SCIENTIFIC RESEARCH OF THE SCO COUNTRIES: SYNERGY AND INTEGRATION

上合组织国家的科学研究：协同和一体化

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这些会议文集结合了会议的材料 – 研究论文和科学工作者的论文报告。 它考察了职业化人格的技术和社会学问题。一些文章涉及人格职业化研究问题的理论和方法论方法和原则。

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CONTENTS

PHARMACEUTICAL SCIENCES

创新企业：国内竞争力
INNOVATIVE ENTERPRISES: DOMESTIC COMPETITIVENESS

Karimov Bulat Nailevich
Candidate of Economic Sciences, Associate Professor
State Scientific Center
Medical Biophysical Center named after A.I. Burnazyan

抽象的。 在本文中，我们将考虑对油气市场企业的竞争力进行评估，在第四次工业革命的当前条件下，这是基于生产数字化的。 "第四次工业"革命的概念越来越流行——它是工业和数字技术的结合，催生了数字工业、智能工厂和工厂。它导致网络物理系统的引入，生产过程的自动化，这直接影响了生产力的提高。数字化是现代创新企业在油气市场竞争力的关键因素。
关键词：竞争力、数字化、石油、天然气、发展、俄罗斯

Abstract. In this article, we will consider the assessment of oil and gas market enterprises in terms of their competitiveness, which in the current conditions of the fourth industrial revolution is based on the digitalization of production. The concept of the "fourth industrial" revolution is gaining more and more popularity - it is a combination of industry and digital technologies, which lead to the creation of digital industries, smart factories and factories. It leads to the introduction of cyber-physical systems, automation of production processes, which directly affects the increase in productivity. It is digitalization that is a key factor in the competitiveness of modern innovative enterprises in the oil and gas market.

Keywords: competitiveness, digitalization, oil, gas, development, Russia

The oil industry plays one of the key roles in the economy of our country. This industry has huge opportunities, not all of which have been realized at the moment. In modern conditions of globalization and the desire of Western companies in this industry to enter new markets, domestic VIOC form their strategies based on a variety of internal and external factors. The competitiveness of any enterprise and VIOC will not be an exception here, it is determined by several factors - this is the presence of a quality management system, which is undoubtedly important, but the presence of competition as such will be even more important. As of January 2021, oil production in the Russian Federation was carried out by 285 organizations, while 104 of them are part of the VIOC structure, which accounted

for a total of 85% of all national oil production at the end of last year. The rest of the market is divided between 187 independent companies and 3 operating on the terms of a production sharing agreement. VIOC has undeniable competitive advantages over small companies, as they have a complete production and marketing cycle. The VIOC structure has a pronounced oligopolistic character.

Starting from 2016, the Federal Antimonopoly Service of the Russian Federation has been considering the possibility of adopting a law "On Peculiarities of the Turnover of Oil and Oil Products in the Russian Federation". Its goal is to limit the power of companies in the oil and gas industry of the domestic economy and transfer more rights to third parties or small companies. The measures contained in the draft law are aimed at curbing actions aimed at restricting competition on the part of market participants, as well as at improving the efficiency of regulating relations related to oil turnover. However, even today we can note some progress in this matter, so over the past 5 years there has been an increase in the share of small companies.
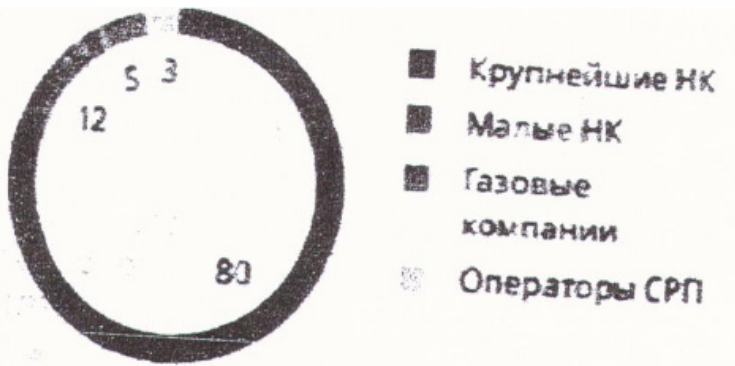
Figure 1. Share of small companies

It is worth recognizing that the vertical integration of companies in the oil industry of our country, although being successfully implemented, is still not without difficulties. All industry players are focused on the development of oil refining and the delivery of petroleum products to the end consumer, however, capitalization is directly related to proven oil reserves [1].

The depletion of reserves in traditional mining areas requires significant financial investments in exploration. Oil business strategies are largely influenced by recent significant changes in the oil industry.

Modern technologies in all areas of the oil industry lead to the evolution of vertical integration. From the information discussed earlier, it is clear that the hallmark of oil companies is their strategies. Obviously, those strategies that were

used in the very recent era of industrial development at the end of the twentieth century are not relevant at the present time - the era of the digital economy and digitalization [2].

The current situation in the industry dictates its own rules of the game, only companies that can extract and process oil more efficiently than others, as well as produce oil products ahead of market requirements, will be able to claim success in the competition. This requires powerful technological tools, and therefore, technological development is one of the main priorities of the company. Key performance indicators of "Gazprom-neft" PJSC in accordance with the development strategy until 2025 are shown in figure 2.

	Key perfor-mance indicator	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
1	Production from high-tech wells, thousand toe	7450	8190	8600	9030	9480	9955	104 50	109 75	115 25	121 00	127 05
	For reference: the share of production of their high-tech wells	17.1 %	19.2 %	19.3 %	19.4 %	19.5 %	20.0 %	21.2 %	23.3 %	25.3 %	27.5 %	30.3 %
2	Expenses for R&D and Technological Strategy, million rubles	596	1670	1770	1930	2130	2180	2430	2540	2640	2750	2900
	For reference: share of R&D and technology strategy costs in revenue	0.06 %	0.19 %	0.18 %	0.18 %	0.19 %	0.18 %	0.18 %	0.17 %	0.17 %	0.16 %	0.16 %
3	Specific consumption of fuel and energy resources for own technological needs and losses toe/toe	0.04 59	0.04 75	0.04 12	0.04 20	0.04 39	0.04 37	0.04 74	0.04 73	0.04 75	0.04 87	0.05 01
	Annual measurement in %		3.7	-13.4	1.9	4.6	-0.5	0.5	-0.1	0.4	2.5	2.9

4	Specific greenhouse gas emissions in CO2 equivalent, t/toe	0.1299	0.1280	0.1159	0.1090	0.1046	0.1015	0.0995	0.0975	0.0965	0.0955	0.0846
	Annual measurement in %		-3.0	-8.0	-6.0	-4.0	-3.0	-2.0	-2.0	-1.0	-1.0	-1.0
5	Growth in the number of used patents and licenses, units	-9	2	2	2	2	2	2	2	2	2	2
6	Labor productivity, million rubles/person	17.7	14.1	15.3	15.5	17.7	19.1	20.5	22.1	23.6	24.9	26.1
	Annual measurement in %		-20.5	8.6	7.6	7.8	7.7	7.7	7.6	6.6	5.7	4.6
7	Share of R&D contracts in the field of oil refining for which package applications were submitted, %	70	70	73	76	79	81	83	85	85	85	85

Figure 2. *Key performance indicators of "Gazprom-neft" PJSC until 2025*

Technological development is one of the company's priorities until 2030. Innovative technologies should contribute to the effective implementation of large-scale projects in the field of oil production, and as a result, will allow us to take a leading position in strategic areas. If we talk about the company's competitive strategies and its position in the market, we cannot ignore the company's constant work to improve product quality, the main goals in this direction are to ensure efficient production and further marketing of products that meet both domestic and all international standards.

Good financial results, new fields, active interaction with the state, along with the fact that the company is successfully fulfilling the goals set in the strategy for 2025 [4], this strategy was supposed to be the goal until 2020, so it is not surprising that the company seeking to take a leading position in its industry, is preparing a development strategy for 2030. The new strategy is a logical continuation of the previous one, however, it will be more focused on the company's market positioning, increasing its flexibility to all external changes and transforming key business processes. By 2030, the company should become a benchmark for other

industry representatives in terms of efficiency, manufacturability and safety, and the company's focus is not only on domestic, but also on the world representatives of the oil and gas industry [5].

The company's development strategy until 2030 implies the implementation of a number of opportunities aimed at improving operational efficiency. This should happen as a result of the development and implementation of advanced modern technological solutions. The company's goal is to unlock the potential of new niches in the market through innovation. Also, it is planned to further develop in the markets and maintain leadership positions in terms of the efficiency of the sales network in the country. The company aims to occupy 70% of the domestic market for catalysts for key secondary oil refining processes, as well as take the lead in the LNG bunkering market in the country. As for the premium segment, the goal here is to enter the top 10 global jet fuel manufacturing companies for the production of lubricants and bitumen products.

Digitalization is the creation of data flows in production, "smart" technologies that speed up managerial decision-making and increase labor productivity at times. All this is already working for the new economy. However, the formation of a developed innovative and creative sector is impossible without taking into account the best world experience.

The most important thing in oil production is to do it as efficiently as possible, without fear of competition. The digital technologies used in the oil industry are directly related to this. They should allow not only to increase production, but also to make it as efficient as possible, including from the point of view of the company's budget. In its competitive strategies, PJSC "Gazpromneft", first of all, aims at digitalization. According to many factors, innovation in all areas of activity has a great impact on the competitiveness of the company, both within the industry and beyond.

In recent years, the company has implemented a large number of digitalization projects, including those using artificial intelligence, analytics, and others. Blockchain-based smart contracts have been developed and implemented. This project concerns aviation fuel refueling. Its implementation will increase the speed and efficiency in financial settlements for refueling aircraft, as well as automate the planning and accounting of fuel supplies. In the domestic market - this is the first advanced experience of this kind. For airlines, blockchain provides an opportunity to avoid financial risks and prepayments. This approach increases efficiency and significantly reduces labor costs. When initiating a smart contract, the customer company transmits through the system to "Gazprom Neft" information about the planned supply, in which the volume and price are fixed. These data are necessary to transfer the TK to the tanker driver. On the specified date, the aircraft commander requests the amount of refueling from the operator, an online application

to the customer's bank reserves the required amount on the account, after which refueling of the aircraft immediately begins. After the service is rendered, funds are debited, and information about the closing of the current application is transmitted to the commercial services of both parties, with all reporting documents attached. This innovation guarantees that transactions will be carried out exclusively according to the scheme approved by both parties, which eliminates the possibility of violation of the terms of the contract and guarantees the transparency of settlements.

The implementation of such projects as part of digital transformation, in cooperation with major partners, allows us to reach a new level of technological and operational efficiency already at this stage. The digitalization of business in the conditions of the modern economy, of course, provides great competitive advantages. The company has opened a digital office in St. Petersburg - "Innovation House", which undoubtedly indicates that the company is betting heavily on technology in its competitive strategies. Based on the results, we can conclude that in the event of further successful implementation of the digital transformation strategy, oil and gas companies will be able to maintain and increase their competitive positions in the oil market, while continuing to reduce costs and increase operating profit.

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神经网络技术在劳动力市场管理人员选拔过程中的应用前景
PROSPECTS FOR THE USE OF NEURAL NETWORKS IN THE PROCESS OF SELECTING MANAGEMENT STAFF IN THE LABOR MARKET

Tretyakov Oleg Vladimirovich
Candidate of Economic Sciences, Head of the Department
Perm National Research Polytechnic University
Perm, Russia

抽象的。 本文分析了使用人工神经网络对管理人员选择过程进行建模的前景。 研究了使用神经网络技术开发营销机制以调节劳动力市场管理人员选择中的调解过程的可能性。 招聘机构等专业机构被视为中介。 在这方面应用数学方法可以增加人事决策的客观性，也可以在招聘机构普遍采用的海量选拔情况下简化人事经理的工作。
关键词：人员选择，人员配备机构，人工神经网络，神经网络技术，管理决策自动化。

Abstract. The article analyzes the prospects for the use of artificial neural networks to model the processes of selection of management staff. Possibilities of using neural network technologies for the development of marketing mechanisms for regulating the processes of mediation in the selection of managerial staff in the labor market are studied. Specialized institutions such as recruitment agencies are considered intermediaries. The application of mathematical methods in this area can increase the objectivity of personnel decisions, as well as simplify the work of personnel managers in the case of mass selection, which is common practice for recruitment agencies.

Keywords: personnel selection, staffing agencies, artificial neural network, neural network technologies, automation of management decisions.

In the process of organizing the activities of any company, the leading place is occupied by the personnel management system, or the so-called personnel management. E. Michaels, H. Handfil-Jones, H. Axelrod, world-famous management practitioners, in their famous book "The War for Talents" note that in the 21st century the demand for highly qualified workers clearly exceeds supply [1, p. 35]. Today, the successful operation of companies depends on the availability of

such personnel. Therefore, employers compete with each other for effective employees who can maximize performance. Under these conditions, the management of any company requires fast and accurate recruitment decisions. The process of personnel management (personnel management) began to be singled out as a separate business process within the company.

The famous foreign researcher Edwin B. Flippo gave the following definition: "Personnel management is the planning, organization, remuneration and integration of people in order to achieve organizational, individual and social goals" [2, p. 303]. A broader interpretation is given by the modern English-language business dictionary: "Human resources management is an administrative discipline related to the recruitment and development of employees, aimed at increasing their value to the organization, including analysis of staffing needs, planning and selection of personnel, selection of people for a place work, orientation and training, salary determination, provision of benefits and incentives, performance evaluation, dispute resolution, communication with all employees at all levels" [3].

Some Russian researchers consider personnel management as an integral part of the innovation management policy, which has the following areas: the development of an enterprise's personnel policy, the selection and placement of personnel, adaptation and stabilization of personnel [4, p. 52]. We agree with the approach according to which personnel management is a personnel management system, which is a combination of a theoretical field of knowledge and a field of practical activity, including planning, search and selection of personnel, its orientation, training and stimulation, adaptation and stabilization aimed at for the company to achieve the goal of acquiring a workforce that satisfies all the requirements, capable of coping with the tasks set with high quality and at minimal cost [5].

The search (selection) of personnel is one of the stages of the personnel management system, which includes the methods used by companies in order to ensure the best composition of potential qualified labor force, from which they can hire candidates if necessary.

Recruitment is carried out sequentially (tab. 1) [6, p. 2-3].

Table 1.

Stages of recruitment

№	Selection process stage	Stage characteristic
1	Development of a recruitment and retention policy, as well as a system that ensures its functioning	Collecting statistics, maintaining documentation on the organizational recruitment process
2	Assessing the organization's current and future workforce needs	The need for labor force for each labor category (functional unit) of the organization should be assessed according to the established priorities. Availability of tools for assessing future labor demand. Conducting a proactive analysis of the impact of significant changes in the organization on the ability of employees to continue their work activities in this company through surveys or individual interviews.
3	Determining the potential workforce in the internal and external environment of the organization, as well as the degree of competition for the proposed vacancy	Satisfying the need for personnel at the expense of the internal personnel reserve. The use of external sources of labor. Development and application of certain strategies for searching and attracting candidates.
4	Position analysis	Definition of the content of the work in terms of knowledge, skills, competencies and experience. Determination of the proposed remuneration for the work performed. The analysis allows you to establish what tasks the employee will face, how he will have to solve them, what personal qualities he needs to have.
5	Determination of the ability of the organization to pay wages and other bonuses, bonuses within a certain period of time	Develop ideas about possible rewards in order to attract potential employees.
6	Determination of the strategy for searching and attracting candidates	It acts as the basis for the following procedures: announcement of a vacancy, contact with a candidate (telephone, through a personal interview).

Completion of the sixth stage of personnel selection enters the beginning of the implementation of the procedure - personnel selection.

One of the most time-consuming and responsible processes in personnel

management is the search and evaluation of the professionalism of future employees of the company. This requires significant experience, professionalism and knowledge of modern assessment methods from managers in order to evaluate a potential employee [7, p. 3]. Evaluation is understood as "a purposeful process of comparing the characteristics of an employee and the requirements of a position or workplace, which allows obtaining information for making further management decisions" [8, p. 115].

Personnel selection in the company is carried out by the personnel department, however, in some cases it is unprofitable for the company to engage in independent search and screening of candidates, and the company may contact a recruitment agency. The personnel (recruiting) agency undertakes the work of finding future employees, conducting interviews and selecting those who will be recommended to the client. A recruiting agency may also provide services such as staff leasing, in which an employee is legally registered with a recruitment agency but works for the client company.

The HR managers of the recruitment agency are directly involved in the search for candidates, conducting interviews and the subsequent selection of future employees, and in fact, the quality of recruitment directly depends on them. In turn, the agency bears both non-material (the reputation of the agency) and material responsibility for the quality of selection: if the proposed employee has not passed the probationary period with the client, the recruitment agency, depending on the specific terms of the contract, can significantly reduce the amount of the invoice.

The evaluation of a potential employee is mainly carried out during the interview, but a sufficient amount of information about the candidate can also be gleaned from the resume. Moreover, any recruitment agency has a resume database that includes employees of both categories: those who have passed the probationary period and those who have not passed it, which makes it possible to use artificial neural networks to simulate recruitment processes.

Neural networks are artificial, multi-layer highly parallel (i.e., with a large number of independently parallel operating elements) logical structures composed of formal neurons. The beginning of the theory of neural networks and neurocomputers was laid by the work of American neurophysiologists W. McCulloch and W. Pitts "The logical calculus of ideas related to nervous activity" (1943), in which they proposed a mathematical model of a biological neuron [9, p. 363-384].

Among the fundamental works, one should also highlight the model of D. Hebb, who in 1949 proposed the learning law, which was the starting point for learning algorithms for artificial neural networks. The further development of the neural network theory was significantly influenced by the monograph "Principles of Neurodynamics" by the American neurophysiologist F. Rosenblatt, in which he described in detail the scheme of the perceptron (a device that simulates the

process of information perception by the human brain). His ideas have been developed in the scientific works of many authors. In 1985-86, the theory of neural networks received a "technological impetus" caused by the possibility of modeling neural networks on affordable and high-performance personal computers that appeared at that time [10].

An artificial neural network is a mathematical model built on the principle of organization and functioning of biological neural networks [11, 12].

Currently, artificial neural networks are widely used in solving a wide variety of problems, especially where conventional algorithmic solutions are ineffective or even impossible. An artificial neural network is a huge distributed parallel processor consisting of elementary information processing units that accumulate experimental knowledge and provide it for further processing. An artificial neural network is similar to the brain in the following parameters: the knowledge used by an artificial neural network in the learning process comes into it from the environment; to accumulate knowledge, synaptic weights are used - connections between neurons. The main advantage of artificial neural networks is that they build a model based on the presented information, i.e. do not need a known model in advance. It is for this reason that artificial neural networks are widely used in those areas of human activity where there are poorly algorithmized tasks [13].

The advantage of using artificial neural networks for classification problems is due to their exceptional ability to model non-linear dependencies with a large number of variables. In addition, in the case of employee evaluation, when the number of classes is two (0 - the employee should not be recommended to the client, 1 - the employee can be recommended to the client), the use of neural networks will not cause difficulties associated with the presentation of data at the output of the network [14, p. 453].

The activity of recruitment agencies is focused on the consumers of the labor force - employers. The potential market, in which employers express their specific demand and employees specify their offer, consists of a number of separate segments. In relation to the labor market, its segmentation is the process of breaking down the supply of labor and the demand for it into groups expressing aggregates that respond in the same way to the same employment incentive. Each of them is characterized by similar needs on the part of consumers, the same properties of the labor force or the same type of behavior of employees. In this study, the segment of the labor market from the standpoint of employers will be considered known, the models under consideration relate to assessing the compliance of personnel with the requirements of employers from this segment [15].

Formally, the mechanism for assessing the candidate's compliance with the requirements of various segments of the labor market and employment can be represented as a mechanism for recognizing how much the constructed candidate's

characteristics vector $X = (x_1, x_2, \ldots x_n)$ reproduces the average image $Y = (y_1, y_2, \ldots y_m)$ requirements of employers from a certain segment of the labor market (the values y_k $k = \overline{1.m}$ can be measured in special rating scales or $y_k \in [0.1]$ $k = \overline{1.m}$ and reflect the severity of a certain requirement) and in general a generalized indicator $\mu \in [0.1]$ of employer satisfaction with this candidate. The vector of candidate characteristics includes the entire range of data obtained at all stages of the standard selection [15, p. 77].

Many of these qualities reflect the analysis of the content of the work, which is carried out on the basis of special questionnaires.

Proven measurement methods are used to measure the characteristics of candidates, in particular, special tests are used. The difficulty lies in the fact that the question of the validity of the selection method, that is, the quality of the measurement and the optimality of this particular set of characteristics for determining the compliance with this position, always remains not fully resolved. Any measuring system must measure exactly what it is designed to measure. The requirements of employers reflect certain criteria for the success of the work. The relevance of performance criteria is determined by the extent to which its use as an index of success correlates with actual success in any given activity. Traditionally, work performance criteria are classified into three main types, reflecting the performance indicator, evaluation data, and personnel information. Unfortunately, employers very often cannot clearly articulate the requirements, perhaps they are not even interested in individual competencies, but in combinations of competencies, it is easier for the employer as a whole to assess the degree of compliance of an employee with a certain position after he has worked in this position. Recruitment agencies monitor the fate of the candidates recommended by them, and know the assessment of the work of these people by employers. The employer assesses compliance with the requirements based on his feelings and experience in this segment of the labor market and employment [15, p. 77].

To formalize the evaluation process, special behavioral scales are developed, for example, rating scales.

Of considerable interest is the construction of a formalized mechanism for recognizing the degree of compliance of a candidate with the requirements of employers, capable of learning in some way, i.e. reproduce and generalize the experience of employers. The very formulation of the problem leads to the fact that the development of such mechanisms can be based on neural network technologies. Let's make a brief reasoning underlying artificial neural networks [16]. These considerations provide some justification for using neural network mechanisms.

Humans solve complex problems of pattern recognition, classification, and decision making with daunting ease. This is done by the nervous system. The nervous system consists of a collection of cells - neurons, which are in contact with

each other with the help of processes - dendrites and axons.

Neurons are specialized cells capable of receiving, processing, encoding, transmitting and storing information, organizing reactions to stimuli, establishing contacts with other neurons and organ cells.

Artificial neural networks consist of artificial neurons, the functionality of which is similar to most of the elementary functions of a biological neuron. These elements are organized in a way that may correspond to some extent to the anatomy of the brain. Despite their superficial similarities, artificial neural networks exhibit a surprising number of properties that are inherent in the brain. For example, they learn from experience, generalize previous cases to new cases, and extract essential properties from incoming redundant information. Artificial neural networks can change their behavior depending on the external environment. Upon presentation of the input signals (perhaps together with the required outputs), they self-adjust (learn) to provide the desired response. Many learning algorithms have been developed, each with its own strengths and weaknesses. The response of the network after training can be somewhat insensitive to small changes in the input signals. This inherent ability to see through noise and distortion is vital to pattern recognition in the real world.

The question of the possibility of constructing, on the basis of neural networks, a formalized mechanism for recognizing the degree of compliance of a candidate with the requirements of employers is reduced to the problem of the possibility of an accurate representation or approximation using a neural network of a mapping that associates the input vector of the candidate's characteristics $X = (x_1, x_2, ... x_n)$ average image $Y = (y_1, y_2, ... y_m)$ of compliance with the requirements of employers from a certain segment of the labor and employment market or (and) in general, a generalized indicator $\mu \in [0.1]$ of employer satisfaction [15, p. 78].

Speaking of neural networks, we are talking about the approximation of functions of many variables using linear operations and superpositions of functions of one variable. Each network consists of formal neurons. The neuron receives a vector of signals x as input, calculates its dot product with the vector of weights, and applies some function of one variable. The result is sent to the inputs of other neurons or passed to the output. Thus, neural networks calculate superpositions of simple functions of one variable and their linear combinations [15, p. 78].

The following statement is a theoretical basis for constructing the functions required by the formulation of the problem based on neural networks.

Theorem 1 [17]. For any set of pairs of input-output vectors of arbitrary dimension (X^k, Y^k), $k = 1, K$ there exists a two-layer homogeneous neural network with serial connections, with sigmoidal $\left(f(c) = \frac{1}{1+e^{-\alpha s}} \right)$ activation functions and with a finite number of neurons, which for each input vector X^k forms the corresponding output vector Y^k.

Thus, a two-layer homogeneous neural network with sigmoidal activation functions is used to represent multidimensional functions of many variables.

To estimate the number of neurons in the hidden layers of homogeneous neural networks, the following formula is used to estimate the required number of synaptic weights N_ω in a multilayer network with sigmoidal transfer functions:

$$\frac{N_y N_p}{1+\log_2(N_p)} \leq N_\omega \leq N_y \left(\frac{N_p}{N_x}\right) \cdot \left(N_x + N_y + 1\right) + N_y, \tag{1}$$

where N_y - output signal dimension;

N_p - number of training sample elements;

N_x - dimension of the input signal. Having estimated the required number of weights, we can calculate the number of neurons in the hidden layers. For example, the number of neurons in a two-layer network will be:

$$N = \frac{N_\omega}{N_x + N_y}, \tag{2}$$

similarly, one can calculate the number of neurons in networks with a large number of layers.

If the number of hidden layers and the number of neurons in each layer are determined, then before applying the network to solve the problem of predicting the compliance of candidates with the requirements of employers from the considered segment of the labor market, it is necessary to set the optimal values of the weight coefficients for each neuron, on each layer of the network. The formation of such optimal weights is called the learning process of the neural network. Training is based on some reference signal-vectors or a reference sample (when it is known which signal is fed to the input of the neural network and which should be the output). This learning process is called supervised learning or learning by reference. In our case, the role of a reference sample will be played by a sample of pairs of sets of characteristics of candidates $X = (x_1, x_2, ..., x_n)$ and success criteria $Y = (y_1, y_2, ..., y_m)$, which are stored in the database recruitment agency.

To solve the problem, a homogeneous multilayer feedforward network without feedback is used, the training of which is carried out according to the backpropagation algorithm. The scheme of operation of such a network is shown in fig. 1 [15, p. 79].
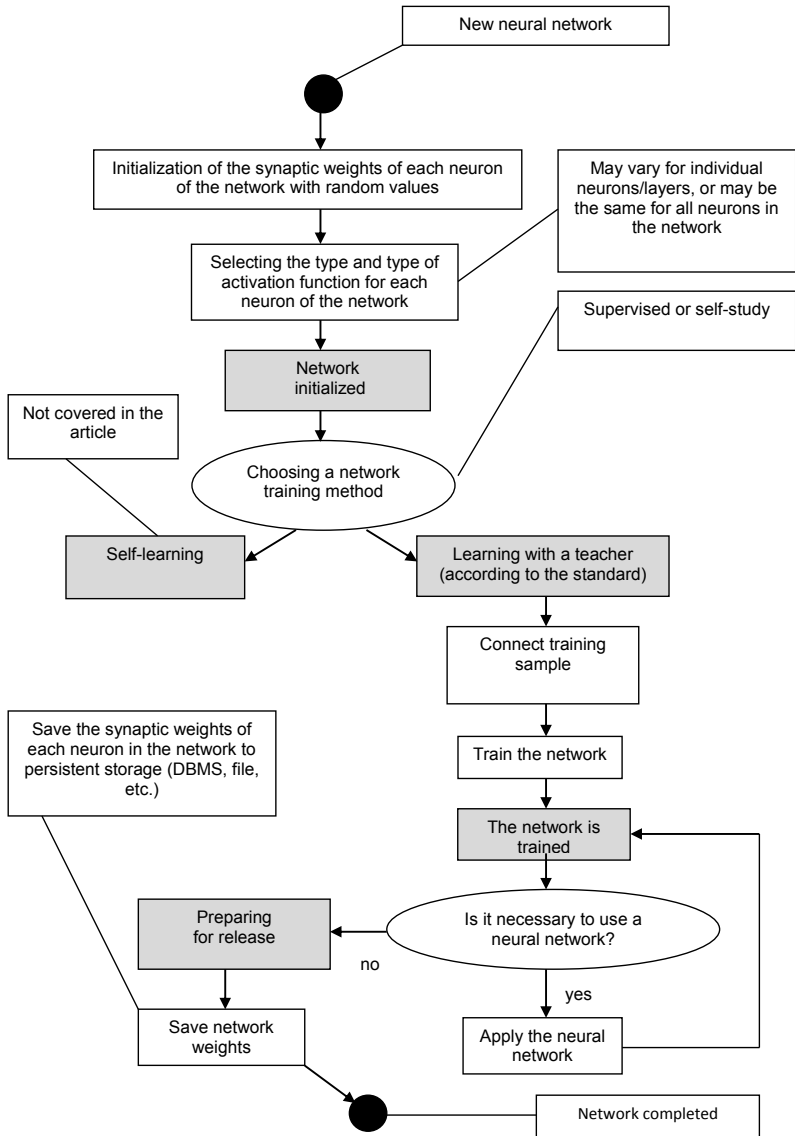
Figure 1. Scheme of the network functioning

The general scheme of the neural network mechanism is shown in fig. 2. [15, p. 80].
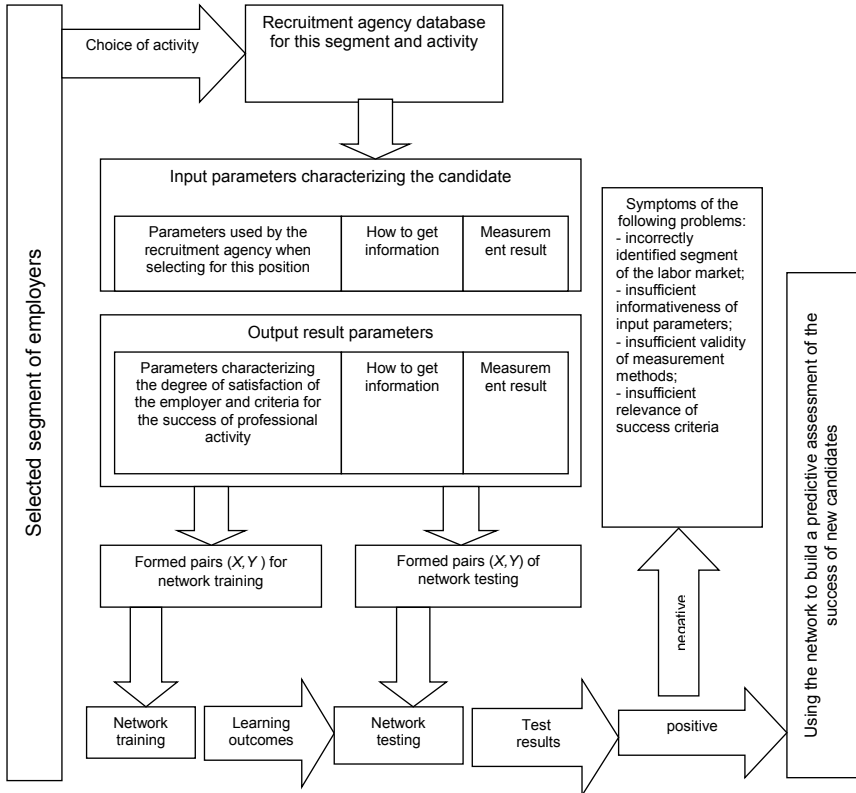
Figure 2. General scheme of the neural network mechanism

It should also be noted that:

- the performance of the neural network mechanism depends on how correctly the segment of the labor market is identified; the input parameters of the candidates are correctly selected; valid and reliable mechanisms for measuring input parameters; relevant parameters of success;

- it is possible to build neural network mechanisms, the output of which for new candidates is a scalar value $\mu \in [0,1]$ of the overall satisfaction of the employer; it is possible to build compositions of neural networks, the output of the first neural network is a multidimensional vector $Y = (y_1, y_2, ..., y_m)$, then this vector as an input is fed to the input of the second neural network, the output of which is the value $\mu \in [0,1]$;

- similar neural network mechanisms can be used in the internal analytical activities of recruitment agencies, for example, they, like special statistical methods,

can solve the problems of the validity and reliability of the measurement methods used, the problems of the relevance of the criteria for the success of professional activity [15, p. 79-80].

Thus, the introduction of the latest intelligent systems in personnel management makes it possible to make a qualitative leap in management and increase the efficiency of personnel selection for productive work in the company. Artificial neural networks have good potential for modeling the recruitment process, but this method also has disadvantages. In the case when a recruiting agency carries out a mass selection of employees and the agency wants to automate this process, it may not be so important to know what effect specific factors have on the classification. If we are talking about the selection of highly qualified personnel, for example, for managerial positions, such information would certainly be useful, because. in this case, the mathematical model can only act as a decision support system, while the final decision on whether the employee can be recommended to the client remains with the HR manager.

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员工激励在食品企业发展管理中的地位
THE PLACE OF STAFF MOTIVATION IN THE MANAGEMENT OF THE DEVELOPMENT OF FOOD ENTERPRISES

Ustyugova Irina Evgenievna
Candidate of Economic Sciences, Associate Professor

Krivenko Elena Ivanovna
Candidate of Economic Sciences, Associate Professor

Stryapcikh Elena Sergeevna
Senior Lecturer

Voronezh State University of Engineering Technology
Voronezh Russia

抽象的。人员激励体系的形成是企业管理任何类型活动的基本组成部分。这是根本，因为动机决定了人的活动，决定了员工的行为特征，从而导致了人员的激活。员工的行为是由一组或复杂的个人动机决定的，这些动机在这些动机中相互作用并决定了他的工作效率。对于每个员工来说，这个集合是个人的，由许多不同的因素决定。组织的激励结构必须具有一定的稳定性、稳定性，但它是可以变化和发展的。为了团结团队，吸引额外的员工，以及留住主要员工，有必要引入劳动力的物质非货币激励政策。这将使员工感到安全和安全，在舒适的条件下工作，学习、发展，从而发展公司。社会一揽子计划的存在将对特定员工的劳动活动和整个企业产生积极影响。员工工作效率提高，劳动生产率提高，劳动纪律加强。所有这一切最终将导致该组织的财务业绩增加。

关键词：管理、发展、激励、人员、组织。

Abstract. The formation of a personnel motivation system is a basic component of the management of an enterprise of any type of activity. And this is fundamental, since motivation determines human activity and determines the characteristics of the employee's behavior, leading to the activation of personnel. The behavior of an employee is determined by a set or complex of individual motives in which they interact and determine the effectiveness of his work. For each employee, this set is individual and is determined by many different factors. The motivational structure of the organization must have a certain stability, stability, but it can change and develop. In order to unite the team, attract additional staff, as well as retain the main staff, it is necessary to introduce a policy of material non-

monetary incentives for labor. This will allow employees to feel secure and safe, work in comfortable conditions, learn, develop and thereby develop the company. The presence of a social package will have a positive impact both on the labor activity of a particular employee and on the enterprise as a whole. The efficiency of employees will increase, labor productivity will increase, and labor discipline will be strengthened. All this, ultimately, will lead to an increase in the financial results of the organization.

***Keywords:** management, development, motivation, personnel, organization.*

The global intensification of economic processes is associated with information, technical and technological changes. In order to remain competitive, many businesses are forced to improve.

Currently, development is the most important element in the activities of most domestic enterprises, as it is associated with the need to modernize the Russian economy as a whole. Development management is becoming a necessary component of company management.

Under development, it is customary to consider the dynamic state of the system (including socio-economic); the process of transforming an object, its transition to a new position; level (degree) of development (maturity) of the subject and system. The positive transformation of the entire enterprise or part of it in the economic context, as a rule, is understood as development.

In an unfavorable economic environment, companies need to strive to prevent wastage of resources, which can be achieved through the formation and implementation of a well-defined organization development strategy, which allows company leaders to achieve their desired profit and profitability targets. Note that the bankruptcy of any enterprise that conducts business activities can be caused by uncoordinated actions of its management and not following a clearly formulated development strategy. In this regard, in recent years, there has been a special interest of the management of enterprises in the development of risk management measures and the desire to create an integrated management system and an effective development strategy.

If necessary, based on the identified problematic aspects of strategic management, it is important to develop proposals for improving the strategy to prevent a decrease in the activity of an economic entity and the possibility, if necessary, of increasing it in a strategic perspective [2].

One of the most relevant areas is the development of human resources of the organization. This problem is considered and studied both at the state, regional and industry levels, and at the micro level - organizations, enterprises. The processes of population reproduction are given great attention by the state, and demographic security is one of the directions for the development of the domestic economy. Or-

ganizations and enterprises act as separate economic entities, which in turn form separate industries and influence the dynamics of the gross regional product, as well as the probabilistic growth of the economy and the main indicators of its efficiency. An organization is not able to become effective and develop further without an effectively functioning personnel management system. The work of people directly affects the economic performance of the organization.

The personnel motivation system includes four groups of employee incentive methods: direct material incentives, indirect material incentives, organizational incentives, moral incentives, which are presented in figure 1.

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                    ┌─────────────────────────────────┐
                    │   Employee incentive methods    │
                    └─────────────────────────────────┘
          ┌──────────────────────┐      ┌──────────────────────┐
          │  Financial incentive │      │ Non-financial incentives │
          └──────────────────────┘      └──────────────────────┘
```

1. Direct material incentives: wages, bonuses, bonuses, gifts.
2. Direct indirect incentives: flexible working hours, valuable gifts, payment for vouchers, extended vacations, shortened working hours.

1. Organizational incentives: growth prospects, career, self-realization as a specialist, participation in corporate events.
2. Moral stimulation: recognition (personal, public), criticism, praise.

Figure 1. Employee incentive methods

Material incentives are a certain system of non-monetary, as well as monetary (but which has a material and material form of expression) employee incentives. One of its main elements is wages, which allows you to influence the efficiency of labor. The higher the wage, the correspondingly, and most of their needs are able to satisfy a person. In the system of monetary motivation, bonuses and bonuses can also be distinguished. Non-monetary forms include extended vacations, valuable gifts, shorter working hours, flexible work hours.

Non-material incentives consist in satisfying the psychological needs of a person, the purpose of which is a moral impact on a person through creating an atmosphere of social harmony around him.

These may include a career, self-realization as a specialist, participation in corporate events, the prospect of growth, criticism, recognition, praise, medical care, vacation, insurance [1].

Through status differences, the boundaries of non-material and material incentives are determined, which consist in incentives that were received by an employee occupying a certain status in the organization, or rather, a separate workplace, as well as privileges for a particular employee. At the moment, there are many forms and methods of incentives, but the management of the organization needs to develop mechanisms for motivating employees and adapt them to the specific conditions and tasks of the organization. The features of the organization must be constantly taken into account (its traditions, history, specifics of activity), and of course, a motivational map should be built individually for each employee.

The object of the study was a regional food industry enterprise, after analyzing the dynamics of the labor resources of which it was revealed that over the past three years the enterprise has experienced a high turnover of personnel. This is mainly due to the violation of labor discipline among workers. The replacement rate in 2020 was 0.06, which indicates that there was a reduction in production volumes and the elimination of some jobs.

In order to increase the saving of material resources, increase the productivity of work (labor) and improve the final results of the enterprise, bonuses are paid to employees.

The following types of awards are used:

- monthly bonus for the main results of economic activity based on the results of work for the same month.

It should be noted that bonuses to workers and permanent staff are carried out for such indicators as:

observance of labor discipline and compliance with safety regulations;

high-quality and timely fulfillment of planned targets, instructions and functional duties;

a noticeable improvement in the quality of work, an increase in the level of responsibility for the assigned area of work, for the manifestation of the creative activity of each employee.

The monthly bonus is 50% of the basic salary. This bonus is accrued monthly in full, provided there are no violations of labor discipline.

- bonuses based on the performance of the company as a whole for the year.

It should be noted that individual workers of the enterprise for work in harmful working conditions with high qualifications are given a salary bonus of 4%. These allowances are established based on the results of a special assessment of the conditions of the trois at the workplace.

Also, the company establishes an additional payment for combining professions and positions, as well as for increasing the volume of work performed. It is up to 30% of the salary for the replaced job. More specific amounts of such surcharges are set by the director. The size may depend on many factors.

The most reliable and obvious moment (method) by which an enterprise can reward its employees is a monetary reward.

In order to raise the culture of work (production) and improve the aesthetic appearance of the organization, the production premises were repaired (internal repair). Employees of the enterprise were also involved in the repair work. Planting green spaces on the territory of the enterprise is directly related to the aesthetic factors of the working area. This affects the thermal regime, improves the air, reduces noise, reduces dust, decorates and creates comfort. The territory has been landscaped, new flower beds have been laid out, and the internal premises (canteens, showers) are being renovated.

To identify the motives of employees, an anonymous survey was conducted, the results of which are presented in figure 2.
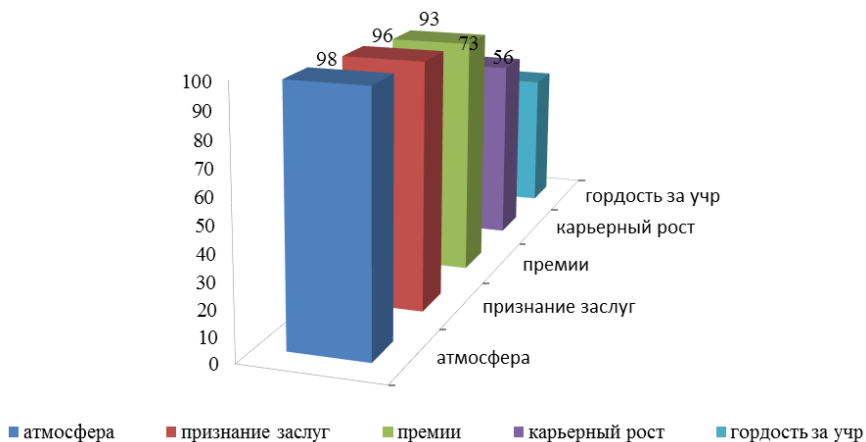
Figure 2. *The main motives of the employees of the organization, %*

Incentive methods are bonuses (93%), professional recognition (96%), and the first place in the survey was the psychological atmosphere in the team (98%). As a rule, many enterprises most often use material methods of stimulation, but as we see from the results of the survey, the psychological component is of great importance for the employees of the enterprise under study, especially for creative professions.

It should be noted that out of all respondents, 80% of respondents answered positively to the question of whether corporate culture influences labor stimulation, and another 20% found it difficult to answer. No negative results were received.

Based on this, we can conclude that corporate culture has a high degree of influence on the stimulation of labor and the work process as a whole.

It should be noted that due to the low level of wages, there is a turnover of staff, which adversely affects the activities of the enterprise.

Personnel motivation is the basis of an effective and productive organization of labor, one of the ways to increase labor motivation is to increase the motivation of department heads, and as a result, increase the motivation of subordinates on the part of department heads.

The main directions for improving the motivation of the personnel of a food enterprise are presented in table 1.

Table 1.
The main directions for improving the motivation of food enterprise personnel

The main directions for improving the motivation of food enterprise personnel
Holding competitions and presenting valuable gifts for employees
Development of a scheme of accruals, deductions, surcharges
Scholarship program
Organization of staff training
Support for employee health measures
Sale of enterprise products of preferential value

After analyzing the system of labor incentives at a food enterprise, it is obvious that the personnel policy of the enterprise is aimed at obtaining decent wages and bonuses for the staff based on performance. However, the staff is dissatisfied with the level of material motivation, as every year management rewards employees less and less. A huge drawback of the system of material incentives is the absence of a direct and clear connection between wages and work results for almost all categories of workers. [3]

To fully stimulate labor in material terms, it is necessary to develop a scheme for calculating deductions/surcharges and convey it to employees. In order to inform employees about the new bonus scheme, it is necessary to display visual information on information stands, hold meetings within each department and communicate this information to employees in an accessible way. Surveys should be conducted in each department, which will reflect the changes that have occurred from the introduction of a new system of staff motivation.

In order to unite the team, attract additional staff, as well as retain the main staff, it is necessary to introduce a policy of material non-monetary incentives for labor. This will allow employees to feel secure and safe, work in comfortable conditions, learn, develop and thereby develop the company.

Thus, the presence of a social package will have a positive impact both on the labor activity of a particular employee and on the enterprise as a whole. Firstly, the efficiency of employees will increase, secondly, labor productivity will increase, and thirdly, labor discipline will be strengthened. All this, ultimately, will lead to an increase in the financial results of the organization.

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公司管理中的品牌：研究的理论方面
BRANDING IN COMPANY MANAGEMENT: THEORETICAL ASPECTS OF THE STUDY

Pryadko Svetlana Nikolaevna
Candidate of Economic Sciences, Associate Professor

Qian Feifan
Undergraduate
Belgorod National Research University

摘要： 本文介绍了有关品牌化问题理论来源的简要研究成果。该研究以两个搜索引擎为基础：Google Scholar 和 Web of Science。指标采用定量指标：出版物和引用的次数；和定性指标：科学出版物的语言和主题专业化。对被引用次数最多的出版物进行有意义的分析，可以确定企业科学主题研究和实践活动的几个发展方向：品牌作为附加值，品牌作为关系主题，品牌作为战略管理工具，品牌作为战略资产。
关键词：品牌，管理，企业，理论分析

Abstract. *The article presents brief results of a study of theoretical sources on the problem of branding. The information base of the study was two search engines: Google Scholar and Web of Science. Quantitative indicators were used as indicators: the number of publications and citations; and qualitative: linguistic and thematic specialization of scientific publications. A meaningful analysis of the most cited publications made it possible to identify several directions for the development of thematic scientific research and practical activities of firms: brand as an added value, brand as a subject of relations, brand as a strategic management tool, brand as a strategic asset.*

Keywords: *branding, management, firm, theoretical analysis*

Introduction

The relevance of the research problem is due to the rapid changes taking place in the world and national economies of many countries, forcing the management of companies to develop anti-crisis scenarios for the development of companies, change existing business models, make changes to current operating activities and look for more effective tools for interaction between the company and the market. One such tool is branding.

Research methodology and design

The study took place in two stages. At the first stage of the study, we carried out a quantitative analysis of secondary information on the research problem in two search engines: Google Scholar and Web of Science. The indicators of the study were: the number of thematic publications, the number of citations, language and thematic specialization.

At the second stage of the study, we carried out a meaningful analysis of the most cited publications and identified areas for the practical use of branding in the practice of company management. The article presents brief results of the study.

Research results

An analysis of the scientific literature on the research problem showed that the concept of "branding" is quite capacious, and is used in the context of managing certain areas of development of firms more and more often. The dynamics of the use of the term in English-language publications of the Google Scholar search engine over the past five years is presented in table 1.

Table 1.

Dynamics of references to the concept of "branding" in the English-language literature of the Google Scholar search engine

Year	Searching results	Thematic publication with the highest citation rates
2016	Results: approximately 64900 (0.05 sec)	Branding in the age of social media. D Holt - Harvard business review, 2016 - academia.edu Cited: 305
2017	Results: approximately 64100 (0.05 sec)	Designing brand identity: an essential guide for the whole branding team. A Wheeler - 2017 - books.google.com Cited: 1372
2018	Results: approximately 61100 (0.03 sec)	Internet-Branding. CF Altobelli, M Sander - 2018 - degruyter.com Cited: 83
2019	Results: approximately 55500 (0.05 sec)	Branding in the era of digital (dis) intermediation. K Gielens, JBEM Steenkamp - International Journal of Research in Marketing, 2019 - Elsevier Cited: 57
2020	Results: approximately 46800 (0.07 sec)	Branding in a hyperconnected world: Refocusing theories and rethinking boundaries. V Swaminathan, A Sorescu- Journal of Sage, 2020 - journals.sagepub.com Cited: 94
2021	Results: approximately 42400 (0.08 sec)	Role of brand experience in shaping brand love. R Joshi, P Garg - International Journal of Consumer Studies, 2021 - Wiley Online Library Cited: 54

According to the presented data, it can be seen that the dynamics of thematic publications on branding issues has a negative value. The maximum number of publications falls on 2016 (64900). The most cited publications are devoted to the problems of Internet branding, digitalization and practical issues of brand development.
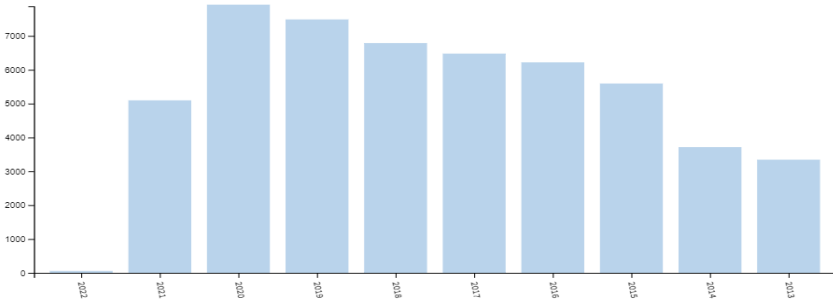
An analysis of scientific publications in the Web of Science Internet search platform showed the presence of 79,320 thematic materials. The top 5 most cited sources are presented in table 2.

Table 2.

List of the most cited branding case study sources in the Web of Science search engine

Period	Number of citations	Most cited publication
JAN 1993	5,200	KELLER, KL CONCEPTUALIZING, MEASURING, AND MANAGING CUSTOMER-BASED BRAND EQUITY JOURNAL OF MARKETING Vol: 57 Issue: 1 P.: 1-22
MAR 1998	3,149	Fournier, S Consumers and their brands: Developing relationship theory in consumer research JOURNAL OF CONSUMER RESEARCH Vol: 24 Issue: 4 P.: 343-373
NOV 1991	2,772	TVERSKY, A; KAHNEMAN, D LOSS AVERSION IN RISKLESS CHOICE - A REFERENCE-DEPENDENT MODEL QUARTERLY JOURNAL OF ECONOMICS Vol: 106 Issue: 4 P.: 1039-1061
AUG 1997	2,582	Aaker, JL Dimensions of brand personality JOURNAL OF MARKETING RESEARCH Vol: 34 Issue: 3 P.: 347-356
MAR 2001	2,383	Muniz, AM; O'Guinn, TC Brand community JOURNAL OF CONSUMER RESEARCH Vol: 27 Issue: 4 P.: 412-432

According to the presented data, it can be seen that the most cited publications were prepared in the 90s of the XX century. At the same time, it should be noted that the citation rate, firstly, cannot be the only true criterion for the indicator of the scientific and practical significance of research and publication; secondly, the number of citations is gradually increasing as the scientific community becomes familiar with the author's research.

The dynamics of thematic scientific publications in the Web of Science search engine in the current period is shown in figure 1.

Figure 1. *Dynamics of thematic scientific publications in the Web of Science search engine*

We also analyzed the linguistic and territorial structure of scientific research in the field of branding (figures 2 and 3).
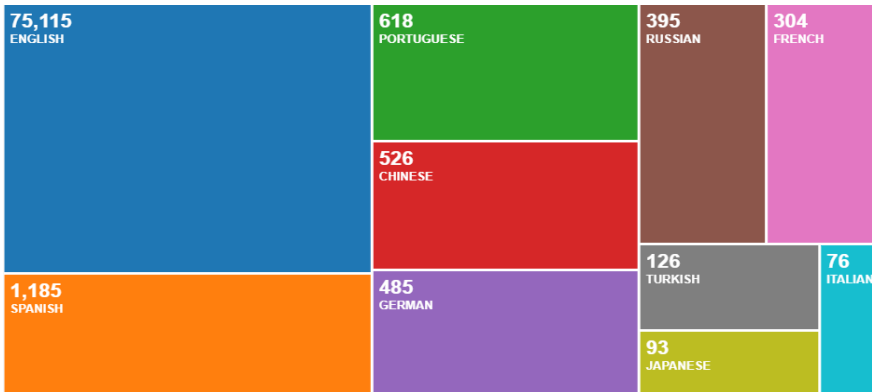
Figure 2. *The language structure of thematic scientific publications in the Web of Science search engine*

According to the presented data, it can be seen that the majority of scientific publications on branding issues are published in English (75,115 publications), with a significant margin - publications in Spanish (1185 publications), Portuguese (618), Chinese (526), German (485) and Russian (395). But it is impossible to unambiguously judge the geographical structure of scientific interest in brand-

ing problems, since English is the generally accepted language for publishing research results all over the world. The territorial structure of thematic publications on branding issues is as follows.
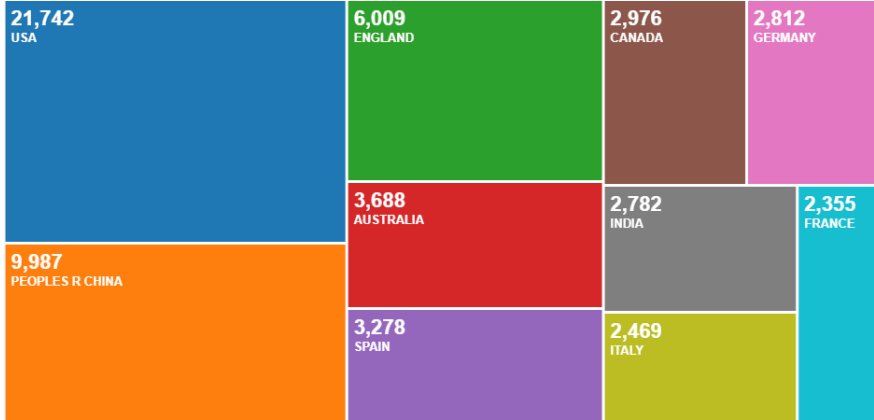
Figure 3. Territorial structure of thematic scientific publications in the Web of Science search engine

According to the presented data, it can be seen that most of the scientific research on branding issues in the analyzed period was carried out in the United States (21742), China (9987), England (6009), Australia (3688), Spain (3278), Canada (2976), etc.

At the second stage of the study, we carried out a meaningful analysis of the most cited sources. An analysis of the most cited publications made it possible to identify several areas in which the main ideas of scientific research and the practical activities of firms in the field of branding are concentrated.

1) Brand as added value. It involves the construction of a branding system and brand management from the standpoint of added value.

2) Brand as a subject of relations. It involves the formation of a system of brand relations with the target audience.

3) Brand as a strategic management tool. It involves the development and implementation of the brand as the leading tool for strategic management.

4) Brand as a strategic asset. It involves the development and use of the brand from the position of an intangible asset of the company.

Thus, according to the presented periodization, it can be seen that in most scientific publications brand management is studied from the position of attracting the added value of a product, service or company. The main scientific methodology of this approach is a set of linguistic, psychological, and, now increasingly,

neuroscientific methods aimed at studying the values of branding objects, assessing the depth and strength of the influence of brand attributes, etc.

In the studies of the brand as a subject of relations and a tool for the company's strategic management, the main methods are also a set of semantic and syntactic research methods.

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国际刑事法院是国际司法的参考吗?
IS THE INTERNATIONAL CRIMINAL COURT A REFERENCE OF INTERNATIONAL JUSTICE?

Skorik Elena Nikolaevna
Candidate of Juridical Sciences, Associate Professor,
Head of the Master's Department
Rostov Institute for Entrepreneur Protection

注解。 这篇文章涉及国际刑事法院的诉讼程序问题。 以关于刚果民主共和国的决定为例，提出了国际司法的公平性和公正性问题。
关键词：国际刑事法院、罗马规约、刚果民主共和国调查。

Annotation. *The article deals with the issues of the proceedings of the International Criminal Court. On the example of the decision on the Democratic Republic of the Congo, questions of fairness and impartiality of international justice are raised.*

Keywords: *International Criminal Court, Rome Statute, Democratic Republic of the Congo investigation.*

The International Criminal Court was established by the Rome Statute [1], which was adopted on 17 July 1998 and entered into force on 1 July 2002.

There are 124 States parties to the Rome Statute of the International Criminal Court. Of these, 34 are African states, 19 are in the Asia-Pacific region, 18 are in Eastern Europe, 28 are countries in Latin America and the Caribbean, 25 are countries in Western Europe and other regions.

The Russian Federation has signed the Rome Statute, but has not yet ratified it and has not been a State Party to the International Criminal Court. On November 16, 2016, the President of the Russian Federation signed a decree "On the intention of the Russian Federation not to become a party to the Rome Statute"[2], which means Russia's withdrawal of the signature under this document.

The International Criminal Court is an independent, permanent judicial body with jurisdiction over those responsible for the most serious crimes of concern to the international community, namely the crimes of genocide, crimes against humanity and war crimes.

In 2003, the International Criminal Court became a reality. A fully functioning

Court has been formed in accordance with the principles laid down in the Rome Statute.

The Democratic Republic of the Congo Inquiry was the first official investigation by the International Criminal Court. These are crimes committed in the DRC during the Second Congo War and its aftermath, including the Ituri and Kivu conflicts. The war began in 1998, and despite a peace agreement between the combatants in 2003, the conflict continued in the eastern parts of the country for several years. In April 2004, the DRC government formally referred the situation in the Congo to the International Criminal Court, and in June 2004 prosecutor Luis Moreno Ocampo formally launched an investigation. Arrest warrants were issued for: Thomas Lubang Dyilo, and Mathieu Ngudjolo Chui, Bosco Ntaganda, Callixte Mbarushimana. Summarized information on the proceedings conducted by the ICC is set out in the table:

Names of the accused	Charges	ICC decision
Thomas Lubanga Dyilo Alleged founder of the Union of Congolese Patriots (UCP) and the Patriotic Forces for the Liberation of the Congo (FPJK); alleged former commander-in-chief of the PPJK from September 2002 until at least the end of 2003.	**Recruitment of children** is a war crime (Art. 8(2)(b)(xxvi) of the Rome Statute); **Conscription of children for military service** is a war crime (Art. 8(2)(b)(xxvi) of the Rome Statute); **Using children to participate in hostilities** is a war crime (Art. 8(2)(b)(xxvi) of the Rome Statute).	14 years in prison

Names of the accused	Charges	ICC decision
Germaine Katanga led the Ituri Patriotic Resistance Front (FRPI) and was appointed Brigadier General of the Armed Forces of the Democratic Republic of the Congo (FARDC).	**Intentional killing** is a war crime (Art. 8(2)(a)(i) of the Rome Statute); **Inhuman acts -** a crime against humanity (art. 7(1)(k) of the Rome Statute); **Inhuman or cruel treatment** is a war crime (art. 8(2)(a)(ii) or (c)(i) of the Rome Statute); **Using children to participate in hostilities** is a war crime (art. 8(2)(b)(xxvi) of the Rome Statute); **Sexual slavery** is a crime against humanity (Art. 7(1) (g) of the Rome Statute).	In December 2012, they were acquitted by Judge Bruno Kotte due to insufficient evidence of the involvement of the accused in these crimes.
Mathieu Ngujolo Chui Army Colonel of the Democratic Republic of the Congo, in the past one of the leaders of the armed group "Nationalist and Integrationist Front" (FNI) and the Ituri Patriotic Resistance Forces (FRPI)	**Sexual slavery** is a war crime (Section 8(2)(b)(xxii) or (e)(vi) of the Rome Statute); **Attacking a civilian population** is a war crime (art. 8(2)(b)(i) or (e)(i) of the Rome Statute); **Plunder** is a war crime (Art. 8(2)(b)(xvi) or (e)(v) of the Rome Statute).	

Names of the accused	Charges	ICC decision
Bosco Ntaganda former member of the Rwandan Patriotic Army and allegedly former Deputy Chief of the General Staff of the Patriotic Forces for the Liberation of the Congo (FPLC), the military wing of the Union of Congolese Patriots.	**Recruitment of children** is a war crime (Art. 8(2)(b)(xxvi) of the Rome Statute); **Conscription of children for military service** is a war crime (Art. 8(2)(b)(xxvi) of the Rome Statute); **Using children to participate in hostilities** is a war crime (art. 8(2)(b)(xxvi) of the Rome Statute); **Murder** is a crime against humanity (para. 1 a) Art. 7 of the Rome Statute); **Rape and sexual slavery** are crimes against humanity (art. 7(1) (g) of the Rome Statute); **Persecution** is a crime against humanity (Art. 7(1) (h) of the Rome Statute); **Murder** is a war crime (Art. 8(2)(c)(i) of the Rome Statute); **Attacking a civilian population** is a war crime (art. 8(2)(e)(i) of the Rome Statute); **Rape and sexual slavery** are war crimes (Art. 8(2)(e)(vi) of the Rome Statute); **Plunder** is a war crime (art. 8(2)(e)(v) of the Rome Statute).	sentenced to 30 years in prison. Ntaganda subsequently appealed his verdict. On 30 March 2021, the ICC Appeals Chamber rejected his appeal and upheld his conviction.

Names of the accused	Charges	ICC decision
Callixte Mbarushimana Rwandan Hutu and former United Nations official (1992-2001)	**Attacking a civilian population** is a war crime (art. 8(2)(b)(i) or (e)(i) of the Rome Statute); **Destruction of property** is a war crime (art. 8(2)(a)(iv) or (e)(xii) of the Rome Statute); **Murder** is a crime against humanity (para. 1 a) Art. 7 of the Rome Statute); **Torture** is a war crime (art. 8(2)(a)(ii) or (c)(i) of the Rome Statute); **Rape** is a crime against humanity (art. 7(1) (g) of the Rome Statute); **Inhuman treatment** is a war crime (Art. 8(2)(a)(ii) of the Rome Statute); **Persecution** is a crime against humanity (Art. 7(1) (h) of the Rome Statute).	The Pre-Trial Chambers by a majority refused to confirm the allegations and ordered Mbarushimana's release from custody.
Sylvester Mudakumura general commander of the military wing of the rebel democratic forces for the liberation of Rwanda (FDLR), known as the Combat Forces of Abakunguzi (FOKA).	**Murder** is a war crime (Art. 8(2)(c)(i) of the Rome Statute); **Mutilation** is a war crime (Art. 8(2)(c)(i) of the Rome Statute); **Ill-treatment** is a war crime (Art. 8(2)(c)(i) of the Rome Statute); **Torture** is a war crime (Art. 8(2)(c)(i) of the Rome Statute); **Insult to personal dignity** is a war crime (Art. 8(2)(c)(ii) of the Rome Statute); **Attacking a civilian population** is a war crime (art. 8(2)(e)(i) of the Rome Statute); **Plunder** is a war crime (art. 8(2)(e)(v) of the Rome Statute); **Rape** is a war crime (Art. 8(2)(e)(vi) of the Rome Statute); **Destruction of property** is a war crime (art. 8(2)(e)(xii) of the Rome Statute).	killed by the security forces of the Democratic Republic of the Congo in the territory of Rutshuru on the night of September 17-18, 2019

According to the Coalition for the ICC, the verdict was "a heavy blow to the victims and affected communities, who placed all their hopes in the Court to achieve justice, given the great harm they suffered during the ethnic war in Ituri"[3].

Obviously, in order to smooth the dissatisfaction of the victims, the Judicial Chamber of the International Criminal Court issued a decision, according to which Bosco Ntaganda was obliged to pay $ 30 million in compensation to the victims of the conflict in the Democratic Republic of the Congo (DRC), who suffered as a result of the actions of one of the leaders of the rebel army. This is the largest amount of compensation in the history of the ICC.

At the same time, the judges acknowledged that Ntaganda himself was insolvent and called on the Trust Fund for Victims of Crime to "contribute as much as possible to compensation, given available resources", and to make efforts to "search for additional funds necessary to pay compensation in full". According to the decision of the judges, the money should not go to payments to individuals, but to finance programs, charitable foundations and projects created to help victims of crime.

Is it possible to recognize the above decisions of the ICC as fair? More than 5 thousand persons received the status of victims. Many of them were infected with HIV after gang rapes by soldiers, were rejected by their families and communities, and do not have access to medicines, psychological and other assistance.

Nevertheless, according to the ICC judges, the conviction of a person in the absence of a solid evidence base, moreover, on the basis of incorrectly applied rules of law, is an unacceptable price in the fight against impunity.In their dissenting opinion, Judges Christine van den Wingart (Belgium) and Howard Morrison (Great Britain) noted that the quality of justice is determined not by the numbers of convictions and acquittals, but, above all, by the fairness of the process.

At the same time, the Russian Foreign Ministry recalled that over 14 years of work, the ICC issued only four verdicts, while spending more than a billion dollars[4].

What can induce nation-states to recognize such justice as an impartial instance, in whose hands should be given both the scales and the punishing sword of Themis?

References

1.   https://www.un.org/ru/documents/decl_conv/conventions/pdf/rome_statute(r).pdf

2. Decree of the President of the Russian Federation of November 16, 2016 N 361-rp "On the intention of the Russian Federation not to become a party to the Rome Statute of the International Criminal Court" // Collected Legislation of the Russian Federation of November 21, 2016. - No. 47. Art. 6630.

3. https://web.archive.org/web/20151121180440/http:// www. haguejusticeportal.net/index.php?id=30

4. https://ria.ru/20161116/1481485239.html

集聚区划界问题（俄罗斯圣彼得堡案例）
PROBLEM OF AGGLOMERATIONS' BORDER DELIMITATION (CASE SAINT PETERSBURG, RUSSIA)

Vulfovich Revekka Mikhailovna
Doctor of Political Sciences, Full Professor
North-west Institute of Management of RANEPA - National School of
Public and Business Administration (Saint Petersburg)

抽象的。 现在，世界上大约 50% 的人口居住在大大小小的城市中。 世界高度城市化，出现了新型的定居系统。 它们大多被称为聚集地，由数十个城市、城镇、村庄组成。 它们与现代交通系统相互连接，包括通勤列车、地铁、有轨电车和其他铁路运输，还与公共汽车和私家车相连。 进一步的发展需要对未来的战略性认识，而集聚边界的划定是这一过程中最为复杂的问题之一。 这篇文章专门讨论这种划界的原则和方法，并以圣彼得堡（俄罗斯）周边地区为例，展示了这种划界的可能性和复杂性。
关键词：城市化，聚居系统，集聚，交通系统，战略，边界划定，圣彼得堡。

Abstract. Now about 50% of the world population live in larger and smaller cities. The world is highly urbanised, and new types of settlement systems appear. Mostly they are called agglomerations and consist of dozens of cities, towns, villages. They are interconnected with modern transport systems including commuter trains, undergrounds, trams, and other rail-transports but also with busses and private cars. Further development needs strategic understanding of the future, and the agglomeration border delimitation is one of the most complicated problems in this process. The article is devoted to principles, methods of such delimitation and shows the possibilities and complications of it on the example of the region around Saint Petersburg (Russia).

Keywords: urbanisation, settlement systems, agglomeration, transport system, strategy, border delimitation, Saint Petersburg.

Introduction

In the modern high urbanized world agglomerations are the most often existing settlements' form. Growing large cities rope other smaller ones, and rural villages in their area into the common development process. Multiple connections – economic, social and first transport – develop between separated settlements in a large

space. As M. Castells wrote the space of places and the space of flows (finance, energy, social, cultural and others) are interconnected and influence each other. During the time the connections become more intensive, and the new integrated space arises. The agglomeration building process is global, the problems connected with it have a common character. One of the problems is the development of a common policy for the whole area and the fulfilment of a common politics inside its borders.

The 10-dimensional[1] political hyperspace of an agglomeration

The analyses of some agglomerations in different countries shows that these systems have multiple power levels which include the central state level (in unitary states); two state levels – the federal and the level of the federation elements (states, Länder, provinces, regions in federal states); one, two or more municipal levels (in all states). All levels are interconnected differently, they create the hierarchical structure in some cases, coordinate their functioning and cooperate during the tasks completion that go beyond the interests of one level. A very modern mechanism of collaboration allows to include citizens into the decision-making process. Interests and ideas of different groups should be considered and reflected in programs and projects implemented within the agglomeration. But political-administrative borders of municipalities and regions give little possibilities for this. So, the problem of political integration of the hyperspace has a great importance in all agglomeration areas of the world. It becomes more difficult because of their large dimensions (territory and population) and uneven distribution of this population (density) and different level of the quality of life. We illustrate the main characteristics of 7 agglomeration examples (table 1).

Table 1.

Examples of large agglomeration. Main characteristics

N	Name of the metro area	Territory	Population / density	Levels of governance
1.	Beijing-Tianjin-Hebei Metropolitan Area, China (Jing-Jin-Ji, 'Jing' 京 for Beijing, 'Jin' 津 for Tianjin and 'Ji' 冀 for the Hebei Province)	217.156 km² (about 2.2% of the total land area of China)	112mln / 515760/ km²	3: Central (China government), regional (province, city of central subordination), municipal
2.	Berlin -Brandenburg Metropolregion, Germany	30.546 km²	6mln / 200/ km²	4: Federal (authorities of FRG), regional (Länder), 2 municipal

[1]Kaku M. Hyperspace: A Scientific Odyssey Through Parallel Universes, Time Warps, and the 10th Dimension. Oxford University Press. 1994; Vulfovich R. The Metropolitan Regions' Governance in the 21st Century: Political Aspect. Herzen University Press. 2001.

3.	Métropole du Grand Paris, France	814 km²	7,2mln / 8598/km²	5: Central (French authorities), regional (metropolis), 3 municipal
4.	London Metropolitan Area, UK	8.382 km²	12,653mln / 1510/ km²	3: Central (UK authorities), regional (Greater London), municipal (London districts, etc.)
5.	New York, NY-NJ-PA Metropolitan Area, USA	11.880 km²	21,045mln / 1711/ km²	4: Federal (US governments), regional (states), 2 municipal (county and special district, municipality
5.	Moscow Agglomeration, RF	26.000 km²	20,0mln /3100 / km²	4: Federal (authorities of the Russian Federation), regional (subject), 2 municipal
7.	Saint Petersburg Agglomeration, RF	SPb 1439 km² (city) + Leningrad Oblast 84.500 km²	5, 427mln / 3,708 /km² + 1,847mln / 20 km²	4: Federal (authorities of the Russian Federation), regional (subject), 1 municipal. (St. Petersburg) + 2 (Leningrad region)

To form the integrated political hyperspace of an agglomeration the authorities need to create practically one more power level common to the whole agglomeration, but it is impossible without the delimitation of the area borders. Among the 7 examples shown above only the Metropole du Grande Paris has the border delimitated by law[2], and the Metropol Region Berlin – Brandenburg has a border delimitated by agreement between both Länder of the Federal Republic of Germany. All other agglomerations practically have no borders at all. They are steadily growing and some of them have different borders for different purposes. One of the examples is the huge Capital Region of Beijing (China) created only for the common development project of the CPC, the other – the Metropolitan Area of New York - New Jersey- Pennsylvania – existing as a statistical unit. At the same time the Tri-state-metropolitan Region with other borders consists of the counties in the states New York, New Jersey and Connecticut, and the Regional Planning Association existing since the 20-s of the last century created all the four Regional Plans[3] for this area. The Greater London agglomeration is defined as the commut-

[2] LAW n° 2015-991 of August 7, 2015 on the new territorial organization of the Republic, August 7, 2015 (LOI n° 2015-991 du 7 août 2015 portant nouvelle organisation territoriale de la République, 7 août 2015) URL: https://www.legifrance.gouv.fr/loda/id/JORFTEXT000030985460/

[3] Regional Planning Association URL: https://rpa.org/

ing area. This means only the territory whose residents commute every day for their working places to Greater London. In Russia the notion "agglomeration" has no normative definition which makes the situation even more complicated.

Russian specialists' delimitation attempts of the agglomeration borders (theory and praxis)

Already in the Soviet Union the research of large urbanized territories was common, one of the most founded descriptions of such areas was made G. M. Lappo whose definition of the urban agglomeration we find in the Great Russian Encyclopaedia[4]. About the same definition of the agglomeration, we find in the "Strategy for the Spatial Development of the Russian Federation on period until 2025"[5]: ""urban agglomeration" is a set of compactly located settlements and territories between them <…>, connected by a joint using infrastructure facilities and joint intensive economic, including labour, and social connections".

The most actual research of this matter was made 2021 by the specialist of the Institute of Urban Economics[6]. They formulate two main approaches to the agglomerations' border delimitation – the unified and the individual approach. As we have already shown earlier differences between large urban agglomerations are very strong from such points of view as the legislative definition of the area and its dimensions, the existence of administrative and sometimes political borders inside the area, and the character of economic, social and transport connections being the main factor of agglomerations' development as complete high integrated systems.

The authors present the detailed and well-founded also with the international experience model for delimitating the borders of agglomerations and analyse the attempts in some regions of Russia to make the delimitation practically. The examples are the Chelyabinsk, Krasnoyarsk, Novosibirsk, Ekaterinburg, Tomsk, and Samara-Tolyatti agglomerations.

The Analytical report[7] describes the most often used methods of the agglomerations' borders delimitation: the detachment algorithm of functional urban areas used as a standard method in the OECD-countries based on the population densities starting from the area core up to periphery; connectivity level criteria based on different factors including transport connectivity (the so called Golz constant – 1,5 hours on the way from the place of living to the place of labour inside the agglomeration borders)[8]; estimation of the periphery residents' share working on

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[4]The Large Russian Encyclopaedia URL: https://bigenc.ru/geography/text/2371705

[5]Strategy for the Spatial Development of the Russian Federation on period until 2025 URL: https://docs.cntd.ru/document/552378463

[6]Institute of Urban Economics. Methods for delimitation of urban agglomerations. Analytical report. Moscow 2021 URL: https://www.urbaneconomics.ru/research/analytics/ieg-predstavlyaet-issledovanie-metodiki-delimitacii-gorodskih-aglomeraciy

[7]Ibid, p. 12–16.

[8]Golz, G. A. Transport and Settlement System. M.: Science, 1981

the core territory; analysis of outdoor advertising spatial distribution.

The use of these methods in Russia is often hampered by the lack of a sufficient volume of relevant and correct statistical data. Perhaps this is the main reason for the lack of serious studies on the delimitation of the borders of Moscow agglomeration and St. Petersburg agglomeration – two largest urbanized regions in Russia. Better results one can reach with "big data" technology, but it is more the future than the present reality.

Saint Petersburg agglomeration. Possibilities of borders delimitation

Now the Saint Petersburg agglomeration becomes larger rapidly and needs the common development strategy. But the territory consists of not only one subject of the Russian Federation – Saint-Petersburg (the Federal City) – but also includes parts of the territory of the other subject – the Leningrad region (oblast). Article 73 of the Russian Constitution transfers full power on the territory of the constituent entities of the Russian Federation to their authorities within the limits established by the Constitution and federal legislation. This means after all, that the City and the Region have their own legislation including the Statute, authorities for the most important functional spheres and different development strategies with goals and ends important for every region.

At the same time some districts (with municipal identity and normative acts) in the Leningrad Region already are parts of the Saint Petersburg agglomeration from the objective point of view. Their territories adjoin the borders of the city, and residents of many settlements not only work in the city, but also take their children there to schools, believing that the quality of education is better in city schools. At the same time, they acquire apartments in settlements of the region due to their lower cost.

We can evaluate the situation better looking at two images of possible variants for borders delimitation in the urban area of Saint Petersburg. The first is much more traditional and includes only some small parts of the Leningrad Region. The radius of the area makes 60 km. The overall situation is not simple also if we have such relatively small area. Saint Petersburg in the borders of the subject of federation cannot be seen as a "normal" city. It is a large agglomeration with 13 inner-city districts and 5 suburb-districts. 9 stand-alone cities such as Pushkin, Pavlowsk, Petrodvorets, Lomonossov, Kronstadt, Kolpino, Sestroretsk, Zelenogorsk, Krasnoje Selo and 21 smaller settlements are the parts of the Federal City. Many of them were built already in the 18[th] century when the history of Saint Petersburg began. In this situation only 5 districts or their parts in the Leningrad Region become parts of the agglomeration: Vsevolozhskiy, Kirovskiy, Tosnenskiy, Gatchinskiy, Vyborgskiy, Lomonosovskiy. The image of the agglomeration is shown on picture 1.
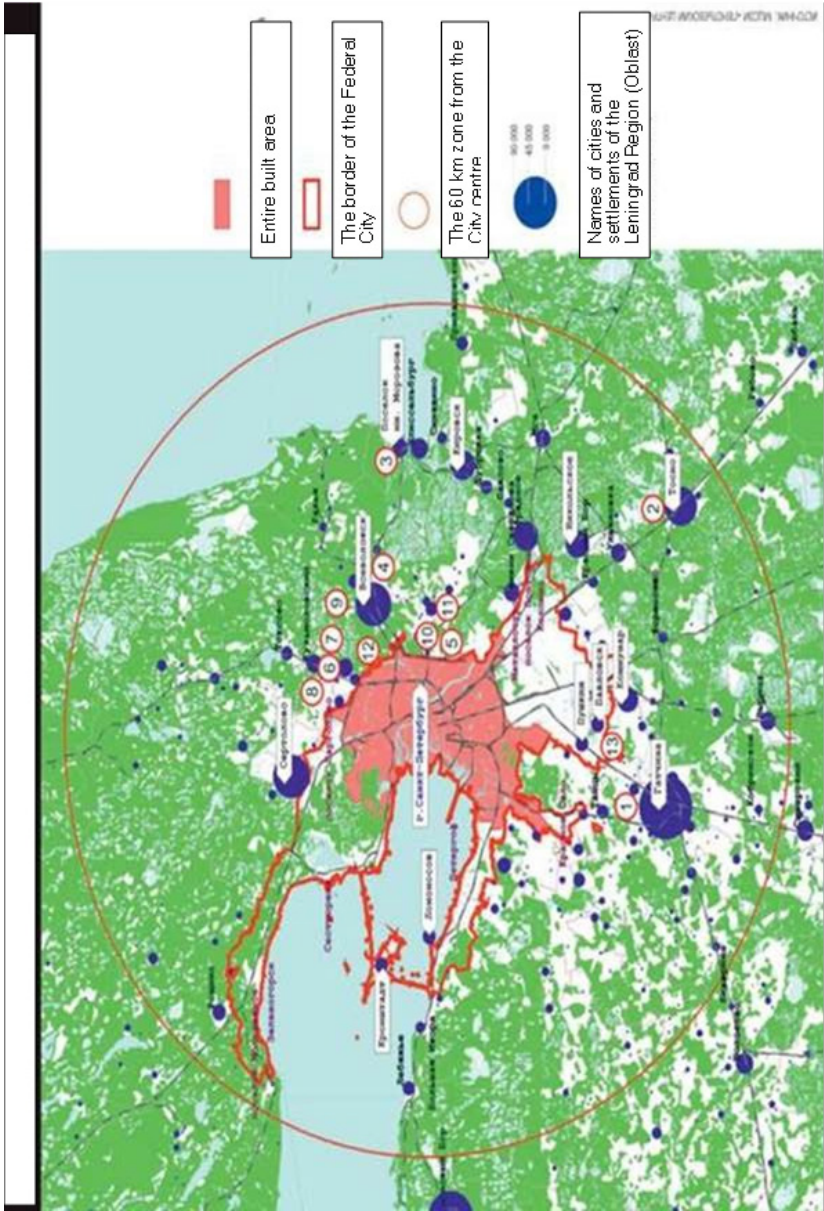
Figure 1. *The structure of the Saint Petersburg agglomeration (radius 60km)*

If we apply the connectivity level method to the borders delimitation of this area, we can state it is possible to commute from the core city to the agglomeration periphery during 1,5 hours In the Federal City and in the surrounding areas exist two separate transport systems, and only some parts of the 60 km zone relate to each other by commuting trains and regular and route buses. The last are commercial transport facilities of bad quality, dangerous because of their low qualified drivers and are not used by students and pensioners because they must pay for a trip. In the regular buses these privileged passengers use the transport cards financed by the City and the Region. Some steps have been made since 2013. The autonomous non-profit organization "Directorate for the Development of the Transport System of St. Petersburg and the Leningrad Region"[9] was established by the Government of the Russian Federation jointly with the Governments of Saint Petersburg and the Leningrad region for the implementation of measures to develop the common transport system of St. Petersburg and the Leningrad region. The Strategy of integrated development of both transport systems till 2030 was created and must be implemented trough these years. Now the first project of the enlarging of the Saint Petersburg's metro system into the Region begins. The metro station building in the town of Kudrovo (Vsevolozhskii district) begins this year.

But there is also the second variant of borders delimitation around Saint Petersburg. The area is much larger and includes not only 6 districts of the Leningrad Region previously named but also the districts Priozerskiy and Vyborgskiy in the North, Kingispeskiy and Slantsevskiy in the West, Luzhskiy and Volosovskiy in the South, Kirishskiy and a part of Volokhovskiy in the East. The radius of the territory is approximately 120-140 km. The existing transport system does not match the Golz constant. But the development of new transport facilities happens very rapidly, and the City of Saint Petersburg is going on to grow. This larger variant of the Saint Petersburg agglomeration is shown on picture 2.

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[9]Directorate for the Development of the Transport System of St. Petersburg and the Leningrad Region URL: https://spbtrd.ru/
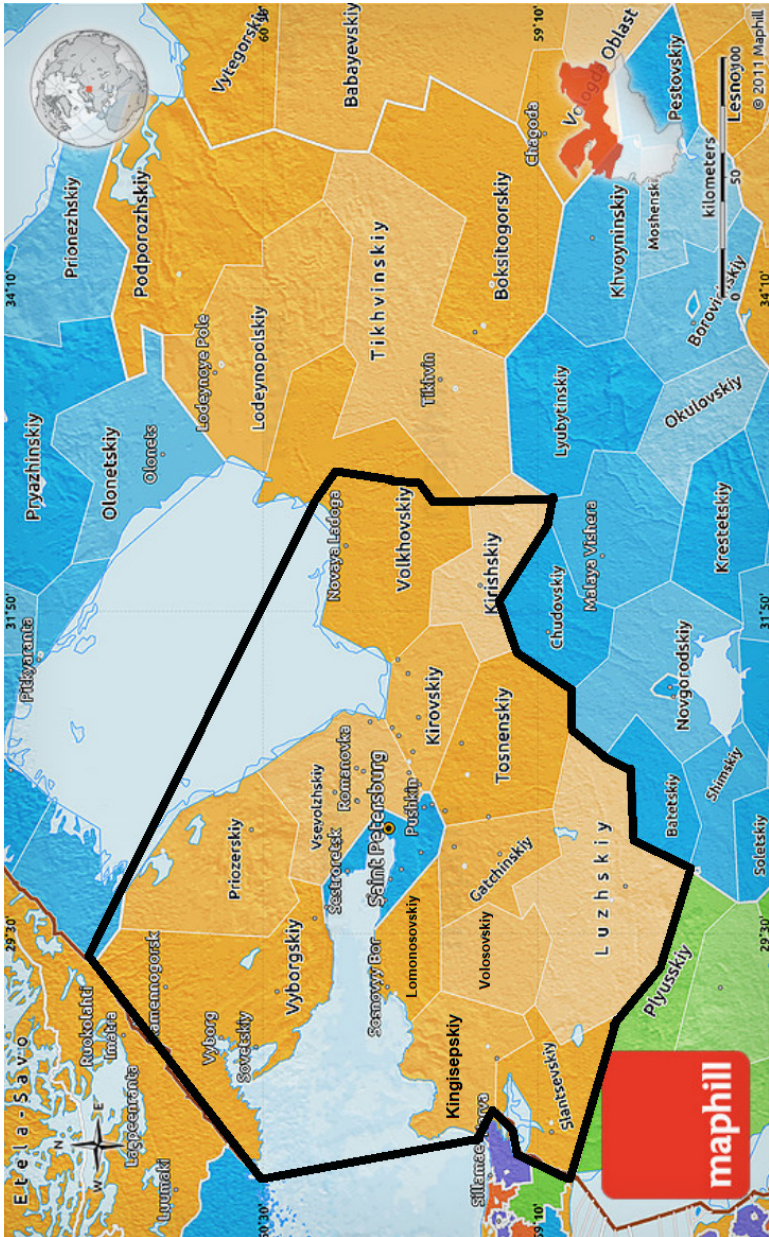
Picture 2. The "large" agglomeration. Saint Petersburg and 14 districts of the Leningrad region

From the political-administrative point of view the rational decision of the agglomeration building problem could be the amalgamation of both subjects of Russian Federation – Saint Petersburg and the Leningrad Region into one with common authorities for administrating the agglomeration territory. But it is too large and the connections economic, social and transport as well are too weak to make the territory function as a whole system. And if 4 eastern districts are not included as we can see on the map, they cannot develop at all.

Conclusions

The analysis of an agglomeration process in Russia in comparative perspective with urban territories in other countries shows many common tendencies but at the same time it is possible to stress the differences. The first one is the absence of the normative definition of an agglomeration in the Russian law. This makes the whole matter indefinite and gives the regions (subjects of Federation) few possibilities to work out strategies for building and developing these systems. In the region around Saint Petersburg the problem is complicated by the presence of an administrative border between the Federal City and the region surrounding it. The region has a large territory, which could be a significant resource for the development of the city. However, the Leningrad region has a small population, and the transport system is not sufficiently developed for intensive commuting.

Two variants of agglomeration border delimitation are possible. The smaller agglomeration with the radius 60 km exists already and the integration of the territory becomes more intensive every year. Some subsystems, for example, transport, have a development strategy common to both regions – Saint Petersburg and the Leningrad Region (Oblast). But the integration process is at the very beginning. The second variant includes the city and most of the surrounding region and has the radius 120-140km. But 4 eastern districts of the region will stay out of development. There is a solution for this problem to amalgamate both regions into one. But the territory is too large and underdeveloped for an agglomeration process. The distance from the agglomeration border to the Leningrad region border in the East is about 200 km, the population of all 4 districts is only 170,5 thousand and the density about 7 per square km. For the City of Saint Petersburg this part of the region will be too heavy burden.

All facts prove the Saint Petersburg agglomeration can become larger in a far future but till the middle of the 21st century it will stay in the borders of the variant one (radius 60km) and the main instruments for its development must be the coordination and the cooperation between Saint Petersburg and the Leningrad region (oblast) in the sphere of strategic planning.

成人烧伤毒血症的强化治疗
INTENSIVE THERAPY OF BURN TOXEMIA IN ADULTS

Muhitdinova Hura Nuritdinovna
Doctor of Medical Sciences, Full Professor
Center for the Development of Professional Qualifications of Medical Workers

抽象的。 对患者的身体数据、主观感觉、阴沟的监测不足以衡量重症监护的有效性。 额外的肠外营养，每天引入 321.4±204 ml 氨基酸，能量容量为 280 kcal/天的葡萄糖不足以补偿能量底物损失，在烧伤后的前 5 天内纠正高代谢 面积2-3A度51.4±19.7%, 3B度11.8±8.9%, IF 92.5±20.8个单位。 第 11 天抗生素治疗的减少伴随着增加抗凝剂给药的需要。 识别的特征可能与一般中毒恶化迹象的出现或伤口表面的状态相关，这需要纠正灌注偏差。
关键词：重症监护，烧伤毒血症，成人。

Abstract. Monitoring of physical data, subjective sensations, gutters of patients are insufficiently objective indicators of the effectiveness of intensive care. Additional parenteral nutrition with the introduction of amino acids 321.4±204 ml per day, glucose with an energy capacity of 280 kcal/day was insufficient to compensate for energy-substrate losses, correction of hypermetabolism in the first 5 days after a burn injury with an area of 2-3A degree 51.4±19.7%, 3B degree 11.8±8.9%, IF 92.5±20.8 units. The decrease in antibiotic therapy on the 11th day was accompanied by the need to increase the administration of the anticoagulant. The identified feature can be associated with the appearance of signs of exacerbation of general intoxication or the state of the wound surface, which required correction of perfusion deviations.

Keywords: intensive care, burn toxemia, adults.

Relevance

Numerous studies have shown that the pathogenesis of burn toxemia is based on the resorption of tissue decay products from the burn wound into the blood and lymph. This process is especially pronounced in the first few days after receiving a burn, when granulations have not yet formed, which are a "wound barrier" on the way of absorption of toxins. The pathogenic effect of the products of proteolysis and fibrinolysis of the wound surface is diverse: they have a direct cardiotoxic,

nephrotoxic, hepatotoxic effect, block the action of insulin and the anticoagulant system of the blood, and sharply worsen the rheological properties of the blood and the function of gas transport. Rejection or removal of necrotic tissue from a burn wound leads to a decrease in temperature within 1-2 days. According to the authors, the use of antibiotics and antipyretic drugs does not significantly affect the temperature response [1-4]. Due to the lack of information on the effectiveness of complex intensive care in the first days after a burn injury, we tried to present the results of intensive care monitoring in the early period of toxemia.

Purpose

To study and evaluate the intensive therapy of the period of toxemia in severe burn injuries in adults.

Material and research methods

The data of monitoring of infusion, analgesic therapy, drug correction, replenishment of hypodysproteinemia, energy-deficient state in 8 patients with severe thermal burns admitted to the Republican Scientific Center for Emergency Medical Care at the age of 41 to 60 years (50.5±7.2 years), including 6 patients men, 2 women. Daily monitoring of the volume of intravenous daily fluid administration, kilocalories (glucose), the frequency of administration of painkillers (including sedatives), anti-inflammatory, vasodilators, antibiotics, heparin, vasopressor (dopamine), vitamin C, the amount of injected cytoflavin in ml/day, amino acids in ml/days, proteins in ml/day. The studies were carried out with 100% physiological need provided by enteral administration throughout the entire period of the study of burn toxemia.

Results and its discussion

The duration of intensive care in the ICU was 13±2.3 days, in the hospital 25.8±8.9 days. The severity of the burn was assessed by calculating the surface area of the damaged skin and the Frank index. Data on the characterization of the severity of damage to the skin surface by the area of the burn 2-3A degree 51.4±19.7%, 3B degree 11.8±8.9%, according to IF 92.5±20.8 units are presented in table 1.

Table 1.
Characteristics of patients

number of pa-tients	age	growth	weight	n.d. in ICU	n.d. in hospi-tal	2-3A deg. burn area	3B deg. burn area	IF
8	50.5 ±7.2	165.7 ±6.2	73.7 ±14.2	13.5 ±2.3	25.8 ±8.9	51.4 ±19.7	11.8 ±8.9	92.5 ±20.8

Figure 1. *Dynamics of the mesor of the circadian rhythm of body temperature*

As shown in fig. 1, the average daily level of body temperature of the patients was within the normative value in the first 5 days, in the following days rising to the highest value of 37.3°C on the 9th day. Evidence of the adequacy of hemodynamic correction was the mesor of the circadian rhythm of systolic blood pressure (SBP) stably within the normal range in the first 4 days (fig. 2). Attention is drawn to the trend towards an increase in SBP to 127 mmHg on day 5, indicating a change in cardiac output, possibly of a compensatory direction due to the limitation of the amount of drug therapy.
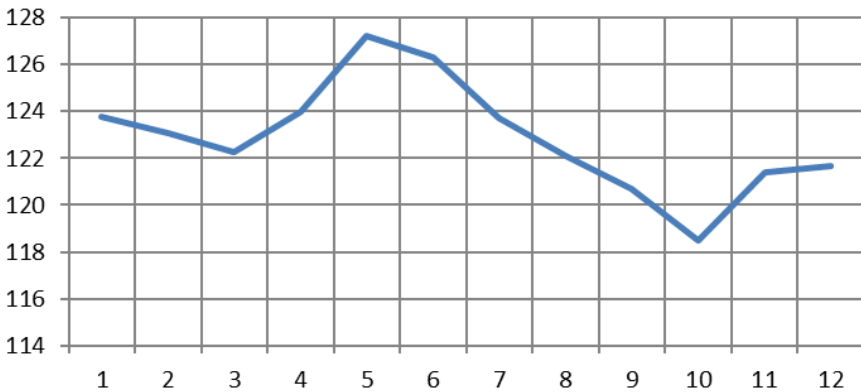
Figure 2. *Dynamics of the mesor of the circadian rhythm of systolic blood pressure (mmHg)*

Table 2.
Infusion therapy (ml per day)

Days	Intravenously liquid, ml/day	Kilocalories/ day	Amino acids ml/day	Protein ml/ day	Number of types of solutions
1	2728.6±804.1	234.3±73.5	35.7±6.2	36.4±6.4	4.3±0.6
2	2645.1±805.6	248.6±72.7	321.4±204.1	54.3±7.6	4.9±1.0
3	2664.3±398.0	285.7±71.8	321.4±204.1	28.6±4.8	4.7±0.9
4	1980.9±502.1	280.0±68.6	321.4±204.1	14.3±2.5	4.1±1.6
5	2132.1±461.6	268.6±81.6	278.6±189.8	122.1±17.5*	4.3±1.1
6	1708.9±200.1	277.1±94.7	214.3±183.7	62.1±8.8	4.1±0.5
7	1654.9±266.7	280.0±125.7	250.0±214.3	0.4±0.1	3.3±0.6
8	1524.6±221.1	257.1±99.6	178.6±104.1	47.9±6.4	3.6±0.6
9	1575.0±508.3	240.0±126.7	125.0±66.7	47.5±7.2	3.3±0.7
10	1673.9±462.4	287.1±83.3	107.1±53.1	28.6±4.0	3.3±0.7
11	1382.2±610.4	406.7±331.1	166.7±66.7	0.0	3.2±0.6
12	1906.25±616.2	200±120	250±125	0	3.75±0.75
13	1729±422.5	160±80	187.5±93.75	0	3.5±0.75

The volume of infusion therapy was the largest in the first three days, amounting to 2728-2664 ml per day with a gradual decrease to a minimum on the 11th day (tab 2). After recovering from burn shock, it was mandatory to supplement entel nutrition with the introduction of parenteral amino acids, glucose in order to correct the energy-deficient state. Albumintransfusion was carried out under the control of biochemical blood tests. Attention is drawn to the increase in the introduction of albumin on the 5th day to 122.1 ± 17.5 ml per day, a gradual decrease and complete cessation on the 11th day of toxemipi. Apparently, additional parenteral nutrition with the introduction of amino acids 321.4±204 ml per day, glucose with an energy capacity of 280 kcal/day was insufficient to compensate for energy-substrate losses, correction of hypermetabolism in the first 5 days after a burn injury with an area of 2-3A degree 51.4±19.7%, 3B degree 11.8±8.9%, IF 92.5±20.8 units.

Table 3.

Medical correction

Days	Anesthesia	Anti-inflammatory	A/B	Heparin	Vit C	Cytoflavin	Vasodilators	Dopamine
1	4.7±1.7	5.9±2.1	2.0±0.3	2.9±0.2	1.4±0.7	0.0	1.3±1.2	0.4±0.5
2	7.0±3.1	5.9±2.7	2.3±0.9	3.1±1.0	1.7±0.7	0.7±1.2	0.9±1.2	0.9±0.5
3	7.4±3.6	5.6±2.9	2.6±0.7	3.3±1.0	2.1±0.8	2.9±1.1	1.7±0.7	0.6±0.2
4	6.4±3.6	5.1±3.3	2.6±0.9	3.4±1.0	2.0±0.6	1.4±1.0	1.6±0.8	0.4±0.1
5	6.0±2.9	4.7±3.4	3.1±0.8	3.4±1.0	1.9±0.8	2.9±1.1	1.6±0.5	0.4±0.1
6	6.3±2.3	5.0±2.0	2.7±1.2	3.3±1.0	2.0±0.6	2.1±1.1	1.4±0.2	0.3±0.4
7	5.3±3.0	4.0±2.6	3.4±1.2	3.1±1.0	2.1±1.1	2.9±1.1	1.3±1.1	0.3±0.1
8	4.4±1.6	3.6±1.8	3.0±1.1	3.3±1.0	1.7±0.9	1.4±2.4	1.1±0.3	0.2±0.1
9	4.2±1.2	3.5±1.5	3.3±1.3	3.2±0.6	1.5±1.0	1.7±0.8	0.7±0.2	0.0
10	4.7±2.3	3.7±2.0	3.4±1.1	3.4±0.5	1.4±1.2	1.4±0.4	0.7±0.2	0
11	2.7±1.8	3.0±1.3	2.5±0.7	3.3±1.1	1.3±1.1	1.7±0.8	0.3±0.1	0.0
12	2.5±1.75	2±1	2.25±0.3	4±1	1±0.5	0	0	0
13	2±1	1.5±0.7	2±0.5	3.5±0.7	1±0.5	0	0	0
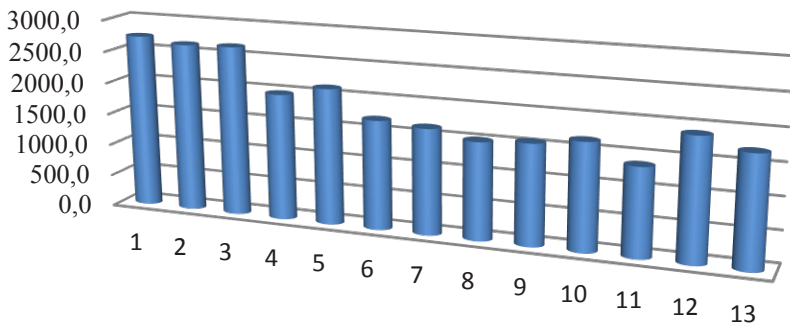
Figure 1. Daily volume of infusion therapy

The volume of infusion therapy in the first three days was more than 2500 ml with a decrease in intravenous administration on day 4 to an average of 1900 ml, in subsequent days gradually decreasing to a minimum of 1382.2 ± 610.4 ml/day on day 11 (tab. 2, fig. 1).
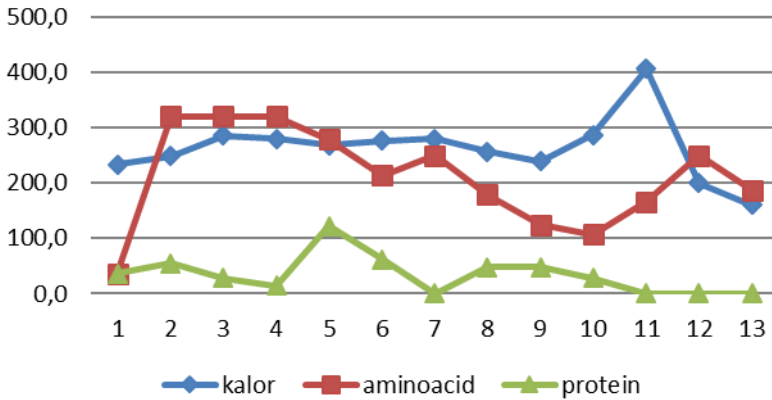
Figure 2. Components of parenteral nutrition

Mandatory components of infusion therapy were amino acids, glucose 20%, albumin 10-20% (fig. 2).
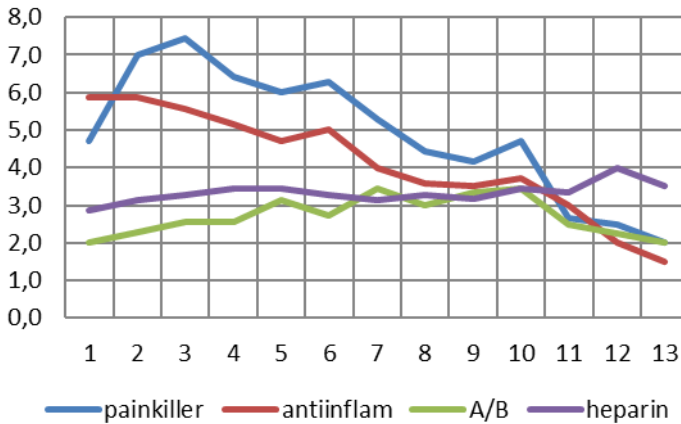
Figure 3. Anti-inflammatory therapy

Attention is drawn to the most active analgesic and anti-inflammatory therapy on days 1-3 with a tendency to decrease in subsequent days to a minimum on day 13 (fig. 3). The frequency of administration of antibiotics, heparin were relatively stable.
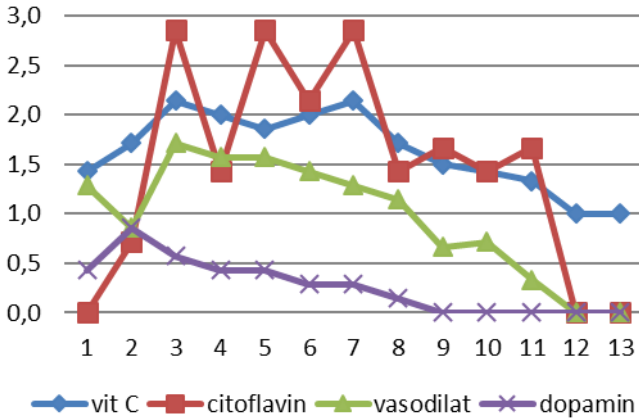
Figure 4. Metabolite therapy

The feasibility of corrective therapy with the introduction of vasodilators, a vasopressor, vitamin C, cytoflavin was determined by the severity of the general condition, the condition of the wound surface, objective physical and clinical signs of blood circulation dynamics, subjective feelings, and patient complaints. A relatively more significant vasodilating correction, the frequency of vitamin C administration, the amount of cytoflavin per ml was carried out on days 3-7. While the maintenance of hemodynamics by the administration of dopamine was maximum on day 2, followed by a decrease and termination of administration on day 9 (fig. 4).

A direct correlation was found between the amount of glucose administered and the frequency of administration of painkillers (0.81) and anti-inflammatory drugs (0.77) on day 1; on day 2, a direct correlation became significantly between the volume of glucose and vasodilators (0.68). A direct strong correlation between the multiplicity of painkillers and anti-inflammatory drugs on day 1 was 0.92, on day 2 - 0.94, on day 3 - 0.98.4-0.98, 5-0.92, 6-0.9, 7- 0.92, 8-0.75.9-0.95.10-0.82, on the 11th day it became insignificant. That is, during the first 10 days, the frequency of analgesic and anti-inflammatory therapy turned out to be in direct interdependence.

On day 1, the direct relationship between the frequency of administration of painkillers and vasodilators was 0.8, reappeared on day 3 - 0.8, 4 - 0.8, 5-0.9, and was not detected on subsequent days. That is, on days 1, 3-5, the stress-protective effect of anesthesia had to be enhanced by the introduction of vasodilators.

An increase in the volume of infusion therapy due to an increase in the types of transfusion media was detected on day 1 (0.72), on day 3 - (0.72), 4-0.71, 8-0.94, however, on the 11th day, an inverse correlation of the studied parameters (-0.79) was found, which can be interpreted as the fact that with a decrease in the volume of infusion therapy, the tendency to introduce various infusion media, including amino acids, remained, as evidenced by the direct relationship of the indicator with the number of types of administered solutions (0.76).

On day 1, a direct strong correlation was observed between the frequency of administration of anti-inflammatory and vasodilator drugs (0.83), which on day 3 was 0.79, on day 4-0.8, on day 5 - 0.85. Of particular interest is a direct strong correlation between antibiotic therapy and the frequency of heparin administration only in 1 day, which amounted to 0.76. However, on the 2nd day there was a direct relationship between the frequency of administration of antibiotics and the vaso-pressor (0.71), which was repeated on the 7th day (0.71). While on the 11th day, a mirror correlation between AB and heparin was found (-0.87). That is, a decrease in antibiotic therapy was accompanied by the need to increase the administration of an anticoagulant. The identified feature can be associated with the appearance of signs of exacerbation of general intoxication or the state of the wound surface, which required correction of perfusion deviations.

On the 2nd day, a strong direct correlation of the volume of intravenous in-fusion and the frequency of heparin (0.8) was revealed, it reappeared only on the 8th day (0.76), and on the 11th day (0.87). The introduction of an anticoagulant contributed to an increase in the antiplatelet effect, improving blood flow and per-fusion. On day 2, the volume of infusion therapy was provided through the cardio-tonic effect of dopamine (0.88). The increase in the variety of fluids administered on day 2 was accompanied by an increase in the frequency of administration of painkillers (0.72), vitamin C (0.74), cytoflavin (0.7). A direct correlation was found for the number of types of solutions with anti-inflammatory (0.91) and anes-thesia (0.93) on day 3, anti-inflammatory (0.7) on day 4, with anesthesia (0.79) on day 5, and also on day 7 with anesthesia (0.7), and with anesthesia on the 10th day (0.84). On the 2nd day, strong direct correlations between the administration of painkillers with vitamin C (0.8), the multiplicity of antibiotics and dopamine (0.7), cytoflavin with the administration of vasodilators (0.88), vasodilators with albumin transfusion (0.93) characterize an attempt at drug containment stress re-sponse to burn injury.

On the 3rd day, the complex nature of corrective actions, such as a direct cor-

relation of the number of types of injected solutions with anti-inflammatory (0.91), with heparin (0.76), with cytoflavin (0.79), with vasodilators (0.76), with proteins (0.8), made it possible to restrain the excessive stress response on the 3rd day, which was expressed in the normal level of the average daily systolic blood pressure of 122 mmHg, and body temperature of 36.9°C.

An increase in the mesor of the circadian rhythm of body temperature on day 9 to 37.3°C, while maintaining the normal value of the average daily SBP at the level of 121 mm Hg, occurred with a tendency to reduce the introduction of calories, amino acids, proteins, painkillers, anti-inflammatory drugs, an unchanged amount of antibacterial drugs and heparin. The decrease in the corrective effect of therapy is confirmed by a decrease in the number of correlations, with the preservation of such as a straight line between glucose and heparin (0.7), pain relief and vitamin C (0.86), anti-inflammatory and vitamin C (0.87). The revealed correlations indicate the expediency of continuing anti-inflammatory, analgesic, vasodilating, dopamine for a longer time, at least the first 10 days of toxemia. At the same time, the tendency to decrease starting from the 5-6th day of toxemia draws attention.

It should be noted that the positive effect of intensive therapy up to 5 days was achieved by drug loading and was characterized by direct correlations between the number of types of solutions with heparin (0.73), with amino acids (0.74), dopamine (0.71), a direct correlation with the frequency of administration painkillers with amino acids (0.83), painkillers with cytoflavin (0.8), anti-inflammatory with vitamin C (0.7), with cytoflavin (0.88), amino acids with vasodilators (0.88), vitamin C with cytoflavin (0.73), with a tendency to reduce the frequency of administration of painkillers and anti-inflammatory drugs, already from the third day. Apparently, the available possibilities for monitoring physical data, subjective sensations, and the gutter of patients are insufficiently objective indicators of the effectiveness of intensive care.

Conclusion

Monitoring of physical data, subjective sensations, complaints of patients are insufficiently objective indicators of the effectiveness of intensive care. Additional parenteral nutrition with the introduction of amino acids 321.4±204 ml per day, glucose with an energy capacity of 280 kcal/day was insufficient to compensate for energy-substrate losses, correction of hypermetabolism in the first 5 days after a burn injury with an area of 2-3A degree 51.4±19.7%, 3B degree 11.8±8.9%, IF 92.5±20.8 units. The decrease in antibiotic therapy on the 11th day was accompanied by the need to increase the administration of the anticoagulant. The identified feature can be associated with the appearance of signs of exacerbation of general intoxication or the state of the wound surface, which required correction of perfusion deviations.

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中老年急性烧伤毒血症的强化治疗
INTENSIVE THERAPY OF ACUTE BURN TOXEMIA IN THE ELDERLY AND SENILE AGE

Muhitdinova Hura Nuritdinovna
Doctor of Medical Sciences, Full Professor

Alauatdinova Gulhan Inyatdinovna
Department assistant

Center for the Development of Professional Qualifications of Medical Workers

抽象的。第一天，73.8±7.2 岁，皮肤表面烧伤面积 2-3A 度 37.5±8.1%，3B 度 – 19±7.3%，IF – 96.8±18.1 un。每日输液治疗量在3230.0±780.0 ml/天以内。在前 10 天，能量底物 – 葡萄糖的引入增加，导致体温降低，身体炎症反应的严重程度降低，并揭示了刺激疗法的主要代谢物方向。在第 10-30 天观察到静脉输注治疗量显着减少 44-60%。 B 复合物的引入伴随着血管加压药的引入减少，这表明在烧伤毒血症的第三个十年中，血管在适应性反应中的代偿参与恢复了。揭示的相关性表征了 61 岁以上人群严重烧伤毒血症中严重应激炎症反应的各种影响和身体代偿反应的复杂性。

关键词：治疗，急性烧伤毒血症，老年人，高龄。

Abstract. *On the first day, at the age of 73.8±7.2 years, with a burn area of the skin surface of 2-3A degree 37.5±8.1%, 3B degree - 19±7.3%, IF - 96.8±18.1 un. volume of daily infusion therapy was within 3230.0±780.0 ml/day. In the first 10 days, an increase in the introduction of an energy substrate - glucose, contributed to a decrease in body temperature, a decrease in the severity of the inflammatory response of the body, and a predominantly metabolite orientation of stimulating therapy was revealed. A significant decrease in the volume of intravenous infusion therapy was observed on days 10-30 by 44-60%. The introduction of the B-complex was accompanied by a decrease in the introduction of a vasopressor, which indicated the restoration of the compensatory participation of vessels in adaptive reactions in the third decade of burn toxemia. The revealed correlations characterize the variety of effects and the complexity of the body's compensatory reactions in severe stress inflammatory response in toxemia of a severe burn injury in people over 61 years of age.*

Keywords: *therapy, acute burn toxemia, elderly, senile age.*

Relevance

Numerous studies have shown that the pathogenesis of burn toxemia is based on the resorption of tissue decay products from the burn wound into the blood and lymph. In the phase of acute burn toxemia, general treatment is aimed at further correction of impaired functions and metabolic processes. In this regard, the fight against developing intoxication, anemia (anemia), a decrease in the amount of protein in the blood plasma (hypoproteinemia), vitamin deficiency and infection is being actively carried out. From the 3rd day, the victim necessarily receives liquid and easily digestible food, as well as some medications through the mouth. The total volume of intravenously infused fluid decreases, but active infusion-transfusion therapy continues. It includes the transfusion of blood, plasma, protein preparations, the introduction of blood-substituting solutions that have a detoxifying effect, liquids containing salts necessary for the body (Ringer's solution, polyionic solutions, sodium bicarbonate solution) or providing its energy needs (hypertonic glucose solutions). The results of studies have shown in the older age group the expediency of complex tactics of intensive therapy for burn disease, which consisted in reducing the volume of surgical interventions, choosing sparing methods of anesthesia and the most rational methods of skin grafting [1-4]. Due to the lack of information on the effectiveness of complex intensive care in the first days after a burn injury in the elderly and senile age, we tried to present the results of intensive care monitoring in the early period of toxemia.

Purpose of the work

To study and evaluate the effectiveness of intensive therapy for burn toxemia in the elderly and senile age.

Material and research methods

The data of monitoring of infusion, analgesic therapy, drug correction, replenishment of hypodysproteinemia, energy deficiency in 8 patients with severe thermal burns admitted to the Republican Scientific Center for Emergency Medical Care at the age of 61 to 85 years (73.8±7.2 years), with the duration of intensive care in the ICU 24.1±10.3 days, in the hospital 47.8±25.9 days. The volume of intravenous daily fluid administration, kilocalories (glucose), the frequency of administration of painkillers (including sedatives), anti-inflammatory, vasodilator, antibiotics, heparin, vasopressor (dopamine in a cardiotonic dose), vitamin B complex (B1, B6), the amount of injected cytoflavin in ml/day, amino acids in ml/day, proteins in ml/day. The studies were carried out with the provision of physiological needs by enteral administration throughout the entire period of the study of burn toxemia.

Results and its discussion

The severity of the burn was assessed by calculating the surface area of the damaged skin and the Frank index. Data on the characteristics of the severity of damage to the skin surface on the area of the burn are presented in table.1.

Table 1.

Characteristics of patients

Age, years	Height, cm	Weight, kg	In ICU, days	In hospital, days	2-3A degree, %	3B degrees, %	IF, units
73,8±7,2	161,5±8,3	66,25±13,8	24,1±10,3	47,8±25,9	37,5±8,1	19±7,3	96,8±18,1

The mean age was 73.8±7.2 years, 25% of 8 patients were male. The severity is due to the area of the burn of the skin surface of 2-3A degree 37.5 ± 8.1%, 3B degree - 19 ± 7.3%, FI - 96.8 ± 18.1 units, acute myocardial infarction was diagnosed in 1 patient, 1 was admitted with acute cerebral insufficiency at the level of coma 1. All patients were transferred to a specialized department with an improvement in their condition.

Table 2.

Infusion therapy

Days	Intravenous liquids, ml/day	Amino acids in ml/day	Calories/day	Proteins, ml/day	Types of solutions
1	3230.0±780.0	0	280.0±140.0	0	2.8±1.7
2	2675.0±400.0	393.8±134.4	245.0±75.0	80.6±20.9	4.0±0.8
3	2079.4±574.4	425.0±112.5	245.0±66.3	65.6±8.4	4.1±0.4
4	2237.5±459.4	481.3±28.1	260.0±70.0	36.3±4.4	4.0±0.5
5	2158.6±350.2	414.3±169.4	257.1±71.8	72.9±8.3	4.1±0.8
6	1992.9±451.8	307.1±136.7	222.9±60.4	69.3±9.2	3.6±0.9
7	2148.6±429.4	378.6±144.9	257.1±71.8	67.1±5.9	3.9±0.5
8	2130.9±532.1	343.1±195.5	274.3±75.1	63.6±9.8	3.7±1.3
9	2073.3±351.1	375.0±166.7	253.3±71.1	119.2±60.6	4.5±0.7
10	1787.7±506.0*	208.3±78.3	200.0±93.3	0	3.7±0.7
11	1955.8±397.5	250.0±150.0	226.7±66.7	63.3±10.6	4.0±0.7
12	1629.6±576.3*	250±100	208±57.6	82±6.6	3±1.2
13	1769±784.8	300±160	208±57.6	0	4±0.8
14	1770±824	250±100	160±96	39±6.4	3.4±1.6
15	1365.0±818.3*	208.3±108.3	166.7±75.6	52.5±7.0	2.8±1.8
16	1376±659.2*	101.6±59.36	128±89.6	55±8	2.8±1.8

17	1532±718.4*	300±160	152±70.4	38±6.8	4±0.8
18	1218±825.6*	200±160	144±68.8	40±6	3±1.2
19	1620±876	250±100	128±89.6	65±7	3.6±1.4
20	1332.5±301.2*	387.5±137.5	130±45	50±7	4±1
21	1262.5±437.5*	312.5±187.5	160±80	0	3.5±0.5
22	1668.7±334.3*	437.5±94	180±70	66.2±9.3	4±1
23	1600±350*	437.5±93.7	180±70	0	3.2±0.7
24	1375±362.5*	375±125	160±80	23.7±5.6	3.2±0.7
25	1537.5±568.7*	312.5±187.5	180±70	0	2.7±1.3
26	1280±495*	287.5±162.5	160±80	62.5±9.7	2.7±1.3
27	1311±390*	312.5±187.5	180±70	63.7±9.6	3.2±1.6
28	1090±309*	250±125	120±40	0	3.7±0.3
29	1553±422*	250±125	140±60	0	4±1
30	1665±609*	375±125	160±80	123.7±13.1	4.5±0.7

*-the change is significant relative to the indicator on the first day.

As shown in tab. 2, on the first day, the volume of daily infusion therapy averaged 3230.0±780.0 ml/day, which corresponds to the volume of anti-shock measures taken, the introduction of crystalloids, colloids. Starting from the 2nd day, parenteral nutrition was started simultaneously with the restoration of enteral compensation for energy losses. In the dynamics in the following days of the period of burn toxemia, there was a tendency to gradually limit the volume of parenteral fluid administration. A significantly significant decrease in the volume of intravenous infusion therapy was noted on day 10 by 44%, 12-49%, by 15-57%, 16-45%, 17-52%, 18-62%, 20-59%, 21-60%, 22-48%, 23-54%, 24-57%, 25-52%, 26-60%, 27-59%, 28-66%, 29-52%, 30-48% ($p < 0.05$, respectively). The introduction of amino acids was limited, averaging 400 ml within 50% of the physiological need for protein. Decrease to 100 ml on the 16th day in parallel with the restriction of glucose solution to 128 kcal/day, the daily volume of infusion therapy to 1376 ± 659 ml per day, a tendency to decrease vasodilators, increase in the B complex and cytoflavin at a normal value of the average daily body temperature (36.7°C), apparently, led to an increased risk of progression of an energy-deficient state, depletion of adaptive resources in patients of this age group. This necessitated an increase in corrective, energy-replenishing therapy in the following days.

Table 3.
*Medicine correction*

Days	Anesthe-sia	Anti-inflam-matory	A/B	Hepa-rin	Vasodi-lators	Dopa-mine	In com-plex	Cytofla-vin
1	6.3±2.4	7.4±2.6	5.3±2.7	1.8±0.8	2.9±1.9	0.3±0.1	1.1±0.2	0
2	6.8±1.3	8.3±2.1	5.0±2.3	2.9±0.9	3.0±0.8	0.5±0.1	2.1±0.7	3.8±0.6
3	6.5±1.0	8.1±1.6	5.1±1.9	2.8±0.8	3.1±1.1	0.2±0.1	2.4±0.3	5.0±0.3
4	5.9±1.1	8.5±1.6	5.9±1.9	2.9±0.9	2.8±1.6	0.4±0.2	2.5±0.3	6.3±0.8
5	7.3±2.4	7.0±1.1	4.6±1.5	2.4±1.1	3.1±1.0	0.3±0.1	2.1±1.1	4.3±1.1
6	6.4±1.6	5.9±1.3	3.9±0.5	2.9±0.7	2.4±1.3	0.4±0.2	2.0±0.6	4.3±2.1
7	6.7±2.2	7.0±2.0	4.3±1.1	2.6±1.2	3.1±1.8	0.4±0.1	2.3±1.6	2.9±0.9
8	6.1±2.4	6.3±1.5	3.9±1.3	3.3±0.6	2.7±1.5	0.3±0.1	2.3±1.6	4.3±1.3
9	5.7±1.0	6.2±2.2	4.5±1.2	3.7±0.8	1.8±1.2	0.3±0.1	2.2±1.6	3.3±0.6
10	5.3±2.0	5.5±2.8	3.2±2.2	3.2±0.6	1.5±1.2	0	1.8±0.8	6.7±1.9
11	4.7±1.4	4.7±2.2	4.2±1.9	3.5±0.7	2.3±0.3	0.2±0.1	2.8±1.4	6.7±2.9
12	4.8±1.7	3.2±1.3	3.2±0.6	3.8±0.7	1.6±0.8	0.2±0.1	1.8±0.7	4±1.4
13	3.8±1.4	3.2±1.6	2.2±1.0	2.8±1.4	1±0.2	0	2.2±1.0	8±2.6
14	4.8±0.6	3.2±0.6	2.2±1.0	2.8±1.0	1±0.2	0.4±0.1	1.8±0.6	6±2.2
15	4.5±1.7	4.7±2.3	3.0±1.0	2.2±1.2	1.2±0.9	0.2±0.1	1.7±1.1	5.0±1.7
16	4.6±1.5	2.4±1.6	2.4±1.5	3.2±0.9	1±0.2	0.2±0.1	2.2±0.3	6±2.2
17	4.8±2.6	3.4±1.12	2.6±1.1	2.8±1.0	1.8±0.7	0.4±0.2	2±0.8	8±2.6
18	4±0.8	3.8±0.6	3.2±1.0	2.6±1.2	1±0.2	0.2±0.1	1.6±0.5	4±1.4
19	4±3.2	2.8±1.6	2.8±1.3	2.8±1.1	1.2±0.5	0.4±0.1	2±0.1	4±1.4
20	3.5±1.25	2.2±1.7	1.7±0.7	2.5±1	1±0.2	0.25±0.1	1.7±0.3	5±1.5
21	3.5±1.5	2. 5±1.2	2.5±1.7	2.7±0.7	1.2±0.2	0.25±0.1	1.5±0.5	5±1.5
22	4±1	3±1	1.5±0.5	3±1	1.2±0.2	0.25±0.1	1.2±0.5	5±1.5
23	3.7±1.2	3±0.5	2.2±0.7	2.7±0.7	1.5±0.5	0.25±0.1	1.2±0.5	5±1.5
24	5.5±2.2	3.2±1.3	2±1	2.2±0.8	1.5±0.7	0.5±0.1	0.7±0.3	2.5±0.7
25	3.7±1.2	2±1.5	1±0.1	2.5±0.7	1±0.5	0.5±0.1	0	0
26	4.7±1.7	3±2	1.7±0.8	2.5±0.7	1.7±0.5	0.2±0.1	1±0.1	0
27	5±2.5	3.2±1.7	2±1.5	2.5±0.7	2±0.2	0.25±0.1	1±0.2	0
28	3±1	1.7±0.8	1.5±0.7	1.7±0.8	1±0.2	0.25±0.1	1±0.2	0
29	3.7±0.7	2.5±1.2	1.7±0.5	2.2±0.3	1.5±0.5	0.25±0.1	0.7±0.2	0
30	3.5±1	1.7±0.6	0.7±0.1	1.7±1.1	1.7±0.5	0.2±0.1	1.2±0.3	0

The number of types of administered solutions was increased in order to increase the efficiency of detoxification, correction of hemodynamics, perfusion of capillaries, replenishment of the energy-deficient state in conditions of excessive hypermetabolism in patients with burn toxemia over 61 years of age to a greater extent. Table 3 presents the indicators of the components of intensive drug therapy for 30 days of the period of acute burn toxemia. The largest volume of complex intensive care (pain relief, anti-inflammatory, antibacterial, vasopressor support) in the first four days gradually decreased in the following days. Draws attention to the trend towards an increase in the introduction of heparin on days 8-12, 16 days. On days 2,3,5,7, the frequency of administration of vasodilators was slightly increased. The greatest administration of dopamine on the 2nd day was of a hemodynamically supportive nature under the conditions of volumetric infusion therapy (tab. 3).
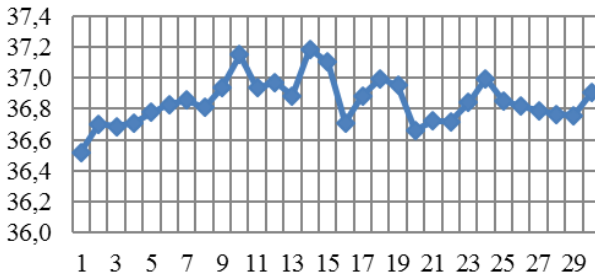
Figure 1. *Dynamics of the mesor of the circadian rhythm of body temperature*

A tendency to an increase in the mesor of the circadian rhythm of body temperature to 37.15°C and 37.2°C on days 10, 14 was revealed, a stable normalization of the indicator after 25 days (fig. 1).
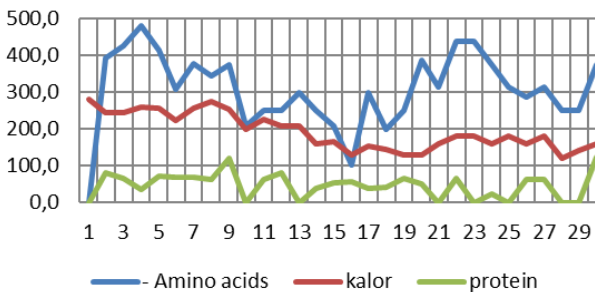
Figure 2. *Parenteral nutrition*

The introduction of glucose 280 ml/day in 1 day, gradually decreased to 150 ml, taking into account the energy compensation enterally. Additional parenteral nutrition with the introduction of amino acids from 455 ml on day 4 made it possible to significantly reduce the tendency to hypoproteinemia and the administration of protein preparations to an average of 50 ml/day (fig. 2).
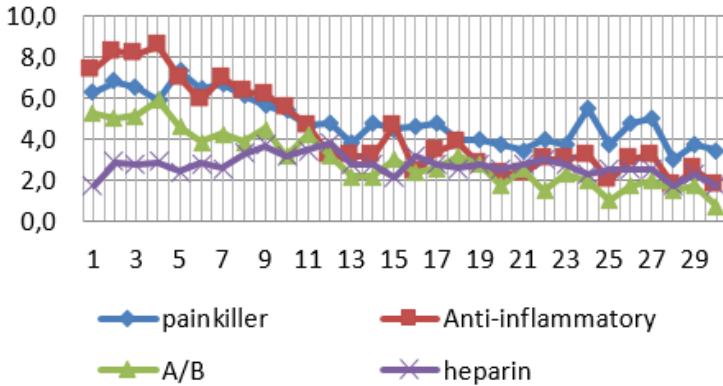

Figure 3. *Medical therapy*

Relatively stable during the study period was the frequency of administration of heparin, vasodilators, dopamine (fig. 4), gradually reduced anti-inflammatory and analgesia, antibiotic therapy (fig. 3).
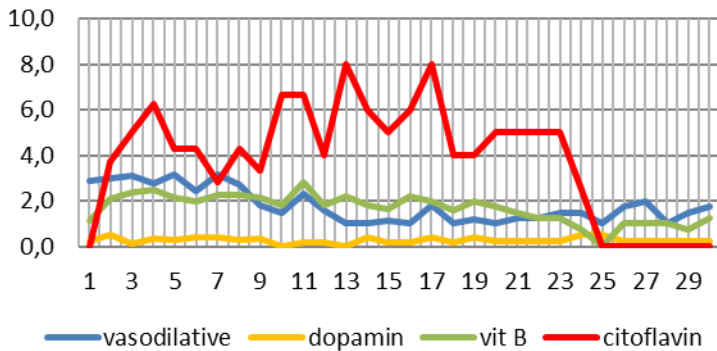

Figure 4. *Correction of capillary blood flow*

In the first 10 days, a strong inverse correlation was found between the administration of glucose and the mesor of the circadian rhythm of body temperature (-0.71), that is, an increase in the introduction of an energy substrate contributed to a decrease in body temperature, a decrease in the severity of the inflammatory response of the body. The number of types of solutions was provided mainly by the addition of amino acids (0.86), proteins (0.76), B-complex vitamins (0.8). In the first decade of toxemia, a negative correlation was found between the daily volume of parenterally administered fluid with heparin (-0.69), with cytoflavin (-0.79), with the average daily level of body temperature (-0.79). A direct correlation between the amount of amino acids and vitamins B complex (0.96) administered, as well as the amount of solutions administered and B complex (0.8) characterized the metabolic orientation of stimulating therapy. At the same time, a positive correlation was observed between anti-inflammatory and antibacterial (0.9), anti-inflammatory and vasodilator (0.7) with a favorable anti-inflammatory effect, as evidenced by the negative relationship between the frequency of administration of anti-inflammatory and T°C (-0.73), vasodilator therapy and body temperature (-0.76). The positive relationship between the change in the introduction of heparin and body temperature (0.68), apparently, is due to an increase in the intake of pyrogenic metabolites from the restored areas of perfusion in the first 10 days of burn toxemia. There was also a direct correlation between anesthesia and antibiotics (0.8), the frequency of administration of analgesic and vasodilator therapy (0.86). In addition, there was a strong direct dependence of anti-inflammatory therapy on antibacterial (0.8) and vasodilating (0.86). As well as anti-inflammatory from antibiotics (0.94) and vasodilators (0.86) with a direct connection between the introduction into the complex and cytoflavin (0.72).

In the second decade, a direct strong correlation was noted between the number of types of parenteral solutions administered and the volume of fluid (0.71). The number of solutions and amino acids (0.78), the volume of intravenous fluid and the introduction of the B complex (0.7). The latter, most likely, was dictated by the need to maintain cellular metabolism under the conditions of indications to enhance detoxification therapy with the introduction of liquid. On days 11-20 of intensive care, direct correlations were found between anti-inflammatory therapy and antibiotics (0.76), anti-inflammatory and average daily body temperature (0.61), synergistic effect of antibacterial and vasodilator drugs (0.74), as well as vasodilators and B- complex (0.66).

In the third decade of burn toxemia, significantly significant positive correlations of calories and heparin (0.7), analgesia and anti-inflammatory (0.82), and negative B complex and dopamine (-0.76) were noted. That is, the introduction of the B-complex caused a decrease in the introduction of the vasopressor, which indicated the restoration of the compensatory participation of vessels in the adaptive capabilities in the third decade of burn toxemia at the age of over 61 years.

Over the entire period (30 days) of monitoring, strong direct correlations were found between the number of administered kilocalories and the volume of intravenous fluid (0.85), the frequency of administration of painkillers (0.8), anti-inflammatory (0.87), antibiotics (0.81), vasodilators (0.84). The increase in intravenous infusion was accompanied by an increase in the frequency of administration of painkillers (0.72), anti-inflammatory (0.81), antibiotics (0.77), and vasodilators (0.77). At the same time, throughout the entire period of toxemia, a direct correlation of painkillers and anti-inflammatory drugs (0.88), pain relief and AB (0.8), pain relief and vasodilators (0.86), as well as a strong direct dependence of anti-inflammatory therapy on antibiotics (0.94), and vasodilators (0.86). As well as a direct relationship between the frequency of administration of the B complex and cytoflavin (0.71). The revealed characterizes the variety of effects and the complexity of the body's compensatory reactions in severe stress inflammatory response in severe burn injury in people over 61 years of age.

Conclusion

On the first day, at the age of 73.8±7.2 years, with a burn area of the skin surface of 2-3A degree 37.5±8.1%, 3B degree - 19±7.3%, IF - 96.8±18.1 unit of daily infusion therapy was within 3230.0±780.0 ml/day. In the first 10 days, an increase in the introduction of an energy substrate - glucose, contributed to a decrease in body temperature, a decrease in the severity of the inflammatory response of the body, and a predominantly metabolite orientation of stimulating therapy was revealed. A significantly significant decrease in the volume of intravenous infusion therapy was observed on the 10th - 30th day by 44 - 60%. The introduction of the B-complex was accompanied by a decrease in the introduction of a vasopressor, which indicated the restoration of the compensatory participation of vessels in adaptive reactions in the third decade of burn toxemia. The revealed correlations characterize the variety of effects and the complexity of the body's compensatory reactions in severe stress inflammatory response in toxemia of a severe burn injury in people over 61 years of age.

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育龄妇女健康生活方式的形成问题
PROBLEMS OF FORMING A HEALTHY LIFESTYLE IN WOMEN OF FERTILE AGE

Karimova Daniya Iusufovna
Doctor of Medical Sciences, Full Professor
Federal Medical Biophysical Center named after A.I. Burnazyan
Moscow, Russia
Zargarova Ayten Eldarovna
Postgraduate
Federal Medical Biophysical Center named after A.I. Burnazyan
Moscow, Russia
Averchenko Rigina Rinatovna
Postgraduate
Federal Medical Biophysical Center named after A.I. Burnazyan
Moscow, Russia
Alsabekova Malika Kazbekovna
Postgraduate
Astrakhan State Medical University

关联。我国医疗保健的预防重点与不断寻找改善年轻一代健康的方法密不可分。在整个综合措施中,预防女性从小就出现生殖障碍和妇科疾病占据了一个特殊的位置。同时,健康生活方式的作用,女孩对其形成技巧的认识也是很大的。

研究目的: 确定与健康生活方式的形成相关的一系列问题,这些问题需要在育龄年轻女性中进行。

材料与方法: 根据专门设计的问卷,对583名15-25岁的女孩进行随机医学和社会研究。收集材料的统计处理通过经典变分统计方法进行,计算广泛的相对值。使用经典变分统计方法对收集的材料进行统计处理,计算广泛的相对值并确定其可靠性 X≥3 x m。

结论。在小学生、中等专业教育机构的学生、女学生、工人群体中,对健康生活方式技能的认识程度不同。作为研究的结果,确定了需要涵盖的一系列问题,制定了作者为帮助讲师准备的演讲厅主题和方法建议,确定了育龄妇女群体以进行差异化的卫生和他们之间的教育工作。

关键词: 健康生活方式 生殖健康 育龄妇女

Relevance. The preventive focus of healthcare in our country is inextricably

linked with the constant search for ways to improve the health of the younger generation. Among the whole complex of measures, a special place is occupied by the prevention of reproductive disorders and gynecological diseases of women from a young age. At the same time, the role of a healthy lifestyle, the awareness of girls about the skills of its formation is great.

Purpose of the study: to identify a range of issues related to the formation of a healthy lifestyle that require their coverage among young women of childbearing age.

Material and methods: according to a specially designed questionnaire, a randomized medical and social study was conducted among 583 girls aged 15-25 years. Statistical processing of the collected material was carried out by methods of classical variational statistics with the calculation of extensive relative values. Statistical processing of the collected material was carried out using the methods of classical variational statistics with the calculation of extensive relative values with the determination of their reliability X≥3 x m.

Conclusions. In groups of schoolchildren, students of secondary specialized educational institutions, female students, workers, a different degree of awareness of healthy lifestyle skills was revealed. As a result of the study, a range of issues that need to be covered was identified, the topics of lecture halls and methodological recommendations prepared by the authors to help lecturers were developed, groups of women of childbearing age were identified for conducting differentiated sanitary and educational work among them.

Keywords: healthy lifestyle, reproductive health, women of childbearing age

According to a specially designed questionnaire, 583 girls aged 15-25 were anonymously interviewed by self-registration. Among them were high school students, SSEI students, female students and young workers.

In terms of optimizing sanitary and educational work among the population, we were primarily interested in the sources from which our respondents draw knowledge about the anatomical and physiological characteristics of their body.

55.4±3.6% of students, 38.3±4.2% of female students, 15.8±2.6% of high school students and 23.7±5.6% of female workers received knowledge from medical workers. 56.3±9.8% of SSEI students, 44.0±11.2% of schoolgirls, 37.7±5.6% of female students and 39.0±7.6% of young workers received knowledge from their teachers.

20.0 ± 3.2% of SSEI students, 40.1 ± 6.7% of high school students and 25.7 ± 4.3% of female students, 23.7 ± 3.3% of factory workers draw medical knowledge through television.

34.8±7.4% of high school students, 5.4±0.9% of SSEI students, 42.8±9.7% of female students and 6.8±1.2% of working women receive the necessary infor-

mation from their parents and their acquaintances. Female workers address their parents less with questions, as this is already an older age group, and among young girls, the group of SSEI students with almost no parental attention differs sharply in their answers.

On the other hand, SSEI students are better than other groups covered by classes in sports sections. They turned out to be 51.8±9.8%, while in all other groups only every 10 girls took part in the work of sports sections.

The rational use of free time, intended for the development of "physical and intellectual forces", the proper organization of leisure and active recreation enriches people's livelihoods. The culture of everyday life has a direct impact on human health.

Most of the girls devote their free time to visiting theaters and cinemas, watching TV shows: 86.2±11.2% of high school students, 91.5±12.4% of workers, 79.2±9.8% of students and 43.6±6.7% of SSEI students. Very many read fiction: 89.5±12.8% of high school students, 81.3±11.4% of female workers. 2 times less than those among SSEI students - 40.0±9.9% and among female students - 40.7±6.9%. But the motivations here are completely different: the former read less because of their low curiosity, the latter due to the fact that they spend a lot of time reading specialized literature on their future profession.

75.4±12.9% of SSEI students, 48.5±8.5% of female students, 58.7±7.9% of schoolgirls are engaged in physical education and hardening of their body.

Of the factors that shape the reproductive health of women and the health of the unborn child, a number of questions were raised. For example, 89.9±14.3% of working women, 83.8±12.3% of high school students, 80.9±10.8% of SSEI students, 68.8±9.8% female students. The answers seem to contradict the level of the girls' educational qualifications. But they most likely answered the question "do you admit the possibility of early sexual activity?".

Remarkably, 18.2±3.6% of high school students, 22.7±4.8% of female students, 45.4±6.4% of SSEI students answered that one can get married before the age of 18, and among factory workers, no one indicated an age under 18. Judging by the statements of the workers, they think so from the moral and ethical ideas that have developed in society. The bulk of the respondents indicated the age group of 18-20 years: 52.7±8.6% female students, 55.0±9.9% high school students, 53.6±7.8% SSEI students and 27.1±4.5% female employees. All other workers believe that the age should be over 20 years.

To the next question, "what is the danger of abortion?" almost all respondents answered: infertility, and 7.2±1.2% of female students, 11.8±3.2% of SSEI students, 14.5±3.6% of high school students indicated that abortion affects a woman's health.

A survey conducted at the time by A.L. Sannikov et al. among adult women

under the age of 35, revealed their higher awareness of the consequences of abortion [1]. According to him, $98.0 \pm 12.3\%$ of the respondents gave correct answers and among the complications of abortion, along with infertility, they indicated that it contributes to inflammation of the female genital organs, can lead to miscarriages, to ectopic pregnancy.

$19.8\pm3.6\%$ of high school students and $13.6\pm2.6\%$ of SSEI students do not know about the harmful consequences of consuming alcoholic beverages. The rest, at our request, transcribed their answers. $55.4\pm8.7\%$ of high school students, $65.4\pm9.4\%$ of SSEI students, $49.1\pm7.6\%$ of female students answered that it is not permissible for a girl, a woman, because it is harmful to the female body, $23.9\pm4.3\%$ of female workers. Harmful for offspring - consider $47.3\pm11.2\%$ of female students, $40.9\pm8.7\%$ of SSEI students and $52.6\pm14.3\%$ of female workers.

$32.3\pm7.9\%$ of female students, $70.9\pm15.7\%$ of SSEI students, $40.4\pm7.4\%$ of high school students were already familiar with the taste of wine before the age of 10 years. $57.7\pm7.9\%$ of female students, $2.4\pm0.9\%$ of high school students, $29.1\pm5.6\%$ of SSEI students recognized the taste of wine at the age of 10–14 years. Among female workers, the answers are completely different.

Before 15 years, none of them had tasted wine, and the first communion at 15-16 years old was in $8.5\pm1.2\%$, at 18-19 years old in $28.8\pm4.9\%$ and over 20 years old - in $5.1\pm1.6\%$. Only $1.8\pm0.8\%$ of SSEI students, $8.5\pm1.2\%$ of high school students and $30.5\pm5.7\%$ of female workers are still not familiar with the taste of wine. These data are correlated with our earlier data collected from adolescent girls [2,3].

We were also interested in the alcoholic attitudes of the girls for the future. How will they feel about friendship with a young man who drinks alcohol? Female students are the most tolerant of this: $29.9\pm4.7\%$ of them, as well as $12.7\pm3.3\%$ of SSEI students, $15.8\pm3.8\%$ of high school students and only $10.2\pm3.3\%$ of workers believe that it is possible to convince them, to re-educate them. All others are negative.

Quite unexpected for us were the answers to the question of how people get infected with venereal diseases. Quite a few respondents did not know the answer: $28.3\pm3.5\%$ of high school students, $27.3\pm4.9\%$ of SSEI students, $24.6\pm3.8\%$ of female students and $8.5\pm\%$ of working women. All the rest indicated among the ways of transmission of sexually transmitted diseases sexual, domestic, or both together, while listing dishes, bedding, etc.

Summing up our surveys, we asked the girls a question: do you know, in the end, that the health and happiness of the future family depends on the observance of a healthy lifestyle, implying a positive answer in advance. Yet 10.0% of SSEI students and one high school student answered don't know.

Conclusions

As a result of the study, a range of issues that need to be covered was identified, the topics of lecture halls and methodological recommendations prepared by the authors to help lecturers were developed, groups of women of childbearing age were identified for conducting differentiated sanitary and educational work among them.

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大疱性表皮松解症与支气管哮喘对 DNA 氧化损伤程度的比较分析
COMPARATIVE ANALYSIS OF THE DEGREE OF OXIDATIVE DAMAGE TO DNA WITH EPIDERMOLYSIS BULLOSA AND BRONCHIAL ASTHMA

Pavlyuchenko Ivan Ivanovich
Doctor of Medical Sciences, Full Professor, Head of Department

Gusaruk Lyubov Ramazanovna
Candidate of Biological Sciences, Associate Professor

Tekutskaya Elena Evgenievna
Candidate of Chemical Sciences, Associate Professor

Kuban State Medical University
Krasnodar, Russia

抽象的
目的。　　比较分析大疱性表皮松解症（EB）和支气管哮喘（BA）的DNA氧化损伤程度。
材料和方法。　DNA 的氧化损伤程度通过血清中的 8-氧鸟嘌呤浓度水平来评估，该浓度是通过酶免疫测定法用单克隆抗体测定的。
结果。　发现EB患者体内修饰碱基8-氧鸟嘌呤的浓度是对照组的1.9倍。　对于BA，该指标与对照相比没有显著变化。
结论。　EB 和 EB 中不同浓度的 8-氧鸟嘌呤表明 EB 中结构 DNA 损伤的严重程度和 BA 中几乎不存在氧化性 DNA 修饰，这可能表明这些疾病在细胞水平上的病理生理障碍机制不同。
关键词：大疱性表皮松解症，支气管哮喘，DNA氧化损伤，8-氧鸟嘌呤。
Abstract

Purpose. To conduct a comparative analysis of the degree of oxidative DNA damage in epidermolysis bullosa (EB) and bronchial asthma (BA).

Materials and methods. The degree of oxidative damage to DNA was assessed by the level of 8-oxoguanine concentration in blood serum, determined by enzyme immunoassay with monoclinal antibodies.

Results. It was found that the concentration of the modified base 8-oxoguanine in patients with EB is 1.9 times higher than in the control group. With BA, this indicator does not change significantly compared with the control.

Conclusion. *Different concentrations of 8-oxoguanine in EB and EB indicate the severity of structural DNA damage in EB and the almost absence of oxidative DNA modification in BA, which may indicate different mechanisms of pathophysiological disorders in these nosologies at the cellular level.*

Keywords: epidermolysis bullosa, bronchial asthma, oxidative damage to DNA, 8-oxoguanine.

Introduction

Epidermolysis bullosa (EB) – Epidermolysis bullosa, is a clinically and genetically heterogeneous group of orphan diseases, including about 30 genotypic and phenotypic forms. All of them are characterized by an innate tendency to form bulls (bubbles) on the skin and mucous membranes of the esophagus, intestines, respiratory, genitourinary systems. Violation of the integrity of the skin occurs even in response to a slight mechanical impact [1]. Erosive and ulcerative defects can persist on the skin from one month to several years, being a predisposing factor to the formation of squamous cell skin cancer - the main cause of premature death of patients [2,3]. Extracutaneous manifestations and their complications in other epithelialized organs make EB a multisystemic disease with high mortality [4, 5].

Bronchial asthma (BA) is a widespread chronic disease affecting 300 million people worldwide. The basis of the pathogenesis of BA is a protracted inflammatory process, including morphological and functional changes in the bronchial tree, characterized by a significant contribution to their development of the hereditary component [6].

Thus, BA and EB belong to multifactorial diseases and, on this basis, arise from the interaction of unfavorable factors of hereditary and non-hereditary nature, the effect of which is eventually summed up. It is known that xenobiotics, highly reactive cellular metabolites, ultraviolet and ionizing radiation lead to the activation of free radical oxidation processes and, as a result, the accumulation of reactive oxygen species (free radicals, hydrogen peroxide, singlet oxygen, etc.) in cells. By causing oxidative modification of various cellular structures, they affect, among other things, its genetic material, leading to damage to the nitrogenous bases of DNA, destabilizing the genome. The most common product of this oxidative modification of nitrogenous bases is 8-oxo-7,8-dihydroguanine (8-oxoG). The reason for this is that it is guanine that has the lowest redox potential of all nitrogenous bases [7].

The body has developed a multi-level system of protection and repair of the genetic apparatus. Formed upon DNA damage, 8-oxoG is eliminated or modified due to the presence of a multifactorial antioxidant defense system and an excision repair system. As a result of the functioning of the enzyme 8-oxoguan-

ine-DNA-*N*-glycosylase, the sequential hydrolysis of the N-glycosidic bond from the 3'end of the damage occurs and the binding of 8-oxoG by the active center occurs. At the same time, the enzyme exhibits a highly specific β-lyase activity against the remaining AP sites, "reversing" 8-oxoG from the DNA molecule. Accumulating in biological fluids, 8-oxoG is one of the best biomarkers of genotoxic oxidative stress in various pathophysiological conditions and diseases [8].

The formation of 8-oxoG in DNA is closely associated with such processes in the body as carcinogenesis, inflammation, aging, and the development of a number of age-related pathologies. According to ESCODD (European Standards Committee on Oxidative DNA Damage), the level of endogenous 8-oxoG in DNA is ~1 8-oxoG per 10^6G. Under genotoxic oxidative stress, this indicator increases several times [9].

Purpose of this work was a comparative assessment of the degree of oxidative DNA damage in patients with EB and BA.

Materials and methods

The degree of oxidative damage to DNA was assessed by the level of 8-oxoG concentration in blood serum in a sample of six EB patients (orphan pathology, a limited number of patients, and difficulties in collecting biomaterial for research), 20 BA patients, and 20 apparently healthy donors. The determination was carried out using monoclonal antibodies to 8-oxoG according to the protocol (DNA Damage, ELISA Kit) by enzyme immunoassay, described in detail earlier [10]. 8-oxoG content was quantified using a pre-built calibration curve, linear in the range of 0.94-60 ng/ml. The sensitivity of the method was 0.59 ng/ml. In each experiment, at least three repetitions were measured, determining the average value.

The significance of differences between samples was assessed using the non-parametric Mann-Whitney U test for small samples. The results were statistically processed (StatPlus software).

Results and discussion

To determine the degree of oxidative damage to DNA, the concentration of 8-oxoG in blood serum was considered. In the control group, this parameter varies from 3.1 to 11.0 ng/ml, averaging 7.7 ± 1.4 ng/ml (Figure).
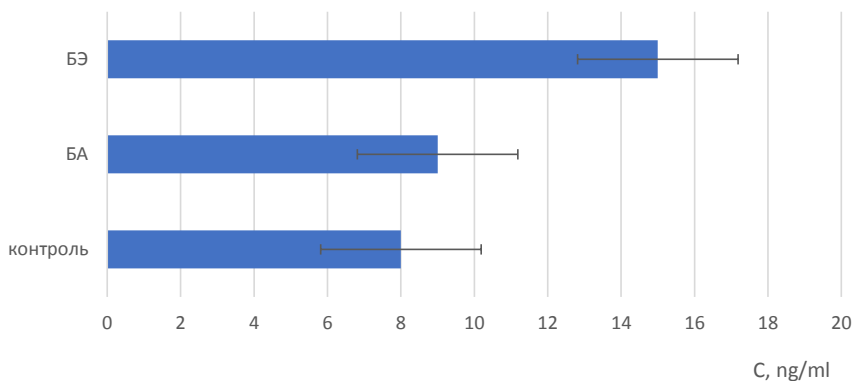
Figure. *The content of 8-oxoG in the blood serum of healthy (control), patients with EB and patients with BA. (U = 1.5; U critical = 3 at p ≤ 0.01; U critical = 7 at p ≤ 0.05). C-concentration of 8-oxoG*

In the group of patients with EB, the level of 8-oxoG varies from 10.0 to 22.2 ng/ml and averages 14.8 ± 2.1 ng/ml, which is 1.9 times higher than in the control. The Mann-Whitney U=1.5 test indicates a small area of overlapping values between the two samples and the reliability of the identified differences ($p \leq 0.01$). In BA, the level of the studied metabolite averaged 9.4 ± 1.7 ng/ml in the sample, which is comparable with the control. This gives reason not to consider BA as a factor of pronounced oxidative stress, which manifests itself at the subcellular level and significantly affects the integrity of the hereditary apparatus.

An almost twofold increase in the concentration of 8-oxoG in EB indicates a significant degree of damage to the structure of the DNA molecule. Since the majority of 8-oxoG is formed as a result of exposure to reactive oxygen species, the genome destabilization observed in this case occurs as a result of the presence of oxidative genotoxic stress, which is formed as a result of activation of free-radical oxidation reactions and insufficiency of antioxidant defense systems.

The main biological consequence of 8-oxoG formation is mutagenesis. Oxidized guanine is able to complementarily combine not only with cytosine, but also with adenine, forming a stable non-canonical (Hoogsteen) oxoG-A pair. In the next cycle of replication, a mutation occurs according to the G/C→T/A [11] transversion type [11]. The defense system developed in the body is designed to restore damage. However, the accumulation of 8-oxoG that occurs in EB can serve as a trigger for mutations that can weaken the processes of excisional repair, preventing the restoration of the DNA structure.

Thus, a statistically significant increase in the level of 8-oxoG and its accumulation in the blood serum of patients with EB indicates that significant destructive genome disorders occur in this pathology, and the cause of these disorders, first of all, is the redundancy of oxidative processes.

Conclusion

An increase in the concentration of 8-oxoG in the biological fluids of the observed patients, which is a molecular marker of genotoxic stress, suggests that EB causes significant oxidative damage to the DNA structure, which disrupts the molecular genetic status of the organism. Perhaps this is one of the reasons for the slowdown in the processes of excisional repair. Identification of the nature of damage to the genetic material of cells in EB can make a certain contribution to further understanding of the etiology and pathogenesis of this pathology. On the contrary, in BA, the amount of the studied metabolite does not differ from the control, and this suggests that repair mechanisms in this pathology, in contrast to EB, are generally preserved, which is probably due to the presence of sufficient reserves of the cellular antioxidant defense system in this category of patients.

There is no conflict of interest

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COVID–19 患者使用糖皮质激素的原则
PRINCIPLES OF GLUCOCORTICOID ADMINISTRATION IN PATIENTS WITH COVID-19

Ivanova Liudmila Alexandrovna
Doctor of Medical Sciences, Full Professor, Head of Department
Kuban State Medical University, Krasnodar, Russia
ORCID ID: 0000-0001-5302-3802
Tanin Ivan Yurievich
Department Assistant
Kuban State Medical University, Krasnodar, Russia
ORCID ID: 0000-0001-8883-3899
Gileva Elena Eduardovna
Head of Department
City Clinical Hospital № 1 of Krasnodar
ORCID ID: 0000-0002-2770-1275

抽象的。 本文讨论了用糖皮质激素药物（GCS）治疗冠状病毒感染（COVID–19）、药物的副作用及其预防、从静脉注射到肌肉注射、再到口服给药、"戒断"综合征的发展。 文章描述了开具抗生素治疗的条件，以及需要联合使用 GCS 和抗生素的条件。 研究的目的 – 分析 GCS 处方治疗 COVID–19 的主要原则：GCS 处方的适应症、给药方案和所需剂量、GCS 处方的副作用。
关键词：糖皮质激素，抗生素，冠状病毒感染（COVID–19），"戒断"综合征。

Abstract. *This article discusses the treatment of coronavirus infection (COVID-19) with glucocorticosteroid drugs (GCS), side effects of drugs and their prevention, transfer from intravenous to intramuscular, and then to oral administration, the development of the "withdrawal" syndrome. The article describes the conditions under which antibiotic therapy is prescribed, as well as the conditions under which the combined use of GCS and antibiotics is necessary.* ***The purpose of the study*** *– to analyze the main principles of GCS prescribing in the treatment of COVID-19: indications for GCS prescribing, administration regimens and required dosages, side effects of GCS prescribing.*

Keywords: *glucocorticosteroids, antibiotics, coronavirus infection (COVID-19), "withdrawal" syndrome.*

Introduction

The SARS-CoV-2 virus causes a coronavirus infection (COVID-19), which is transmitted between people by airborne droplets and contact [1, 16].

More than 5 million people in the world died from COVID-19, more than 266 thousand in Russia, of which more than 8 thousand people in the Krasnodar Territory [2].

Scientists and doctors around the world are faced with the urgent need to develop effective treatment and prevention of COVID-19.

According to WHO recommendations and interim guidelines for (COVID-19) of the Ministry of Health of the Russian Federation (version 15. - 22.02.2022), antiviral, antithrombotic, glucocorticosteroid drugs (GCS), antibacterial therapy are mainly used in the treatment of coronavirus infection. Interleukin-6 receptor antagonists are prescribed along with GCS to stop the cytokine storm in critically ill patients [3].

Material and methods

In cases of severe and critical course of COVID-19 disease (confirmation may be an increase in ferritin, procalcitonin, CRP), systemic corticosteroids are used [3, 4]. Their appointment is justified even when the course of the disease was not initially diagnosed as severe, but suddenly the patient's condition worsened.

Several main groups of drugs are used for COVID-19: immunosuppressive, anti-allergic, anti-inflammatory and anti-shock. All these properties have GCS.

The severe course of the disease is determined by the presence of at least one of the following criteria:
- blood saturation at ≤ 93%
- respiratory rate is > 30 per minute in adults;
- there are symptoms of respiratory failure [6, 8].

The critical course in COVID 19 is determined in the following cases: the development of sepsis and septic shock, the use of mechanical ventilation or catecholamine infusion, acute respiratory distress syndrome (ARDS) [3, 21, 22].

The cytokine storm in COVID 19 significantly worsens the prognosis and is associated with the risk of developing ARDS and sepsis [21]. In such cases, the use of GCS is justified and shown, which inhibit all phases of inflammation, as well as the synthesis of almost all pro-inflammatory mediators [3, 4. 5].

After applying GCS, the therapeutic effect occurs after a few hours. At the same time, the main activity of GCS develops after a decrease in their concentration in the blood [4].

Results and its discussion

For the treatment of pneumonia with respiratory failure or ARDS, "cytokine storm", the use of different schemes for the administration of GCS is recommended. Dexamethasone is prescribed (starting dose of 16 or more mg/day intravenously with a frequency of administration 1-2 times/day), methylprednisolone

(125 mg intravenously every 6-12 hours or 250 mg intravenously simultaneously) [3]. The macrophage activation syndrome is characterized by an increase in the levels of ferritin and CRP in the blood, as well as the development of two- or three-pronged cytopenia. In this case, the following GCS regimens are used: methylprednisolone 125 mg or dexamethasone 20 mg intravenously every 6-12 hours. The dose is titrated daily [3].

• The maximum initial dose of GCS is administered until the condition stabilizes. Criteria for stabilization of the patient's condition: the disappearance of fever, a stable decrease in ferritin (by at least 15%), CRP, activity of alanine aminotransferase, aspartate aminotransferase, and serum lactate dehydrogenase [7]. Glucocorticoids inhibit the secretion of CRH (corticotropin-releasing hormone) and ACTH (adrenocorticotropic hormone) by a negative feedback mechanism. Long-term treatment with GCS leads to slow atrophy of the adrenal glands. Acute withdrawal of corticosteroids can lead to relative adrenal insufficiency. Adrenal atrophy and the development of SCAI (secondary chronic adrenal insufficiency) should be expected in patients taking > 30 mg glucocorticoids per day in terms of hydrocortisone (~ 7.5 mg prednisolone or 0.75 mg dexamethasone tablets) for more than 3 weeks! The intake of glucocorticoids in a dose exceeding the physiological need can cause exogenous hypercorticism, the so-called drug Cushing. The diagnosis is confirmed on the basis of the appearance of characteristic complaints and physical examination data, as well as laboratory changes: cortisol and ACTH levels are suppressed, hypokalemia in 30.5% of cases (potassium <4 mmol/l), hypercholesterolemia in 66.6% of cases (cholesterol $\geq$ 6.3 mmol/l) [3, 5].

• History of GCS use, presence of hypothyroidism, liver cirrhosis, hypoalbuminemia, autoimmune hepatitis, thyroiditis, autoimmune hypoparathyroidism, advanced and senile age increase the effect of GCS.

• In such patients, drug-induced hypercortisolism develops at lower doses of GCS, and withdrawal syndrome, acute adrenal insufficiency, sympathetic-adrenal crises develop much more often with acute withdrawal of GCS.

• Patients who initially received high and very high doses of parenteral dexazone (16-32 mg per day) are initially recommended to switch from intravenous to intramuscular administration, provided that CRP and/or ferritin levels are steadily decreasing. In the event of an increase in the levels of these indicators after the next decrease in the dose of GCS, it is necessary to return to the previous dose and stay there until the trend towards a decrease in CRP and/or ferritin. Then reduce the dose by 10-15% every 4 days [8, 9, 10, 14, 15].

When the dose of tableted prednisolone reaches 5 mg in patients who received medium, high and very high doses of GCS, a further dose reduction is made by 1 mg per month, since the recovery period of the hypothalamic-pituitary-adrenal function can be delayed up to one year [20, 21, 22].

When taking high doses of GCS and abrupt withdrawal, a "withdrawal" syndrome (not due to hypocorticism) may develop. There are several types of "withdrawal" syndrome in patients treated with GCS for a long time:

Type I: both laboratory and clinical signs of impaired hypothalamic-pituitary-adrenal function are present. Adrenocorticotropic hormone (ACTH) and cortisol levels are suppressed. In this case, GCS replacement therapy is needed.

In type II (the most frequently observed), symptoms appear due to an inadequately rapid decrease in the dose of glucocorticoids: arthralgia, malaise, fatigue, depression, fever, etc. In such cases, it is necessary to slow down the intensity of reducing the dose of glucocorticoids.

Type III: dependence on glucocorticoids develops. The clinical picture in this case is not due to the activity of the disease. The function of the hypothalamic-pituitary-adrenal axis is normal. However, for the relief of clinical symptoms, it is necessary to use physiological doses of glucocorticoids (approximately 5 mg of prednisolone or 4 mg of methylprednisolone, or 0.5 mg of dexazone per day in tablets) [4, 5].

Type IV: Patients have laboratory evidence of hypothalamic-pituitary-adrenal axis suppression: ACTH and cortisol levels are suppressed. In this case, short-term GCS replacement therapy is prescribed.

It is also possible the occurrence of acute adrenal insufficiency, sympathoadrenal crises with severe rhythm disturbances and uncontrolled hemodynamics.

All conditions develop, as a rule, in the range from midnight - to 4-5 o'clock in the morning, when these disorders are aggravated by low levels of cortisol according to its circadian rhythm. It is urgent to return to GCS. It is recommended to study electrolytes and calculate the dose and method of administration of potassium and magnesium, depending on the severity of hypokalemia and hypomagnesemia [12]. In a biochemical blood test, potassium less than <4 mmol/l is considered hypokalemia (target serum potassium values are 4–5.1 mmol/l) [12]. Hypomagnesaemia is considered to be less than <0.85 mmol/l (target serum magnesium values of 0.85–1.07 mmol/l) [12]. At blood potassium levels of less than 4 mmol/l against the background of developed GCS withdrawal syndromes, sympathoadrenal crises, rhythm disturbances, there is a need for parenteral (intravenous) administration of potassium preparations and, as a rule, magnesium. After the withdrawal of crises, it is recommended to switch to oral forms of these drugs - potassium and magnesium aspartate for a long time [12, 13].

A timely return to taking GCS will prevent the risk of death of the patient from cardiovascular insufficiency, severe arrhythmias up to polytopic extrasystole, flutter and atrial fibrillation.

An example of the transition from parenteral to oral administration of GCS.

4 mg of dexazone in 1 ampoule = 30 mg of prednisolone in 1 ampoule [4, 5].

30 mg ampoule prednisolone = 5 mg prednisolone per 1 tablet [4, 5]. This dosage of prednisolone tablets should be administered the next day after the withdrawal of 4 mg ampoule dexazone. Reception schemes may be different. For example, 5 mg at 7:00 and 2.5 mg at 12:00, or 5 mg at 7-8:00 and 2.5 mg at 18:00, or 5 mg at 7-8:00; 1.25 mg at 13-14:00, 1.25 mg at 19-20:00). Dose reduction is carried out by 1 mg every 2-4 weeks [8, 9, 10, 14, 15].

It is possible to assess the likelihood of developing primary adrenal insufficiency as a result of long-term suppression of GCS adrenal function by a complete blood count: the development of relative lymphocytosis, anemia, and eosinophilia. The possibility of GC discontinuation should not be assessed by the results of laboratory tests of cortisol, ACTH, aldosterone and plasma renin activity, but should be based on clinical data and the patient's well-being. It will be possible to assess whether the HPA function has recovered in terms of cortisol and ACTH levels only after the complete abolition of GCS. Even with the normalization of the state against the background of the complete abolition of GCS, it must be remembered that in any case, relative hypocorticism develops, which can manifest itself in any stressful situation. Therefore, any, even a small surgical intervention in the future should be accompanied by glucocorticosteroid therapy. During the period of weakening the effect of glucocorticoids due to a decrease in the daily dose, in the absence of contraindications, ascorbic acid is prescribed at a dose of 0.5 g, alpha-tocopherol - 0.4 g per day. Both drugs are taken simultaneously with meals once a day, for a long time. Due to the antioxidant effect of these drugs, the anti-inflammatory effect of glucocorticosteroid hormones is enhanced, the process of lipid peroxidation is suppressed, and cell membranes are stabilized. There is hope for the restoration of the work of the adrenal glands [10, 14].

Conclusions

Thus, we can formulate the following principles for prescribing glucocorticoids in patients with COVID-19:

1. Strict adherence to indications for the appointment of HA (development of macrophage activation syndrome and hemophagocytic lymphohistiocytosis in patients with severe and critical condition). Administration of GCS to patients with COVID-19 who do not meet criteria for severe or critical illness is not recommended. Glucocorticoids save the lives of patients with COVID-19. But it is always necessary to remember that these drugs disrupt all types of metabolism and the treatment of complications that have developed can take the rest of the patient's life.

2. The duration of administration of the maximum doses of HA depends on the severity of the patient's condition and should only be assessed by experienced physicians.

3. A gradual decrease in the dose of HA is recommended to avoid the de-

velopment of the "withdrawal" syndrome, adrenal insufficiency of central origin, sympathoadrenal crises.

4. Only collegial management of patients both in the hospital and in the clinic by doctors of different specialties will help to cope with the complications of taking GCS.

Research transparency

The study was not sponsored. The authors are solely responsible for providing the final version of the manuscript for publication.

Declaration of financial and other relationships

All authors participated in the development of the concept and design of the study and in writing the manuscript. The final version of the manuscript was approved by all authors. The authors did not receive a fee for the study.

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子宫体癌患者的死亡风险取决于肿瘤的组织学类型和癌细胞的分化程度
THE RISK OF DEATH IN PATIENTS WITH UTERINE BODY CANCER DEPENDING ON THE HISTOLOGICAL TYPE OF TUMOR AND THE DEGREE OF DIFFERENTIATION OF CANCER CELLS

Kovalenko Nadezhda Vital'evna
Candidate od Medical Sciences, Chief Physician
Volgograd Regional Clinical Oncology Center, Volgograd, Russia
Demidova Aleksandra Aleksandrovna
Candidate od Medical Sciences, Head of Department
Rostov State Medical University, Rostov-on-Don, Russia
Gladkikh Oleg Nikolaevich
surgeon-oncologist
Regional Consultative and Diagnostic Center, Rostov-on-Don, Russia
Domashenko Elena Vladimirovna
Candidate od Medical Sciences, obstetrician-gynecologist
Regional Consultative and Diagnostic Center, Rostov-on-Don, Russia

注解。 对 5148 名患者国家癌症登记处数据的统计分析揭示了生存和死亡时间的特征，这取决于子宫体恶性上皮肿瘤的组织学类型和肿瘤细胞的分化程度。
关键词：子宫体癌，子宫内膜癌，罕见的子宫体癌，死亡风险。

Annotation. *Statistical analysis of the data of the State Cancer Registry in 5148 patients revealed features of survival and timing of death, depending on the histological type of malignant epithelial tumors of the uterine body and the degree of differentiation of tumor cells.*

Keywords: *uterine body cancer, endometrial cancer, rare forms of uterine body cancer, risk of death.*

Introduction

In Russia, in recent years, uterine cancer has firmly taken the second position in terms of prevalence in the structure of oncological diseases of the reproductive system of women, pushing cervical cancer [1]. The state registry for cancer of the uterine body takes into account the age of patients at registration, the morphological type of the tumor, the degree of differentiation of tumor cells and the date of death of the patient. In the classification of molecular genetic types of endomet-

rial cancer developed in 2019, presented in the Atlas of the Cancer Genome, along with gene mutations and defects in signaling pathways, the histological type of the tumor and the degree of differentiation are present as system-forming factors, which emphasizes their high classification significance [2,3] .

Purpose

To evaluate the dynamics of survival of patients with uterine body cancer in a cohort study, taking into account the histological type of tumor and the degree of differentiation of cancer cells.

Materials and research methods

For the period 2000-2019 data on 5148 patients diagnosed with uterine cancer (C54 according to ICD10) were analyzed. With the help of frequency analysis, the structure of morphological types of malignant epithelial tumors of the body of the uterus was revealed, the frequency of gradations of the degree of tumor differentiation was determined. The International Histological Classification of Endometrial Cancer (WHO classification), 4th edition, 2013, was used for this.

Survival of patients with cancer of the body of the uterus was analyzed by the method of compiling tables of life times and the method of Kaplan-Meier multiplier estimates. The difference in cumulative survival depending on the tumor morphotype or degree of differentiation was assessed using a nonparametric logarithmic rank test. Cox's regression analysis made it possible to characterize the strength of the influence of factors on survival. Using the method of logistic regression, a predictive model of lethal outcome was built and risk values were calculated for various combinations of input parameters. For statistical data analysis, STATISTICA 12.0 software (StatSoft, USA) was used.

Research results

The results of the analysis of the structure of histological types of uterine cancer in 5148 patients living in the Rostov region, registered in specialized oncological institutions, are presented in Table 1.

Table 1.

The structure of histological types of malignant epithelial tumors of the uterine body in patients for 2000-2019

Histological type	Morphological code	Abs.	%
Endometrial adenocarcinoma	8380/3	4836	93,9
Serous cancer	8441/3	196	3,8
Clear cell cancer	8310/3	69	1,3
Mixed adenocarcinoma	8323/3	17	0,3

Variant of malignant epithelial tumor with squamous metaplasia	8570/3	23	0,5
Mucinous cancer	8480/3	3	0,06
Undifferentiated cancer	8020/3	3	0,06
Small cell neuroendocrine cancer	8041/3	1	0,02
Total		5148	100,0

The structure of uterine body cancer was characterized by morphological heterogeneity and was predominantly represented by endometrial carcinoma (93,9%). Among 4836 cases of the endometrioid form of the disease, adenocarcinoma in the glandular polyp, according to the results of a morphological study, was established in 87 patients (1,7%). Rare forms of uterine body cancer were histologically identified in 312 women (6,1%) and presented as serous (3,8%), clear cell (1,3%), mucinous (0,06%), undifferentiated cancer (0,06%), a variant with squamous metaplasia (0,5%).

Among the patients, highly differentiated carcinoma (G1) was detected in 774 (15%), moderately differentiated (G2) in 3604 (70%) and poorly differentiated (G3) endometrial adenocarcinoma in 770 (15%) patients.

The distribution of patients depending on two factors - the tumor morphotype and its degree of differentiation is presented in Table 2.

Table 2.

Distribution of patients with uterine body cancer depending on the histological type of tumor and its degree of differentiation

Morphotype	Degree of differentiation					
	G1		G2		G3	
	Абс.	%	Абс.	%	Абс.	%
Endometrial adenocarcinoma	757	15,7	3402	70,3	677	14,0
Rare endometrial forms	17	5,5	202	64,7	93	29,8
p	p<0,001		p=0,04		p<0,001	

Among patients of two subgroups, depending on the histological type of tumor, moderate differentiation of cancer cells was most often observed. However, in rare forms of uterine body cancer, compared with endometrial adenocarcinomas, highly differentiated tumors were less common (5,5% vs. 15,7%, p<0,001), and poorly differentiated tumors were more common (29,8% vs. 14%, p<0,001). In rare forms of cancer of the uterine body, a high frequency of poorly differentiated G3 gradation is a known fact [3]. But in the classification of molecular genetic types

of endometrial cancer, when ranking the risk of an unfavorable outcome of the disease, only a combination of a non-endometrial tumor and G3 gradation is considered [3]. Meanwhile, these two signs, as our observation has shown, provide for other combinations. Thus, moderate tumor differentiation was predominantly observed in the region in patients with non-endometrial adenocarcinoma (64,7%). Using the Kaplan-Meier method, in dynamics over 20 years, observations of changes in the cumulative proportion of survivors characterized the survival function. At G1, the cumulative survival rate over 20 years of follow-up decreased from 100% to 76,9%, at G2 from 100% to 53%, and at G3 from 100% to 47,8%. Differences in overall survival in the three subgroups were statistically significant (p<0,001). The median survival was reached only at G3 and was 12,7 years.

According to the results of Cox regression analysis, the odds ratio of death in patients with rare forms of uterine body cancer compared with endometrial carcinoma increased by 3 times (exp(B)=3,4; Wald 5,7; p=0,001), and with gradation G3 compared with G2 – 10,7 times (exp(B)=10,7; Wald 11,9; p<0,0001).

For the entire population group of women with uterine cancer, the turning point in time for increased risk of death according to the exponential model was a period of 15,1 years. After reaching this point in time, the risk of developing a lethal outcome increased sharply.

Using the logistic regression method, we created a model that allows us to calculate the risk of death 10 years after the oncological registration of a patient with uterine body cancer, taking into account the morphotype and degree of tumor differentiation. The logistic regression model had a general mathematical expression $P=exp(z)/(1+exp(z))$, where the coefficients of the Z function were calculated based on the results of the analysis of population data. It was found that $Z=0,73*X1+0,79*X2-3,03$, where X1 is the ranking of the presence (1) or absence (0) of a rare form of uterine body cancer, X2 is the degree of differentiation of tumor cells (1,2,3). Using the obtained formula, the probability of developing a lethal outcome in patients with various combinations of predictors was calculated. Risk values are presented in Table 3.

Table 3.

Probability of developing a lethal outcome 10 years after the oncological registration of a patient with uterine body cancer, taking into account the morphotype and degree of tumor differentiation

Morphotype	Degree of differentiation		
	G1	**G2**	**G3**
Endometrial adenocarcinoma	0,1	0,19	0,34
Rare endometrial forms	0,18	0,33	0,52

With endometrial adenocarcinoma, the risk of death within 10 years from the start of specialized treatment with a change in gradation from G1 to G3 increased from 0,1 to 0,34, and in rare forms of cancer from 0,18 to 0,52. That is, with endometrial adenocarcinoma and low-grade G3 cancer, every third patient dies after 10 years, and with a rare form of cancer and the same differentiation, every second.

In patients with serous cancer of the uterine body, a lethal outcome over 20 years of follow-up occurred in 40 (43%) cases. The overall cumulative survival of patients with serous cancer decreased over 20 years from 100% to 47,3% and was statistically significantly lower compared with patients with endometrial carcinoma (p<0,001). Over a five-year period, the cumulative proportion of patients with serous cancer decreased to 0,7, and with endometrial cancer to 0,86, over a ten-year period - to 0,59 and 0,77, respectively. The risk of death in patients with serous cancer of the uterine body increased at 8,6 years and at 12,9 years.

In patients with clear cell carcinoma of the uterine body, a lethal outcome over 20 years of follow-up occurred in 9 (30%) cases out of 30. The overall cumulative survival of patients with serous cancer decreased over 20 years from 100% to 45,5% and was statistically significantly lower in compared with patients with endometrial carcinoma (p=0,035). Over a five-year period, the cumulative proportion of patients with clear cell cancer decreased to 0,69, and with endometrial cancer to 0,86, over a ten-year period - to 0,46 and 0,77, respectively. According to the exponential model, the risk of death in patients with clear cell carcinoma of the uterine body increased at 2,47 years and at 7,41 years.

Conclusion

The dependence of the survival rate of patients with uterine body cancer at the population level for 2000-2019 was detailed from the histological structure of the carcinoma, the degree of tumor differentiation. The fact of a relatively high frequency of moderate differentiation of cancer cells in rare forms of uterine body cancer (64,7%) was found, which led to the development of a prognostic model taking into account these predictors and their combinations. In rare forms of cancer of the body of the uterus, the risk of death must be ranked depending on the degree of differentiation of tumor cells.

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微创膀胱切除术中激光治疗安全模式的发展
DEVELOPMENT OF A SAFE MODE OF LASER TREATMENT IN MINIMALLY INVASIVE CYSTECTOMY TECHNOLOGY

Tukenov Evgeny Sergeevich
Candidate of Medical Sciences, Oncology Surgeon, maxillo-facial surgeon, Chief of surgery
SBHI NSO "CP No. 24".
Novosibirsk, Russia
Semennikova Nina Vladimirovna
Candidate of Medical Sciences, Associate Professor
Altai State Medical University, Barnaul, Russia

抽象的。目标是在设计用于治疗神经根囊肿的新微创技术 – 经瘘和穿孔通路时，在实验和临床中开发二极管激光对囊肿包裹物的安全模式效果。建议的方法包括牙髓治疗或牙齿修复的所有阶段，它们是骨囊肿的来源。这部分处理被赋予了潜在价值，并为处理的最后阶段根尖部分的完全干燥创造条件 – 通道的气密密封，是消除液体和水分的基础，确保阻塞传染源。这些条件是通过从囊肿中抽吸液体并通过瘘管或通过在其前庭或口腔侧打孔 1–2 使其壳凝固来提供的。为了进一步消除残留的囊肿膜和对骨腔的消毒，在 4–5 分钟内将 1–3 ml 光敏剂注入囊腔腔内，排出并再次照射输出功率为 0.5 W、640–650 nm 的二极管激光和25–30秒的长度。在抽吸和凝固控制湿度通道结束后，如果完全执行，现代内生材料填充干燥
关键词：牙源性囊肿，二极管激光，消融，光动力疗法，牙周组织，膀胱切除术。

Abstract. Goal is to develop safe mode effects of diode laser on the wrapper of the cyst in the experiment and clinic when designing a new minim invasive technology for the treatment of radicular cysts - transfistular and transperforation access. The proposed methodology includes all the stages of the Endodontic treatment or retritmenta teeth, which are sources of bone cysts. This component of treatment is given to the underlying value and creating conditions for the full drying in the apical part of the roots of the final phase of treatment-the hermetic sealing of channels, is the Foundation for eliminating liquids and moisture ensure the blockade of the source of infection. These conditions are provided by aspiration of fluid from the cyst and coagulation of its shell through the fistula, or through

hole punching 1-2 in its vestibular or oral side. To further eliminate remnants of membranes of cysts and sterilization of the bone cavity injected into the cavity of the cyst 1-3 ml of photosensitizer in 4-5 minutes, drained and irradiated again diode laser output power 0.5 W, 640-650 nm and the length of 25-30 sec. After the end of aspiration and coagulation controlled humidity channels and, if fully carried out, modern endogermetic materials filling drying

Keywords: odontogenous cyst, diode laser, ablation, photodynamic therapy, periodontal tissue, cystectomy.

The classical methods of surgical treatment of radicular cysts of the jaw bones, proposed by Partsch back in 1882, such as Partsch I (cystotomy) and Partsch II (cystectomy), are widely used in the clinic at the present time [1;2;3] in the form of various modified versions . However, despite the great experience of specialists in this field, the number of various complications and recurrences after the treatment of jaw cysts is decreasing. However, it still remains within 7% - 18% [3;4], an even higher figure is presented in similar studies by other scientists - from 24% to 56% [5;6]. Carrying out cystectomy is limited by the extent of the spread of the cyst, the risk of completely or partially destroying important anatomical formations due to the inability to remove the cyst membrane when it fuses with surrounding tissues. One of the most appropriate ways to improve the quality of treatment is minimal surgical invasion, which ensures the safety of organs and tissues in the area of the pathological focus and the recovery of patients in the shortest possible time [7;8;9]. Therefore, further improvement and search for more effective methods and means of treatment and prevention of radicular and follicular cysts continues to be one of the most important areas of dentistry and maxillofacial surgery.

The purpose of the work is to determine the parameters of the safe mode of the diode laser exposure to the cyst membrane in the experiment and clinic during transfistular and perforation cystectomy.

Materials and methods

The minimally invasive technique of laser cystectomy is intended for the treatment of radicular cysts with a diameter of up to 2.0 cm and includes all stages of endodontic treatment or retreatment of teeth - sources of apical cysts. This final component of antibacterial treatment of root canals is of primary importance, and the absence of moisture in the periapical zone of the roots during its final stage, reliable sealing of the canals, is the basis for eliminating microleakage and ensuring conditions for blocking the source of infection. This was ensured by aspiration of fluid from the cyst cavity and coagulation of its membrane through the fistula or through 1-2 perforations in its vestibular or oral wall. To completely eliminate the remnants of the cyst membranes and sterilize the bone cavity, 1–3 ml of a photosensitizer was injected into the cyst cavity for 3–5 minutes, if necessary,

the cavities were additionally dried and irradiated with a diode laser with a power of 0.5 W, 640–650 nm and a duration of 25–30 sec. After the end of aspiration and coagulation, the humidity and cleanliness of the canals were controlled with paper points and iodinol, and, provided they were completely dry and there was no change in the staining intensity, they were filled with modern endo-sealants. The manipulation ended with the introduction of osteoconductors-osteoinductors into the cavity in the form of a gel with osteotropic antibiotics and application of ointment compositions with antimicrobial, dehydration and anti-inflammatory properties to the perforation area [9] (Figure 1).
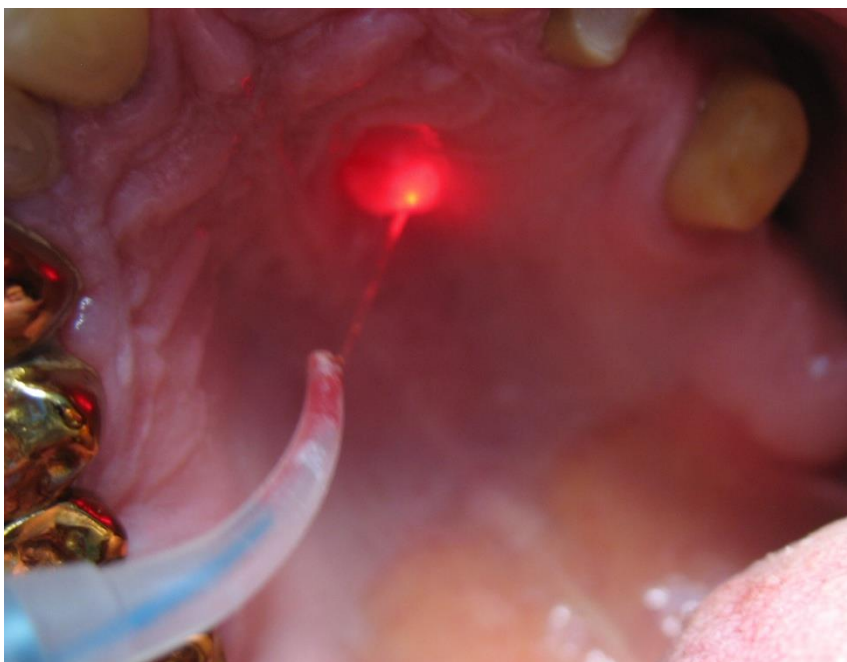
Figure 1. *Method of coagulation of the cyst membrane with a diode laser through a perforation*

The final restoration of the tooth crown was carried out using intracanal posts, as well as pin tabs, artificial crowns.

To determine the most rational indicators of the impact of diode laser radiation on the cyst membrane on biomannequins (maxillary bones of pigs) of the area of the floor of the maxillary sinus, artificial bone cavities up to 2.0 cm were formed with a cutter, which were delimited only by the sinus mucosa (Figures 2 a, b)

a   b
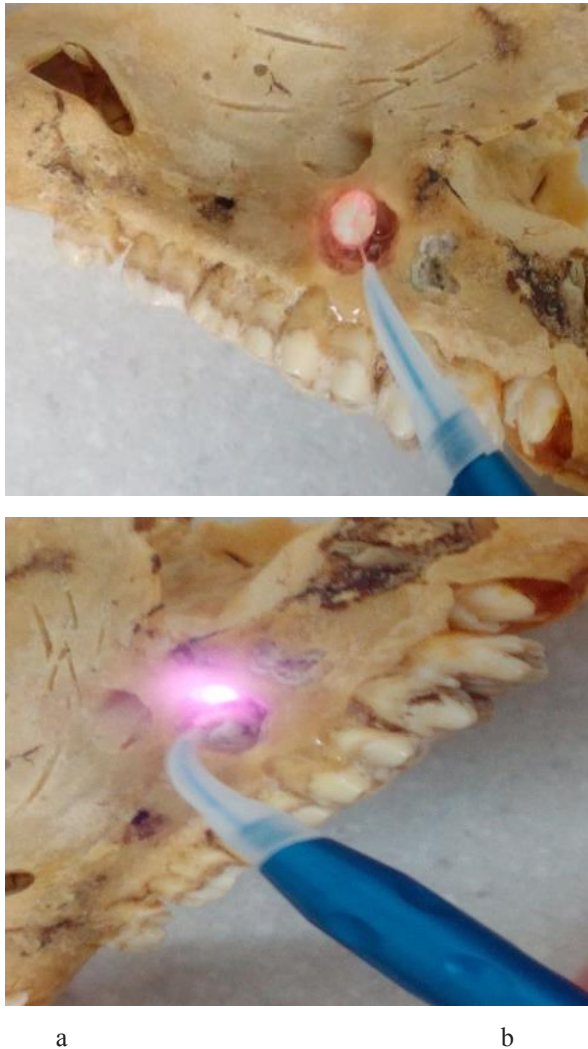
Figure 2. Experimental study using cyst shells in continuous and pulse-periodic modes

Then the cyst shell was placed in the cavity (pieces of cyst shells removed during the cystectomy operation). After that, the cyst membrane was coagulated with a diode laser with an output power of 1.0, 1.5, 2.0, 2.5 and 3.0 W, 10 Hz, with an exposure of 1-2, 2-3, 3-4 and 5 seconds at each power in continuous mode and

1.0, 1.5, 2.0 W, 10Hz, 50 ms in a similar exposure in repetitively pulsed mode. For complete destruction of the tissue components of the cystic membrane, the depth of its coagulation should be at least 80% of its thickness. In order to control the degree of damage during laser cystectomy on the adjacent tissues, we used the method of measuring temperature using an infrared laser thermometer - "Kelvin" tm (CJSC "Euromix", Moscow). Trademark certificate No. 251631) in accordance with the available instructions for its use. The laser beam was directed and placed on the surface of the gums, the measurement result was recorded on the screen, followed by entering the results into the research protocol during laser coagulation of the cyst tissues in the continuous mode of operation of the device, 970 nm, 3.0 W, 1-2 sec × 2-3 times , with an interval between impacts of 1 second (Figure 3)
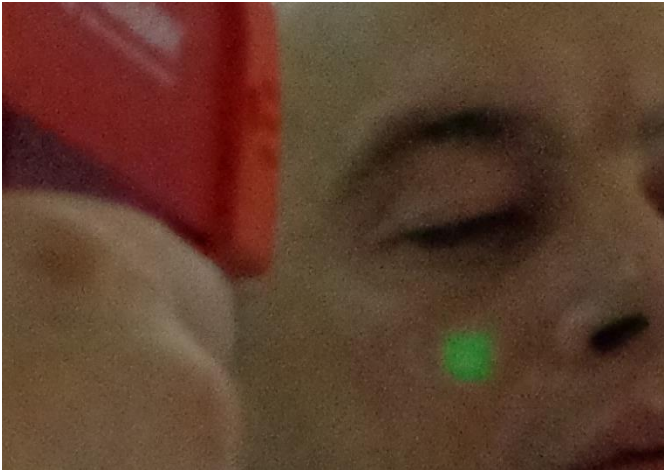
Figure 3. Measurement of tissue temperature using a laser device

Light microscopy and morphometric study were carried out on 12 experimental biomodels in 2 groups: group 1 - using continuous coagulation; group 2 - with the use of coagulation in a pulse-periodic mode. In group 1, the total number of studies was 37 cases, in group 2 - 36 studies. The shells of cysts coagulated with a diode laser in different modes were fixed in 10% neutral formalin solution and embedded in paraffin in accordance with established standards. A microtome was used to make sections of the required thickness of 5–6 µm. The preparations were stained with hematoxylin and eosin using the Van Gieson method. Preparations were analyzed and images were fixed using a "Biolam" light microscope at magnification (approx. 10 × vol. 20 × nozzle 0.5; 1.0; magnification 100-200). Photographs of preparations through a light microscope were taken with a "Sony DSC-P

73" camera. To measure the depth of coagulation necrosis, the "NIS-Elements D3.0" computer morphometric program (Nikon, Melville, NY) was used, and a microscope eyepiece ruler was also used [10].

Statistical processing

The obtained digital indicators were processed by the methods of mathematical statistics, which was carried out on a personal computer based on the "AMD Athlon" processor and the Excel 2016 application software package for Windows XP. With a normal distribution and equality of sample variances, Student's t-test was used to compare the means. Otherwise, the nonparametric Vann-Withny U-test for independent selection groups and Wilcoxon's T-test for linked samples were used. The critical level of statistically significant indicators when testing the null hypothesis was set at $p \leq 0.05$.

Research results and discussion

In the experimental group No. 1-5 models (39 observations), when using a repetitively pulsed form of the energy of the action of a diode laser, the parameters of the destructive depth of the tissues of the cyst membrane were established, which were statistically significant ($p < 0.002$): 1 - with laser coagulation of the cyst membrane at power – 0.5 W 2 sec. × 3 times with an interval of 1 second, the depth of the coagulate was the smallest (382.76 ± 2.75) μm), the deepest tissue coagulation was detected in model No. 5 using a power of 2.0 W 4 sec × 3-4 times (970.87 ± 7.87 μm). The obtained data of the experiment on biomannequins are presented in Table 1.

Table 1.

The depth of the coagulate of the shell of the apical cysts by a diode laser in a repetitively pulsed mode in the experiment, (M ± m)

model no.	1	2	3	4	5
Average measurement value, μm	290,80 ± 2,78[×] 282,87 ± 2,44 (min.)	417,81 ± 2,50[×]	520,70 ± 3,17 [×]	623,77 ± 4,74[×]	770,63 ± 3,78 [×] 789,87 ± 7,78 (max.g)

Note. [×]- statistically significant indicators in groups (U-test Mann-Witny, p = 0.002)

In the study of temperature effects on the mucous membrane of the maxillary sinus, the maximum rise in temperature of 50 0C with reversible thermal damage to surrounding tissues was observed in the 5th research model. In the second batch (37 experiments) of experimental studies, the volume of laser coagulation was studied in a continuous mode at the same power indicators and exposure interval. It was revealed that the studied parameters, corresponding to the studies of the fifth model of series No. 1, were obtained under the influence of 1–2 sec. × 3 times with

a power of 3.0W. On these preparations, insignificant carbonization of the coagulated components of the shell of the radicular and follicular cysts was determined (Figure 4 a, b), the zone of coagulation damage was detected on all the studied preparations in the form of an area. It was actively saturated with the dye. In the studied preparations, there was a slight edema, moderate leukocyte infiltration, unexpressed plethora of blood vessels; along the periphery of the coagulation area, collapsed vessels filled with a small amount of coagulation substrate were determined.

a   b
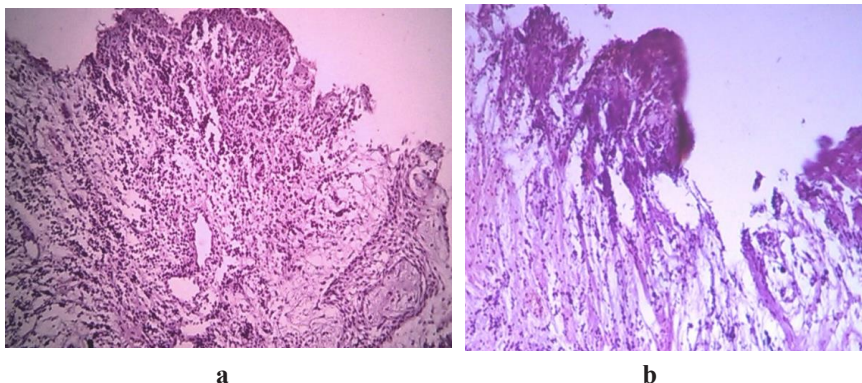
Figure 4. a, b. Cyst wall after laser exposure - damage to its entire thickness: a - cyst wall - zone of coagulation destruction with pronounced predominantly lymphocytic inflammatory infiltration, on the right side - a layer of stratified squamous epithelium, plunging into the thickness of the wall. – Stained with heptoxylin-eosin. A magnification of 100, b - zone of coagulation destruction and carbonization, pronounced infiltration of tissue structures of the cyst by macrophages and leukocytes. Stained with hematoxylin-eosin, magnification of 100 times

Other indicators of more intense damage after the action of the laser in the first series of the experiment in the mode of 1 sec. × 3 times the power of 2.0 W, the wavelength of 970 nm is not installed. The coagulation zone in the largest dimension was equal to 0.99 mm division on the scale of the eyepiece-ruler of the microscope. This was confirmed by computer morphometry data - the volume of necrotic damage was localized within the thickness of the sections of cyst membranes - the average maximum depth was within 979.87 ± 7.78 μm (p=0.002) (Figure 5). Therefore, coagulation with a 970 nm diode laser in a repetitively pulsed mode is 1–2 sec. × 3 times and a power of 2.0 W did not cause an irreversible destructive effect and destruction of the constituent components of the periodontal tissues and mucous membrane of the maxillary sinus floor and the floor of the nasal cavity adjacent to the cyst membrane.
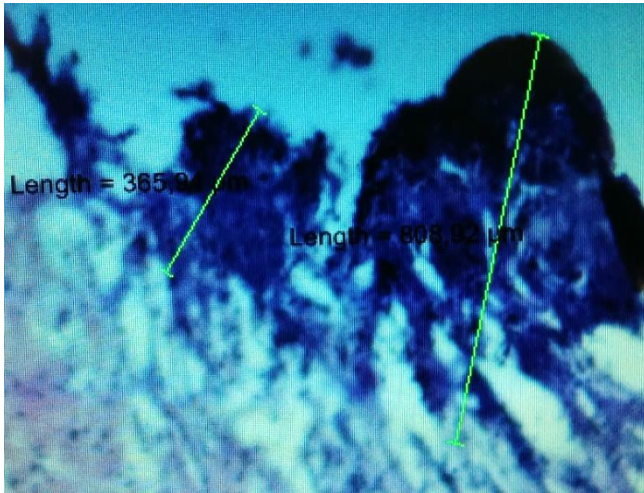
Figure 5. *Measurement of the zone of coagulation destruction group 1. Stained with hematoxylin-eosin, magnification of 40 times (using the computer morphometric program "NIS-Elements D 3.0")*

To control laser exposure in a safe mode in 43 patients of the main group using the original technique of laser cystectomy, temperature indicators were monitored with an infrared laser in the mucosa of the alveolar process of the upper jaw and the alveolar part of the lower jaw at the level of localization of the cystic defect. The analysis of the data obtained showed that during the coagulation of the cyst membrane, a short-term (2.1 ± 0.10) sec.) statistically significant (p=0.001) temperature increase by 8.7 ± 2.1 0C was recorded on the surface of the adjacent tissues. The highest value of the measured temperature parameters in the area of the mucous membrane of the arch of the vestibule of the oral cavity, and, accordingly, the mucous membrane of the maxillary sinus during the time interval of the operation of laser cystectomy averaged 41.51 ± 0.20 ^{0}C for 2.10 ± 0,10 seconds (p=0.001).

Conclusion

The data obtained in the course of experimental studies and using a minimally invasive method of laser cystectomy in the treatment of patients allow us to prove that the established algorithm for the parameters of laser destruction of the epithelial and connective tissue components of the cystic membrane is the most favorable and safe for the patient. The technique of transperforation and transfistula use of diode laser energy with parameters of 2.0 W, 10 Hz, 50 ms (pulse-periodic) and

3.0 W (continuous mode), 970 nm, 10 Hz, light-conducting fiber diameter 200-400 µm with duration of contact with the tissues of the cyst membrane 1-2 seconds x 2-3 times with an interruption of exposure for 1 second when performing the original approach for the treatment of apical cysts of the jaw bones with a volume within 2.0x2.0x2.0 cm of various localization does not cause irreversible damage to periodontal tissues, the mucous membrane of the lower part of the maxillary sinus and the bottom nasal cavity in direct contact with the cyst membrane. Therefore, its use in a polyclinic can be considered rational and expedient.

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12. Tarasenko S. V., Patent for the invention 2020 Method for tooth removal using laser radiation

塔吉克斯坦共和国股骨颈骨质疏松症和低能量骨折
OSTEOPOROSIS AND LOW-ENERGY FEMORAL NECK FRACTURES IN THE REPUBLIC OF TAJIKISTAN

Inoyatova Nigina Azizovna
Candidate of Medical Sciences, Associate Professor

Sayidova Nilufar Samandarovna
Internship doctor

Bakhtibekov Mansur Tabrezovich
Internship doctor

Avicenna Tajik State Medical University, Tajikistan

摘要。 骨质疏松症是最常见的疾病之一，其特征是人口的残疾和死亡率，尤其是 65 岁以上的人群。 最严重的问题与股骨颈骨折有关，在一些国家，包括塔吉克斯坦共和国，其发生频率仍未得到探索。
关键词： 骨质疏松 股骨颈低能量骨折 假体

Abstrat. *Osteoporosis is one of the most common diseases characterized by disability and mortality of the population, in particular those over 65 years of age. The most acute issue is in relation to femoral neck fractures, the frequency of which in some countries still remains unexplored, including in the Republic of Tajikistan.*

Keywords: *osteoporosis, low-energy fractures of the femoral neck, endoprosthetics*

Introduction

In the age of high technology, mankind has achieved significant success in improving the pathogenesis of many diseases, which contributes to the improvement of methods for treating various pathologies. However, despite the achievements of mankind in medicine, especially in matters of vaccination and timely revaccination, which contribute to the prevention of infectious diseases, there is an increase in non-communicable diseases.

According to the materials of the World Congress on Osteoporosis (OP), this is one of the most common diseases, which, along with cardiovascular pathology, diabetes mellitus and oncological diseases, occupies a leading place in the structure

of morbidity and mortality of the population [1]. OP is the most common metabolic disease of bone tissue, characterized by a violation of its structure in the form of a decrease in mass and strength, which often causes fractures, especially of the spine, hip joints and wrist, with the subsequent need for surgical intervention [2].

According to the WHO today, osteoporosis ranks 4th among non-communicable diseases (WHO 1998). This distribution is characterized by the prevalence of disability and mortality in the population. The International Osteoporosis Foundation (IOF) includes doctors from the following specialties: endocrinologists, traumatologists and orthopedists, as well as rheumatologists. However, given the prevalence of the disease and disability, a more expanded interdisciplinary approach is needed.

The lack of awareness of physicians about the prevalence of osteoporosis is exacerbated by the absence of clinical signs. In 50% of cases, patients do not have pain syndrome; it is not for nothing that osteoporosis is called the "silent killer". In the practical health care of many developing countries, the prevention of osteoporosis has not yet been established at a sufficient level, including the Republic of Tajikistan. Unfortunately, due to the lack of a comprehensive examination of patients, as a rule, complications of osteoporosis progress, one of them is femoral neck fractures (FNF). As a rule, FNF is more often observed in elderly patients. According to some authors, the incidence of femoral neck fractures ranges from 46 to 54% of all hip fractures, with the most common type being a verbal fracture and accounting for 34–46% [4].

Fall analysis indicates the development of fractures with minor low-energy trauma, that is, with a simple fall on the trochanteric region. Elderly patients who have sustained a trochanteric fracture due to low-energy trauma often have comorbid injuries such as fractures of the distal radius metaepiphysis and fractures of the proximal humerus. Multiple fractures are noted as a consequence of a decrease in bone mineral density in systemic osteoporosis [5].

According to international experts, by 2025, a two-fold increase in the incidence of fractures of the proximal femur worldwide is predicted. According to statistical reports and researchers, the number of victims worldwide with fractures of the femoral neck by the end of the twentieth century was 1.3 million, and by 2025, 13.5 million low-energy fractures or fractures due to falls will occur worldwide every year [3]. With the aging of the population and the emergence of "old" populations, in which more than 25% of the population belongs to the age group over 65 years, the number of low-energy fractures will increase by 23% by 2030 [4]. And in 2050, the frequency of these damages is predicted - 40.5 million per year. In turn, an increase in life expectancy can also lead to an increase in FNF [6].

In this connection, the problem of osteoporosis among the population is of considerable interest in terms of reducing overall mortality, and in this regard, it is of interest to study the prevalence of FNF in the Republic of Tajikistan.

Purpose of the study

To study the incidence of hip fracture (FNF) in patients in the Republic of Tajikistan.

Materials and methods

On the basis of the State Institution of the Medical Center "Istiklol" in the Department of Traumatology and Orthopedics, 252 records of patients hospitalized for surgery - "Hip Arthroplasty" were retrospectively analyzed in the period from 2017-2020. Of these, 128 (50.8%) patients were men and 124 (49.2%) - women, aged 19 to 86 years, whose average age was 54±1.01. According to the anamnesis, the first fracture was detected in 51%, the 2nd and 3rd fracture in 49% of patients. During hospitalization, all patients underwent laboratory research methods, including: complete blood count, general urinalysis, fasting blood sugar, glycosylated hemoglobin, biochemical blood test (liver and kidney tests, total cholesterol, Ca, P, ion. Ca, vitamin D3, radiography of the hip joint, densitometry.

All patients underwent anterior external arthroplasty using a MERIL (USA) prosthesis.

Statistical processing and mathematical analysis were carried out using the program Statistica 8.0, Excel 2017.

Results and discussion

According to the analysis of records of patients, patients were hospitalized for hip fractures of various degrees, the cause of which was established osteoporosis - 22 (36.9%), injuries 75 (23.8%), congenital dislocations of the hip - 13 (16.25 %) people, coxarthrosis in 113 patients (76.16%), aseptic necrosis in 22 (12.79%) patients, ankylosis in 3 patients (1.74%) and arthrosis in 4 patients (2.34%).

Densitometry was performed in 184 patients, according to which 117 (64%) patients with signs of osteopenia and osteoporosis were identified, the average age of patients was 61.42±0.75. Among the identified patients, various degrees of osteopenic syndrome are observed, in 17 (14.5%) patients in all 3 areas of the examination, in 25 (21.4%) people in 2 standard areas and in 75 (64.1%) patients only in the 1st standard zone.

In 119 (47.2%) patients, the levels of calcium, phosphorus, ionized calcium, and vitamin D levels were studied. When analyzing these results, it was found that in patients with signs of osteopinic syndrome, the indicators were reduced compared to those with normal bone mineral density. The level of vitamin D was reduced in all studied patients compared to the reference values. Data analysis revealed a number of comorbidities in patients (diabetes mellitus, pathology of the gastrointestinal tract, chronic kidney and blood diseases), which can be the cause of secondary osteoporosis.

Endoprosthesis replacement of the hip joint was performed after compensating for comorbidity.

The presence of surgical interventions by years was also analyzed. (tab.1)

Table 1.

Endoprosthesis replacement of the hip joint in patients with hip fracture for the period 2017-2020

Year/sex	men		women	
	<60 years old	*>60 years old*	*<60 years old*	*>60 years old*
2017	14 (10,9%)	23 (17,9%)	13 (10,4%)	27 (21,7%)
2018	13 (10,1%)	22 (17,1%)	11 (8,9%)	21 (16,9%)
2019	10(7,8%)	22(17,1%)	10 (8,1%)	19 (15,3%)
2020	6 (4,6%)	18 (14%)	6 (4,8%)	17 (13,7%)

After a retrospective analysis, a trend towards a decrease in surgical interventions over the years was found (data are shown in the table). I would like to note the trend towards an increase in the detection and treatment of osteoporosis.

Thus, the problem of osteoporosis is still relevant and measures of prevention and timely detection should be strengthened.

Conclusion

1. The incidence of FNF is 76.2% in Dushanbe

2. Timely detection and treatment of osteoporosis is necessary to reduce the incidence of FNF.

3. Widespread densitometry at any age in order to determine the cause of osteoporosis.

4. Patients with diabetes are also at high risk of FNF.

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儿童后部可逆性脑病综合征。 临床病例及文献复习
POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME IN CHILDREN. CLINICAL CASES AND LITERATURE REVIEW

Savina Ekaterina Sergeevna
Doctor Anesthesiologist-Resuscitator
St. Petersburg Clinical Scientific and Practical Center for Specialized Types of Medical Care (Oncological)
Pulkina Olga Nikolaevna
Candidate of Medical Sciences, Head of Department
St. Petersburg Children's Infectious Diseases Hospital №3

抽象的。 本综述总结了俄罗斯和国外关于肿瘤血液病患儿后部可逆性脑病综合征的患病率、临床表现、诊断和治疗的文献资料，并提出了我们自己对该综合征患儿的临床观察。
关键词：后部可逆性脑病综合征，血管源性脑水肿，动脉高血压，意识障碍

Abstract. *This review summarizes the literature data from Russian and foreign sources on the prevalence, clinical manifestations, diagnosis and treatment of posterior reversible encephalopathy syndrome in children with oncohematological diseases, and presents our own clinical observations of children with this syndrome.*

Keywords: *posterior reversible encephalopathy syndrome, vasogenic cerebral edema, arterial hypertension, impaired consciousness.*

Differential diagnostic search for the causes of impaired consciousness in pediatric patients with oncohematological diseases is a difficult task for the clinician. The outcome of the disease directly depends on how quickly and correctly the syndrome that caused the impairment of consciousness is diagnosed and the emergency care is provided in a timely manner. One of the possible causes of impaired consciousness in children of oncohematological profile is the syndrome of posterior reversible encephalopathy.

The syndrome of posterior reversible encephalopathy was first described in 1996 by Hichey et al.[1] Hichey described this syndrome based on an analysis of 15 adult medical records from the New England Medical Center in Boston and St. Anne's Hospital in Paris. The authors noticed a similar clinical picture

in patients admitted to clinics with various acute conditions: headache, impaired consciousness, convulsions, visual disturbances in combination with white matter edema of the brain, mainly in the posterior sections according to MRI. All patients received antihypertensive therapy as treatment, neurological symptoms resolved within two weeks. This condition is called Posterior reversible encephalopathy syndrome (PRES). [1]

To date, there is no official statistics on the prevalence of this syndrome in the Russian Federation, only isolated cases are reported, as a result, there is no clinical alertness of specialists. With late diagnosis and therapy, severe irreversible neurological deficit develops in 30% of cases [2].

In this article, we would like to share two clinical observations of pediatric patients with posterior reversible encephalopathy syndrome suffering from oncohematological diseases.

Clinical case № 1. Patient V., 13 years old, suffering from T-lymphoblastic lymphoma with mediastinal involvement, has been ill since February 2020. She was admitted to the ICU on March 22, 2020 from the pediatric oncology department for acute impairment of consciousness for 3-5 minutes on the 27th day of therapy, including steroid hormones. From the anamnesis it is known that the child has no concomitant pathology, episodes of impaired consciousness were not previously noted. During the last week, there were complaints of headache, mainly in the temporal areas of a "pressing nature". The patient was admitted to the intensive care unit in a clear consciousness with symptoms of retrograde amnesia, BP 160/98 mmHg, other indicators of vital functions were normal. The patient was examined for diagnostic purposes. Clinical and biochemical blood tests, including electrolyte concentrations, are normal. According to the EEG, ECHO-KG, ECG, no pathology was detected. A CT scan of the brain was performed: a decrease in the density of white matter in the convexital sections of the left frontal lobe, in both splenial and occipital lobes - edema? She was examined by specialists: by a cardiologist - labile arterial hypertension, by an ophthalmologist - there is no evidence of optic nerve congestion, by a neurologist - damage to the parietal lobes: bilateral sensitive ataxia, an MRI was recommended to clarify the nature of the process in the brain. According to MRI: MR-picture of areas of vasogenic edema with predominant localization in the parietal and occipital lobes of the brain, most likely posterior reversible encephalopathy syndrome (PRES) (fig. 1, fig. 2). Given the changes found, the therapy of the underlying disease was stopped and postponed, planned antihypertensive therapy (metoprolol 50 mg 3 times a day, lazortan 25 mg 1 time a day), decongestant therapy (acetazolamide 250 mg 1 time a day) was selected and prescribed. Against the background of the ongoing symptomatic therapy, the attacks of loss of consciousness did not recur, there was a regression of the existing neurological symptoms. On the control MRI

after 14 days - residual effects of PRES, which allowed to continue the therapy of the underlying disease. (fig. 3, fig. 4).

Clinical case № 2. Patient A., 15 years old, with a diagnosis of T-lymphoblastic lymphoma with mediastinal involvement, has been ill since August 2020. He was admitted to the ICU on 10.08.2020 from the pediatric oncology department on the 29th day of therapy, including steroid hormones, due to the development of generalized tonic-clonic seizures. From the anamnesis it is known that the child has no concomitant diseases, during the last week there were complaints of an increase in BP to 150/90 mmHg, for which he received planned antihypertensive therapy with enalapril 10 mg 1 time per day. In the ICU, there was a recovery of consciousness with symptoms of retrograde amnesia, an increase in BP to 164/111 mmHg, other indicators of vital functions were normal. Over the next 4 hours, the development of three repeated generalized tonic-clonic seizures with the restoration of clear consciousness in the interictal period was noted. In order to diagnose the cause of convulsive seizures, the patient was examined by specialists: a neurologist - the clinical picture is represented by cerebral symptoms, symptoms of damage to the left parietal lobe (acalculia), right frontal lobe (left-sided pyramidal syndrome), cerebellar syndrome (dysmetria), left occipital lobe (hemianopsia), convulsive syndrome; an ophthalmologist - there is no data for stagnation of the optic nerve head. Conducted instrumental examination: EEG - in the right parieto-posterior temporal region recorded epileptiform activity in the form of complexes "sharp-slow wave"; ECG, ECHO-KG - a variant of the norm. Laboratory in the clinical and biochemical analysis of blood, including the level of electrolytes - without pathological changes. Taking into account the medical history and available clinical experience, examination data from related specialists and instrumental data, a preliminary diagnosis of posterior reversible encephalopathy syndrome was established, and a decision was made to conduct an urgent MRI of the brain. According to MRI data: the MRI picture of structural changes in the subcortical regions of the occipital, frontal, temporal and parietal lobes corresponds to PRES (fig. 5, fig. 6). Given the existing changes, the therapy of the underlying disease was stopped and postponed. Anticonvulsant therapy (valproic acid 25 mg/kg/day) was prescribed, planned antihypertensive therapy was corrected (metoprolol 50 mg 3 times a day, enalapril 10 mg 3 times a day), decongestant therapy (acetazolamide 250 mg 1 time per day). Against the background of ongoing symptomatic therapy, the control MRI of the brain showed positive dynamics after 7 days (fig. 7, fig. 8), convulsive seizures did not recur, which made it possible to continue the therapy of the underlying disease. Thus, posterior reversible encephalopathy syndrome is a potentially reversible condition with timely diagnosis and adequate symptomatic therapy.

Posterior reversible encephalopathy syndrome is a specific clinical and neuroradiological syndrome that is quite rare in clinical practice.

According to information from The Kids`Inpatient Database for 2016, out of 6266285 hospitalizations, 825 hospitalizations were associated with the development of PRES, which is 0.04% [3]. Despite the described symptoms of this syndrome, untimely recognized cases of the syndrome with the development of lethal outcomes persist [3-7].

Khan et.al reported severe multi-organ dysfunction, the immediate cause of which was the posterior reversible encephalopathy syndrome, which led to death. [5]

The clinical picture of this syndrome develops acutely or subacutely and includes non-specific clinical signs: headache, nausea and vomiting, various degrees of impaired consciousness, visual disturbances, visual hallucinations, convulsive syndrome, which can be represented by both generalized convulsive seizures and non-convulsive paroxysms. [8, 9-15] Wu T. et al. report the development of myelopathic syndrome associated with the involvement of the spinal cord in the pathological process. [10]

PRES has specific neuroradiological patterns, the most characteristic of which is a symmetrical edema of the posterior white matter of both hemispheres of the brain, mainly in the parieto-occipital region [1], however, isolated damage to the parietal or occipital regions, frontal lobes, cerebellar hemisphere, basal ganglia, brain stem, and spinal cord is possible. [6]

The best method for visualizing these changes is MRI. The most common MRI findings are punctate or confluent lesions on PD and T2 weighted images. [11, 19]

According to studies, the absence of changes in the brain according to the results of computed tomography does not rule out the diagnosis and requires an MRI. [2]

The etiology of posterior reversible encephalopathy syndrome has not been studied, but this syndrome accompanies many pathological conditions. According to various literature sources, there are descriptions of the syndrome in systemic connective tissue diseases, kidney diseases, preeclampsia, eclampsia, after operations for resection of tumors of the posterior cranial fossa, oncological diseases, organ transplantation, arterial hypertension, diabetes insipidus, hemolytic-uremic syndrome, sepsis, pronounced electrolyte disorders (in particular, hypomagnesemia and hypocalcemia), massive blood transfusions, high-dose steroid therapy, with the use of certain cytostatics, the introduction of granulocyte colony-stimulating factor, intravenous immunoglobulin therapy, the same syndrome is described in patients on hemodialysis. [1, 3, 5, 8, 12-15]

Tambasco N. et al in 2016 notes that in the pediatric population, PRES is most common in oncohematological diseases. Based on the analysis of 111 medical records, it was demonstrated that children suffering from leukemia and lymphomas are most susceptible to developing PRES, and 50% of them developed posterior

reversible encephalopathy syndrome at the induction stage using drugs such as vincristine, steroids, L-asparginase, daunomycin, intrathecal methotrexate, cytarabine. 80% of patients also had arterial hypertension greater than the 95th percentile of the BP distribution curve in the population. [7]

There are conflicting data in the literature about the age of children with PRES. According to Khan SJ et. al. the average age of children with oncohematological diseases and developed PRES is 7 years. [5] According to Thavamani A et. al in the pediatric population, the median age of children with PRES is 13 years. [3] Tambasco N. et al indicate a mean age of 9 +/- 3.7 years in children with cancer. [7]

Khan SJ et. al. emphasize that arterial hypertension and the use of high doses of steroids are key risk factors for the development of PRES in children with oncology. [5]

According to the data presented by the authors of Dmitry Rogachev NMRC PHOI in 2017, in children with oncohematological diseases, the leading trigger factor for the development of PRES is arterial hypertension in combination with the use of immunosuppressants, which was observed in 6 out of 7 observed children with this syndrome. [17]

The pathogenesis of PRES remains debatable and has two main theories: the first theory is associated with impaired autoregulation of cerebral blood flow against the background of a sharp increase in blood pressure, which causes vasospasm, reduced cerebral blood flow, ischemia and subsequently leads to vasogenic edema in the border zones of arterial pools. The second theory is associated with endothelial dysfunction and severe vasodilation, which leads to extravasation of fluid into the interstitium. [12, 18]

Anastasopoulou S. et al. in 2019, based on the observation of 52 patients with acute lymphoblastic leukemia and PRES, they note that seizures are the most common clinical manifestation of posterior recurrent encephalopathy syndrome: they were observed in 43 patients in the observed group. Generalized seizures were noted in 26 patients, partial seizures in 10 patients, partial seizures with secondary generalization in 7 patients. In 19 cases, the convulsive syndrome recurred. Of the other neurological manifestations of the syndrome, the authors indicate impaired consciousness, headache of varying intensity, visual impairment. The authors also draw attention to the fact that 41 patients (78.8%) had arterial hypertension above the 95th percentile, 8 of them received antihypertensive therapy before the development of PRES. [2]

Thavamani A et al. 2019 also point to the role of arterial hypertension in the development of posterior reversible encephalopathy syndrome [7].

Based on data from The Kids'Inpatient Database for 2016, up to 75% of pediatric cancer patients had a history of arterial hypertension prior to the development of PRES[3].

Many authors consider arterial hypertension as a complication associated with the use of specific drugs for the treatment of oncohematological diseases (in particular, cyclosporine, corticosteroids) [3, 4, 16].

Among pediatric patients hospitalized with various diagnoses in US hospitals, the incidence of PRES in children with arterial hypertension is 0.6%, which makes it a key risk factor in the development of this syndrome. [3]

With timely diagnosis and adequate symptomatic therapy, PRES is reversible in 70% of cases. Neuroradiological changes regress completely or almost completely in the range from 2 weeks to 1 month according to Olliver M. et al. [6]

However, 5 to 19% of patients may have an irreversible neurological deficit. [6]

According to a prospective follow-up of 24 pediatric patients diagnosed with PRES for 2 years, the development of irreversible neurological deficit was noted in the group of children with recurrent PRES. [4] According to observations of Tambasco N. et al. mortality in case of late diagnosis of PRES in oncohematological patients reaches 17%. [7]

Symptomatic therapy for posterior reversible encephalopathy syndrome includes antihypertensive therapy, the most commonly prescribed drug is nifedipine [2], but there are also data in the literature on the successful use of clonidine, amlodipine, beta-blockers, ACE inhibitors. [1, 2, 7, 19]

Anticonvulsant therapy includes: benzodiazepines for the relief of a convulsive attack and planned therapy with levitiracetam, fosphenytoin, valproates. [3, 8, 12]

According to several authors, the development of PRES in patients with oncohematological diseases requires a temporary suspension of chemotherapy as one of the trigger factors, which in itself increases the risk of progression of the underlying disease. [5, 7]. This issue requires further study.

According to the largest retrospective study published to date by Thavamani A. Et al. 2019, the costs of hospitalization and effective treatment of PRES in pediatric patients significantly exceed the costs of hospitalization and treatment of other pathologies, which is probably due to the difficulties in diagnosing this condition, the length of stay in the hospital, the need for neuroimaging and the significant use of hospital resources. [3]

Conclusion

Thus, the available literature data and clinical observations indicate that the syndrome of posterior reversible encephalopathy is a potentially reversible condition with timely diagnosis and adequate symptomatic therapy. It is necessary to take into account the possibility of its development in the presence of risk factors, to include it in the differential diagnostic search for the development of impaired consciousness in patients with oncological profile. Routine control of blood pressure in children with oncohematological diseases, in particular leukemia and

lymphoma, and the timely appointment of planned antihypertensive therapy may be promising areas for the prevention of this condition and require further monitoring and study.
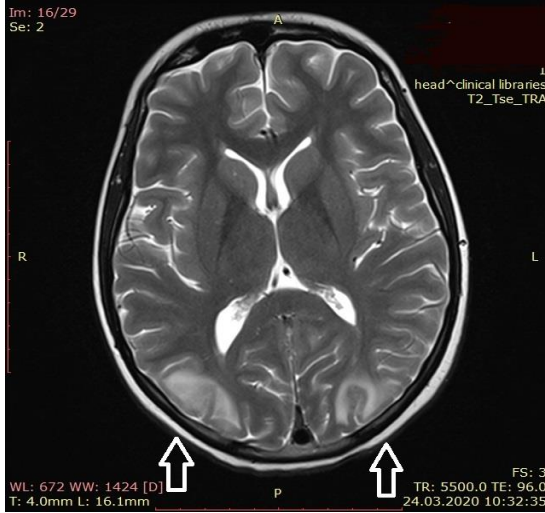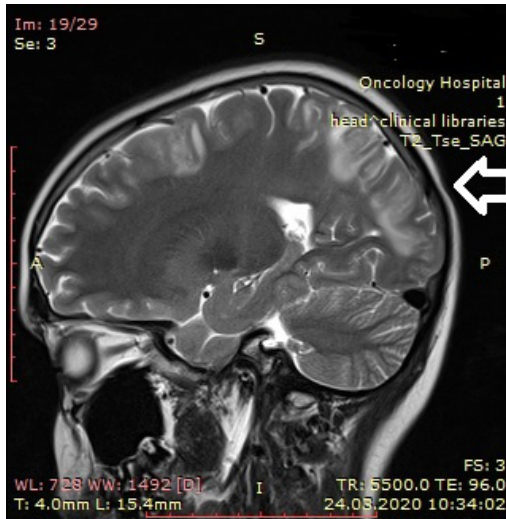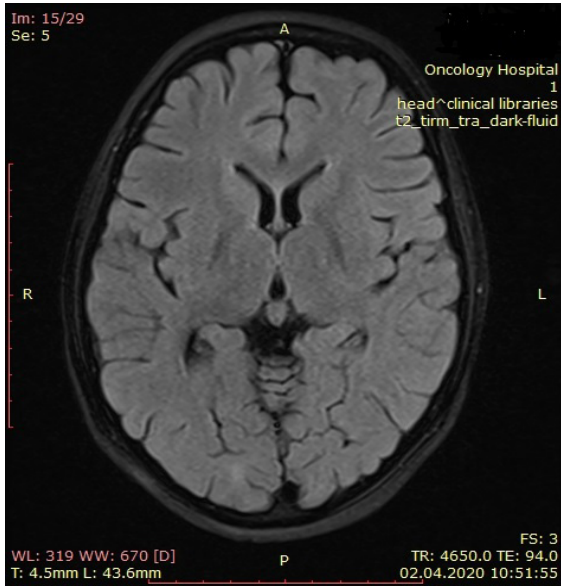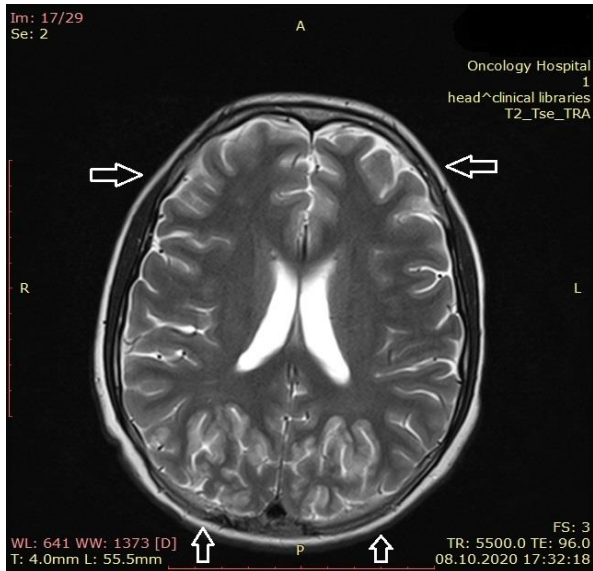
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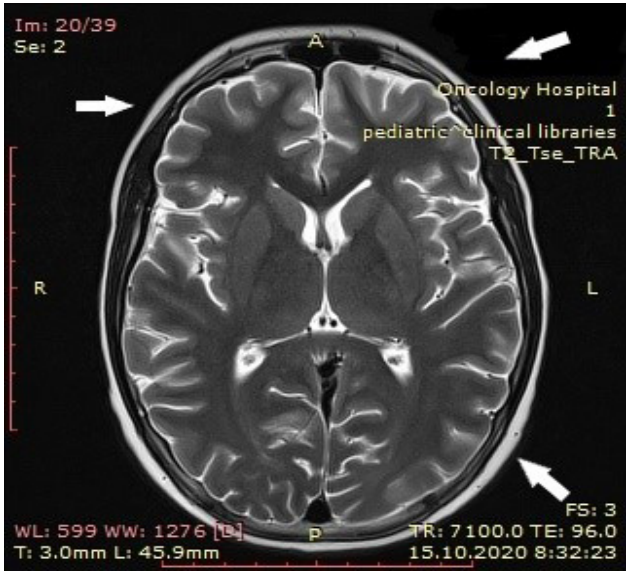
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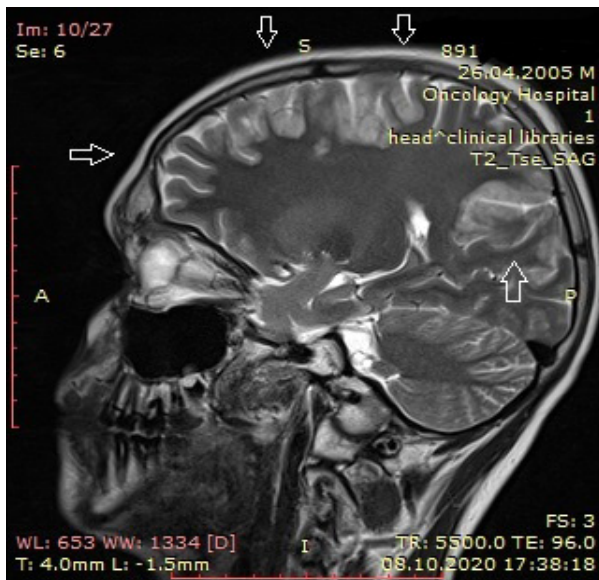
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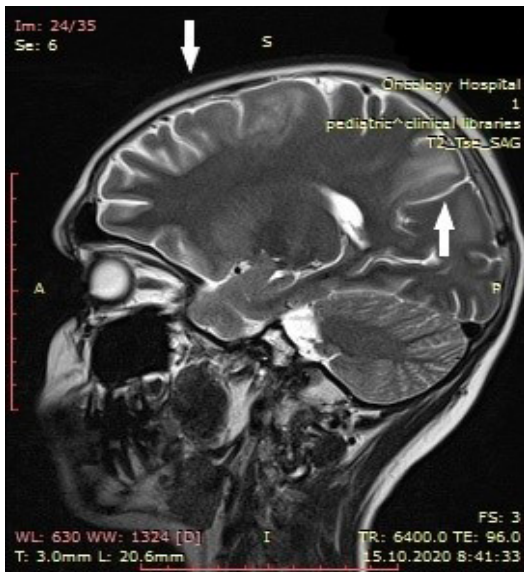
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大鼠小肠和胰腺缺血再灌注损伤的差异
DIFFERENCE OF ISCHEMIA AND REPERFUSION DAMAGE IN SMALL INTESTINE AND PANCREAS IN RATS

Firsova Tatiana Ivanovna
postgraduate
Belgorod State National Research University
Alekhin Sergey Alexandrovich
Candidate of Medical Sciences, Associate Professor
Kursk State Medical University
Bezhina Elena Nikolaevna
postgraduate
Kursk State Medical University

抽象的。 本文介绍了小肠和胰腺组织对缺血/再灌注损伤的反应差异。 获得的数据使我们能够了解胰腺急性炎症的原因，其血管中的血流减少。
关键词：缺血，容量灌注率，再灌注，胰腺，小肠。

Abstract. *The article presents difference of tissue response of small intestine and pancreas to the ischemia/reperfusion injury. The data obtained allow us to understand the causes of acute inflammation of the pancreas with a decrease in blood flow in its vessels.*

Keywords: *ischemia, volume perfusion rate, reperfusion, pancreas, small intestine.*

Introduction

Ischemic and reperfusion tissue injuries in acute surgical diseases, united by the common name acute abdomen, are of critical importance. The pancreas is no exception, and in the genesis of the destructive lesion of the gland tissue, suprasporeal ischemia of the acinar apparatus plays no less a role than the effect of stopping blood flow in the development of structural and functional damage to intestinal tissues in mesenteric thrombosis [2, 5, 6, 7, 9, 12].

The role of ischemia in the development of acute pancreatitis as a consequence of developing mitochondrial dysfunction has been noted in various studies, but recently reports have begun to appear about the possibility of the formation of acute destructive pancreatitis as a complication of cardiac surgery with a decrease

in organ perfusion against the background of artificial circulation. The role of ischemia as the main factor in the development of destruction of the intestinal wall in acute mesenteric thrombosis is beyond doubt [4, 8, 10, 11].

We have previously conducted studies of the rate of volumetric blood flow in the pancreas against the background of a canalicular hypertension model of acute destructive pancreatitis. It was found that the maximum decrease in blood flow is observed by the first day, which is manifested by pronounced destructive phenomena in the stroma of the organ [1, 3].

However, it is not possible to conduct a comparative analysis of blood flow data in the microcirculation in the canalicular-hypertensive model of acute pancreatitis and the model of mesenteric thrombosis due to the difference in the mechanisms of etiopathogenesis.

In this connection, the purpose of our study was to study the rate of volumetric perfusion in the microcirculation of the pancreas in the vascular model of acute pancreatitis and small intestine tissue in the model of segmental mesenteric thrombosis.

Materials and methods

The study was performed on 24 female white rats that were in a state of fasting for 48 hours with free access to water, weighing 280-300 g.

Research design

The animals were divided into 4 groups

Group A (6 animals) model of 30-minute pancreatic ischemia of a rat

Group B (6 animals) model of 30-minute ischemia/reperfusion of the rat pancreas

Group C (6 animals) a model of 30-minute ischemia of the rat small intestine

Group D (6 animals) model of 30-minute ischemia/reperfusion of rat small intestine

All studies and interventions were performed under general anesthesia (zoletil 100 at a dose of 60 mg/kg + chloral hydrate at a dose of 125 mg/kg intraperitoneally).

Acute pancreatitis was reproduced by ligation of pancreatic arteries for 30 minutes.

The model of segmental mesenteric thrombosis was reproduced according to the developed technique by ligation of the arteries for 30 minutes.

Reperfusion was reproduced by resuming blood flow when removing ligatures for a period of 30 minutes.

The velocity of volumetric blood flow was determined by laser doppler flowmetry with an invasive TSD144 sensor using the Biopac system software and hardware complex, software module AcqKnowledge 4.2.0. The data obtained were expressed in perfusion units (PE).

Results and their discussion

In preliminary studies, we have repeatedly noted significant variability in the rate of volumetric blood flow in the abdominal organs in the studied animals, de-

pending on the nature of food and the phases of digestion.

We managed to achieve standardization of indicators in studies with fasting for 48 hours, free access to water and separate keeping of animals.

When using 48-hour fasting, we managed to stabilize the blood flow rate in the microcirculaion of the pancreas at the level of 418.09 ± 39.11 PE, this indicator was later used as the baseline level of perfusion, while against the background of active digestion, the perfusion rate can rise to the level of 1500 ± 276.34 PE.

The data obtained earlier indicate a variation in the perfusion parameters of the microcirculation of both the pancreas and the small intestine, depending on different perfusion zones and as they move away from the central to peripheral areas [3].

In general, understanding the processes of changing the perfusion rate and comparing it when using a variety of indicators in different perfusion zones is significantly difficult, and therefore we use an integral indicator as a result of different perfusion rates in different zones of one tissue site.

Studies of the rate of volumetric perfusion in the pancreatic and small intestine tissue were performed on a vascular model of acute pancreatitis and a model of segmental mesenteric thrombosis during an episode of deep ischemia with complete cessation of blood flow in the pancreatic vessels and an isolated segment of the small intestine for a period of 30 minutes, as well as during the restoration of blood flow for 1, 3, 7, 15, 30 and 60 minutes of reperfusion.
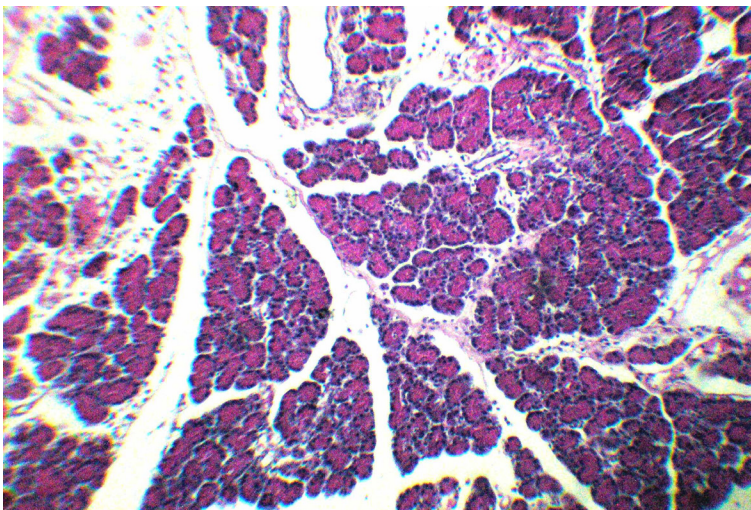
Diagram 1.
"Destructive changes in the pancreas in deep 30 -minute ischemia/reperfusion injury . G+E, magnification X100"

The study revealed a difference in the response of the pancreatic microcirculation to an episode of deep ischemia. The initial perfusion parameters were at the level of 418.09 ± 39.11 PE, with the cessation of blood flow in the vessels of the pancreas, the rate of volumetric perfusion decreased to detectable values. Throughout the entire period of ischemia, the blood flow rate in the microcirculation was at the same level.

The first minute of restoration of blood flow in the vessels of the pancreas was characterized by an increase in perfusion to a level of 50.46 ± 10.18 PE. By the third and seventh minutes of reperfusion, there was a distinct increase in blood flow velocity to values of 87.15 ± 12.83 PE and 103.74 ± 10.47 PE, respectively. And by the 15th minute, the blood flow rate in the microcirculation increases to a level of 151.35 ± 8.27 PE.

In the course of the work, it was revealed that the increase in blood flow velocity during reperfusion is noted only up to the 30th minute, while further restoration of blood flow is reduced by its fall, which is expressed in the level of volumetric blood flow velocity of 333.21 ± 26.32 PE at the 30th minute and 266.69 ± 18.79 PE at the 60th minute.

The pronounced damaging effect of an episode of deep ischemia lasting 30 minutes followed by a 30-minute reperfusion on the pancreatic tissue, unlike the tissues of the small intestine, is also manifested at the microscopic level, which primarily affects the formation of interstitial edema. During histological examination in the pancreas, the phenomena of venous fullness and hemorrhage are noted.

Reperfusion during a 30-minute episode leads to the progression of destructive changes, despite the increase in the rate of volumetric perfusion from 418.09 ± 39.11 to 333.21 ± 26.32 PE. Structurally, this is manifested in cytoplasmic homogenization of pancreatic cells with vacuolization of zymogenic zones. In the stroma, pronounced swelling of the interlobular spaces and disorganization of the lobules of the pancreas are formed (Diagram 1).

In the course of the study, we found that there is no episode of transient hyperemia in the pancreas during the restoration of blood flow after an episode of deep 30-minute ischemia, characteristic of small intestine tissue, and instead of this increase in blood flow velocity in the vascular model of acute pancreatitis, there is a decrease in perfusion of pancreatic tissue to the level of 266.69 ± 18.79 PE (Diagram 2).
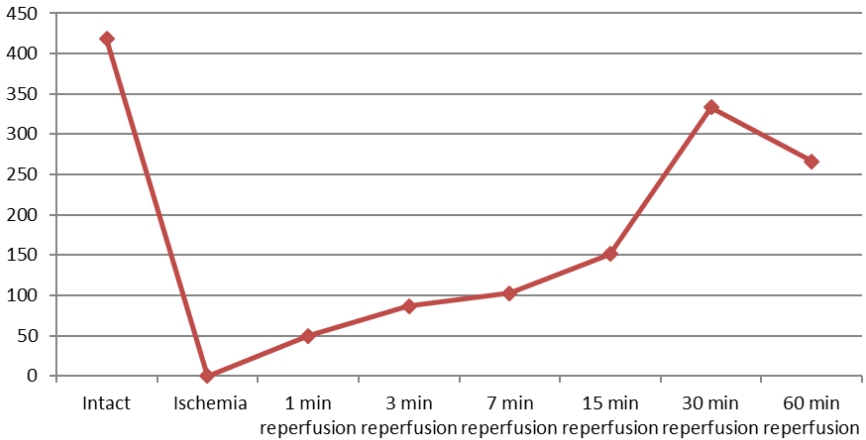
Diagram 2

"The rate of blood flow in the microcirculation of the rat pancreas during an episode of deep 30-minute ischemia and reperfusion"

Thus, in the course of the study, the difference in the reaction of the microcirculation of the rat pancreas in response to an episode of deep 30-minute ischemia with subsequent restoration of blood flow was established.

Conclusions

The data obtained in the course of the work indicate a pronounced damaging effect of an episode of deep 30-minute ischemia and 30-minute reperfusion on both pancreatic tissue and small intestine tissue, however, the resulting reaction of restoring blood flow at the 60th minute is significantly different, which, in our opinion, is one of the main causes of the development of acute pancreatic necrosis with the formation of a systemic inflammatory response syndrome.

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从时间生物学的角度来看，功能性 Stange 和 Gench 呼气测试作为 COVID-19 大流行期间患有缺血性心脏病的第二成熟女性对缺氧的抵抗力的标志物

FUNCTIONAL STANGE AND GENCH BREATH TESTS FROM THE STANDPOINT OF CHRONOBIOLOGY AS MARKERS OF THE RESISTANCE OF WOMEN OF THE SECOND MATURITY WITH ISCHEMIC HEART DISEASE TO HYPOXIA DURING THE COVID-19 PANDEMIC

Boyarskaya Larisa Aleksandrovna
Candidate of Medical Sciences, Associate Professor, Chief Physician
Tyumen hospital of FMBA of Russia,
Tyumen State Medical University, Tyumen
Prokopyev Nikolay Yakovlevich
Doctor of Medical Sciences, Full Professor, Honored Innovator of
Russia, Honored Worker of Science and Education,
Academician of the RANS
Tyumen State Medical University, Tyumen
Ananyev Vladimir Nikolaevich
Doctor of Medical Sciences, Full Professor
Institute of Biomedical Problems of the RAS, Moscow
Toropygin Pyotr Yurievich
Candidate of Medical Sciences, Head of the Therapeutic Department
Tyumen Hospital FMBA Russia, Tyumen
Ananeva Olga Vasilevna
Doctor of Medical Sciences, Full Professor
Tyumen State Medical University, Tyumen

抽象的。作者为 24 名西伯利亚第二成熟期 47.4 ± 1.7 岁的女性设定了研究目标，这些女性患有慢性缺血性心脏病 (IHD)，在 Covid-19 大流行期间，在时间生物学方面没有心力衰竭的迹象，研究在积极言语影响下吸气和呼气对缺氧的抵抗力，以创造一个占主导地位的AA院士Ukhtomsky 在使用音乐伴奏方面。经女性口头同意，每周 3 次，每次 8、12、16 和 20 小时，根据 Stange 和 Gench 呼气试验进行抗缺氧的时间生物学研究。得出的结论是，在执业医师进行有限检查的条件下评估呼吸系统的活动时，上述测试以其简单性和可访问性，客观地了解了身体的功能。即使存在 IHD 形

式的躯体疾病，使用　　Ukhtomsky　　显性也有助于显着提高呼吸系统的功能。
关键词：第二成熟女性、缺血性心脏病、抗缺氧性、Covid-19 大流行。

Abstract. The authors set the goal of the study in 24 women of the period of the second maturity of Siberia 47.4 ± 1.7 years old, with chronic ischemic heart disease (IHD) without signs of heart failure, during the Covid-19 pandemic, in chronobiological terms, to study resistance to hypoxia on inhalation and exhalation under the influence of positive verbal influence to create a dominant Academician A.A. Ukhtomsky in terms of using musical accompaniment. With the oral consent of women at 8, 12, 16 and 20 hours 3 times a week, a chronobiological study of resistance to hypoxia was performed according to Stange and Gench breath tests. It is concluded that in assessing the activity of the respiratory system in conditions of limited examination by a practicing physician, the above tests, with their simplicity and accessibility, give an objective idea of the functional capabilities of the body. The use of the Ukhtomsky dominant contributes to a significant increase in the functionality of the respiratory system, even despite the presence of a somatic disease in the form of IHD.

Keywords: women of the second maturity, ischemic heart disease, resistance to hypoxia, Covid-19 pandemic.

Relevance

Over the past years, the issues of the clinic, diagnosis, treatment and prevention of the Covid-19 coronavirus have been the subject of constant discussions on the pages of the periodical press. It remains a fact that the Covid-19 coronavirus pandemic has made significant changes in the habitual lifestyle of every person, including those with various somatic diseases, in particular the cardiovascular system (CVS) [4, 5, 7, 15, 18, 21, 28], significantly changing the quality of life [12] and often ending in death [2, 16, 26].

The SARS-CoV-2 pathogen that causes Covid-19 is an infection that affects the human respiratory system [11, 20, 23, 25, 30].

In addition, the virus also has a negative effect on CVS, causing serious complications such as exacerbations of ischemic heart disease (IHD), myocardial infarction (MI), cardiac arrhythmias, and thrombosis [6, 19]. Thus, in particular, CVS complications occur in 20-25% and cause death in 40% of patients [9, 24].

In the context of the globalization of the disease and due to the high contagiousness of Covid-19, the Government of the Russian Federation made the only right decision to introduce a strict self-isolation regime in our country, which, of course, significantly reduced the level of physical activity of each person, including patients with CVS diseases. Long-term self-isolation in conditions of limited living space, significant and sometimes complete restriction of motor activity significantly affected the functional state of CVS. The infection primarily chose

the heart as one of the targets, the functional significance of which in the overall structure of human life can hardly be overestimated [8, 10, 17, 22].

In the available literature, we have not found studies that shed light on the effect of a long-term regime of self-isolation in women of the second maturity living in Siberia, suffering from IHD without signs of chronic heart failure, on the chronobiological indicators of the function of external respiration in the form of breath holding on inhalation and exhalation, firstly, under the influence of simultaneous positive verbal suggestion to create a dominant Academician A.A. Ukhtomsky and, secondly, against the background of pleasant musical accompaniment. It should be noted that when assessing the physical development of a person, an obligatory item of examination is the analysis of his resistance to hypoxia.

In this study, we did not address the clinical presentation of IHD and respiratory failure.

Purpose: in women of the period of the second maturity of Siberia during the Covid-19 pandemic, in chronobiological terms, to study resistance to hypoxia during inhalation and exhalation under the influence of positive verbal influence to create an academician A.A. Ukhtomsky dominant in terms of using musical accompaniment.

Material and methods

In 24 women of the second maturity of 47.4 ± 1.7 years, who are hospitalized in the therapeutic department of the Tyumen hospital FSBHCI NSMC FMBA of Russia for the chronic course of IHD without signs of heart failure, with their oral consent, chronobiological (in 8, 12, 16 and 20 hours 3 times a week) study of resistance to hypoxia using the Stange and Gench samples. From the anamnesis, it was established that the duration of IHD disease was 6.2 ± 1.4 years.

The assessment of the functional state of the respiratory system was carried out by studying many indicators, of which in this report we share the duration of an arbitrary breath holding (in seconds) during inhalation and exhalation. The Stange test and the Gench test were used in a state of physiological rest in a sitting position and after a positive 8-10 minute verbal suggestion and, secondly, against the background of pleasant musical accompaniment.

The Stange test was chosen by us due to two cumulative factors. Firstly, due to the fact that it allows quickly and safely for a person to determine the general functional state of the respiratory system, resistance to hypoxia and hypercapnia. Secondly, it has methodological simplicity of implementation and mass availability, does not require special equipment, which is important in conditions of self-isolation. We consider it important to note that the correctness of the test was controlled by palpation determining the beginning of reflex contractions of the diaphragm before the end of arbitrary apnea. The test with arbitrary breath holding on exhalation (Genchi) was performed according to the generally accepted method.

When using the dominant of the Russian physiologist Alexei Alekseevich Ukhtomsky (1875-1942), we proceeded from the fact that the human brain during wakefulness works on certain algorithms that require constant updating.

Ukhtomsky first introduced the concept of "dominant" into scientific use in 1904, and published the results of its application in 1923. In his opinion, the dominant is the excitability of the nerve centers, while inhibition phenomena are widely observed in the rest of the nervous system [29]. The main property of the dominant is the capture of motor pathways to the muscles in its subordination, which is easily explained by the need to move for the implementation of the dominant. The dominant neurocenter (DN) has a number of specific properties. Among them, for example, resistance and increased excitability of neurons. The increased excitability of the dominant DN predetermines the ability of the neurons of the dominant DN to respond to excitations to which they have not previously reacted (the dominant DN "attracts" excitations radiating through the central nervous system). Dominant DN has a depressing effect on competing centers.

We assumed that the process of updating neural connections in the brain would be better if it was stimulated with the help of breathing, in particular, an arbitrary breath holding on inhalation and exhalation to musical accompaniment and verbal suggestion to create a dominant according to A.A. Ukhtomsky. An unresolved issue in such a situation is to identify the individual characteristics of the physiological and psychological adaptation of women suffering from IHD by studying their functional tests with breath holding when applying positive verbal suggestion against the background of musical accompaniment.

For 8-10 minutes, the woman was calmly told that without much effort and without visible tension, so to speak, effortlessly, she could hold her breath for 10-15 seconds longer than she did at rest in everyday life. During the period of positive suggestion and direct determination of the duration of arbitrary breath holding, the music of V.A. Mozart "Rondo Alla Turca" – "Turkish Rondo".

We made the assumption that, even if short in time, but precisely the positive nature of suggestion against the background of musical accompaniment, it can be that irritant for the brain, which, in accordance with the teachings of Academician A.A. Ukhtomsky about the dominant, programs it for a more pronounced and time-stable preservation of the function of the respiratory system.

The results of the study were processed on a personal computer using modern electronic programs (STATISTICA). The assessment of the significance of differences was carried out using Student's t test.

During the study, the principles of voluntariness, the rights and freedoms of the individual, guaranteed by articles 21 and 22 of the Constitution of the Russian Federation, as well as the Order of the Ministry of Health and Social Development of Russia № 774n dated August 31, 2010 "On the Ethics Council" were observed. The study was also conducted in compliance with the ethical standards set out in the Declaration of Helsinki and the Directives of the European Community (8/609EC) and the informed oral consent of women.

Results and discussion

By observing the protective regime in the therapeutic department, we tried to protect women with IHD as much as possible from external negative influences and tried to make their stay in the ward not only as comfortable as possible, but also useful in terms of self-education. In this regard, when studying the resistance of women to hypoxia, we, firstly, explained to them the methodology and progress of the study and its practical importance. Secondly, they taught how to perform tests. Thirdly, they pointed to the normative values of the studied indicators and carried out their interpretation.

The resistance of the female body with IHD to hypoxia according to the results of the Stange test

We emphasize that the Stange and Gench tests for rapid assessment of the function of external respiration have firmly entered clinical practice and have taken a worthy and honorable place in it due to safety and ease of execution [1, 3, 13, 27].

For normative values of arbitrary breath holding on inspiration in women, 35-45 seconds are taken.

As a result of the study, firstly, it was found (tab. 1) that the duration of arbitrary breath holding on inspiration in women of the second maturity in a state of physical rest during the day and week was at a level below the standard values.
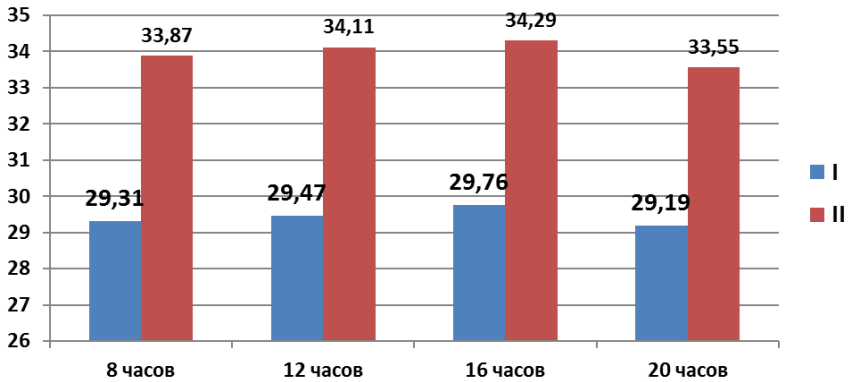
Chronobiological indicators of resistance to hypoxia in women of the second maturity according to the results of the Stange test in conditions of self-isolation in a state of physiological rest (I) and after combined (II) positive suggestion and music (M±m)

Day of the week	Examination time			
	At 8 o'clock	At 12 o'clock	At 16 o'clock	At 20 o'clock
Monday	I. 29.43±1.16 II. 33.96±1.18 Growth 4.53	I. 29.57±1.15 II. 34.29±1.18 Growth 4.72	I. 29.94±1.16 II. 34.87±1.19 Growth 4.93	I. 29.35±1.14 II. 33.77±1.17 Growth 4.42
Wednesday	I. 29.38±1.15 II. 33.87±1.17 Growth 4.49	I. 29.50±1.16 II. 34.16±1.17 Growth 4.66	I. 29.86±1.16 II. 34.59±1.15 Growth 4.73	I. 29.22±1.15 II. 33.63±1.16 Growth 4.41
Friday	I. 29.13±1.14 II. 33.79±1.13 Growth 4.66	I. 29.34±1.16 II. 33.89±1.15 Growth 4.55	I. 29.48±1.16 II. 33.43±1.15 Growth 3.95	I. 29.02±1.14 II. 33.27±1.12 Growth 4.25
Averages	I. 29.31±1.15 II. 33.87±1.17	I. 29.47±1.16 II. 34.11±1.17	I. 29.76±1.16 II. 34.29±1.15	I. 29.19±1.14 II. 33.55±1.15

Secondly, during the day and week, the duration of the amplitude of arbitrary breath holding on inspiration at rest ranged from 29.02 seconds to 29.94 seconds, i.e. its range was 0.92 seconds. Thirdly, the maximum breath holding during the day and the week took place at 4 pm, while the minimum duration of breath holding on inspiration was found at 8 and 8 pm, and in absolute terms, the duration of breath holding during these hours was almost the same ($p > 0.05$).

A significant ($p < 0.05$) increase in the duration of voluntary breath holding on inspiration was revealed after we used the Ukhtomsky dominant, both during daylight hours and during the week of the study (fig. 1).

Figure 1. *The level of the mean value (mesor) of the duration of voluntary breath holding on inspiration in women of the second maturity with IHD during the Covid-19 pandemic during the day at physical rest (I) and after using the Ukhtomsky dominant (II)*

The resistance of the female body to hypoxia according to the results of the Gench test

The results of the study of the resistance of women to hypoxia according to the Gench test testified (tab. 2) that, firstly, in all of them it was assessed as unsatisfactory, because it went beyond the normative values of 30-39 sec.

Table 2.

Chronobiological indicators of resistance to hypoxia in women of the second maturity according to the results of the Gench test in conditions of self-isolation in a state of physiological rest (I) and after combined (II) positive suggestion and music (M±m)

Day of the week	Examination time			
	At 8 o'clock	At 12 o'clock	At 16 o'clock	At 20 o'clock
Monday	I. 23.43±1.16 II. 28.76±1.18 Growth 5.33	I. 24.07±1.16 II. 29.14±1.18 Growth 5.07	I. 24.69±1.16 II. 29.56±1.18 Growth 4.87	I. 23.31±1.16 II. 28.43±1.18 Growth 5.12
Wednesday	I. 23.12±1.16 II. 28.64±1.18 Growth 5.52	I. 23.71±1.16 II. 28.90±1.18 Growth 5.19	I. 24.16±1.16 II. 29.23±1.18 Growth 5.07	I. 23.03±1.16 II. 28.32±1.18 Growth 5.29
Friday	I. 22.77±1.16 II. 28.35±1.18 Growth 5.58	I. 23.29±1.16 II. 28.44±1.18 Growth 5.15	I. 24.09±1.16 II. 29.16±1.18 Growth 5.07	I. 22.31±1.16 II. 28.20±1.18 Growth 5.89
Averages	I. 23.10±1.15 II. 28.58±1.17	I. 23.69±1.16 II. 28.82±1.17	I. 24.31±1.16 II. 29.31±1.15	I. 22.88±1.14 II. 28.31±1.15

Secondly, during daylight hours, the maximum values of voluntary breath holding on exhalation were recorded at 16:00 (fig. 5), while the minimum values were at 8:00 in the morning and at 20:00. The amplitude of the spread in the duration of breath holding on exhalation ranged from 22.31 to 24.69 seconds, i.e. 2.38 sec. It is noteworthy that the Ukhtomsky dominant contributed to a significant ($p < 0.05$) increase in the resistance of the women's body to hypoxia, practically bringing it closer to the normative values (fig. 2).
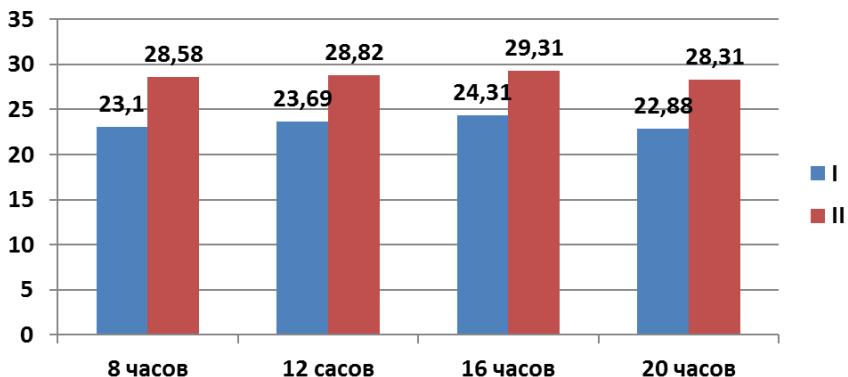
Figure 2. The level of the mean value (mesor) of the duration of voluntary breath holding on expiration in women of the second maturity with IHD during the Covid-19 pandemic during the day at physical rest (I) and after using the Ukhtomsky dominant (II)

Conclusions

1. Self-isolation with IHD in the context of the Covid-19 pandemic is a kind of stress-induced state of the real life of a woman of the period of the second maturity, which occurs during her stay in conditions of not only a closed room, but also physical inactivity and hypokinesia associated with this, is a prerequisite for changes in the mechanisms of regulation of the functioning of the cardiorespiratory system.

2. The presence of cumulative factors, including the age period of ontogenesis, approaching the elderly; the presence of a somatic long-term disease in the form of IHD; forced self-isolation due to the Covid-19 coronavirus pandemic and the relative hypokinesia associated with it, significantly contributed to the decrease in the resistance of the female body to hypoxia.

3. The study during the day and week of the chronobiological values of the resistance of women to hypoxia according to the Stange and Gench tests in a state

of physical rest and after using the Ukhtomsky dominant in the form of a positive verbal suggestion against the background of music testified to its favorable effect on the function of external respiration. It is concluded that in assessing the activity of the respiratory system in conditions of limited examination possibilities, by a practicing physician, the above tests, with their simplicity and accessibility, give an objective idea of the functional capabilities of the body. The use of the Ukhtomsky dominant, its simplicity and accessibility, contributes to a significant increase in the functionality of the respiratory system, even despite the presence of a somatic disease in the form of IHD.

4. Testing the body of women of the second maturity in chronobiological terms during the day and week allows us to conclude that at 12 and especially at 16 o'clock in the afternoon the respiratory system operates in a mode of high functionality, which should be taken into account during the treatment process. At the same time, we must not forget that if the body is not "nourished" by the dominant influence, the functional capabilities begin to gradually dry up.

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Research transparency. The study was not sponsored. The authors are solely responsible for providing the final version of the manuscript for publication.

Declaration of financial and other relationships. All authors were involved in the development of the topic, data collection, study design, and writing the manuscript. The final version of the manuscript was agreed and approved by all authors. The authors did not receive a fee for the study.

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肝细胞培养工艺的优化
OPTIMIZATION OF THE HEPATOCYTE CULTIVATION PROCESS

Inozemtsev Pavel Olegovich
Candidate of Pharmaceutical Sciences
Senior Research Officer of Department of Biomedical Research and
Technology Irkutsk Scientific Center of the Siberian Branch of the
Russian Academy of Sciences
ORCID iD 0000-0002-6623-0998
Lepekhova Svetlana Alexandrovna
Doctor of Biological Sciences
Head of Department of Biomedical Research and Technology Irkutsk
Scientific Center of the Siberian Branch of the Russian Academy of
Sciences
ORCID iD 0000-0002-7961-4421
Inozemtsev Evgeny Olegovich
Candidate of Medical Sciences
Assistant of the Department of Hospital Surgery
Irkutsk State Medical University
ORCID iD 0000-0001-6804-0357

结果。由于根据 M. Berry 等人的肝脏原位两阶段酶处理从成熟肝脏中分离肝细胞的方法的组合。获得新生儿分离的肝细胞。揭示了细胞活力与培养基 pH 值之间的直接密切相关性，工作溶液的最佳 pH 值设定为 7.6。由以上数据可知，培养第5天，HGF含量最高。第 5 天调节肽的量显着增加至 46.8 (38.4–50.0) ng/ml，而第 2 天为 14.3 (13–15.6) ng/ml (pU = 0.003)。

结论。通过选择培养条件，获得具有高度活力的2–5个细胞的微片段悬浮液。在Ficoll梯度中分离细胞后，平均从一克肝组织中分离出800万个细胞(8.6 (7.4–10)×106；n = 7)。 50 ml 悬浮液含有 4000 万个细胞(40.5 (38–43)×106；n = 7)。分离纯化后的细胞存活率为 98.8 (98.3–99.3)% (n = 15)。揭示了工作溶液酸化与离体胚胎肝细胞活力下降之间的关系(r = +0.71；p < 0.05)，工作溶液的最适pH值为7.6。

关键词：生物技术，细胞培养，肝细胞，HGF

Introduction. *The clinical application of bioartificial liver support systems is still limited due to technical problems associated with the complexity of the*

application, storage, transportation of hepatocytes. One of the directions in solving this problem is the cultivation of cells and tissues in artificial nutrient media, with the production of biologically active substances, which are increasingly being used in medicine.

Purpose. Selection of optimal conditions for culturing embryonic liver cells, contributing to the maximum accumulation of hepatocyte growth factor.

Materials and methods. We used embryonic liver cells of neonatal rat pups. Cultivation was carried out under standard conditions. Cell culture was performed on RPMI, 199, Hanks nutrient media. At all stages of cultivation, the content of the HGF regulatory peptide in the culture medium was evaluated in dynamics, according to which the proliferative activity of cultured cells was judged.

Result. As a result of a combination of methods for isolating hepatocytes from a mature liver according to the two-stage enzymatic treatment of the liver in situ according to M. Berry et al. neonatal isolated hepatocytes were obtained. A direct close correlation between cell viability and the pH value of the medium was revealed, and the optimal pH value of the working solutions was set equal to 7.6. From the above data it follows that on the 5th day of cultivation, the content of HGF was maximum. A significant increase in the amount of the regulatory peptide on the 5th day to 46.8 (38.4–50.0) ng/ml was revealed versus 14.3 (13–15.6) ng/ml on the 2nd day ($pU = 0.003$).

Conclusion. By selecting the cultivation conditions, a suspension of microfragments of 2–5 cells with a high degree of viability was obtained. After separation of cells in a ficoll gradient, 8 million cells were isolated on average from one gram of liver tissue ($8.6 (7.4–10) \times 10^6$; $n = 7$). 50 ml of suspension contained 40 million cells ($40.5 (38–43) \times 10^6$; $n = 7$). The degree of cell viability after isolation and purification was 98.8 (98.3–99.3)% ($n = 15$). The relationship between acidification of working solutions and a decrease in the viability of the isolated embryonic liver cells ($r = +0.71$; $p < 0.05$) was revealed, and the optimal pH value of the working solutions was set to 7.6.

Keywords: biotechnology, cell culture, hepatocytes, HGF

The clinical application of bioartificial liver support systems is still limited due to technical problems associated with the complexity of the application, storage, and transportation of hepatocytes [1]. One of the directions in solving this problem is the cultivation of cells and tissues in artificial nutrient media, with the production of biologically active substances, which are increasingly used in medicine. To obtain a culture of embryonic liver cells, the technology of mixed disaggregation of embryonic liver tissue was used [2, 3]. We additionally proposed polyfocal intraparenchymal injection of a collagenase solution with subsequent manual mechanical separation of stromal elements under visual control.

We sought to obtain not isolated hepatocytes, but microfragments containing associations of up to 10 hepatocytes and non-parenchymal cells. According to the initial hypothesis, the resulting cells produce hepatotropic factors, the leading role among which belongs to the hepatocyte growth factor produced by Kupffer and Ito cells [4,5], for this reason we considered it important to maintain cellular cooperation. The proposed method made it possible to obtain cells with a higher viability than using known methods (pU < 0.00001) and significantly increased the yield of cell numbers (table 1).

Table 1.

Comparative characteristics of methods with an assessment of the number and viability of cells isolated from 1 g of liver (median, quartiles)

№	Cell isolation method	Cell viability (%)	Number of cells obtained from 1 g of liver tissue ($\times 10^8$)
1.	isolated hepatocytes	41.9 (38.6–44.4)*	7.2 (6.4–7.3)*
2	embryonic hepatocytes	90.5 (89.5–96.3)	10.9 (9.8–11.6)

Note: * $-p_U < 0.00001$ – significance of differences compared with the results of applying the original method; ** – calculation of the absolute number of cells is difficult due to the large size of liver tissue fragments.

Histological examination of the material, immediately after isolation, before purification of the cell suspension using a discontinuous Ficoll gradient, revealed that the cellular composition was represented by polygonal embryonic hepatocytes, which were mostly located in groups of 2–4 cells, macrophages, and cellular detritus. The nuclei of hepatocytes were spherical in shape and located in the center of the cytoplasm. Heterochromatin and nucleoli were poorly visible. The cytoplasm looked homogeneous dark, without any inclusions. Thus, 2 types of cells were obtained: isolated hepatocytes with a viability of 41.9% and embryonic liver cells, which immediately after isolation represented associations of cells with a viability of 90.5%, with an increase in the number of cells isolated from 1 g of embryonic liver tissue. The cellular composition was represented by polygonal-shaped embryonic hepatocytes with clearly visible nuclei without damage, macrophages and hematopoietic cells. The isolated cells were mostly located in groups of 2–4 cells.

To remove cellular debris, peripheral blood elements, hematopoietic cells of the embryonic liver, large fragments, damaged cells from the obtained cell suspension, centrifugation was performed in an intermittent Ficoll gradient. The next stage of work included the selection of optimal conditions for culturing embryonic liver cells.

When working with cells, attention was paid to the acidification of the pH of nutrient media after immersion of a suspension of isolated cells in them (pH of standard nutrient media RPMI, 199, Hanks, which led to a decrease in the yield of viable cells (table 2).

Table 2.

Dynamics of changes in the viability of liver cells in the process of dissociation and pH of working solutions

Cell viability after isolation (%)	n	medium pH initial	medium pH final	p	r
40–70	8	7.3 (7.1–7.3)	6.8 (6.6–6.9)	$p_U < 0.05$	+ 0.70
71–86	8	7.4 (7.4–7.4)	7.2 (7.1–7.3)	$p_U < 0.05$	$p < 0.05$
87–99	8	7.6 (7.6–7.6)	7.4(7.4–7.4)	–	

Note: The significance of differences was determined in comparison with cell viability in the range of 86–99%.

A direct close correlation was found between cell viability and the pH value of the medium (r = +0.70; p < 0.05).

A change in the pH value of the nutrient medium was revealed when a suspension of cells was placed in it, and their viability was assessed after a short-term incubation in a nutrient medium with a given pH value, which was determined after the introduction of a suspension of donor material (table 3).

Table 3.

Change in the pH value of the nutrient medium when a suspension of isolated liver cells is placed in it and the viability of cells incubated in a thermostat at 37 ^{0}C for 1 hour at given pH values

№	Initial pH of the nutrient medium	pH after placement of the cell suspension	pH of the nutrient medium after adding the cell suspension	Cell viability after 1 hour of cultivation (%)
2.1	7.2 *	6.9 (6.8–6.9) **	6.9	63 (61.2–67.1) ○
2.2	7.4	7.1 (7.0–7.1) **	7.2	79.3 (75.4–81.6) ○
2.3	7.6	7.4 (7.4–7.4)	7.4	92.8 (89.2-96.2)
2.4	7.8	7.6 (7.5–7.6)**	7.6	76.5 (72.5–80.3) ○

Note: * – pH of the standard nutrient medium RPMI, 199 and Hanks; ** – the significance of the differences was determined in comparison with pH = 7.6 – $p_U < 0,00001.$; the significance of differences in cell viability was determined in comparison with pH 7.4; ○ – $p_U < 0.00001.$

To do this, cells with the same viability and in the same volume were placed in a cultivation medium with a variation in the initial pH of the medium (table 3.) and briefly (1 hour) incubated at 37 °C.

In all observations, there was a decrease in the pH value. Thus, at initial values in the medium of 7.6–7.8, acidification was 0.2, and at pH = 7.2–7.4, acidification was more pronounced (0.3). Incubation in a medium with a pH value of 7.4 made it possible to preserve the cells with the maximum degree of viability. Therefore, the initial pH of the cultivation medium, taking into account the regular acidification of the medium (0.2), should be 7.6.

Optimization of cultivation conditions made it possible to obtain a suspension of microfragments of 2–5 cells with a high degree of viability. After separation of cells in a ficoll gradient, 8 million cells were isolated on average from one gram of liver tissue (8.6 (7.4–10) × 106; n = 7). 50 ml of suspension contained 40 million cells (40.5 (38–43) × 106; n = 7). The degree of cell viability after isolation and purification was 98.8 (98.3–99.3)% (n = 15). We have revealed the relationship between acidification of working solutions and a decrease in the viability of isolated embryonic liver cells (r = +0.71; p < 0.05), the optimal pH value of working solutions was set to 7.6; culturing was used to achieve the acquisition of maximum proliferative activity by hepatocytes. Cultivation was carried out under standard conditions; To assess the functional activity of liver cells in culture, we assessed the level of albumin in the culture medium. This indicator was unchanged in the dynamics of observation: on the first day of cultivation, the level of albumin was 8.0 (6.5–9.0) g/l, on the 5th day - 8.7 (6.2–10.0) g /l.; during the cultivation of liver cells, at all stages of cultivation, the dynamics of the content of the regulatory peptide in the cultivation medium was monitored, according to which the proliferative activity of the cultured cells was judged.

Upon reaching the highest concentration of the HGF regulatory peptide in the culture medium, the viability of the embryonic liver cells was assessed as high and the readiness of the cells was considered to be maximum.

Liver cell culture can be considered as a source of obtaining regulatory peptides, which is one of the promising directions in the creation of drugs for the correction and prevention of liver failure [6,7].

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NOTES

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