[22] Rogers, S. (1992). Skin thickness in psoriasis. *Clinical and experimental dermatology,* 17(5), 324-327. doi: 10.1111/j.1365-2230.1992.tb00221.x

[23] Selcuk, A., Bulucu, F., Kalafat, F., Cakar, M., Demirbas, S., Karaman, M., ... & Arslan, E. (2013). Skinfold thickness as a predictor of arterial stiffness: obesity and fatness linked to higher stiffness measurements in hypertensive patients. *Clinical and Experimental Hypertension*, 35(6), 459-464. doi: 10.3109/10641963.2012.746357

[24] Shalom, G., Zisman, D., Babaev, M., Horev, A., Tiosano, S., Schonmann, Y., ... & Cohen, A. D. (2018). Psoriasis in Israel: demographic, epidemiology, and healthcare services utilization. *International journal of dermatology,* 57(9), 1068-1074. doi: 10.1111/ijd.14130

[25] Surendar, J., Indulekha, K., Deepa, M., Mohan, V., & Pradeepa, R. (2016). Association of adiposity, measured by skinfold thickness, with parental history of diabetes in a South Indian population: data from CURES-114. *Postgraduate medical journal,* 92(1089), 379-385. doi: 10.1136/postgradmedj-2015-133363

[26] Vikdahl, M., Carlsson, M., Linder, J., Forsgren, L., & Haglin, L. (2014). Weight gain and increased central obesity in the early phase of Parkinson's disease. *Clinical nutrition*, 33(6), 1132-1139. doi: 10.1016/j.clnu.2013.12.012

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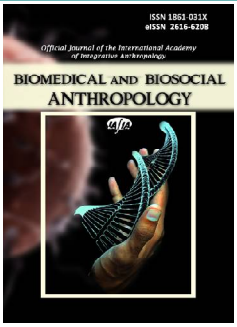

Evaluation of the effectiveness of a proposed approach to treat infertility against the background of uterine leiomyoma, which includes treatment with a releasing hormone agonist, hysteroresectoscopy or conservative myomectomy, and pre-pregnancy treatment in assisted reproductive technology programs

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There is much discussion about the effect of uterine leiomyomas on the outcomes of assisted reproductive technologies (ART). This study aimed to analyze the effectiveness of in vitro fertilization following the use of a therapy scheme we propose to treat infertility with the background of uterine leiomyoma. The therapy scheme includes the use of a releasing hormone agonist, hysteroresectoscopy or conservative myomectomy and pre-pregnancy pre-treatment. The clinical study involved 175 women of reproductive age who had been diagnosed with uterine leiomyoma, and were divided into the groups as follows. The treatment group A included 137 women with uterine leiomyoma, and was further divided into subgroups. Subgroup A1 included 55 women with uterine leiomyoma after conservative myomectomy who underwent the proposed treatment scheme (TS); A2 included 45 women with uterine leiomyoma after hysteroresectoscopy who underwent the TS; A3 included 37 women with uterine leiomyoma who underwent the TS but not the surgical removal of uterine leiomyoma. Control group B included 38 women with uterine leiomyoma after conservative myomectomy. All patients with intramural and submucosal myoma nodules underwent a hormonal preparatory treatment with a gonadotropin-releasing hormone (GnRH) agonist (Diphereline 3.75 mg intramuscularly once every 28 days for 3 months) prior to the myomectomy. After the surgery, patients were prescribed a combination therapy with a vitamin complex FT 500 plus, vitamin D3 and Pelvidol for three months before and during controlled ovarian stimulation (COS) protocol up to the follicle puncture. We determined that the incidence of pregnancy was the lowest (37.8 %) in women with infertility against the background of uterine leiomyoma, who surgically treated for the myomas, but underwent pre-pregnancy pre-treatment. The frequency of pregnancy did not differ between the A1 and A2 treatment groups, and was on average 7.0 % higher than in the control group, and 11.0 % higher than in the A3 group. The relative incidence of clinical pregnancies was the highest in A1 (45.5 %) and A2 (44.4 %) treatment groups. The frequency of live births in the A1 group was significantly higher than in A3 group (by 14.0 %), while the relative number of term live births in the A1 group exceeded that of A3 group by 26.0 %. Thus, both proposed therapy schemes to treat infertility against the background of uterine leiomyoma, which include the use of a releasing hormone agonist, either a conservative myomectomy or hysteroresectoscopy and pre-pregnancy pre-treatment in addition to the ART protocol with a multi-vitamin complex with inositol, vitamin D3, alpha-lipoic acid and magnesium, had the equivalent effects on the incidence of clinical pregnancy, however the frequency of live births was highest after conservative myomectomy (84.0 %).

Keywords: *uterine leiomyoma, myomectomy, pre-pregnancy treatment, effectiveness.*

Introduction

Current research data addressing the issue of uterine leiomyoma and its impact on female reproductive function indicate that uterine leiomyoma is a hormone-dependent benign formation of the myometrium. The tumor develops

from an abnormal cell that, after it mutates, gains the ability to grow uncontrollably. Uterine leiomyomas occur in up to 60 % of women under the age of 40 and in 80 % of women under 50 [17]. At the same time, uterine leiomyomas are found in 5 to 10 % of women with infertility and in 1-3 % of cases this pathology is the only factor contributing to infertility [1]. Uterine leiomyoma is also the cause of approximately 7 % of recurring miscarriages [15].

Sub-mucosal and intramural myomas in particular cause deformation of the lumen of the uterus and are the specific types of uterine leiomyomas that can reduce fertility [23]. Studies link the presence of sub-mucosal myomas to impaired fertility as well as pregnancy loss, but the effects of intramural myomas on reproductive outcomes are less clear [16].

Some studies failed to demonstrate an association between intramural myomas and successful *in vitro* fertilization [11], while the others conclude that the presence of intramural myomas reduces the effectiveness of *in vitro* fertilization cycles [17]. A meta-analysis study by Sunkara et al. revealed that intramural localization of myomas reduces the incidence of clinical pregnancy and fertility rate (0.85 and 0.79, respectively) in the cycles of *in vitro* fertilization [19]. There is still no consensus on the practicability of conservative myomectomy to treat these types of leiomyomas [12, 13, 24]. This surgical intervention can be performed, depending on the indications, using vaginal, trans-cervical, laparoscopic or abdominal access. However, surgical treatment can sometimes lead to infertility or deterioration of reproductive function if the connective tissue forms on the pelvic organs or scars form on the uterus. There are conflicting opinions on the effect of surgical treatment (conservative myomectomy) on the restoration of fertility. In particular, Zepiridis et al. [24] showed improved infertility treatment outcomes after any type of conservative myomectomy, while Samejima et al. [18] found that conservative myomectomy can address the issue of infertility only if the myomas were the only cause of infertility, in particular due to their sub-mucosal localization, and the removal of intramural nodules may not affect the effectiveness of infertility treatment. A combination therapy (aGnRH, pre-pregnancy treatment) increases the effectiveness of conservative myomectomy.

The aim of the study was to analyze the effectiveness of *in vitro* fertilization following a treatment for infertility against the background of uterine leiomyoma using a proposed scheme which includes administration of a releasing hormone agonist, hysteroresectoscopy or conservative myomectomy and pre-pregnancy treatment.

Materials and methods

The clinical study was performed during 2014-2020 at the medical center "The Clinic of Professor Stefan Khmil". The study group included 175 women of reproductive age who were diagnosed with uterine leiomyoma. The patients were divided into the treatment group A, which included 137 women with uterine leiomyoma, and control group B, 38 women with uterine leiomyoma after conservative myomectomy. The group A was further sub-divided into the following subgroups: A1 - 55 women with uterine leiomyoma after conservative myomectomy who underwent treatment according to the proposed TS, A2 - 45 women with uterine leiomyoma after hysteroresescopy and TS, and A3 - 37 women with uterine leiomyoma who did undergo surgical removal of uterine leiomyoma but were administered the medication part of the TS (Fig. 1).

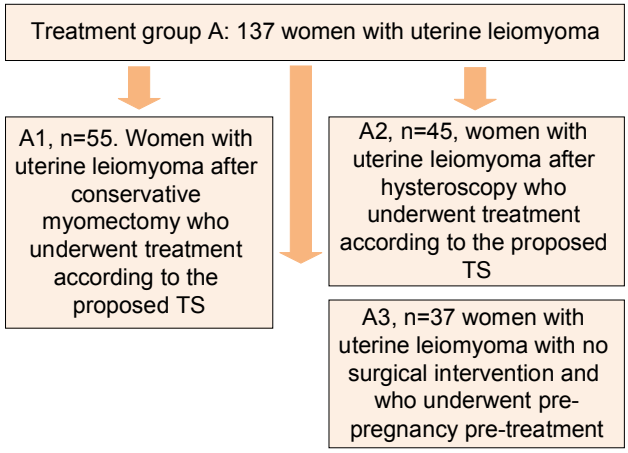

Fig. 1. Composition of the treatment group and its sub-groups.

All patients with sub-mucosal, intramural and subserosal localization of the myoma nodules underwent hormonal pre-treatment with gonadotropin-releasing hormone (GnRH) agonists (*Diphereline* 3.75 mg intramuscularly once every 28 days for 3 months) before myomectomy. Such preoperative treatment with GnRH agonists is intended to reduce the size of myomas, supporting the organ-sparing approach. Surgical interventions were performed using different methods, depending on the localization of myomas.

Patients of the group A2 underwent hysteroresectoscopy, a modern organ-sparing minimally invasive surgical method to treat patients with uterine leiomyoma. Patients with sub-mucosal myomas were treated in one stage, and those with sub-mucosal/intramural localization of the myoma nodules, in two stages. Hysteroresectoscopy was performed on the 6^{th} to 10^{th} day of the menstrual cycle in the dorsal lithotomy position using mechanical and electrosurgical approaches with a hystero-resectoscope (Karl Storz) under a general anesthesia.

The operating field was pre-treated with antiseptic solutions, the cervix was exposed in mirrors in aseptic conditions; the anterior lip was gripped and stabilized using ball tips forceps. Os direction and length of the uterus were measured using a uterine probe, the degree of cervical canal extension using a Hegar 8 dilator. After that, a hysteroscope was inserted into the uterine cavity. Prior to the surgery, the condition of the uterine cavity and endometrium, angles of the uterus, openings of the fallopian tubes, the cervical canal and the presence and location of pathological formations, were examined and evaluated under a video camera control.

The choice of a surgery method was determined by localization and size of the myomas:

- mechanical surgery using a cutting loop was used to remove sub-mucosal myomas on a thin stalk, located on the uterine floor;
- electrosurgical approach with a loop electrode was used for resection of myoma nodules on a wide stalk with a sub-mucosal/intramural and sub-mucosal localization.

Following the surgery, all patients were prescribed appropriate hemostatic, antibacterial and hormonal therapy.

The other treatment groups of patients underwent conservative myomectomy with removal of intramural and subserosal myomas using laparotomy and laparoscopic approach.

After the surgery, all patients were prescribed a combination therapy for three months before the TS and, in the controlled ovarian stimulation (COS) protocol, before the follicle puncture. The combination therapy included: vitamin complex *FT 500 plus* (inositol (vitamin B8) - 2000 mg, vitamin C - 160 mg, vitamin E - 12 mg, folic acid - 400 μg, selenium - 55 μg, glutathione - 50 mg, zinc - 10 mg, and lutein - 3 mg), 1 sachet once a day for 3 months; vitamin D3 (in the form of *Eutilia vitamin D3*) 2000 IU 1- 2 times/day, depending on the 25(OH)D levels, for 3 months; and *Pelvidol* (alpha-lipoic acid - 600 mg and magnesium - 241.2 mg), 1 tablet once a day for 3 months.

Superovulation in the patients was stimulated with a recombinant gonadotropin corifollitropin-alpha *Elonva* starting on days 2-3 of the menstrual cycle. This drug has a prolonged effect produced by a modification of the carboxy-terminal peptide subunit of the beta chain of human FSH. On days 5-7 of the protocol, depending on the ovarian response, when the follicle size reached 14-15 mm, gonadotropin-releasing hormone antagonist (aGnRH) *Orgalutran* 0.25 mg/day was administered. On day 8 after *Elonva* administration, the stimulation was continued with a recombinant FSH *Puregon* and urinary medication *Menopur* until the final maturation of the oocytes (3 follicles at > 18 mm). Releasing hormone agonist *Diphereline* used was as a trigger (0.2 mg/mL once in the control group, and 0.2 mg/mL once and additionally 0.1 mg/mL after 12 hours in the treatment group). The duration of COS and medicine administration, including the ovulation trigger, were determined by ultrasound and hormone monitoring.

Follicle puncture and follicular fluid aspiration were performed under the control of a trans-vaginal sensor with Cook probes (USA) 36 h after ovulation trigger administration in a manipulation room. On day 5-6 the eggs were fertilized and embryos were cultured with subsequent vitrification in the IVF laboratory. One or 2 embryos were transferred into the uterine cavity using a Cook catheter, the remaining embryos were vitrified. Subsequently, the patients were prescribed a maintenance therapy with progesterone drugs to a positive β-HCG result. With a positive pregnancy result, the pre-pregnancy treatment was maintained for up to 10-12 weeks.

Ultrasound examination of the pelvic organs was performed on all patients included in the study using the *Voluson E8 Expert* system at the initial and each subsequent visit during COS, as well as for several days following the follicular puncture; and 28 days after the embryo transfer to visualize it in the uterine cavity and verify foetal heartbeat.

All patients received a standard comprehensive obstetric clinical and laboratory examination according to local protocols approved both in the Clinic for the management of patients with uterine infertility and by the Regulation of the Ministry of Health of Ukraine № 787 from 09.09.2013 "On the approval of the use of assisted reproductive technologies in Ukraine". This study utilises results of standard clinical and laboratory tests which were performed according to appropriate documents (local orders) regulating outpatient and inpatient obstetric and gynaecological care before and after myomectomy. The study was carried out in accordance with the principles of the Helsinki Declaration of Human Rights, the Council of Europe Convention on Human Rights and Biomedicine as well as relevant laws of Ukraine.

Statistical analysis was performed using a licensed software Statistica (version 10; Statsoft, USA). Quantitative values were compared using parametric statistics (the mean and standard error). The differences between parameters were considered statistically significant differences at $p<0.05$.

Results

We used several parameters to evaluate the effectiveness of the proposed scheme to treat infertility against the background of uterine leiomyoma, and which includes administration of a releasing hormone agonist, hysteroresectoscopy or conservative myomectomy and pre-pregnancy pre-treatment. We found that the incidence of pregnancy was the lowest (37.8 %) in women with infertility against the background of uterine leiomyoma, who did not undergo surgical myoma removal, but underwent pre-pregnancy pre-treatment. The frequency of pregnancy was not significantly different between the A1 and A2 treatment group and was on average 7.0 % higher than in the control group, as well as 11.0 % higher than in the A3 group.

It should be noted that in women with infertility against the background of uterine leiomyoma, who did not have myoma resection, but received pre-pregnancy pre-treatment, the relative number of biochemical pregnancies was 21.4 %, which significantly exceeded the same value in the patients with uterine leiomyoma who underwent conservative myomectomy together with the proposed treatment scheme (3.7 %) and in patients with uterine leiomyoma after hysteroscopy and the proposed treatment scheme (9.0%), as well as the values in the control group (12.5 %). Ectopic pregnancies were diagnosed in 1 woman each of the groups A1 and A3.

The relative incidence of clinical pregnancy was the highest in the A1 (45.5 %) and A2 (44.4 %) treatment groups, exceeding the same value in the A3 group, as well as control

Table 1. Clinical results in the study groups of patients (n,%).

Parameters	A1 group, n=55	A2 group, n=45	A3 group, n=37	Control group, n=38
Frequency of pregnancy	27 (49.1 %)	22 (48.9 %)	14 (37.8 %)	16 (42.1 %)
Frequency of biochemical pregnancy	1 (3.7 %)	2 (9.0 %)	3 (21.4 %)	2 (12.5 %)
Frequency of ectopic pregnancy	1 (3.7 %)	0 (0 %)	1 (7.1 %)	0 (0 %)
Frequency of clinical pregnancy	25 (45.5 %)	20 (44.4 %)	10 (27.0 %)	14 (36.8 %)
Frequency of aborted pregnancy	4 (16.0 %)	2 (10.0 %)	3 (30.0 %)	3 (21.4 %)
Frequency of a multiple pregnancy	4 (16.0 %)	3 (15.0 %)	1 (10.0 %)	2 (14.3 %)
Frequency of live birth	21 (84.0 %)	15 (75.0 %)	7 (70.0 %)	11 (78.6 %)
Frequency of term delivery	19 (76.0 %)	14 (70.0 %)	5 (50.0 %)	9 (64.3 %)
Frequency of a preterm delivery of live foetus	2 (8.0 %)	1 (5.0 %)	2 (20.0 %)	2 (14.3 %)

group. Among clinical pregnancies, the lowest proportion of aborted pregnancies was recorded in women with uterine leiomyoma who underwent hysteroresescopy and TS (10.0 %); it was lower compared to the A1 and A2 groups by 6.0 % and 20.0 %, respectively, and to the control group by 11.4 %.

The lowest incidence of a multiple pregnancy was diagnosed in the group of women without surgical removal of uterine leiomyoma and pre-pregnancy pre-treatment (in 1 patient), while this value was comparably similar among other groups and ranged from 14.3 to 16.0 %. It should be noted, that in women who underwent surgery and pre-pregnancy pre-treatment according to the COS protocol, the frequency of live births did not differ from the control group, while it was even slightly higher (5.4 %) in the A1 group. The frequency of live births in the A1 group was significantly higher than in A3 group (by 14.0 %), while the relative number of term deliveries in the A1 group exceeded the same value in the A3 group by 26.0 %. Preterm deliveries with live fetuses were observed in 20.0 % of patients of the A3 group, which was higher compared to the A1 (by 12.0 %) and A2 (by 15.0 %) groups, as well as control group (by 5.7 %) (Table 1).

Discussion

Results of this study indicate the highest frequency of clinical pregnancy and the frequency of live birth were observed in women with uterine leiomyoma after conservative myomectomy who received the proposed treatment scheme. These results correspond to a number of other studies, which confirm higher effectiveness of *in vitro* fertilization after conservative myomectomy with removal of intramural and subserosal myomas [20]. For instance, Martynova et al. [14] found that patients who underwent laparoscopic myomectomy for intramural (or combined with subserosal) nodules with a diameter of over 4 cm before *in vitro* fertilization, the frequency of pregnancy was comparable to that in patients without uterine myomas, which confirms the need for myomectomy.

However, some studies indicate absence of a positive effect of conservative myomectomy on the results of *in vitro* fertilization caused by the changes in uterine blood supply and endometrial receptivity [11]. In this study, we found almost the same frequency of clinical pregnancy in women of the A1 and A2 groups, but women who underwent hysteroresectoscopy of uterine leiomyoma and received the proposed treatment scheme had a slightly lower incidence live foetus births. Hysteroresectoscopy is known to have advantages such as organ preservation, significant reduction of surgical trauma, short duration of the surgery, and unproblematic postoperative period [10]. However, some research findings point out to a decrease in ovulatory activity after various cavitary interventions on the uterus or fallopian tubes [3, 7, 8]. Some authors that suggest that the risk scar tissue development in the uterine cavity after one hysteroscopy reaches 16 %, and after three or more up to 32 %, which leads to atrophic transformation of the preserved endometrium [2, 21], which may lower efficiency of *in vitro* fertilization. At the same time, the lowest incidence of clinical pregnancy in women of the A3 group, who did not undergo surgical removal of myomas, is fully warranted because of deformation of the uterine cavity, which leads to decreased blood flow, inflammatory changes and imbalance of pro- and antioxidant processes.

It should also be noted that patients in the groups A1, A2 and A3 underwent a course of pre-pregnancy pre-treatment before and into the COS protocol up to the follicle puncture. This combined therapy included inositol as part of the *FT 500 plus* vitamin complex, vitamin D3 in *Eutilia vitamin D3* and alpha-lipoic acid together with magnesium as components of *Pelvidol*. Research findings suggest that the use of medications with antioxidant properties allows not only to normalize the processes of free radical oxidation, which are activated in the cases of uterine leiomyoma, but also to balance the production of reproductive hormones [6, 9]. In addition, inositol and vitamin D3-containing medications enhance the efficiency of *in vitro* fertilization and increase the frequency of pregnancy by improving the quality of eggs and embryos, [22, 25]. Alpha-lipoic acid exhibits immunomodulatory and antioxidant activity, which improves embryo implantation and stimulates the production of local mediators that facilitate implantation. For instance, a study by Canosa et al. [5] showed that the intake of inositol,

alpha-lipoic and folic acids had a beneficial effect on the molecular organization of *zona pellucida* during follicle maturation, which is physiologically rearranged during oocyte maturation [4].

Conclusions

In women with infertility against the background of uterine leiomyoma, the proposed treatment scheme, which includes either a conservative myomectomy or hysteroresectoscopy, administration a releasing hormone agonist and pre-pregnancy treatment for ART with a vitamin complex, vitamin D, inositol, lipoic acid and magnesium, has similar effects on the incidence of clinical pregnancy, but the frequency of live births is highest after conservative myomectomy (84.0%).

References

[1] Ahdad-Yata, N., Fernandez, H., Nazac, A., Lesavre, M., Pourcelot, A. G., & Capmas, P. (2016). Fertility after hysteroscopic resection of submucosal myoma in infertile women. *J. Gynecol. Obstet. Biol. Reprod.*, 45(6), 563-570. doi: 10.1016/j.jgyn.2015.06.028

[2] Ahmadi, F., Siahbazi, S., Akhbari, F., Eslami, B., & Vosough, A. (2013). Hysterosalpingography finding in intra uterine adhesion (Asherman' s syndrome): a pictorial essay. *Int. J. Fertil. Steril.,* 7(3), 155-160. PMCID: PMC3914485.

[3] Bendifallah, S., Brun, J. L., & Fernandez, H. (2011). Myomectomy for infertile women: the role of surgery. *J. Gynecol. Obstet. Biol. Reprod*. (Paris), 40(8), 885-901. doi: 10.1016/j.jgyn.2011.09.014

[4] Canosa, S., Adriaenssens, T., Coucke, W., Dalmasso, P., Revelli, A., Benedetto, C., & Smitz, J. (2017). Zona pellucida gene mRNA expression in human oocytes is related to oocyte maturity, zona inner layer retardance and fertilization competence. *Mol. Hum. Reprod.*, 23(5), 292-303. doi: 10.1093/molehr/gax008

[5] Canosa, S., Paschero, C., Carosso, A., Leoncini, S., Mercaldo, N., Gennarelli, G., ..., & Revelli, A. (2020). Effect of a combination of myo-inositol, alpha-lipoic acid, and folic acid on oocyte morphology and embryo morphokinetics in non-PCOS overweight/obese patients undergoing IVF: a pilot, prospective, randomized study. *J. Clin. Med.*, 9(9), 2949. doi: 10.3390/jcm9092949

[6] Diamanti-Kandarakis, E., & Dunaif, A. (2012). Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. *Endocr. Rev*., 33(6), 981-1030. doi: 10.1210/er.2011-1034

[7] Hackethal, A., Westermann, A., Tchartchian, G., Oehmke, F., Tinneberg, H. R., Muenstedt, K., & Bojahr, B. (2011). Laparoscopic myomectomy in patients with uterine myomas associated with infertility. *Minim. Invasive Ther. Allied. Technol.,* 20(6), 338-345. doi: 10.3109/13645706.2010.541922

[8] Hrubosova, E. (2011). Uterine fibroids and their treatment. *Ceska Gynekol.*, 76(2), 152-157.

[9] Jayagopal, V., Kilpatrick, E. S., Jennings, P. E., Hepburn, D. A., & Atkin, S. L. (2003). The biological variation of testosterone and sex hormone-binding globulin (SHBG) in polycystic ovarian syndrome: implications for SHBG as a surrogate marker of insulin resistance. *JCEM.*, 88(4), 1528-1533. doi: 10.1210/jc.2002-020557

[10] Khmil, S. V., Drozdovska, Yu. B., Khmil, M. S., & Chudiyovych, N. Ya. (2018). Ефективність гістерорезектоскопії у жінок з безпліддям на фоні лейоміоми матки в програмах допоміжних репродуктивних технологій [Effectiveness of hysterorezectoscopy in women with infertility and uterine fibroids in programs of assisted reproductive technologies]. *Вісник соціальної гігієни та організації охорони здоров'я України - Bulletin of social hygiene and health care organization of Ukraine,* 4(78), 51-55. doi: 10.11603/1681-2786.2018.4.10030

[11] Klatsky, P. C., Lane, D. E., Ryan, I. P., & Fujimoto, V. Y. (2007). The effect of fibroids without cavity involvement on ART outcomes independent of ovarian age. *Hum. Reprod*., 22(2), 521-526. doi: 10.1093/humrep/del370

[12] Kroon, B., Johnson, N., Chapman, M., Yazdani, A., & Hart, R. (2011). Fibroids in infertility-consensus statement from ACCEPT (Australasian CREI Consensus Expert Panel on Trial evidence). *Aust. N. Z. J. Obstet. Gyneaecol.,* 51(4), 289-295. doi: 10.1111/j.1479-828X.2011.01300.x

[13] Marret, H., Fritel, X., Ouldamer, L., Bendifallah, S., Brun, J. L., De Jesus, I., ..., & Fernandez, H. (2012). Therapeutic management of uterine fibroid tumors: updated French guidelines. *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 165(2), 156-164. doi: 10.1016/j.ejogrb.2012.07.030

[14] Martynova, A. Ye., Smolnikova, V. Yu., Demura, T. A., & Kogan, Ye. A. (2013). Эффективность программы ЭКО у женщин с миомой матки в зависимости от морфофункционального состояния эндометрия [The effectiveness of the IVF program in women with uterine myoma, depending on the morphofunctional state of the endometrium]. *Акушерство и гинекология - Obstetrics and Gynecology*, (2), 57-61.

[15] Olive, D. L. (2011). The surgical treatment of fibroids for infertility. *Semin. Reprod. Med.,* 29(2), 113-123. doi: 10.1055/s-0031-1272473

[16] Penzias, A. S. (2012). Recurrent IVF failure: other factors. *Fertil. Steril.,* 97(5), 1033-1038. doi: 10.1016/j.fertnstert.2012.03.017

[17] Pier, B. D., & Bates, G. W. (2015). Potential causes of subfertility in patients with intramural fibroids. *Fertil. Res. Pract.,* (1), 12. doi: 10.1186/s40738-015-0005-2

[18] Samejima, T., Koga, K., Nakae, H., Wada-Hiraike, O., Fujimoto, A., Fujii, T., & Osuga, Y. (2015). Identifying patients who can improve fertility with myomectomy. *Eur. J. Obstet. Gynecol. Reprod. Biol.*, (185), 28-32. doi: 10.1016/j.ejogrb.2014.11.033

[19] Sunkara, S. K., Khairy, M., El-Toukhy, T., Khalaf, Y., & Coomarasamy, A. (2010). The effect of intramural fibroids without uterine cavity involvement on the outcome of IVF treatment: a systematic review and meta-analysis. *Hum. Reprod.,* 25(2), 418-429. doi: 10.1093/humrep/dep396

[20] Surrey, E. S., Minjarez, D. A., Stevens, J. M., & Schoolcraft, W. B. (2005). Effect of myomectomy on the outcome of assisted reproductive technologies. *Fertil. Steril.*, 83(5), 1473-1479. doi: 10.1016/j.fertnstert.2004.11.045

[21] Takai, I. U., Kwayabura, A. S., Ugwa, E. A., Idrissa, A., Obed, J. Y., & Bukar, M. (2015). A 10-year review of the clinical presentation and treatment outcome of Asherman's syndrome at a center with limited resources. *Ann. Med. Health Sci. Res.,* 5(6), 442-446. doi: 10.4103/2141-9248.177984

[22] Unfer, V., Facchinetti, F., Orru, B., Giordani, B., & Nestler, J. (2017). Myo-inositol effects in women with PCOS: a meta-

analysis of randomized controlled trials. *Endocr. Connect.,* 6(8), 647-658. doi: 10.1530/EC-17-0243

[23] Yoshida, M., & Miyake, T. (2019). The outcomes of uterine myomectomy in infertile patients with uterine leiomyomas. *Ann. Infert. Rep. Endocrin.*, 2(1), 1014.

[24] Zepiridis, L. I., Grimbizis, G. F., & Tarlatzis, B. C. (2016). Infertility and uterine fibroids. *Best. Pract. Res. Clin. Obstet. Gynaecol.*, (34), 66-73. doi: 10.1016/j.bpobgyn.2015.12.001

[25] Zhao, J., Liu, S., Wang, Y., Wang, P., Qu, D., Liu, M., ..., & Li, Y. (2019). Vitamin D improves the outcome of in vitro fertilization (IVF) in infertile women with polycystic ovary syndrome and insulin resistance. *Minerva Med.,* 110(3), 199-208. doi: 10.23736/S0026-4806.18.05946-3

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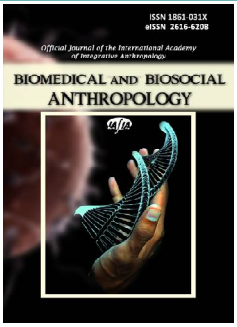

Evaluation of the effectiveness of early intervention methods in newborns who have suffered hypoxic-ischemic CNS damage

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Timely diagnosis of cerebral disorders both in the prenatal period and in the early neonatal period, as well as early rehabilitation treatment is the basis for the prevention of childhood disability. To this end, the so-called Early Intervention System is being introduced in Ukraine. The effectiveness of early intervention techniques directly depends on timely diagnosis and correctly chosen intervention tactics. Given the high neuroplasticity of the developing brain, it is advisable to start the elements of neurodevelopmental therapy from infancy. The aim of the work is to evaluate the effectiveness of methods of early intervention in children of the first 3 months of life who have suffered hypoxic-ischemic CNS damage in the neonatal period, by assessing the main indicators of psycho-motor development. 101 children who were treated in the neonatal pathology department due to hypoxic-ischemic CNS damage and did not have concomitant somatic pathology were examined. The children were in the ward for rehabilitation. To assess the effectiveness of comprehensive rehabilitation in young children, it is advisable to use adapted for Ukraine scale of Munich functional developmental diagnostics, which allows to assess the child's development in all major areas, its harmony and effectiveness of rehabilitation measures during the first 3 years of life. Statistical processing of the obtained results should be performed in the license package "Statistica 6.1 for Windows". Timely diagnosis of cerebral disorders both in the prenatal period and in the early neonatal period, as well as early rehabilitation treatment is the basis for the prevention of childhood disability. Given the high neuroplasticity of the developing brain, it is advisable to start the elements of neurodevelopmental therapy from infancy. The effectiveness of the methods recommended for use depends on timely diagnosis and correctly chosen intervention tactics. Assessment of the effectiveness of care for children at risk of deviant psychomotor development should be based on the application of the criteria and scales recommended by international expert groups, which are adapted in our country. Signs of full-fledged early intervention in the region are: perinatal diagnosis of congenital pathology, timely provision of medical and rehabilitation, social and special pedagogical services to children aged 0 to 3 years and their families. In order to achieve the set goals, in our opinion, the priority measures should be steps to implement the national protocol for care for children with perinatal CNS injuries, approval and implementation in Ukraine of the modern International Classification of Functioning, Life and Health Restrictions, providing medical care, rehabilitation and social services for young children.

Keywords: *early intervention, newborns, hypoxic-ischemic encephalopathy, assessment of psychomotor development, rehabilitation of young children, effectiveness.*

Introduction

Unfavorable onset of life in the neonatal period can cause a variety of health problems, ranging from moderate developmental delays to severe disabling diseases, which in turn leads to problems with adaptation in society in adulthood [9, 28]. According to international experts, in the future the annual income of persons who had adverse circumstances at birth will be 1/4 lower than the average, which is 2 times higher than the cost of their early

rehabilitation and education [24]. Scientific data show that early childhood is not only a period of special sensitivity to various risk factors, but also an important period in life, when a set of therapeutic measures gives a double return, and the negative effect of risk factors is mitigated [28]. The positive effect of comprehensive care for the child in the first years of life will be manifested in the future in the form of better health, well-being, higher learning ability and higher income. Services and measures to maintain the health of young children are an important condition for preserving the potential of each individual throughout his life and the potential of the generation as a whole [9].

The incidence of the nervous system, which leads to disability and maladaptation of children, in 70-80 % of cases due to perinatal factors. Among the factors affecting children in the perinatal period, hypoxia is one of the most common [1, 4, 5]. In essence, hypoxic-ischemic encephalopathy (HIE) is a post-stroke encephalopathy [1, 5, 16]. HIE is a term used to describe a set of complex physiological, cellular and molecular changes that occur due to impaired oxygen supply to the brain [8]. HIE causes severe lifelong morbidity, including cerebral palsy and premature mortality [4, 19]. According to Barashnev Y. I. [3], timely diagnosis of cerebral disorders both in the prenatal period and in the early neonatal period, as well as early rehabilitation treatment is the basis for the prevention of childhood disability.

To this end, the so-called Early Intervention System is being introduced in Ukraine. Early intervention - all types of activities aimed at child development and parental support, which are carried out immediately and immediately after determining the status and level of development of the child (European Organization for Early Intervention, 1993) [10, 28]. The Early intervention program was first developed in the United States and Western Europe for children in their first 3 years of life. Its purpose is to detect deviations in the child's development as early as possible and provide appropriate assistance to the child and his family [2]. Early intervention is aimed at developing all the basic skills of the child. These include motor development, cognitive and communication skills, self-care and the development of the socio-emotional sphere. The philosophy of early intervention is based on the focus on the family in which the child lives, the priority of the child's interests, respect for its problems, taking into account the circumstances of life and family values [9, 13].

There are no official statistics on the number of children in need of early intervention in Ukraine. The experience of developed countries shows that 13-18 % of children in the first 3 years of life have developmental disabilities and need qualified care [28]. In Ukraine, to assess the adequacy of motor development of the child, health workers are guided by the order of the Ministry of Health № 149 "Clinical protocol of medical care for a healthy child under 3 years" from 2008 [21]. The international assessment of the state of assistance to children also indicates the need to further improve the provision of assistance to children with disabilities (recommendations of the UN Committee on the Rights of the Child 2011 and 2014) [10]. The development of the Concept of Social Pediatrics in Ukraine (Resolution of the Committee of the Verkhovna Rada of January 13, 2015 № 96-VIII) is a logical consequence of these recommendations [20]. Priority areas, according to this Concept are: prevention of disabling pathology in children; formation of a single rehabilitation space around the child and his family by forming a single system of rehabilitation institutions at different levels.

Rehabilitation of children with organic damage to the nervous system aims to prevent or reduce the effects of organic damage to the CNS and improve the social integration of the child. To achieve this goal, it is advisable to involve in the process of diagnosis and recovery of the child a multidisciplinary team of specialists, in particular, a neonatologist, neurologist, medical psychologist, ophthalmologist, orthopedist and physical therapist [20, 22]. The main provisions of specialized care for children are reflected in the "Unified clinical protocol of primary, secondary (specialized) and tertiary (highly specialized) medical care and medical rehabilitation of children with movement disorders" [22].

To work with newborns and young children, it is advisable to use a comprehensive approach to neurorehabilitation. An individual rehabilitation program is developed for each child depending on its needs and capabilities [3, 6]. A prerequisite is a comprehensive examination of the child to determine the nature and extent of brain damage, determine the functional state of the child, the presence of concomitant somatic pathology and associated disorders in order to plan further individual rehabilitation program [6, 15, 21].

In perinatal neurology, the combinations of the author's neurodeveloping methods and techniques of classical massage and therapeutic physical training are generally accepted. Neurodevelopmental therapy (NDT), aimed at suppressing the activity of pathological tonic reflexes, translational reactions and motor stereotypes with the subsequent restoration of statics and motor skills [17, 18]. To achieve optimal sensory-motor and intellectual development, it is recommended to combine methods of physical impact with the so-called sensory integration of the child, ie to influence different areas of perception (sight, hearing, touch) for better adaptation of the child in the environment [20, 22].

The aim of the work is to evaluate the effectiveness of methods of early intervention in children of the first 3 months of life who have suffered hypoxic-ischemic CNS damage in the neonatal period, by assessing the main indicators of psycho-motor development.

Materials and methods

For the purpose of the greatest efficiency of carrying out methods of early intervention it is expedient to carry out diagnostics of the psychoneurological status of the child

with the use of valid scales before the beginning of procedures. The vast majority of methods for assessing the neurological status of the newborn are aimed at determining the level of consciousness [6, 20] or assessing the motor area [20, 22]. At the same time, insufficient attention is paid to psycho-emotional and pre-speech development, which does not give a complete picture of the child's neurological status and possible prognosis. After reaching the 1st year, the range of diagnostic capabilities is significantly expanded [17, 26]. Currently, the Munich Functional Diagnosis of Development (MFDD) meets the requirements for the assessment of children from birth to 3 years of age [6, 7]. This technique is aimed at early diagnosis of abnormalities in the development of the child for a special correction of the identified pathological changes. First of all, the method assesses the level of development of the motor functional system. However, it is possible to assess the state of perceptual, cognitive, linguistic functional systems and the state of social interaction. The diagnostic scale determines the degree of maturity of individual functional brain systems according to the concept of developmental neurology. The results of the Munich diagnostic determine the degree of compliance of the child's development with his passport age, as well as his psychophysical age, which is a unique criterion that gives an objective assessment of corrective measures. In children with organic lesions of the nervous system, according to the Munich Diagnosis of Development, functional systems develop unevenly, which disrupts their interaction [7]. The results of the examination with the help of MFDD, along with a clinical neurological examination, become the basis for the development of an individual rehabilitation program for a specific child with organic damage to the nervous system [6, 10].

Test card for assessing the physical and neuropsychological development of a child in the first year of life according to the protocol of the Munich Functional Diagnosis of Child Development is used to test and determine the psychological age of a child in the first year of life on scales: crawling, sitting, leaning, grasping, perception, expressive speech, language comprehension, social age. The function of language comprehension is assessed from the 10th month of life [11, 20]. The test card for assessing the physical and neuropsychological development of a child 2-3 years of age contains assessment scales for the age of uprightness, age of fine motor skills, perception (understanding of relationships), age of active speech, language comprehension and social age. The presence or absence of the skill is assessed at the age when it is acquired by 95 % of children with a normal rate of development. Both cards are interconnected, which allows you to monitor the development of each child from birth to 3 years. This, in turn, allows professionals at different stages of helping children to understand the degree of development and dynamics of the formation of individual skills and the general level of development of the child, avoiding subjective judgments.

101 children who were treated in the neonatal pathology department of the Children's Regional Clinical Hospital due to hypoxic-ischemic CNS damage and did not have concomitant somatic pathology were examined. The children were in the ward for rehabilitation treatment at the age of 1 to 3 months. The course of early rehabilitation was determined by the pediatric neurologist individually and contained elements of neurodevelopmental therapy, selected according to age, general and local massage, physical therapy and elements of sensory integration. The main criteria in the choice of early intervention procedures were the main national and international recommendations [20, 22, 27].

To assess the effectiveness of rehabilitation in children in the first 3 months of life, the scale was adapted to the appropriate age. The presence of each skill was evaluated in 1 point, and the absence - 0 points, respectively. Thus, the skill "Crawling" according to MFDD can be assessed from 0 to 4 points at the end of the 1st month of life. At 3 months, the child can acquire 2 more skills related to the development of crawling, ie the maximum can be estimated at 6 points. The "Seat" function in the first month of a child's life can have a range of 0-4 points, and at the end of the 2nd from 0 to 5 points, respectively. Thus, the child's skills are calculated for each of the categories.

To perform statistical processing of the results obtained during the work, a licensed standard package of multidimensional statistical analysis applications "Statistica 6.1 for Windows" (intellectual property of the Center for New Information Technologies of National Pirogov Memorial Medical University, Vinnytsya, licensed № BXXR901E245722FA) was used.

Results

The first group consisted of 48 children who suffered from encephalopathy of hypoxic-ischemic origin of moderate and severe degree and after withdrawal from the acute period, in addition to drug therapy according to the protocol received a course of early rehabilitation in the form of neurodevelopmental therapy and correctional massage with elements. In addition, an appropriate sensory background was created for each child in order to avoid excessive light, sound and sensory stimuli. Children

Table 1. The main indicators of physical development of children in the study groups (M±m).

Indicators	1 group (n=48)	2 group (n=53)	p
Body weight at birth (g)	3105±182	3040±160	>0.05
Gestational age (weeks)	37.33±2.81	38.7±1.45	>0.05
Full-term (%)	75.01±6.25	71.73±6.17	>0.05
Apgar score 1min. (points)	2.732±0.13	2.661±0.105	>0.05
Apgar score 5min. (points)	5.068±0.143	5.983±0.062	<0.001

Notes: p - the reliability of the differences between the 1st and 2nd groups.

Table 2. Indicators of psychomotor development of children of the studied groups at the beginning (1st month) and at the end (3rd month) of the recovery period (M±m).

Indicators	1 group (n=48)		p	2 group (n=53)		p	p_1	p_2
	1 month	3 month		1 month	3 month			
Crawling	1.854±0.89	3.271±1.003	>0.05	1.962±1.107	2.415±1.083	>0.05	>0.05	>0.05
Sitting	1,354±0,731	2.875±0.850	=0.090	1.603±0.936	2.188±0.984	>0.05	>0.05	>0.05
Walking	1.020±0.532	2.166±0.661	=0.090	1.113±0.601	1.452±0.753	>0.05	>0.05	>0.05
Grasping	1.354±0.782	2.250±0.621	>0.05	1.622±0.851	1.924±0.772	>0.05	>0.05	>0.05
Expressive speech	1.312±0.683	2.354±0.775	>0.05	1.433±0.680	1.867±0.705	>0.05	>0.05	>0.05
Social age	1.229±0.615	2.104±0.562	>0.05	1.207±0.627	1.641±0.726	>0.05	>0.05	>0.05
Age of perception	0.875±0.541	2.229±0.763	=0.070	1.056±0.662	1.792±0.918	>0.05	>0.05	>0.05

Notes: p - the significance of differences between 1 and 3 months in the 1st or 2nd groups; p_1 - the reliability of the differences in the indicators of the 1st month between the 1st and 2nd groups; p_2 - significance of differences in the indicators of the 3rd month between the 1st and 2nd groups.

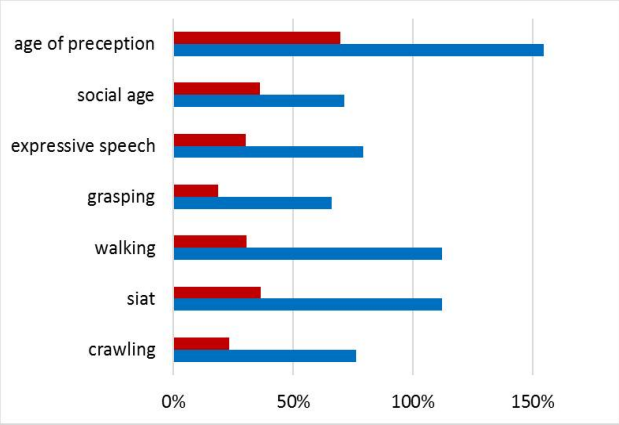

Fig. 1. The ratio of growth of the main indicators of development. Blue shows the results in the 1st group, red - in the 2nd group.

of the 2nd group (n=53) also had encephalopathy of appropriate severity and were registered in the follow-up office (Table 1). The course of early rehabilitation was not carried out for various reasons (mainly due to the parents' refusal to be hospitalized). Both groups of children did not have somatic pathology, which could significantly affect the neurological status. To exclude the influence of additional factors, the main and control groups included children who did not need at the time of the study of drug therapy with drugs that affect the central nervous system. Both groups of children were registered at the dispensary in the follow-up room of the Vinnytsia Regional Children's Clinical Hospital to monitor the health and psychomotor development of children.

Assessment of psychomotor development on a scale was conducted at the end of the 1st month of life and in 3 full months (Table 2).

In each of the groups there was an improvement in all points of development in a full 3 months. For a more accurate view of the improvement of development in the full 3 months, the increase in the main indicators of development was estimated as a percentage (compared to previous data) (Fig. 1).

Discussion

According to the results, both groups of children had similar starting positions according to the Munich Functional Diagnosis of Development. After a comprehensive rehabilitation program of Early Intervention in the Department of Neonatal Pathology, the neurological status of children improved in all categories. The most pronounced changes were observed in the motor area (skills of crawling, sitting and walking). Grasping skills, expressive speech and social age were restored at a slower pace. At the same time, the characteristics that assess the age of perception, ie visual and auditory responses, also progressed more intensively. This may be due to the elements of sensory integration that were part of the early rehabilitation complex.

In the group of children who were not able to receive comprehensive treatment immediately after undergoing HIE, basic functions were restored at a slower pace. Moreover, the motor reflex sphere suffered the most. It is likely that the identified differences may be predictors of delays in motor, mental or speech development in old age. Accordingly, it is advisable to monitor children at risk during the first years of life for timely detection of deviations and their correction.

According to a British study [15] on the impact of early development programs on children at high perinatal risk, the greatest effect was exerted by complex programs with an impact on the motor, cognitive and sensory areas. According to the authors, corrective massage and elements of neurodevelopmental therapy (NDT) meet the principles of recurrence and enrichment of the environment around the baby with motor stimuli. In preschool, such children showed better cognitive abilities compared to those who had similar circumstances at birth but did not have access to early rehabilitation. However, excessive sensory stimuli can have a negative effect on behavior at the age of 2 years. According to our observations, in the short run, the motor sphere improves in the first place in comparison with communication skills. While after 2 years of age the differences in motor development between the two groups

of children are less noticeable. Most likely, with age, the effectiveness of the impact on the motor sphere decreases, which requires further observation. Spittle A. and Treyvaud K. [25] emphasize the importance of selecting a set of procedures that affect different areas of development. In addition, they point out the importance of education and involvement in the early rehabilitation of the child's parents, as well as the creation of a favorable sensory environment at home. No component of early intervention can be identified as the most effective.

Italian authors used EEG data to assess the effects of newborn massage and obtained improvements in its structure [12]. Their programs for "enrichment of motor space" have shown a positive impact on both motor and mental development in the long run [23].

The authors of a large systematic review of 2016 on early intervention note that the impact on the damaged brain in the neonatal period is required as early as possible due to its high plasticity [14]. They also note the greatest effect of the early intervention system on cognitive development compared to motor in the long run. While our results 3 months after the intervention showed a predominant effect on motor area and perception. Such data may also indicate an inextricable link between the quality of perception and mental development. Which in turn shows the need to include in the rehabilitation system elements of sensory integration. Hadders-Algra M. et al. [14] showed that the isolated use of neurodevelopmental therapy or other author's techniques does not give the desired result. While the combination of different influences improves both the motor and cognitive spheres of the child's development, similar to our results. The authors note that the system of early intervention gives greater prospects to full-term infants who have suffered from encephalopathy. While premature births with periventricular leukomalacia, quite often give a picture of cerebral palsy in old age. The review also emphasizes the importance not only of periodic professional rehabilitation courses, but also of enriching the child's living environment and teaching parents the elements of early intervention. The main conclusions of the authors, analyzing 13 major works in the world at that time on early intervention, are as follows: early intervention affects motor and mental development, the dosage of intervention is crucial and parental involvement in the rehabilitation of the child improves family well-being. Our conclusions on the early effects of the intervention system are quite consistent with those presented and need to be continued in the longer term.

At present, there is no consensus in the world on specific recommendations on the scope and methods of early intervention. But the work carried out to assess various areas of child development after the application of interventions in different countries, like ours, give encouraging results. Most authors are inclined to believe that early intervention should be started as soon as the child's condition allows and selected according to its needs [25]. Existing normative documents in Ukraine on the rehabilitation of children with organic CNS damage apply mainly to those who have already developed neurodevelopmental disorders [20, 22]. Clinical guidelines for infants with a high potential risk of motor, mental or speech developmental disorders need to be developed immediately.

Conclusions

1. Adverse onset of life, in particular perinatal hypoxic-ischemic encephalopathies, is one of the factors of poor adaptation in society, high morbidity and low future incomes.

2. The system of early intervention (Earlyintervention-programs) is generally accepted in the civilized world. Its principles and principles should be implemented in Ukraine for the purpose of social adaptation of children who have suffered perinatal CNS damage.

3. To assess the effectiveness of comprehensive rehabilitation in young children, it is advisable to use adapted for Ukraine scale of Munich functional developmental diagnostics, which allows to assess the child's development in all major areas, its harmony and effectiveness of rehabilitation measures during the first 3 years of life.

4. The development of a national Early Intervention Strategy is relevant and in line with current trends.

5. One of the possible options for solving this problem may be the creation of follow-up departments at children's institutions of the III level of medical care. But their effective functioning is possible under the condition of full-fledged work as centers of early intervention with proper staffing and technical support.

References

[1] Aikardi, Z. H., Martin, B., Kristofer, G. Turko, K. S., Gerasimov, A. P., Barashkova, S. V., ... & Skoromets, A. A. (2013). *Заболевания нервной системы у детей [Diseases of the nervous system in children]*. М.: Издательство Панфилова; БИНОМ Лаборатория знаний - M.: Panfilov Publishing House; BINOM Knowledge Laboratory.

[2] Badheka, R., Barad, N. K., & Sankhla, C. S. (2018). Pediatric movement disorders. *Neurology India*, 66(7), 59-67. doi: 10.4103/0028-3886.226447

[3] Barashnev, Iu. I. (1997). Компенсация нарушенных функций ЦНС и значение стимулирующей терапии при перинатальных повреждениях головного мозга новорожденных [Compensation of impaired central nervous system functions and the importance of stimulating therapy in perinatal brain damage in newborns]. *Российский вестник перинатологии и педиатрии - Russian Bulletin of Perinatology and Pediatrics,* (6), 7-13.

[4] Berezhnyi, V. V. (2013). *Педіатрія: національний підручник [Pediatrics: a national textbook]*. Київ: б, (2013) - Kyiv: b, (2013).

[5] Busl, K. M., & Greer, D. M. (2010). Hypoxic-ischemic brain injury: pathophysiology, neuropathology and mechanisms. *NeuroRehabilitation,* 26(1), 5-13. doi: 10.3233/NRE-2010-0531

[6] Ciuraj, M., Kieszczynska, K., Doroniewicz, I., & Lipowicz, A. (2019, June). *Subjective and Objective Assessment of Developmental Dysfunction in Children Aged 0-3 Years-Comparative Study.* In International Conference on Information Technologies in Biomedicine (pp. 382-391). Springer, Cham.

doi: 10.1007/978-3-030-23762-2_34

[7] Clinical Practice Guideline: Report of the Recommendations. (2006). Motor Disorders, Assessment and Intervention for Young Children (Age 0-3 Years). New York State Department of Health, P.O. Box 2000, Albany, New York 12220.

[8] Cowan, F., Rutherford, M., Groenendaal, F., Eken, P., Mercuri, E., Bydder, G. M., ... & de Vries, L. S. (2003). Origin and timing of brain lesions in term infants with neonatal encephalopathy. *The Lancet,* 361(9359), 736-742. doi: 10.1016/S0140-6736(03)12658-X

[9] Detsyk, O. Z., & Melnyk, R. M. (2017). Вплив появи важкохворої дитини на соціальний статус її родини [The influence of the appearance of a seriously ill child on the social status of her family]. *Україна. Здоров'я нації - Ukraine. The health of the nation,* (1), 16-21.

[10] Dobrova-Krol, N. (2014). Раннее вмешательство: ключевые аспекты и международный опыт [Early intervention: key aspects and international experience]. URL:http://www.unicef.org/ukraine/ukr/Early_Intervention_Concept_RUS.pdf (date of the application: 1.05. 2018).

[11] Gajewska, E., Sobieska, M., & Samborski, W. (2006). Correlates between Munich Functional Development Diagnostics and postural reactivity findings based on seven provovoked postural reactions modus Vojta during the first period of child's life. In *Annales Academiae Medicae Stetinensis* (Vol. 52, No. 3, pp. 67-70). PMID: 17385350

[12] Guzzetta, A., D'acunto, M. G., Carotenuto, M., Berardi, N., Bancale, A., Biagioni, E., ... & Cioni, G. (2011). The effects of preterm infant massage on brain electrical activity. *Developmental Medicine & Child Neurology,* 53, 46-51. doi: 10.1111/j.1469-8749.2011.04065.x

[13] Hackworth, N. J., Berthelsen, D., Matthews, J., Westrupp, E. M., Cann, W., Ukoumunne, O. C., ... & Nicholson, J. M. (2017). Impact of a brief group intervention to enhance parenting and the home learning environment for children aged 6-36 months: A cluster randomised controlled trial. *Prevention Science,* 18(3), 337-349. doi: 10.1007/s11121-017-0753-9

[14] Hadders-Algra, M., Boxum, A. G., Hielkema, T., & Hamer, E. G. (2017). Effect of early intervention in infants at very high risk of cerebral palsy: a systematic review. *Developmental Medicine & Child Neurology,* 59(3), 246-258. doi: 10.1111/dmcn.13331

[15] Hutchon, B., Gibbs, D., Harniess, P., Jary, S., Crossley, S. L., Moffat, J. V., ... & Basu, A. P. (2019). Early intervention programmes for infants at high risk of atypical neurodevelopmental outcome. *Developmental Medicine & Child Neurology,* 61(12), 1362-1367. doi: 10.1111/dmcn.14187

[16] Johnston, M. V., Fatemi, A., Wilson, M. A., & Northington, F. (2011). Treatment advances in neonatal neuroprotection and neurointensive care. The Lancet Neurology, 10(4), 372-382. doi: 10.1016/S1474-4422(11)70016-3

[17] Koy, A., Lin, J. P., Sanger, T. D., Marks, W. A., Mink, J. W., & Timmermann, L. (2016). Advances in management of movement disorders in children. *The Lancet Neurology,* 15(7), 719-735. doi: 10.1016/S1474-4422(16)00132-0

[18] Landsem, I. P., Handegard, B. H., Ulvund, S. E., Kaaresen, P. I., & Ronning, J. A. (2015). Early intervention influences positively quality of life as reported by prematurely born children at age nine and their parents; a randomized clinical trial. *Health and quality of life outcomes*, 13(1), 1-11. doi: 10.1186/s12955-015-0221-9

[19] Liu, J., Li, J., & Gu, M. (2007). The correlation between myocardial function and cerebral hemodynamics in term infants with hypoxic-ischemic encephalopathy. *Journal of tropical pediatrics,* 53(1), 44-48. doi: 10.1093/tropej/fml053

[20] Martyniuk, V. Yu. (2016). *Основи соціальної педіатрії. Навчально-методичний посібник: у 2-х т [Fundamentals of social pediatrics. Training manual: in 2 volumes].* К.: ФОП Верес О.І. - К.: FOP Veres O.I.

[21] Ministry of Health of Ukraine. (2008). Про затвердження Клінічного протоколу медичного догляду за здоровою дитиною віком до 3-х років [On approval of the Clinical Protocol of medical care for a healthy child under 3 years of age]. Нормативно-директивні документи МОЗ України. Наказ № 149 від 20.03.2008 - Regulatory documents of the Ministry of Health of Ukraine. Order № 149 of 20.03.2008.

[22] Ministry of Health of Ukraine. (2013). Про затвердження клінічних настанов та Уніфікованого клінічного протоколу медичної допомоги та медичної реабілітації "Церебральний параліч та інші органічні ураження головного мозку у дітей, які супроводжуються руховими порушеннями" [About the statement of clinical instructions and the Unified clinical protocol of medical care and medical rehabilitation "Cerebral palsy and other organic defeats of a brain at children which are followed by motor disturbances"]. Нормативно-директивні документи МОЗ України. Наказ № 286 від 09.04.2013 - Regulatory documents of the Ministry of Health of Ukraine. Order № 286 of 09.04.2013.

[23] Morgan, C., Novak, I., Dale, R. C., Guzzetta, A., & Badawi, N. (2016). Single blind randomised controlled trial of GAME (Goals Activity Motor Enrichment) in infants at high risk of cerebral palsy. *Research in Developmental Disabilities*, 55, 256-267. doi: 10.1016/j.ridd.2016.04.005

[24] Richter, L. M., Daelmans, B., Lombardi, J., Heymann, J., Boo, F. L., Behrman, J. R., ... & Lancet Early Childhood Development Series Steering Committee. (2017). Investing in the foundation of sustainable development: pathways to scale up for early childhood development. *The Lancet,* 389(10064), 103-118. doi: 10.1016/S0140-6736(16)31698-1

[25] Spittle, A., & Treyvaud, K. (2016). The role of early developmental intervention to influence neurobehavioral outcomes of children born preterm. In *Seminars in perinatology* (Vol. 40, No 8, pp. 542-548). WB Saunders. doi: 10.1053/j.semperi.2016.09.006

[26] Spittle, A., Orton, J., Anderson, P. J., Boyd, R., & Doyle, L. W. (2015). Early developmental intervention programmes provided post hospital discharge to prevent motor and cognitive impairment in preterm infants. *Cochrane Database of Systematic Reviews*, (11), CD005495. doi: 10.1002/14651858.CD005495.pub4

[27] United Nations Office on Drugs and Crime's. (2017). Compilation of Evidence-Based Family Skills Training Programmes. URL: https://www.issup.net/knowledge-share/publications/2017-08/compilation-evidence-based-family-skills-training-programmes (date of the application: 10.10. 2019).

[28] Voronenko, Yu. V., Hoida, N. H., & Moiseienko, R. O. (2015). Сучасні аспекти розвитку системи медико-соціальних послуг для уразливих груп дітей в Україні [Modern aspects of the development of the system of medical and social services for vulnerable groups of children in Ukraine]. *Український медичний часопис - Ukrainian medical journal*, (1), 14-18.

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Requirements for writing this section are general, as well as for all international scientific publications. The data is presented clearly, in the form of short descriptions, and must be illustrated by color graphics (no more than 4) or drawings (no more than 8) and tables (no more than 4), the information is not duplicated.

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In the discussion, it is necessary to summarize and analyze the results, as possible, compare them with the data of other researchers. It is necessary to highlight the novelty and possible theoretical or practical significance of the results of the research. You should not repeat the information already listed in the "Introduction" section. At the end of the discussion, a separate paragraph should reflect the prospects for using the results obtained by the author.

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