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RESULTS AND PROSPECTS OF WORK OF THE REFERENCE CENTER FOR MONITORING RICKETTSIOSIS OF FBIS "OMSK RESEARCH INSTITUTE OF NATURAL FOCAL INFECTIONS" OF ROSPOTREBNADZOR

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In 2018, on the basis of the Federal Budget Institution of Science "Omsk Research Institute of Natural Focal Infections" of Rospotrebnadzor, a reference center for monitoring rickettsiosis (RCR) was established. The RCR staff monitored the infectious morbidity of Siberian tick-borne typhus (STT) in the period from 1979 to 2018 in 17 constituent entities of the Russian Federation. In accordance with the risk-oriented approach to prevention, differentiation of the territories of the Russian Federation endemic by STT was conducted with the allocation of epidemiological zones of low, average, above average, high and very high risk of infection of the population. The prognosis of the epidemic situation development for 2019 for endemic rickettsiosis is made on the basis of the estimated number of small mammals and ixodic ticks. The analysis of laboratory diagnostics and monitoring of tick-borne spotted fever rickettsiosis in the territories of 19 subjects of four federal districts of the Russian Federation was carried out. It is promising to clarify the spectrum of rickettsial pathogens in regions endemic by tick-borne rickettsiosis, especially in areas with no registered morbidity.

Key words: *Siberian tick-borne typhus, tick-borne rickettsiosis, Rickettsia sibirica subsp. sibirica, ixodic ticks, epidemiology, monitoring of natural foci.*

In accordance with the order of Rospotrebnadzor No. 1116 dated 01.12.2017 "On improving the monitoring system, laboratory diagnostics of infectious and parasitic diseases and indication of PBA in the Russian Federation", on the basis of the Omsk Research Institute of Natural Focal Infections of Rospotrebnadzor (order No. 14 dated 02.02.2018), a reference center for monitoring rickettsiosis (RCR) was established to provide consulting, methodical and practical assistance to bodies and institutions of Rospotrebnadzor and medical organizations of subjects of the Russian Federation on issues of epidemiology, prevention and diagnosis of natural focal rickettsiosis. Currently, according to the staff list, the RCR includes 13 people, 10 of them are research scientists, including 2 doctors and 5 candidates of medical sciences.

In the Russian Federation, in accordance with form No. 2 of statistical reporting, the incidence of rickettsiosis is officially recorded in the following nosological forms: rickettsiosis (total), epidemic typhus, Brill disease, Q fever, Siberian tick-borne typhus (STT), Astrakhan spotted fever (ASF), human granulocytic anaplasmosis (HGA), and human monocytotropic ehrlichiosis (HME).

On the territory of the Republic of Crimea, since the 30-ies of the previous century, the incidences of Marseilles (Mediterranean) fever have been registered [1], which after joining this territory with the Russian Federation is recorded in form No. 2 entitled "rickettsiosis". It is therefore necessary to introduce an official registration of this nosological form called "Marseilles fever".

Currently, Siberian tick-borne typhus caused by *Rickettsia sibirica* subsp. *sibirica* has been registered on the territory of 17 subjects of Ural, Siberian, and Far Eastern Federal Districts of the Russian Federation. The RCR staff conducted monitoring of STT infectious morbidity in the Russian Federation for the period from 1979 to 2018. During this period, 76,384 cases of STT were registered in the Russian Federation. A gradual increase in morbidity was observed from 0.2 in 1979 to 2.0 per 100,000 population (‰) in 1999, i.e. by 10 times, after which the highest rate for the whole period was recorded in 2001: 2.4‰ (3,460 cases) [2]. From 2002 to 2018, the STT morbidity rate decreased, ranging from 1.0 to 1.8‰ (from 1,365 to 1,797 cases). At the same time, there was an increase in the incidence of STT in Western Siberia: from 0.9‰ in 1979 to 10.3‰ in 2000, i.e. by 11.4 times.

In 2012–2016, up to 98.2% of cases of STT diseases in Western Siberia were registered in three regions of the Russian Federation: Altai Krai, Novosibirsk Oblast, and the Altai Republic. The STT morbidity rate in Altai Krai during this period amounted to 20.9–27.0‰, in Novosibirsk Oblast 6.2–9.5‰, in the Altai Republic 68.7–102.3‰.

In Omsk Oblast, in 2014 and 2015, 4 cases of STT (0.10‰) were registered for the first time.

In accordance with the risk-based approach to the prevention of STT, the differentiation of focal areas with the allocation of zones of low, average, above average, high and very high risk of infection of the population was carried out on the basis of the analysis of long-term data on the intensity of the epidemic process in 301 administrative districts of 17 subjects of the Russian Federation (Figure 1).

The ranking was carried out according to the long-time average annual indicators of the STT morbidity rate for 2000–2018 [3]. Grading of the morbidity levels rating scale was carried out using the method of determining the median confidence intervals [4]. Low risk of infection is characterized by long-time average annual indicators equal to or less than 5.8 per 100,000 population, average risk from 5.8 to 9.7‰, above average from 9.8 to 16.3‰, high from 16.4 to 30.4‰, very high ≥30.5‰.

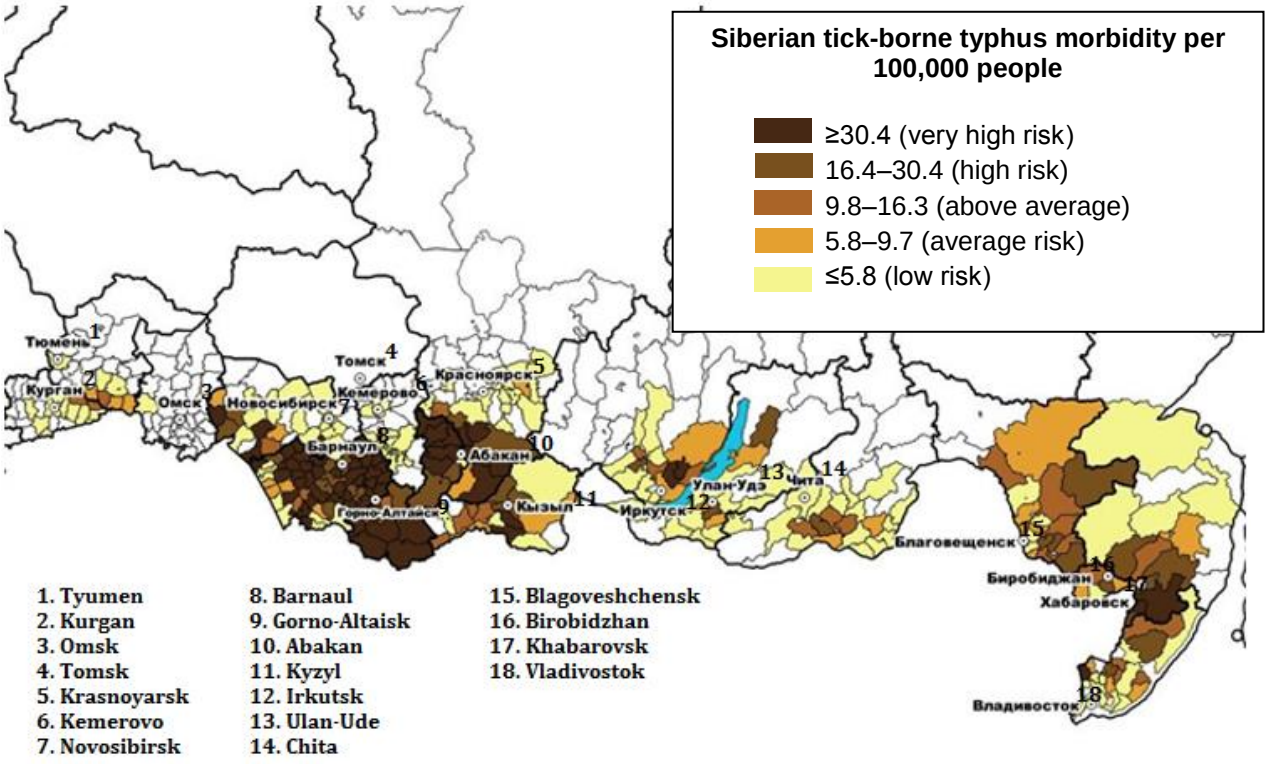

Figure 1. Siberian tick-borne typhus morbidity in the regions of Ural, Siberian and Far Eastern Federal Districts for 2000–2017 (per 100,000 population).

In the analysis of epidemiological risks in the STT foci, it should be taken into account that in Western Siberia tick-borne rickettsiosis can be caused not only by *R. sibirica* subsp. *sibirica,* but also by *R. heilongjiangensis*, as well as by recently described rickettsia *R. raoultii* and *Candidatus* Rickettsia tarasevichiae [2].

In 2018, as part of the advisory and methodological assistance, the analysis of the case of tick-borne rickettsiosis with a fatal outcome in Krasnoyarsk Krai was carried out. The etiology of this disease was retrospectively established. The case of mixed infection caused by *R. sibirica* and *Ca. R. tarasevichiae was verified using a complex of molecular biological methods (PCR sequencing)* for the first time [5]. Fragments of the OmpA, gltA and ompB genes (GenBank numbers MK048467–MK048475) of these two types of rickettsia were found in the blood and brain of a child who died of tick-borne rickettsiosis.

The forecast of the development of the epidemic situation in 2019 for STT, ASF, and Marseilles fever is made on the basis of the estimated number of small mammals (ixodic ticks feeders) and ixodic ticks (vectors). In the Southern Federal District, the exacerbation of the epidemic situation is possible due to endemic rickettsiosis such as Marseilles fever caused by *R. conorii* subsp. *conorii* and ASF caused by *R. conorii* subsp. *caspia*, with vectors – ixodic ticks of the genus *Rhipicephalus.* In the STT foci in the territories of the Central Federal District, the Siberian Federal District, and the Far Eastern Federal District, the epidemic situation will remain stable. Some subjects of the Siberian Federal District (Krasnoyarsk Krai, Irkutsk Oblast) and the Far Eastern Federal District (Primorsky Krai and Khabarovsk Krai) will be exceptions, on their territory, the epidemic situation will be tense. In

general, in 2019, the activity of natural foci of rickettsiosis will remain at the same level in the territory of the Russian Federation.

The analysis of the state of laboratory diagnostics and monitoring of rickettsiosis of the tick-borne spotted fever group (STT, ASF, and Mediterranean fever), HGA, HME, and Q fever was conducted in the territory of 19 subjects of four federal districts of the Russian Federation.

The staff of the reference center developed an approach to assess the effectiveness and compare the work of the FBHI "Centre of Hygiene and Epidemiology" in the constituent entities of the Russian Federation with the official registration of STT and ASF, based on a complex assessment of 12 indicators (registration of morbidity, laboratory diagnostics, screening of causative agents in ixodic ticks, forecast of the number of Ixodes ticks, etc.) according to the point rating system. In 2018, the work was carried out fuller in the Altai Republic, Krasnoyarsk Krai, the Jewish Autonomous Oblast, the Republic of Khakassia, Novosibirsk Oblast, Tyumen Oblast, Omsk Oblast and Altai Krai. The absence of registration of STT cases in the endemic territory of Kurgan Oblast for the last six years (2013–2018) needs to be clarified; in the period from 2007 to 2012, from 3 to 29 cases of this infection were registered annually.

The staff of the reference center analyzed the state of laboratory diagnostics of tick-borne rickettsiosis in the Russian Federation. Currently, there is no commercial production of domestic drugs for serum diagnostics of these infections by regulated methods (agglutination assay – AA, complement fixation test – CFT, indirect hemagglutination test – IHAT, indirect immunofluorescence test – IIFT, enzyme immunoassay – EIA) [6]. In this regard, for the diagnosis of STT, the RCR is studying the possibility of using the EIA test system "Indirect immunoenzyme assay to test IgG and/or IgM antibodies against *Rickettsia conorii* in human serum" produced by Vircell (Spain), authorized by Roszdravnadzor for the diagnosis of Marseilles fever.

In order to detect DNA of rickettsia of the tick-borne spotted fever group, a "Reagent kit for amplification of DNA of *Rickettsia spp.*" (Isogene Lab. ltd.) or "Reagent kit for amplification of DNA of *Rickettsia species* by real-time PCR" (AO "Vector-Best") with subsequent identification of *R. sibirica* and *R. heilongjiangensis* by real-time PCR (test set "RealBest DNA of *Rickettsia sibirica*/*Rickettsia heilongjiangensis*", AO "Vector-Best") can be recommended.

The staff of the RCR carry out the development and introduction into practice of new diagnostic drugs, algorithms and methods of laboratory diagnostics. Experimental series of the EIA test system for detection of antibodies to rickettsia of the tick-borne spotted fever group developed by the staff of the reference center are being tested (Patent for invention No. 2477860 C2, 2013). The staff carries out accumulation of biomass and preparation of corpuscular antigens for IIFT from different types of rickettsia of the tick-borne spotted fever group (*R. conorii, R. sibirica* and *R. raoultii*) with the use of Vero and Hep-2 cell lines infected with strains from the Institute work collection.

Molecular biological and serological methods were used to investigate field (ixodic ticks) and clinical (human blood serum) material from Omsk Oblast, Novosibirsk Oblast, Ulyanovsk Oblast and Krasnoyarsk Krai. 124 blood serums of patients were studied for STT with the help of CFT and PCR. 42 blood serums of patients were investigated for epidemic typhus with the help of CFT.

1,652 ixodic ticks removed from humans were investigated by the PCR method in order to carry out instant diagnosis of rickettsia for the choice of tactics of emergency preventive measures.

Thus, on the basis of the established reference center for monitoring of rickettsiosis, a retrospective analysis of the STT morbidity in the Russian Federation in the period from 1979 to 2018 was carried out. A complex, risk-based approach has been developed, including monitoring the intensity of the epidemic process, forecasting adverse trends, optimization of timely prevention measures with taking into account the varying levels of risk of infection of the population. The prognosis of the epidemic situation development for 2019 for endemic rickettsiosis is made on the basis of the estimated number of small mammals and ixodic ticks. The analysis of laboratory diagnostics and monitoring of tick-borne spotted fever rickettsiosis in the territories of 19 subjects of four federal districts of the Russian Federation was carried out. An approach is developed to assess the effectiveness and compare the work of the FBHI "Centre of Hygiene and Epidemiology" in the territories with the official registration of STT and other tick-borne rickettsiosis. The obtained results can be used to provide consulting, methodical and practical assistance to bodies and organizations of Rospotrebnadzor and other institutions in order to increase the effectiveness of preventive and anti-epidemic measures within the sphere of planned work and in the foci of tick-borne rickettsiosis.

One of the promising directions of the RCR is the in-depth study of the epidemiological and epizootological situation in the territories with the absence of registration of the morbidity of Siberian tick-borne typhus, Astrakhan spotted fever, and Marseilles fever, where at the same time other endemic rickettsiosis caused by recently described rickettsia species may occur; their detection was

not possible before due to imperfect laboratory diagnosis.

Conflict of interest. The authors declare that there is no conflict of interest.

References:

1. Alymov A.Ya. Marseilles fever. *Soviet medicine*. 1939;13:30–33.
2. Rudakov N.V., Shpynov S.N., Samoilenko I.E., Obert A.S. *Tick-borne rickettsiosis and rickettsia of the group of tick-borne spotted fever in Russia*. Omsk: Omsk Scientific Bulletin;2011: 232.
3. Rudakov N.V., Samoilenko I.E., Reshetnikova T.A., Saveliev D.A., Kumpan L.V. Modern condition of siberian tick typhus foci. *Public Health and Life Environment*. 2018;6(303):49-53.
4. GOST R ISO 16269-7-2004. *Statistical representation of data. Median. Determination of point estimation and confidence intervals*. M.; 2004.
5. Rudakov N.V., Samoilenko I.E., Shtrek S.V., Kumpan L.V., Kostrykina T.V., Gurieva L.S., Lents P.A., Igolkina Ya.P., Rar V.A., Zhirakovskaya E.V., Tkachev S., Tikunova N.V. The case of tick-borne rickettsiosis with a fatal outsome in Krasnoyarsk Krai. *Materials of the IV National Congress of Bacteriologists and the International Symposium "Microorganisms and Biosphere "MICROBIOS-2018""*. Omsk; 2018: 59-60.
6. Rudakov N.V., Samoilenko I.E., Reshetnikova T.A. The problems of laboratory diagnostic of rickettsiosis of group spotted tick-bite fever in Russia. *Russian Clinical Laboratory Diagnostics*. 2015;1:50-52.

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ANALYSIS OF STAFF HEALTH RISK FROM THE IMPACT OF PHYSICAL FACTORS OF PRODUCTION ENVIRONMENT IN THE CONDITIONS OF PROVISION OF HIGH-TECHNOLOGY MEDICAL CARE

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The article presents the analysis and assessment of health risk of medical staff of the sanatorium from a complex of workplace factors of physical and chemical nature. Special attention is paid to the problem of occupational risk from electromagnetic exposure at workplaces for maintenance of physiotherapy devices. The results of the study allow to identify three groups of workplace factors with different occupational risk ratios and to propose measures for the protection of medical staff.

Key words: *occupational risk, electromagnetic fields, workplace, hygienic standard of the workplace factor.*

The scientific literature devoted to the study of occupational health issues of medical workers presents mainly the study of working conditions of surgeons, anesthesiologists, dentists, and emergency doctors. At the same time, workplaces of the staff of diagnostic and rehabilitation prophylactic units were studied to a lesser extent and mainly for doctors of functional diagnostics. Meanwhile, being engaged in recovery and rehabilitation of many thousands of patients annually, the staff of physiotherapy departments are at risk of negative impact of labor process factors themselves [1].

In accordance with modern approaches to occupational health and medicine, the occupational risk refers to the probability of injury to health or death associated with the performance of labor responsibilities under an employment contract and in other cases prescribed by law.

The concept of risk is widely used in domestic and international practice and research on occupational health. Quantifying the effects of a particular human exposure allows medical and economic forecasts over a long period [2, 3].

The concept of risk is formalised in the Russian legislation by the Federal Law "On Technical Regulation" of 27.12.2002 No. 184-FZ, where risk is considered to be the probability of causing harm to life or health of citizens, property of natural or legal persons, state or municipal property, the environment, life or health of animals and plants, taking into account the gravity of the harm. Currently, there are quite a lot of normative legal acts describing the definition and use of risks of influence of chemical, radiation and physical factors on a person. The practice and strategy of risk management are defined in the resolution "On the use of risk assessment methodology for environmental and public health quality management in the Russian Federation" dated 10.11.1997 Nos. 25 and 03-19/24-3486. At the moment, the definition of risk from exposure to the chemical factor on the population is considered to be the most developed in the regulatory documentation. However, there are documents on the influence of physical factors such as electromagnetic fields (EMF). The main document used in this work is the methodological recommendations "Assessment of the health risk of the population under the influence of variable electromagnetic fields (up to 300 GHz) in conditions of populated areas" (MR 2.1.10.0061—12).

Lack of development of the issue of risk of impact of physical factors and absence of normative documentation on occupational health of medical workers of physiotherapy departments largely causes relevance of this area of research. The large volume of physiotherapeutic and computer equipment in a typical department of this profile predetermines the need to study the influence of harmful physical factors of the working environment on medical staff [4, 5, 6].

At the same time, it should be borne in mind that the morbidity of medical workers with temporary incapacity to labor remains high (93.2–114.7 cases per 100 workers, which exceeds the average level of morbidity of workers in the country) [7].

The study objective was to carry out a complex hygienic assessment of the occupational risk of medical staff in the combined application of physiotherapeutic procedures in one of the sanatorium-resort institutions of Altai Krai. The main tasks of the study were to carry out measurements of physical, radiation and chemical factors of the production environment at workplaces of medical staff and to calculate the degree of occupational risk of employees in accordance with a priori assessment models.

Materials and methods

The paper used the results of measurements of physical factors of the working environment of medical staff in the physiotherapy department of medical institution "Sanatorium of the Central Union of the Russian Federation" in Belokurikha of Altai Krai. Measurements of EMF were carried out by means of electromagnetometer BE-meter with antenna AT-004 (for measuring EMF from computers and monitors), as well as electromagnetometers of radio-frequency range PZ-34 and PZ-42 with isotropic antenna converters. The Meteoscop-M device was used to measure microclimate parameters (temperature, relative humidity, and air velocity). Light parameters were measured by the TKA-PKM-09 light meter-flicker meter-brightness meter. The ANT-3M gas analyzer measured the content of harmful substances in the air of the working area. The Ecophysica-110A sound meter was used to measure the equivalent noise level. The MAS-01 small air ion counter measured the concentration of positive and negative polarity air ions and unipolarity coefficient. The TKA-PKM-13 UV radiometer measured the intensity of ultraviolet radiation. Studies of the radiation factor at workplaces (efficiency of the ambient dose equivalent of gamma radiation and the equivalent equilibrium volumentric activity of radon in the air of the working area) were performed using the DRBP-03, DKS-96 dosimeters-radiometers and the Alfarad-plus ARP measuring radonometric complex. The total number of measurements of physical, chemical and radiation factors at 150 workplaces of medical staff amounted to 2,568.

To assess the risk, an approved calculation method was used to calculate the probability of the meningioma occurrence under the influence of electromagnetic radiation using the mathematical model with the subsequent definition of the risk index, its changes depending on the job tenure (MR 2.1.10.0061–12 "Assessment of the health risk of the population under the influence of variable electromagnetic fields (up to 300 GHz) in conditions of populated areas").

Results and discussion

In the physiotherapy department of MU "Sanatorium of the Central Union of the Russian Federation" in Belokurikha, a lot of specialized medical equipment operating from domestic electric power network is used. Many of these devices are EMF generators by definition (e.g. magnetic therapy devices). In particular, the following medical devices were used at the workplaces under study: UZT-1.01F, Polimag-01, Amplipuls-8, Diamag, ALT-Uzor2K, RIKTA, ALIMP-1. Workplaces equipped with devices that are not physiotherapeutic in nature were also studied (ultrasound, chromatograph). These devices generate electromagnetic fields of various frequencies, which affects the choice of measurement mode (Table 1).

Table 1

Characteristics of frequency ranges of electromagnetic fields generated by various physiotherapeutic devices

Device	Frequency
Ultrasonic therapy unit UZT-1.01F	0.88 MHz
Magnetic therapy unit Polimag-01	1–75 Hz and 1–16 Hz
Device Amplipuls-8	5 kHz
Magnetic therapy unit Diamag (Almag-03)	7 Hz, 30 Hz
Laser therapy apparatus ALT-Uzor2K	50 Hz
Laser therapy apparatus RIKTA	50 Hz
Magnetic therapy unit ALIMP	10–160 Hz

In modern researches in the field of occupational health of medical staff, numerous data are given on discrepancy of microclimate and state of light environment to normative documents [8, 9, 10]. The most commonly mentioned harmful factors are air temperature and illumination at the workplace. Many workplaces are equipped with personal computers often without grounding, which leads to increased exposure to EMF in workplaces.

Most of workplaces did not meet sanitary standards in the following indicators: working area air temperature (55.6% of all workplaces), artificial illumination (84.5%), light pulsation coefficient (46.7%), negative polarity air ions concentration (57.8%), unipolarity coefficient (80%).

Higher levels of EMF compared to hygienic standards were recorded in workplaces provided with electronic physiotherapy equipment, diagnostic devices (such as ultrasound, gas analyzer, etc.), or personal computers. For example, EMF levels several times higher than the standard levels were recorded in workplaces with magnetic therapy units (Table 2). SanPiN

2.2.4.3359–16 "Sanitary and epidemiological requirements for physical factors in workplaces" was used to assess the impact. The Polimag-01, Diamag (Almag-03), and ALIMP-1 devices are used for magnetic therapy, the Amplipuls-8 device is used for amplipulse therapy.

Table 2

Examples of workplaces in physiotherapy rooms with recorded excess of EMF levels in comparison with hygienic standards

Equipment at the workplace	Measurement level, m	Variable electromagnetic field intensity, V/m			Magnetic field intensity, nT		
		5 Hz – 2 kHz	2–400 kHz	background 50 Hz	5 Hz – 2 kHz	2–400 kHz	background 50 Hz
Polimag-01	0.5	14.4	0.385	46.1	170	5.09	2220
	1.0	61.5[1)]	0.413	124	754	22.5	10500[4)]
	1.5	31.2[1)]	0.379	46.6	243	6.25	3810
Amplipuls-8	0.5	2.25	1.72	75	22	2.88	223
	1.0	4.93	16.2[3)]	99.4	65	4.31	1920
	1.5	0.815	1.44	34.6	8	2.88	350
Diamag (Almag-03)	0.5	33.34	0.385	113	15	2.96	328
	1.0	11.9	0.433	181	674[2)]	16	5080
	1.5	4.16	0.375	59.6	55	55	520
ALIMP-1	0.5	19.4	0.452	3.07	2010[2)]	4.25	773
	1.0	27.6[1)]	0.425	4.1	1520[2)]	16.7	455
	1.5	9.97	0.38	3.75	657[2)]	2.98	276

Notes:

1) According to SanPiN 2.2.4.3359-16, the permissible exposure limit (PEL) is 25 V/m;

2) According to SanPiN 2.2.4.3359-16, PEL is 250 nT;

3) According to SanPiN 2.2.4.3359-16, PEL is 2.5 V/m;

4) According to SanPiN 2.2.4.3359-16, PEL is 10000 nT.

It should be noted that the results of the conducted studies of the radiation factor at the workplaces in the radon therapy department show that the equivalent equilibrium volumentric activity of radon fluctuated in the range of 25–109 Bq/m³, the rate of ambient dose equivalent of gamma radiation – in the range of 0.15–0.18 μSv/h, which corresponded to hygienic standards according to NRB-99/2009.

Time-weighted average concentrations of harmful chemicals in the air of the working area during mud treatment (hydrogen sulphide in the interval of 2.9–3.5 mg/m³) and paraffin therapy (saturated hydrocarbons in the interval of 29.3–43.2 mg/m³) did not exceed the maximum permissible concentrations for these substances: 10 mg/m³ for hydrogen sulphide and 300 mg/m³ for saturated hydrocarbons.

The risk index did not exceed 0.05 for all studied workplaces in the CLD department, which corresponds to the acceptable risk. At the exposure to an electric field of 1.33 V/m, the risk index will exceed 0.05 and can be classified as moderate from 37 years of job tenure. The workplaces of medical staff of the physiotherapy department are also characterized by an acceptable risk of meningioma development, except for two workplaces with electric field expositions of 6.33 and 11.9 V/m. Work on the first of them is characterized by the occurrence of moderate risk on reaching 10 years of job tenure, and on the second one on reaching the sixth year already and high risk on reaching 30 years of job tenure.

It should be noted that the values obtained during the measurements of the electric field do not exceed the standard of 25 V/m, however, the risk indices obtained in some workplaces suggest preventive measures to prevent the occurrence of meningioma, in particular, to reduce the intensity of the electric field in the workplace to the values that provide an acceptable risk throughout the entire period of service.

In the first phase of the assessment of workplaces of medical staff in the physiotherapy department, three groups of hazards were identified: physical factors of non-ionizing nature (variable electromagnetic field intensity (ranges of 5 Hz – 2 kHz and 2–400 kHz), magnetic field intensity (range of 5 Hz – 2 kHz), concentration of positive and negative air ions, unipolarity coefficient, working area air temperature, illumination, light pulsation coefficient), chemical factors (hydrogen sulphide, saturated hydrocarbons), and ionizing radiation produced by radon. The concentration of the investigated chemicals in the air of the working area did not

exceed the maximum permissible concentration. The radon equivalent equilibrium volumentric activity and efficiency of the ambient dose equivalent of gamma radiation also did not exceed the levels defined by regulatory documents.

Measurements of physical factors have shown numerous cases of exceedance of standard levels. Among the physical factors under analysis, the electromagnetic field is of particular interest as the factor actively studied by modern science, the mechanism and consequences of which are still understudied. It was decided to use a risk-oriented model to assess the harmful effects of electromagnetic radiation. The result was a moderate risk value. It follows that it is recommended to develop and carry out preventive measures for these workplaces taking into account the midterm and short-term prospects (1–3 years). A planned review is recommended at least every three years, and a review of occupational risk is recommended every year.

Conclusion

As a result of hygienic assessment of occupational risks of sanatorium staff in conditions of application of radon therapy and carrying out physiotherapy procedures, it was revealed that the obtained values of individual annual effective irradiation doses from short-lived daughter products of radon isotopes in air varied from 3.7 mSv/year to 8.6 mSv/year. Such results show the necessity of personalized study of components of natural radiation background for sanatorium staff with the use of integral methods of assessment of radon EEVA and its DP, both in the workplaces and in residential buildings. The workplaces of medical staff of physiotherapy departments with exposure to non-ionizing electromagnetic radiation are characterized by an acceptable risk of meningioma development, except for two workplaces with electric field expositions of 6.33 and 11.9 V/m.

Conflict of interest. The authors declare that there is no conflict of interest.

References:

1. Balandovich B.A., Krasikov A.A., Kudryavsky C.I., Nagornyak A.S., Tulin N.Yu. Complex hygienic evaluation of working conditions of medical personnel for physiotherapeutic procedures. *Bulletin of Medical Science*. 2017;1(5):10-13.

2. Balandovich B.A., Potseluev N.Yu., Krasikov A.A., Tulin N.Yu., Nagornyak A.S., Pashkov A.P., Zhukova O.V., Filippova S.P., Shved O.I., Shults K.V. Hygienic assessment of risk of exposure to electromagnetic fields of radio-frequency range. *Bulletin of Medical Science*. 2018;4(12):3-8.

3. Saldan I.P., Nagornyak A.S., Balandovich B.A., Potseluev N. Yu., Krasikov A.A., Tulin N.Yu., Kudryavskii S.I. Hygienic aspects of the medical worker's safety and the problem of the evaluating professional risk. *Hygiene and sanitation*. 2019;1:49-54.

4. Saldan I.P., Balandovich B.A., Poceluev N.Yu., Nagornyak A.S., Krasikov A.A., Tulin N.Yu. Health risks for workers from occupational exposure to radon and electromagnetic radiation. *Radiation and Risk (Bulletin of the National Radiation and Epidemiological Registry)*. 2018;4:133-140.

5. Saldan I.P., Balandovich B.A., Potseluev N.Yu., Kudryavskiy S.I., Nagornyak A.S. Hygienic assessment of occupational risks medical personnel during physiotherapy treatments. *Population Health and Life Environment*. 2017;7:26-29.

6. Dubel E.V., Unguryanu T.N. Hygienic assessment of working conditions for medical personnel in clinical and paraclinical departments of the hospital. *Hygiene and Sanitation*. 2016;1:53-57.

7. Zaitseva N.V., Trusov P.V., Shur P.Z., Kiryanov D.A., Chigvintsev V.M., Tsinker M.Yu. Methodical approaches to health risk assessment of heterogeneous environmental factors based on evolutionary models. *Health Risk Analysis*. 2013;1:15-23.

8. Xu XS, Zhang LA, Sun QF, Qin YC, Yu NL. Estimation of the occupational exposure dose for medical diagnostic X-ray workers in Jiangsu, China, using a retrospective dosimetry method. *J Radiat Res*. 2018;59:141-148.

9. Shah SG, Farrow A. Systematic literature review of adverse reproductive outcomes associated with physiotherapists' occupational exposures to non-ionising radiation. *J Occup Health*. 2014;5:323-331.

10. Andrikopoulos A, Adamopoulos A, Seimenis I, Koutsojannis C. Microwave diathermy in physiotherapy units: a survey on spatial and time heterogeneity of the electromagnetic field. *J Radiol Prot*. 2017;2:27-41.

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ASSESSMENT OF OCCUPATIONAL RISK TO HEALTH OF MINING WORKERS FROM EXPOSURE TO ORE AND ROCK DUST AND TOXIC SUBSTANCES

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Kemerovo Oblast is one of the main mining regions of the country. The mining industry of the region is characterized by difficult working conditions, the impact on workers of a complex of adverse production factors, which determines a high risk of occupational diseases development. The article presents a hygienic assessment of factors of the production environment of employees of the main professional groups of the enterprise for the iron ore extraction: dust loading and toxic substances content in the air of the working area. The classes of working conditions are defined. On the basis of calculation of risks of occupational diseases formation, professional groups of miners most susceptible to influence of unfavorable factors of production environment were determined. The medical and preventive, as well as organizational and technical measures aimed at reducing the levels of risk and preserving the health of workers are proposed.

Key words: *mining enterprise, ore and rock dust, toxic substances, classes of working conditions, occupational risk, preventive measures.*

The mining industry is the basis for the formation of the country's budget. Russia produces 48 types of mineral raw materials, which makes it the absolute leader among 166 mining countries. Russia owns about 40% of the world's iron ore deposits, which corresponds to almost 65 billion tons of ore. Every year our country accounts for 15% of world iron ore production [1, 2]. The largest number of deposits in Russia is in the Siberian Federal District and Far Eastern Federal District. They account for about 75% of all recorded mineral resources [3].

Kemerovo Oblast is one of the main mining regions of the country. The mining and smelting industry of the region, along with the coal one, is the basic branch of economy of the Kuznetsk Basin, it accounts for about 30% of all industrial production of the region [4]. Widespread underground mining in the region causes the high relevance of the issue of saving labor resources in this industry. Adverse working conditions increase the risk of developing not only occupational diseases, but also work-related diseases, aggravate their medical and social consequences, reduce labor potential of the society [5, 6]. Despite significant modernization, the mining industry continues to be characterized by difficult working conditions, the impact on workers of a complex of adverse production factors, which determines the high risk of development of occupational diseases [7, 8, 9, 10, 11].

Materials and methods

The hygienic assessment of production factors at workplaces of employees of the Tashtagol Iron-Ore Mine was carried out using workplaces attestation maps with attached protocols of measurements and assessments and summary statements on the working conditions of occupational groups. The working conditions of workers of the main professions were studied: underground miner (underground transport area No. 11), drilling rig operator (drill area No. 9), loading machine operator (cutting operations area No. 6), vibratory driver operator (winning area No. 1), shaft worker (cutting operations area No. 6), shaft worker (pre-production mining area No. 10), duty electrical maintenance fitter (maintenance and repair area No. 4). The analysis of working conditions was carried out on the basis of the "Guide on hygienic assessment of factors of working environment and work load. Criteria and Classification of Working Conditions: R 2.2.2006-05" [12]. The risk of formation of occupational pathology from the impact of ore and rock dust was calculated for work experience of 5, 15, 25 years according to the method of A.P. Mikhailuts et al. [13]. The risk of chronic intoxication associated with toxic substances was determined on the basis of an exponential relationship between the frequency of exceedance of the threshold limit value (TLV) and probability of occurrence of chronic toxic effect according to the method of A.M. Oleshchenko et al. [14].

Results and discussion

The Tashtagol field is located in the south of Kemerovo Oblast within the municipal entity of the city of Tashtagol. The Tashtagol branch of OAO "Evrazruda" carries out the field development with the underground method. Currently, mining

works are carried out on seven floors of the mine, winning and mining operations have reached a depth of 895 meters from the initial surface.

Preparation of the field is carried out by shaft workers of the pre-production mining area No. 10, development by shaft workers of the cutting operations area No. 6 and drilling rig operators of the drill area No. 9. Loading machine operators and vibratory driver operators (winning area No. 1), underground miners (underground transport area No. 11), and electrical maintenance fitters (maintenance and repair area No. 4) are also involved in the development of the field.

Mining drilling equipment is used for underground ore mining: deep-drilling machines NKR-100M; drilling rigs UBSh-207, UPB; drills PT-48, PP-54, PK-60; scraper hoists LS-30, LS-77; moveable underground transport: mobile vibratory delivery unit (MVDU), rock loading machine (PPM-5).

The air of working areas of the main professional groups of the mining enterprise is characterized by the presence of siliceous ore and rock dust (with SiO_2 content from 2 to 10%). Table 1 presents a hygienic assessment of air dusting in the working areas of main occupational groups.

Table 1

Hygienic assessment of air dusting levels in the working areas of main occupational groups

Occupational group	TLV, mg/m^3	Actual level, mg/m^3	Duration of exposure, h
Underground miner (underground transport area No. 11)	4.0	13.9	8
Drilling rig operator (drill area No. 9)	4.0	30.7	7.2
Loading machine operator (cutting operations area No. 6)	4.0	16.9	7.2
Vibratory driver operator (winning area No. 1)	4.0	43.2	7.2
Shaft worker (cutting operations area No. 6)	4.0	39.4	7.2
Shaft worker (pre-production mining area No. 10)	4.0	28.3	7.2
Duty electrical maintenance fitter (maintenance and repair area No. 4)	4.0	5.9	7.2

At workplaces of all occupational groups, there is a prolonged (7.2–8 hours) exposure of siliceous dust on the body of miners. The shaft worker of the cutting operations area No. 6 and vibratory driver operator of the winning area No. 1 have a level of siliceous dust in the air of the working area exceeding TLV by 9.8 and 10.8 times respectively. At workplaces of the drilling rig operator of the drill area No. 9 and shaft worker of the pre-production mining area No. 10, the content of siliceous dust exceeds TLV by 7–7.7 times. The third group of specialities included the loading machine operator of the cutting operations area No. 6, underground miner of the underground transport area No. 11, and duty electrical maintenance fitter of the maintenance and repair area No. 4, the dust content in the air of the working area of which exceeded TLV by 3.5–4.2 times.

Thus, the 3rd class of working conditions (harmful) of the 3rd degree (3.3) is set for the vibratory driver operator (winning area No. 1), drilling rig operator, shaft worker of the cutting operations area No. 6, and shaft worker of the pre-production mining area No. 10, other occupational groups have the 3rd (harmful) class of working conditions of the second and first degree (3.2 and 3.1).

The air of the working area of main occupational groups of workers of the mining enterprise is characterized by the content of toxic substances. Tables 2 and 3 provide a hygienic assessment of carbon monoxide and nitrogen oxide content in the air of the working areas of main occupational groups.

Exceeding of the carbon monoxide TLV level was detected only at the workplace of the vibratory driver operator (winning area No. 1) during certain technological operations. In the air of the working areas of other occupational groups, the level of carbon monoxide was recorded in concentrations significantly below TLV. The longest duration of carbon monoxide exposure on the body of workers (7.2 h) was found at the workplaces of the drilling rig operator (drill area No. 9), loading machine operator (cutting operations area No. 6), shaft worker (cutting operations area No. 6).

Table 2

Hygienic assessment of carbon monoxide content in the air of the working areas of main occupational groups

Occupational group	TLV, mg/m³	Actual level, mg/m³	Duration of exposure, h
Underground miner (underground transport area No. 11)	20.0	3.47–4.53	2–6
Drilling rig operator (drill area No. 9)	20.0	4.52	7.2
Loading machine operator (cutting operations area No. 6)	20.0	3.72	7.2
Vibratory driver operator (winning area No. 1)	20.0	9.52–27.0	1–1.4
Shaft worker (cutting operations area No. 6)	20.0	3.72	7.2
Shaft worker (pre-production mining area No. 10)	20.0	3.68–5.03	3.2–4
Duty electrical maintenance fitter (maintenance and repair area No. 4)	20.0	9.52–14.4	3–4.2

Table 3

Hygienic assessment of nitrogen oxide content in the air of the working areas of main occupational groups

Occupational group	TLV, mg/m³	Actual level, mg/m³	Duration of exposure, h
Underground miner (underground transport area No. 11)	5.0	0.54–0.94	2–6
Drilling rig operator (drill area No. 9)	5.0	0.29	7.2
Loading machine operator (cutting operations area No. 6)	5.0	0.40	7.2
Vibratory driver operator (winning area No. 1)	5.0	0.80–2.07	1–1.4
Shaft worker (cutting operations area No. 6)	5.0	0.40	7.2
Shaft worker (pre-production mining area No. 10)	5.0	0.67–0.68	3.2–4.0
Duty electrical maintenance fitter (maintenance and repair area No. 4)	5.0	0.94	7.2

The nitrogen oxide content did not exceed TLV at any workplace. The longest duration of nitrogen oxide exposure (7.2 h) was detected in the drilling rig operator (drill area No. 9), loading machine operator (cutting operations area No. 6), shaft worker (cutting operations area No. 6), duty electrical maintenance fitter (maintenance and repair area No. 4).

The increase in concentrations of carbon monoxide and nitrogen oxide was observed during blasting.

The presence of manganese in the air of the working area of the duty electrical maintenance fitter (maintenance and repair area No. 4) was revealed only during electric arc welding. At other workplaces, manganese in the air of the working areas was not detected.

In two occupational groups (the vibratory driver operator and the duty electrical maintenance fitter), the total effect of toxic substances of unidirectional action was more than 1 (1.84 and 1.34 respectively).

Thus, the 3rd (harmful) class of working conditions of the 1st degree (3.1) on the content of toxic substances in the air of the working area is determined in the following occupational groups: the vibratory driver operator (winning area No. 1) and duty electrical maintenance fitter (maintenance and repair area No. 4). In other occupational groups, working conditions corresponded to class 2 (acceptable working conditions).

Calculation of the occupational risk of dust etiology for the health of mining workers showed that with a work experience of 5 years it is in the range from 0.04 to 0.18 (in fractions per unity); with an experience of 15 years – from 0.05 to 0.46; with an experience of 25 years – from 0.06 to 0.58. The highest risk levels are observed in occupational groups of shaft workers (cutting operations area

No. 6 and pre-production mining area No. 10) and vibratory driver operators of the winning area No. 1 (0.56 and 0.58 respectively). The lowest risk is noted in occupational groups of duty electrical maintenance fitters (maintenance and repair area No. 4) and underground miners (underground transport area No. 11).

The risk of chronic intoxication of mining workers associated with the content of toxic substances in the air of the working area was determined in the range from 0.029 to 0.185 (in fractions per unity). The highest risk levels were identified in the occupational group of vibratory driver operators of the winning area No. 1: 0.185; the lowest – in the groups of shaft workers (0.037–0.059) and drilling rig operators (0.029). The specific weight of nitrogen oxides in the risk of chronic intoxication was 69.0– 83.1%.

Conclusion

In the operation of mining equipment and technological transport, ore and rock dust and toxic substances have a complex impact on the workers of the mining enterprise. The use of the methodology for assessing the risk of impact of production factors on the health of workers in regions with a developed extractive industry is necessary to obtain information on quantitative relationships and dependence, to reach more complete and qualitative use of information for management decisions to improve health and hygiene working conditions and prevent occupational diseases.

In order to reduce the risk of development of occupational and work-related diseases in mining enterprises, it is recommended to reduce the number of people occupied in harmful and dangerous working conditions, to increase the efficiency of the use of individual protection equipment, to use modern technological equipment [15]. It is necessary to ensure constant control over the activities of all structural divisions in order to improve the organization of the system of labor protection and industrial safety in the conduct of work on the mining enterprises. This requires systematization and analysis of the main problems existing in the mining industry [16, 17, 18]. All forms of protection based on time parameters (rational working and rest regimes, reduced work day, additional leave) with obligatory monitoring of employees' health are recommended as necessary measures to prevent health problems [19, 20].

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References:

1. Kondratyev V.B. The role of mining industry in economy. *Mining Industry Journal*. 2017;1(131): -15.

2. Gurova A.M., Tyunin A.I. Development of mining industry in Russia. *Modern problems of social sciences and humanities*. 2016;6(8):105-108.

3. Savchenko I.A., Karelina M.G. Statistical analysis of mining industry of Russia. *Application of mathematics in economic and technical research*. 2015;1(5):92-95.

4. Kislitsyna V.V., Korsakova T.G., Motuz I.Yu. Features of working conditions and occupational risk of workers engaged in open coal mining. *International Journal of Applied and Fundamental Research*. 2013;4:52-55.

5. Golovkova N.P., Chebotarev A.G., Leskina L.M., Khelkovskii-Sergeev N.A., Ershov V.P., Kotova N.I., Koroleva E.P., Makeeva L.G., Pasekov A.N. Occupational branch of medicine as the basis for preservation of health of workers. *Russian Journal of Occupational Health and Industrial Ecology*. 2013;6:25-29.

6. Zaitseva N.V., Ustinova O.Yu., Alekseev V.B., Ulanova T.S., Vlasova E.M., Nosov A.E. Peculiarities of production-related diseases in miners employed at deep mining of chromic ores. *Russian Journal of Occupational Health and Industrial Ecology*. 2018;10:6-12.

7. Korshunov G.M., Cherkai Z.N., Mukhina N.V., Gridina E.B., Skudarnov S.M. Occupational diseases of workers in the mining industry. *Mining Informational and Analytical Bulletin (scientific and technical journal)*. 2012;2-5:5-10.

8. Rukavishnikov V.S., Shayakhmetov S.F., Pankov V.A., Kolycheva I.V. Health of workers in the mining industry of Siberia and the Far North. *Russian Journal of Occupational Health and Industrial Ecology*. 2004;6:6-10.

9. Pototskii E.P., Zavodnova V.M. Assessment of occupational risk taking into account the combined impact of adverse factors at mining and smelting enterprises. *Gornyi Zhurnal*. 2015;5:88-90.

10. Bukhtiyarov I.V., Denisov E.I., Lagutina G.N., Pfaf V.F., Chesalin P.V., Stepanyan I.V. Criteria and algorithms of work-relatedness assessment of workers' health disorders. *Russian Journal of Occupational Health and Industrial Ecology*. 2018;8:4-12.

11. Tsetsegmaa T., Boldmaa N. Occupational safety and health in mining industry of Mongolia: current situation and development prospects (in terms of the coal sector). *Baikal Research Journal*. 2015;5:16-17.

12. *Guide on hygienic assessment of factors of working environment and work load.* Criteria and Classification of Working Conditions: P 2.2.2006-05. M.; 2005: 156.

13. Mikhailuts A.P., Pershin A.N., Tsigelnik M.I. *Calculation of individual risks of occupational chronic diseases and poisoning, safe work experience*: methodological recommendations. Kemerovo; 2000: 28.

14. Oleshchenko A.M., Surzhikov D.V., Bolshakov V.V., Kislitsyna V.V., Mikhailuts A.P., Shavlova O.P. *Assessment of impact of production factors on the health of workers at the colliery and heat-power engineering enterprises*: methodological recommendations. Kemerovo; 2003: 28.

15. Karnachyev I.P., Levashov S.P., Shkrabak R.V., Cheltybashev A.A. On the concept of occupational risk management in the sphere of occupational health and safety of employees of industrial enterprises of Russia. *Gornyi Zhurnal*. 2018;4:87-92.

16. Petrov B.A. Mining industry: state of supervision, accident rate, injuries, problems of industrial safety. *Mining Informational and Analytical Bulletin (scientific and technical journal)*. 2008;2:38-51.

17. Domingues MSQ, Baptista ALF, Diogo MT. Engineering complex systems applied to risk management in the mining industry. *International journal of mining science and technology*. 2017;4(27):611-616.

18. Väyrynen S, Häkkinen K, Niskanen T. *Integrated occupational safety and health management: solutions and industial cases*. Springer international publishing, Switzerland; 2015: 301.

19. Bakusic J, Lenderink A, Lambreghts S, Vandenbroeck S, Verbeek J, Curti S, Mattioli S, Godderis L. Different approaches for early recognition and prevention of new and emerging work-related diseases. *Occupational and Environmental Medicine*. 2017;74(Suppl 1):A53.

20. Boschman JS, Brand T, Frings-Dresen MHW, Molen van der HF. Improving the assessment of occupational diseases by occupational physicians. *Occupational Medicine*. 2017;67:13-19.

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HYGIENIC ASSESSMENT OF NUTRITION SAFETY OF RURAL POPULATION OF THE REGION UNDER THE CONDITIONS OF TECHNICAL REGULATION OF FOOD PRODUCTS

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The article presents the results of research on the problem of food safety in Altai Krai under the conditions of the relevant technical regulations. Particular attention is paid to the nutrition of the rural population, as well as to the problem of analysis and evaluation of nitrate pollution of various types of vegetable products in the region.
Key words: *hygienic assessment, food safety, rural population, food products, technical regulation, nitrates.*

Nutrition of different population groups of the Russian Federation is an important problem at the regional level caused, on the one hand, by the technical regulation of food products that came into force after adoption of relevant technical regulations at the level of the Customs Union, in the future the EAEU, and on the other hand, associated with numerous environmental and social risk factors affecting the safety of consumed products. So, according to Rospotrebnadzor, at the turn of 20th and 21st centuries in Russia, from 12% to 15% of the studied samples of dairy products and from 7% to 10% of meat products did not meet sanitary standards for bacteriological indexes. From 1.5% to 10.0% of food samples contained heavy metals, including mercury, lead, cadmium, copper, zinc [3, 4, 10]. Changing nutritional conditions contributed to the deterioration of the health status of the population. Thus, according to the results of the study of the structure of actual nutrition in different regions of the country (Kaluga Oblast, Tula Oblast, Ryazan Oblast, Bryansk Oblast, Sverdlovsk Oblast, Chelyabinsk Oblast, etc.) carried out by the Institute of Nutrition of RAMS, it was found that the country's average protein deficiency per capita exceeded 25.0%; ascorbic acid deficiency was detected in 70–80% of the surveyed, and a deep deficiency of this vitamin reached 30–40%; in one third of the surveyed, there was a lack of vitamins of group B, PP, folic acid, and vitamin A.

In many cases, multivitamin deficiency was combined with iron deficiency, causing widespread iron deficiency anemia. At the same time, in the studied population groups, there was an excess consumption of animal fats, deficiency of polyunsaturated fatty acids and dietary fibers among the population of risk groups.

The above negative trends are also characteristic of Altai Krai, on the example of which the work on a complex assessment of food safety of rural population was carried out in this study. It should be noted that the structure of the administrative and territorial division of Altai Krai has significant specific differences from most regions of Russia. The region consists of 12 urban districts and 59 municipal districts, the largest number in the Russian Federation due to a significant proportion of the rural population. For comparison, it is possible to cite data showing that on average in Russia the region accounts for 25 districts. An important contribution to the pollution of food in Altai Krai was made by the agricultural sector, during the development of virgin and fallow lands, it flooded Altai Krai with pesticides and mineral fertilizers [1, 3, 4, 5, 10]. According to many authors, in the last 10 years, the content of nitrates has increased in some vegetable crops by 5–10 times, and the content of nitrates in vegetables grown in the closed ground has reached 5–10 g/kg [10]. Children are particularly sensitive to the high content of nitrates, in this case, they are more likely to experience viral diseases (3.4 times), diseases of the ear and mastoid process (2 times), pneumonia (3.5 times), infectious diseases of the skin and subcutaneous tissue (6.1 times).

In the conditions of technical regulation, the problem of food safety is most significant in connection with the relatively free movement of food products between the territories bordering among themselves. Altai Krai is one of the border territories with Kazakhstan. This also causes the need to control the quality and safety of food products and food raw materials in circulation on the territory of the region.

It should be noted that the measures taken to prevent pollution of food products by xenobiotics and to inform the population of the region on rational nutrition are not fully effective in part of the prevention of alimentary-dependent diseases (ADD). A complex assessment of the nutritional status of the Altai Krai population will allow to substantiate a set of measures for further improvement of the prevention of ADD, which

determined the relevance of this study.

The aim of the work was to systemically substantiate a set of measures to improve nutrition and prevent alimentary-dependent diseases in the population of Altai Krai for the regional level implementation.

Research tasks:

1. To carry out a complex analysis of the actual nutrition of the population of Altai Krai in modern conditions.
2. To carry out a hygienic assessment of food safety of the population of the region and quality of food products according to the indicators regulated by the current normative documentation.
3. To evaluate the system of preventive measures aimed at reducing the negative impact of the nutrition factor on the person.
4. To substantiate the need to develop and adopt the program of nutrition optimization of the Altai Krai population at the regional level.
5. To develop recommendations on improving the system of laboratory control and prevention of alimentary-dependent diseases.

Materials and methods

This study was carried out on the basis of the Federal State Budgetary Educational Institution of Higher Education "Altai State Medical University" of the Ministry of Health of the Russian Federation in accordance with the plan of research works of the university.

The laboratory part of the study was carried out on the basis of the laboratories of the "Center of Hygiene and Epidemiology in Altai Krai", as well as of the Institute of Occupational Health and Industrial Ecology of FSBEI HE ASMU of the Ministry of Health of the Russian Federation.

In order to carry out a hygienic study, groups of food products were identified to search for the content of xenobiotics, including nitrates, to subsequently assess the contamination of food products in circulation on the territory of the region.

The studies were carried out in the period from 2013 to 2018, retrospective data for analysis were taken for the period of 2006—2016.

Food products produced and sold on the territory of Altai Krai were identified as the object of research. A total of 683 food samples were investigated. Determination of nitrates in vegetables was carried out by the ionometric method (505 samples) and capillary electrophoresis (178 samples).

The subject of the study was nutrition and health of the population of Altai Krai, hygienic aspects of nutrition of the population.

The research materials were statistically processed. The choice of statistical processing methods was determined by the nature of the distribution of the studied features, the type of data (quantitative or qualitative), and the design of the study [7, 8].

The article shows the average values of nitrate content indices in fruit and vegetable products in the form of median and 95th percentile when determined by the ionometric method.

Results and discussion

A complex hygienic assessment of the actual nutrition of the population of Altai Krai was carried out on the basis of available data on the level of consumption of certain groups of products by the region population in order to establish the sufficiency of intake of certain nutrients necessary for full and quality life into the human body. The data are publicly available on the website of the Administration of the Federal State Statistics Service for Altai Krai and the Altai Republic [11, 12]. The analysis of the actual nutrition of the Altai Krai population shows insufficient consumption of meat (92–99% of the recommended level), vegetables (73–85% of the recommended level), fruits (48–53% of the recommended level), fish (59–72% of the recommended level) and excess consumption of bread (60–77% above the recommended level), potatoes (44–52% above the recommended level), sugar, including confectionery products (43–67% above the recommended level).

Comparative analysis of the average per capita consumption of food by the Altai Krai population and the recommended values shows a decrease in consumption of vegetables and melons by 15–27%, fruits and berries by 41–47%; excess consumption of vegetable oil by 19–43%; bread products by 57–74%, potatoes by 45–53%, sugar by 39–63%, eggs by 29%.

Thus, the diet of the population of Altai Krai is insufficiently balanced in the main groups of products necessary to maintain the health of the population in optimal condition.

A hygienic assessment of food safety of the Altai Krai population for the period from 2009 to 2016 was made on the basis of official data of the Administration of Rospotrebnadzor for Altai Krai [11, 12].

The largest specific weight of samples that did not meet the hygienic standards for physical and chemical indicators was noted in the following food groups: "melons" – 25%; "baby food products" – 7%; "fruits and berries" – 5.3%; "dietary supplements" – 4.9%; "fat-and-oil products, animal and fish oils" – 4.8%; "poultry, eggs and products of their processing" – 4.4%. Indicators of radiation safety (specific activity of technogenic radionuclides of caesium-137 and strontium-90) in food products met the hygienic

standards.

In the process of carrying out laboratory tests of food products, the groups of food products most exposed to contamination of chemical and biological nature have been established. Basically, these are culinary products produced by non-traditional technology, mushrooms, soft drinks, sugar, fat plant products that did not meet the hygienic standards for sanitary and chemical indicators. Food products not meeting the hygienic standards for microbiological indicators included mushrooms, dietary supplements, wild food products, fish, and fish products.

To determine the content of nitrates, we conducted a study of greens and vegetables grown and marketed in rural areas of Altai Krai (cucumber, tomato, cabbage, beet, onion, potato, zucchini, pepper, carrot) by the ionometric method.

The principle of the method is based on extraction of nitrates by an aluminum potassium sulfate solution followed by measurement of nitrate concentration using the ion-selective nitrate electrode. The method is express. To accelerate the analysis, the juice of the analyzed products diluted with the aluminum potassium sulfate solution can be used instead of the extract. When analyzing cabbage, to destroy impurities interfering with the determination of nitrates, they are additionally oxidized with potassium permanganate.

Electrodes were prepared for work. For this purpose, the membrane nitrate ion-selective electrode and the silver-chloride electrode are prepared for operation in accordance with the instructions attached to the electrodes. Before working, the membrane of the ion-selective electrode was soiled for 24 h in a solution of potassium nitrate or sodium nitrate CNO3–=0.1 mole/dm3 at a temperature of 20+/–5℃.

With the help of this method, 505 samples of vegetables were investigated, excess nitrate content was found in 132 of them, which amounted to 26.14% of the total number of examined samples. As a result of the analysis of the obtained laboratory data, the products most exposed to nitrate contamination have been identified. Exceeding the level of TLV of nitrates was recorded in samples of vegetables such as cucumber, tomato, onion, beet, potato.

Table 1

Nitrate content in some types of fruit and vegetable products by median and 95th percentile.

Type of product	TLV	Petropavlovsky		Zavyalovsky		Barnaul		Ust-Pristansky	
		Median	95th percentile	Median	95th percentile	Median	95th percentile	Median	95th percentile
Potato	250	131.5	283.4	130	284	156	298.4	113	279.3
Carrot	400	91	198.75	105	231.3	134	258.2	107	227.05
Bulb onion	80	67	151.5	79.25	123.5	66	129.7	67	106.1
Bell pepper	250	153.5	248.2	122	250.2	146	284.25	140	259.7
Cucumber	400	262	469.2	271	468.75	319.5	514	244	513.85
Tomato	300	185	474.5	201	384.55	236	406.6	243	510
Beet	1400	902	4784.2	713.5	2100.4	881.5	1860.6	732.5	1811.6
Cabbage	900	438.5	755.8	334	486.95	414.5	534.9	188	599.35

The obtained data show the level of nitrate content in some types of fruit and vegetable products depending on the district in which the product was sampled.

Median of nitrate content in potatoes was 131.5 mg/kg for Petropavlovsky District (95th percentile: 283.4 mg/kg), for Zavyalovsky District 130 mg/kg (95th percentile: 283.4 mg/kg), for Ust-Pristansky District 113 mg/kg (95th percentile: 279.3 mg/kg), for Barnaul 156 mg/kg (95th percentile: 298.4 mg/kg). The average content of nitrates in the product was 63.7% of TLV. The greatest nitrate content by median 156 mg/kg was observed in Barnaul.

Median of nitrate content in bulb onion was 67 mg/kg for Petropavlovsky District (95th percentile: 151.5 mg/kg), for Zavyalovsky District 79.25 mg/kg (95th percentile: 123.5 mg/kg), for Ust-Pristansky District 67 mg/kg (95th percentile: 106.1 mg/kg), for Barnaul 66 mg/kg (95th percentile: 129.7 mg/kg). The average content of nitrates in the product was 88.8% of TLV. The greatest content by median in this type of product is in Zavyalovsky District (79.25 mg/kg).

According to the content of nitrates in beet, the median was 902 mg/kg for Petropavlovsky District (95th percentile: 4784.2 mg/kg), for Zavyalovsky District 713.5 mg/kg (95th percentile: 2100.4 mg/kg), for Ust-Pristansky District 732.5 mg/kg (95th percentile: 1811.6 mg/kg), for Barnaul 881.5

mg/kg (95th percentile: 1860.6 mg/kg). The average content of nitrates in the product was 88.8% of TLV. The greatest content by median in this type of product is in Petropavlovsky District (79.25 mg/kg).

Conclusion

The results of the conducted research allowed to reveal modern mechanisms of influence of nitrates on the state of health of the population of the agrarian region on the basis of monitoring and control of nitrate content in products on the example of four territories of Altai Krai: Barnaul, Petropavlovsky District, Zavyalovsky District, and Ust-Pristansky District. In addition, tasks were identified for improving approaches to control the content of nitrates in food products and prospects for improving control on the risk-based approach to the implementation of sanitary and epidemiological supervision (control) of food safety.

Based on the data obtained from the fruit and vegetable research showing the level of contamination of each product with nitrates, it can be concluded that, in general, there is an unfavorable picture of nitrate content in certain products. In each area studied, there is a product that is most exposed to nitrate contamination. It is beet in Petropavlovsky District, bulb onion in Zavyalovsky District. Among the most nitrate-contaminated fruit and vegetable products, there are cucumber, tomato, potato, bulb onion, and beet.

The present picture showing the real situation of pollution of food products by chemical contaminants justifies the need to develop and adopt a program of optimization of nutrition of the Altai Krai population at the regional level.

The final results of implementation of the program of safe food in the region are the bringing of measurement means in laboratories responsible for the study of food products and food raw materials in compliance with modern developments; introduction of new, more modern laboratory methods and research methods; improvement of nutrition quality of the Altai Krai population through providing microbiological and chemical food safety, including the safe content of nitrates in plant products, rational and balanced nutrition by raising public awareness of food products related to healthy diets.

Conflict of interest. The authors declare that there is no conflict of interest.

References:

1. Deryagina V.P. *Development of methods of analysis of nitrates and nitrites in food products and a hygienic assessment of ways to reduce their content in industrial and culinary processing*: author's abstract ... of the Candidate of Biological Sciences. Moscow; 1994. The link is active on 28.04.2019. http://medical-diss.com/medicina/razrabotka-metodov-analiza-nitratov-i-nitritov-v-pischevyh-produktah-i-gigienicheskaya-otsenka-sposobov-snizheniya-ih-sodixzz4gpabmDKe.

2. GOST 29270-95G. Interstate standard. *Fruit and vegetable processing products. Methods for determination of nitrates*.

3. Kislitsyna L.V. Assessment of chemical contaminants content in food products of residents of Primorsky Krai. *Health. Medical ecology. Science*. 2011;46(3):36-42.

4. Istomin A.V. et al. Hygienic problems of safety and optimization of population nutrition. *Materials of the X Congress of Hygienists and Sanitary Doctors*. M.; 2007: 856-859.

5. Istomin A.V. *Scientific and applied hygienic aspects of nutrition rationalization of the population of certain regions of Russia*: dissertation... of the Doctor of Medical Sciences. M.; 1995: 330.

6. Korolev A.A. *Nutrition hygiene*. M.: Academy; 2008: 528.

7. MR 2.1.10.0062-12. *Quantitative assessment of non-carcinogenic risk from chemicals based on evolutionary modelling*. The link is active on 28.04.2019.
http://docs.cntd.ru/document/1200095225

8. MU 2.3.7.2519—09. *Determination of exposure and risk assessment of exposure to chemical contaminants of food products on the population*. Methodological guidelines. M.: Federal Center of Hygiene and Epidemiology of Rospotrebnadzor; 2010: 27. Annex 5.

9. *Methodological guidelines for determination of nitrates and nitrites in crop production*. Date of introduction 01.01.1990. The link is active on 28.04.2019.
http://docs.cntd.ru/document/1200000148

10. Onishchenko G.G., Zaitseva N.V., Mai I.V. et al.; ed. G.G. Onishchenko, N.V. Zaitseva. *Analysis of health risk in the strategy of state social and economic development*. M.; Perm; 2014: 738.

11. *On the state of sanitary-epidemiological well-being in the Russian Federation in 2013: State report*. Barnaul, 2013.

12. *On the state of sanitary-epidemiological well-being in the Russian Federation in 2015: State report*. Barnaul, 2015.

13. *Official website of the Federal State Statistics Service for Altai Krai and the Altai Republic.* The link is active on 01.08.2017. http://akstat.gks.ru/wps/wcm/connect/rosstat_ts/akstat/resources/929513804e9856abb99cbba638e2bbf1/%D0%9F%D0%BE%D1%82%D1%80.%D0%BF%D1%80%D0%BE%D0%B4.%D0%BF%D0%B8%D1%82%D0%B0%D0%BD%D0%B8%D1%8F.htm

14. R 2.1.10.1920-04. *Guidance on the assessment of public health risks from exposure to environmentally*

polluting chemicals. 2004. The link is active on 28.04.2019.
http://docs.cntd.ru/document/1200037399

15. Federal Law of the Russian Federation No. 52-FZ of 30.03.1999. "On Sanitary and Epidemiological Welfare of the Population". The link is active on 28.04.2019. http://docs.cntd.ru/document/901729631

16. Federal Law of the Russian Federation No. 29-FZ of 02.01.2000. "On the quality and safety of food products (as amended on April 23, 2018)". The link is active on 28.04.2019. http://docs.cntd.ru/document/901751351

17. Federal Law of the Russian Federation No. 184-FZ of 27.12.2002. "On Technical Regulation (as amended on July 29, 2017)". The link is active on 28.04.2019.
http://docs.cntd.ru/document/901836556

18. Shur P.Z., Kiryanov D.A., Atiskova N.G., Chigvintsev V.M., Khrushcheva E.V. Substantiation of permissible levels of nitrate content in crop production according to health risk criteria. *Population Health and Life Environment*. 2013;11(248):47-48.

19. Habermeyer M, Roth A, Guth S, Eisenbrand G, Diel P, Engel K-H, et al. Nitrate and nitrite in the diet: how to assess their benefit and risk for human health *Molecular Nutrition and Food Research*. 2015;59(1):106-128.

20. Reijnders L. Food safety, environmental improvement and economic efficiency in the Netherlands. *British Food Journal*. 2004;106(5):388-405.

21. Ximenes MI, Rath S, Reyes FG. Polarographic determination of nitrate in vegetables. *Talanta*. 2000;51:49-56.

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S-NITROSOGLUTATHIONE INCREASES THE EXPRESSION OF MMP-1 PROTEIN IN CELLS OF THE HT1080 LINE IN HYPOXIC HYPOXIA

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The effect of the synthetic antioxidant S-nitrosoglutathione (GSNO) on the expression of matrix metalloproteinase-1 protein (MMP-1) in human fibrosarcoma cells HT1080 in hypoxic hypoxia was studied. In hypoxic hypoxia, GSNO suppressed the expression of MMP-1 protein in cells of the HT1080 line. At the same time, hyperexpression of superoxide dismutase 2 (SOD-2) increased, and hyperexpression of catalase reduced the expression of MMP-1 protein in cells of the HT1080 line.

Key words: *matrix metalloproteinase, S-nitrosoglutathione, hypoxia, cell culture.*

Matrix metalloproteinases play a key role in regulation of intercellular interactions by splitting components of the extracellular matrix and releasing cytokines deposited in the matrix [1]. MMP play a key role in pathogenesis of various diseases: premature birth [2], stroke [3], and metastasis of tumors [4]. The study of possibilities of pharmacological correction of MMP expression will allow to develop effective methods of control over the matrix metalloproteinases system in pathological processes [5].

It was previously shown that hypoxic hypoxia stimulates the expression of MMP-1 in HT1080 cells, while SOD-2 increases and catalase reduces the expression of mRNA and MMP-1 protein [6]. It was also found that the synthetic antioxidant S-nitrosoglutathione (GSNO) suppresses the expression of mRNA of MMP-1 [7].

The work objective was to assess the effect of synthetic antioxidant GSNO on the expression of MMP-1 protein in human fibrosarcoma cells of the HT1080 line in hypoxic hypoxia on the background of hyperexpression of SOD-2 and catalase.

Materials and methods

Cell culture. Additional copies of MMP-1, SOD-2 and catalase genes were introduced into cells of the HT1080 line of human fibrosarcoma (ATCC cat. No. CCL-121) with the help of the vector; three modified HT1080 cell lines were obtained: HT1080-MMP1 contained increased number of copies of MMP-1 genes; HT1080-MMP1SOD2 contained increased number of copies of MMP-1 and SOD-2 genes; HT1080-MMP1SOD2CAT contained increased number of copies of MMP-1, SOD-2 and catalase genes. Each experiment was carried out three times.

Hypoxic hypoxia. Prepared gas mixtures were used: normoxic (21 v% of oxygen, 5 v% of carbon dioxide, 74 v% of nitrogen) and hypoxic (1 v% of oxygen, 5 v% of carbon dioxide, 94 v% of nitrogen).

Synthesis of S-nitrosoglutathione (GSNO) was performed on the day of study. 1 ml of 200 mM-solution of sodium nitrate (cat. No. S2252, Sigma-Aldrich, USA) was mixed with 1 ml of 200 mM-solution of L-cysteine (cat. No. W326305, Sigma-Aldrich, USA), it was incubated in the dark on ice for 10 minutes. Then we added 2 ml of 1 M solution of potassium phosphate dibasic. GSNO aqueous solution was added to the nutrient medium to achieve its concentration of 500 μmol/l in the medium, then incubated 1 h under normoxic conditions, the medium was replaced with a medium free of GSNO.

Experiment. After 24 h of exposure of cells in hypoxic gas mixture, the expression of MMP-1 protein was evaluated with Western blot using rabbit polyclonal antibodies (Millipore, cat. No. AB8105) and secondary goat antibodies (Invitrogen, cat. No. A-11069). Densitometric analysis of Western blot results was carried out using the ImageJ version 1.47a program (National Institutes of Health).

Statistical analysis. Statistical analysis was performed using the SigmaPlot 11.0 statistical package (Systat Software Inc., USA). The differences were estimated according to the Student's t-test. The differences were considered significant at 5% ($p<0.05$).

Results and discussion

In hypoxic hypoxia, GSNO in the culture medium suppressed the expression of MMP-1 protein in HT1080-MMP1 cells (Figure 1). This indicates the possible antioxidant effect of GSNO in the signal cascade of regulation of MMP-1 expression.

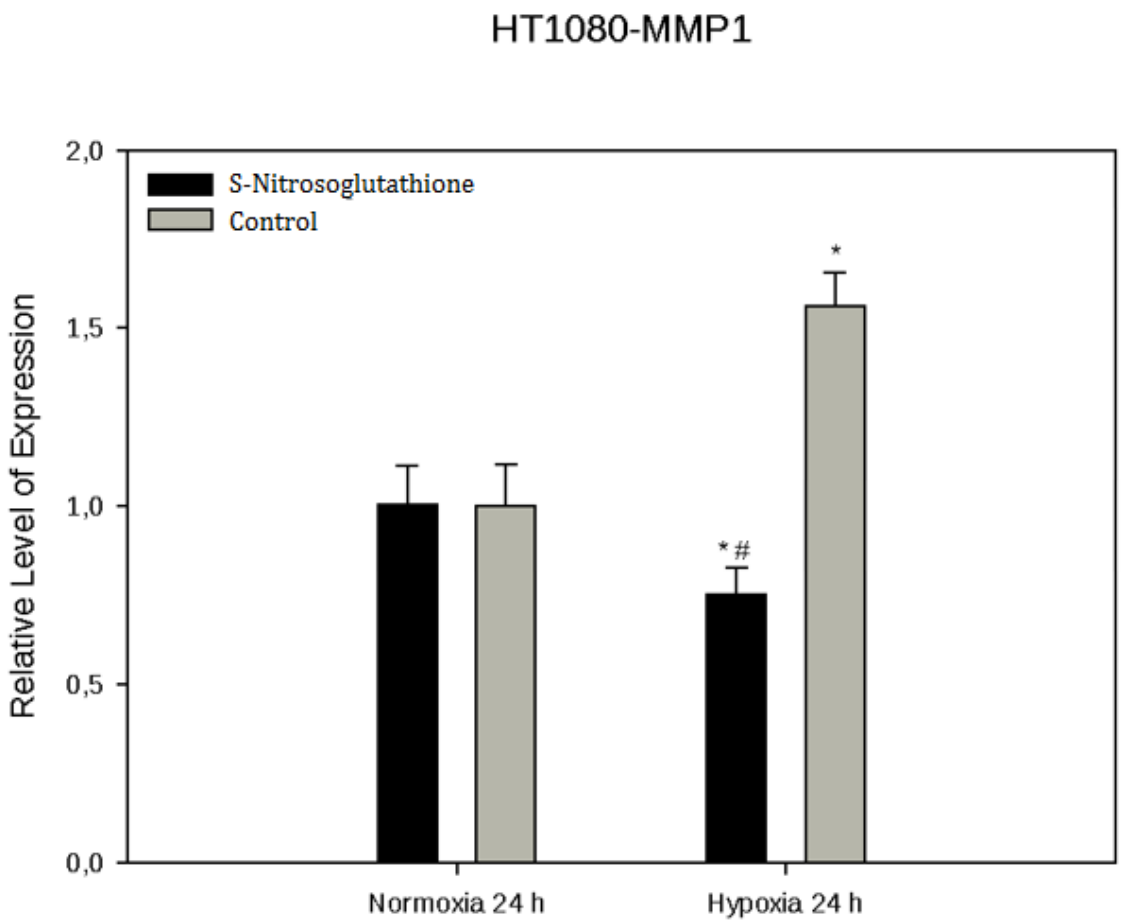

Figure 1. Effect of hypoxic hypoxia and 500 μM solution of S-nitrosoglutathione (GSNO) on MMP-1 protein expression in HT1080-MMP1 cell culture.

*P<0.001 – reliability of differences in the level of MMP-1 protein expression in normoxia and hypoxia.

#P<0.001 – reliability of differences in the level of MMP-1 protein expression under the action of S-nitrosoglutathione in comparison with control.

Hyperexpression of the mitochondrial form of superoxide dismutase (SOD-2) increased the synthesis of MMP-1 protein under normoxic conditions, which, apparently, was caused by increased generation of H_2O_2 [8]. At the same time, GSNO increased the MMP-1 protein expression in normoxic conditions, but suppressed the MMP-1 protein expression in hypoxic hypoxia (Figure 2). Perhaps, this difference was due not only to the antioxidant effect of GSNO, but also to the properties of this agent as a NO donor triggering a nitrosative signaling cascade [9].

Hyperexpression of catalase in HT1080 cells neutralized the effect of SOD-2 on the MMP-1 protein expression, which, apparently, is due to the splitting of H_2O_2 [10]. GSNO suppressed MMP-1 expression under hypoxic hypoxia (Figure 3).

Thus, in HT1080 cells, GSNO suppresses not only the synthesis of mRNA of MMP-1 [7], but also the synthesis of MMP-1 protein. The effect of GSNO on MMP-1 protein expression in HT1080 line cells is more pronounced in hypoxic hypoxia compared to normoxia.

A possible mechanism for induction of the synthesis of MMP-1 is a cascade of mitogen-activated kinase (MAPK), including kinase ERK 1/2 and JNK. In this case, JNK phosphorylates the transcription factors of the Jun family (c-Jun, JunD) [11], and ERK 1/2 phosphorylates the transcription factors of the Jun (c-Jun) and Fos family (Fra-1, Fra-2, c-Fos), as well as the transcription factor of the Ets family (Ets-1) [12]. Jun-Jun and Jun-Fos dimers translocate into the nucleus, where they enhance gene transcription. MMP transcription is enhanced by AP-1 and Ets [13].

The established pattern of MMP-1 protein expression reaction in hypoxic hypoxia should be taken into account when studying pharmacological correction of matrix metalloproteinases expression, in particular, in case of study of antioxidants and nitrosylating agents.

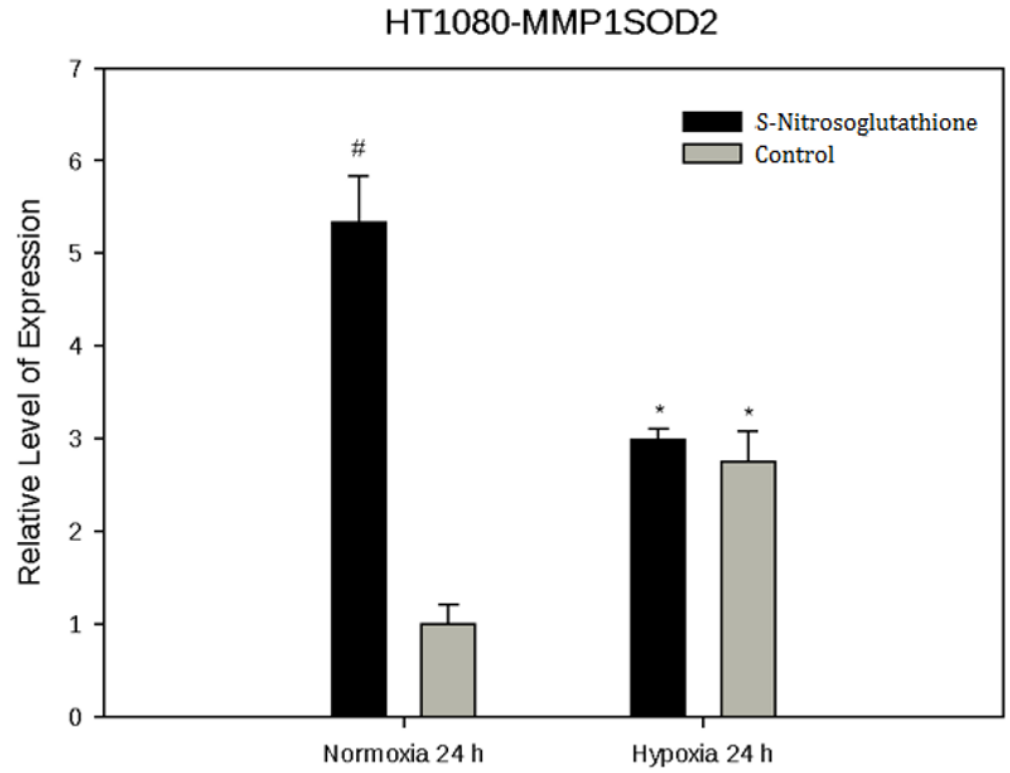

Figure 2. Effect of hypoxia and 500 μM solution of S-nitrosoglutathione (GSNO) on MMP-1 protein expression in HT1080-MMP1SOD2 cell culture.

*P<0.001 – reliability of differences in the level of MMP-1 protein expression in normoxia and hypoxia.
#P<0.001 – reliability of differences in the level of MMP-1 protein expression under the action of S-nitrosoglutathione in comparison with control.

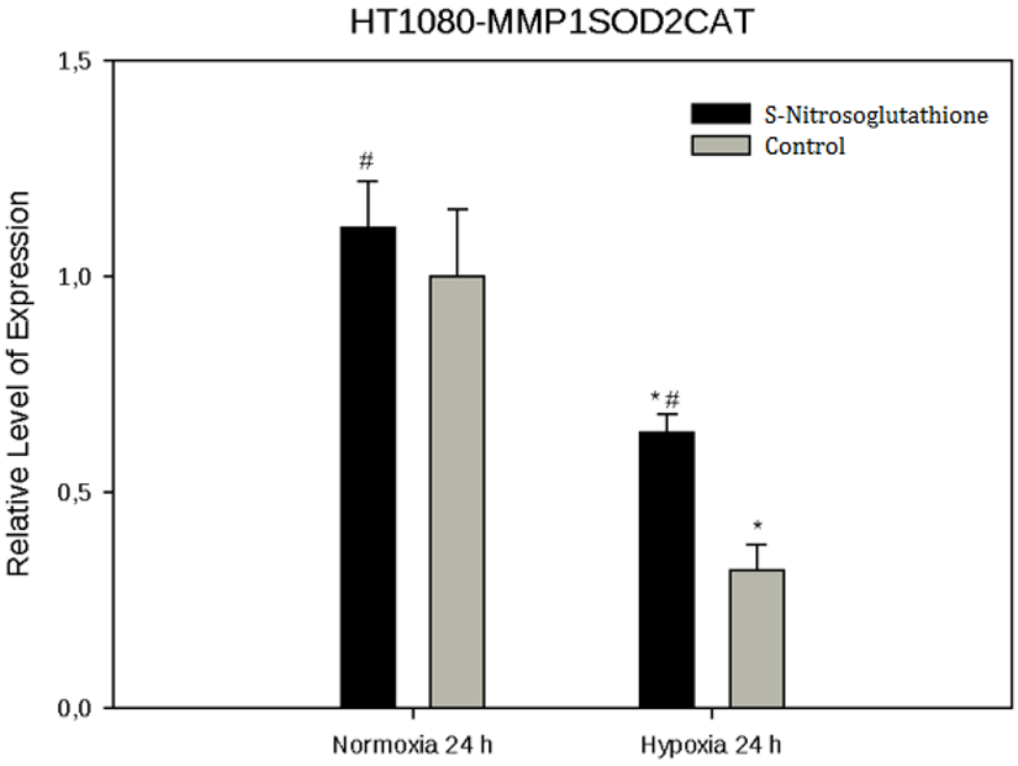

Figure 3. Effect of hypoxic hypoxia and 500 μM solution of S-nitrosoglutathione on MMP-1 protein expression in HT1080-MMP1SOD2CAT cell culture.

*P<0.001 – reliability of differences in the level of MMP-1 protein expression in normoxia and hypoxia.
#P<0.001 – reliability of differences in the level of MMP-1 protein expression under the action of S-nitrosoglutathione in comparison with control.

Conclusion

In hypoxic hypoxia, GSNO suppressed the expression of MMP-1 protein in cells of the HT1080 line. At the same time, hyperexpression of superoxide dismutase 2 (SOD-2) increased, and hyperexpression of catalase decreased the expression of MMP-1 protein in cells of the HT1080 line.

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References:

1. Sukhikh GT, Kan NE, Tyutyunnik VL. et al. The role of extracellular inducer of matrix metalloproteinases in premature rupture of membranes. *J. Matern. Fetal Neonatal Med*. 2016; 29(4): 656-659.

2. Frost JA, Geppert TD, Cobb MH. et al. A requirement for extracellular signal-regulated kinase (ERK) function in the activation of AP-1 by Ha-Ras, phorbol 12-myristate 13-acetate, and serum. *Proc. Natl. Acad. Sci. USA*. 1994; 91: 3844-3848.

3. Onisto M, Garbisa S, Caenazzo C. et al. Reverse transcription-polymerase chain reaction phenotyping of metalloproteinases and inhibitors involved in tumor matrix invasion. *Diagn. Mol. Pathol*. 1993;2:74-80.

4. Turner RJ, Sharp FR. Implications of MMP9 for blood brain barrier disruption and hemorrhagic transformation following ischemic stroke. *Front. Cell Neurosci*. 2016;10:56.

5. Candido S, Abrams SL, Steelman LS. et al. Roles of NGAL and MMP-9 in the tumor microenvironment and sensitivity to targeted therapy. *Biochim. Biophys. Acta*. 2016; 1863(3):438-448. doi: 10.1016/j.bbamcr.2015.08.010

6. Barreto SC, Hopkins CA, Bhowmick M. et al. Extracellular matrix in obesity – cancer interactions. *Horm. Mol. Biol. Clin. Investig*. 2015;22(2):63-77.

7. Chaudhary AK, Pandya S, Ghosh K. et al. Matrix metalloproteinase and its drug targets therapy in solid and hematological malignancies: an overview. *Mutat. Res*. 2013; 753(1):7-23.

8. Korenovskii YV, El'chaninova SA. Effects of S-nitrosoglutathione on the Expression of MMP-1 mRNA in HT1080 cells during hypoxic hypoxia. *Bull. Exp. Biol. Med*. 2016;160(3):319-321.

9. Roebuck KA, Rahman A, Lakshminarayanan V. et al. H2O2 and tumor necrosis factor-α activate intercellular adhesion molecule 1 (ICAM-1) gene transcription through distinct cis-regulatory elements within the ICAM-1 promoter. *J. Biol. Chem*. 1995;270:18966-18974.

10. Shi M, Yang H, Motley ED. et al. Overexpression of Cu/Zn-superoxide dismutase and/or catalase in mice inhibits aorta smooth muscle cell proliferation. *Am. J. Hypertens*. 2004;17(5 Pt 1):450-456.

11. Korenovskii Y.V., El'chaninova S.A. Effect of hypoxia on the expression of matrix metalloproteinase-1 in HT1080 line cells. *Izvestiya of Altai State University*. 2013;79(3/2):31-33.

12. Hemachandra LP, Shin DH, Dier U. et al. Mitochondrial superoxide dismutase has a pro-tumorigenic role in ovarian clear cell carcinoma. *Cancer Res*. 2015;75(22):4973-4984.

13. Won JS, Annamalai B, Choi S. et al. S-nitrosoglutathione reduces tau hyper-phosphorylation and provides neuroprotection in rat model of chronic cerebral hypoperfusion. *Brain Res*. 2015;1624:359-369.

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SYSTEMIC HEMOSTATIC EFFECTS OF FIBRIN-MONOMER AND THEIR MORPHOLOGICAL MANIFESTATIONS IN DOSED LIVER INJURY IN THE EXPERIMENT

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The article presents clarifying results of previously discovered hemostatic effects of different doses of fibrin-monomer in the experiment "in vivo" in dosed liver injury.
Research objective. To study systemic hemostatic effects of fibrin-monomer in parenchymatous bleeding and their morphological manifestations in the area of injury.
Materials and methods. In the experiment on male Chinchilla breed rabbits, along with placebo, hemostatic effects of fibrin-monomer (FM) solution at doses of 0.25 and 2.5 mg/kg with intravenous (i.v.) administration were studied. 1 hour after the administration of drugs, a standard liver injury was applied and the volume and rate of blood loss was estimated. The study of the hemostasis system included determination of number of platelets, fibrinogen concentration, D-dimer level in blood plasma, calibrated thrombography indicators. The condition of the wound surface of the liver was assessed macro- and microscopically.
Results and conclusions. Preliminary administration of FM at doses of 0.25 and 2.5 mg/kg led to a decrease in blood loss after the dosed injury by 6.3 and 7.8 times, respectively, compared to placebo without changing the level of thrombin generation in blood plasma. FM at a high dose (2.5 mg/kg) minimized blood loss, probably by activating the coagulation properties of blood and thrombogenesis, as illustrated by a 7-fold increase in D-dimer level. Regardless of the administered dose of FM, massive thrombotic overlays consisting of thick branching fibrin threads were observed at the site of liver tissue damage. The obtained data indicate the presence of unique hemostatic properties at the site of tissue damage in low dose FM (0.25 mg/kg), which opens the potential to create a new generation of hemostatic drugs of systemic action.
Key words: *hemostasis system, fibrin-monomer, liver injury, blood loss model, systemic hemostatic effect, morphology.*

The hemostasis system is a complex self-organized system of maintaining blood colloidal state for the purpose of adequate blood supply to organs. In modern clinical practice, hemostasis disorders associated with extensive bleeding in urgent conditions, surgical interventions, obstetric pathologies are very common; it explains the high interest of scientists and doctors of different specialties to this problem [1].

It is known that at present there are a number of medications with proven efficacy and explainable systemic hemostatic action [2]. At the same time, the use of most of them involves increased thrombotic potential, which, however, in addition to the therapeutic effect, does not exclude the risk of arterial and/or venous thrombosis [3]. This circumstance seems to be an incentive to search for effective antihemorrhagic drugs with systemic action. Fibrin-monomer (FM) (synonym – desAABB-fibrinogen) can become one of the new hemostatic agents promising for the development. In classical representation, the main function of fibrin-monomer, as a product of fibrinogen proteolysis by thrombin, consists in autopolymerization and formation of the blood clot base [4, 5]. Earlier in experiments "in vivo", we have shown that FM taken at a physiological dose [6] has a pronounced hemostatic effect in its intravenous administration an hour before application of liver injuries [7]. However, the mechanisms through which this effect is realized remain unclear so far, which served as the basis for the study.

The research objective was to study the systemic hemostatic effects of fibrin-monomer in parenchymatous bleeding and their morphological manifestations at the injury site.

Materials and methods

The studies were carried out on 39 healthy male Chinchilla rabbits weighing 3.0-4.5 kg, contained in standard vivarium conditions. The method of block randomization formed 3 experimental groups (Figure 1).

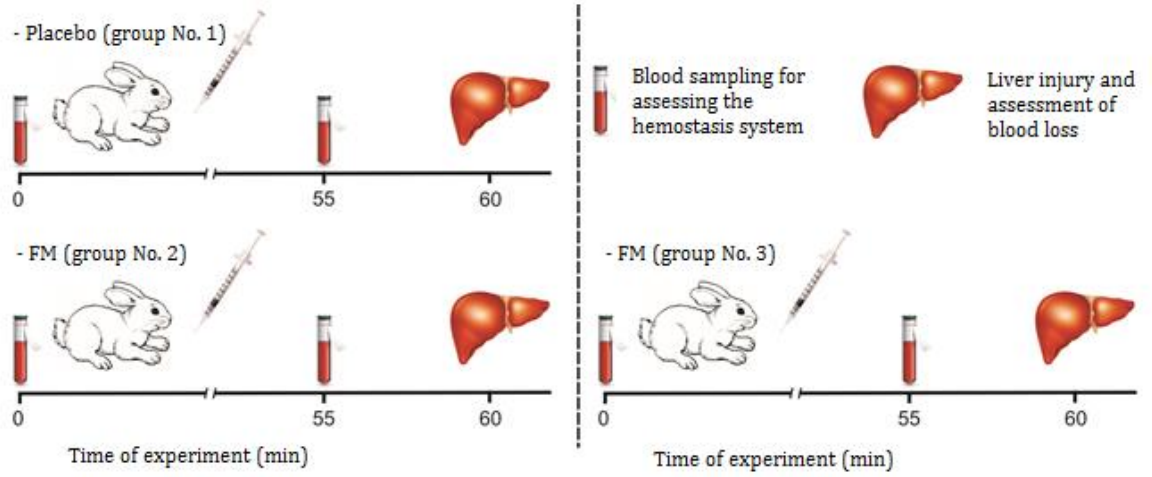

Figure 1. Design of studies of the hemostatic effect of fibrin-monomer in experiment with dosed liver injury.

Animals of group No. 1 (n=11) were injected with a placebo solution in the marginal ear vein (4.0 M urea solution corresponding to its concentration in a FM solution) in the volume of 0.5 ml; animals of group No. 2 (n=15) were injected with a FM solution at a dose of 0.25 mg/kg; accordingly, animals of group No. 3 (n=13) – a FM solution at a dose of 2.5 mg/kg. One hour after administration of drugs, under general anesthesia (the Telazole drug (Zoetis Inc firm)), laparotomy was performed and dosed liver injury was applied in accordance with the approved procedure [8]. After the injury, using gauze pads, the nature of bleeding was assessed by the volume of blood loss in % of the estimated circulating blood volume (% of CBV) taking into account the animal body weight, as well as by the blood loss rate per unit of time (mg/s) [9]. To study the hemostasis system, animal blood was obtained after an incision of the marginal ear vein (gravity) twice: before the administration of drugs (initially) and before the liver injury (Figure 1). Blood for calculating the number of platelets was stabilized by potassium salt of the ethylene diamine tetraacetatic acid, for the study of other parameters – by 0.11 M (3.8%) solution of sodium citrate (the ratio of blood to stabilizer 9:1).

The estimation of hemocoagulation parameters included the calculation of platelets in venous blood using the Drew3 hematological analyzer (Drew Scientific Inc.), determination of fibrinogen concentration on the Thrombostat 2 coagulometer (Behnk Electronik, with the use of a set of reagents "Tech-Fibrinogen-test" of the Technology-Standard firm), D-dimer level in blood plasma (the NycoCard® D-Dimer test system of the Axis-Shield PoC AS firm with the use of the NycoCard Reader II analyzer-reflectometer), and Hemker thrombin generation test using the Fluoroskan Ascent tablet fluorimeter (ThermoFisher SCIENTIFIC) with the software Thrombinoscope 3.0.0.26.

For histological examination, pieces of liver tissue were taken, including wound and undamaged surfaces. The material was placed in histology containers, labeled and fixed in a 10% solution of neutral formalin by Lilly. Processing of the material was carried out by isopropyl alcohol with the help of the TISSUE-TEK VIPTM6 Spin Tissue Processor (the Sakkura firm), the material was poured into paraffin (the BiOvitrum firm) by means of the TISSUE-TEK TEC 5 Tissue Embedding Console (the Sakkura firm). Histological slices 4-5 μm thick were obtained using the Accu-Cut SRM Semi-automatic Rotary Microtome (the Sakkura firm), preparations were colored in the TISSUE-TEK Prisma Automated Slide Stainer (Sakkura, Japan) (coloring with haematoxylin and eosin), preparations were put under the film in the TISSUE-TEK Automated Coverslipper (the Sakkura firm). Morphometric measurements were carried out using the VideoTest – Morphology 5.2 licensed package of morphometric programs.

The distribution of the obtained indications was estimated by the Shapiro–Wilk test, differences between groups depending on the distribution – by the Student's t-test, Mann–Whitney U-test; to estimate sample variances, the Fisher F-test was used. The differences were considered significant at the level of statistical significance p£0.05. The results were processed by the Statistica 10.0 program. The data are presented in the form of median (Me), the 25th and 75th percentiles (Me [Q25÷Q75]).

All animal studies approved by the local ethical committee of FSBEI HE "AGMU" of the Ministry of Health of the Russian Federation were conducted in accordance with Directive 86/609/EEC, the Declaration of Helsinki, and the "Animal experimentation legislations" [10].

Results and discussion

The results of experiments showed that the volume of blood loss in groups of animals No. 2 and No. 3 after i.v. introduction of FM was 6.3 times (1.6 [1.0÷3.0] % of CBV; p=0.001) and 7.8 times (1.3 [0.6÷1.6] % of CBV; p=0.0005) less by median respectively in comparison with the placebo group (group No. 1) (10.1 [4.1÷13.5] % of CBV) (Figure 2).

It can also be noted that the rate of blood loss after the dosed liver injury in group No. 3 (5.2 [3.5÷9.1] mg/s; p=0.03) was 4.9 times less than in the placebo group (25.7 [5.5÷36.5] mg/s) (Figure 2).

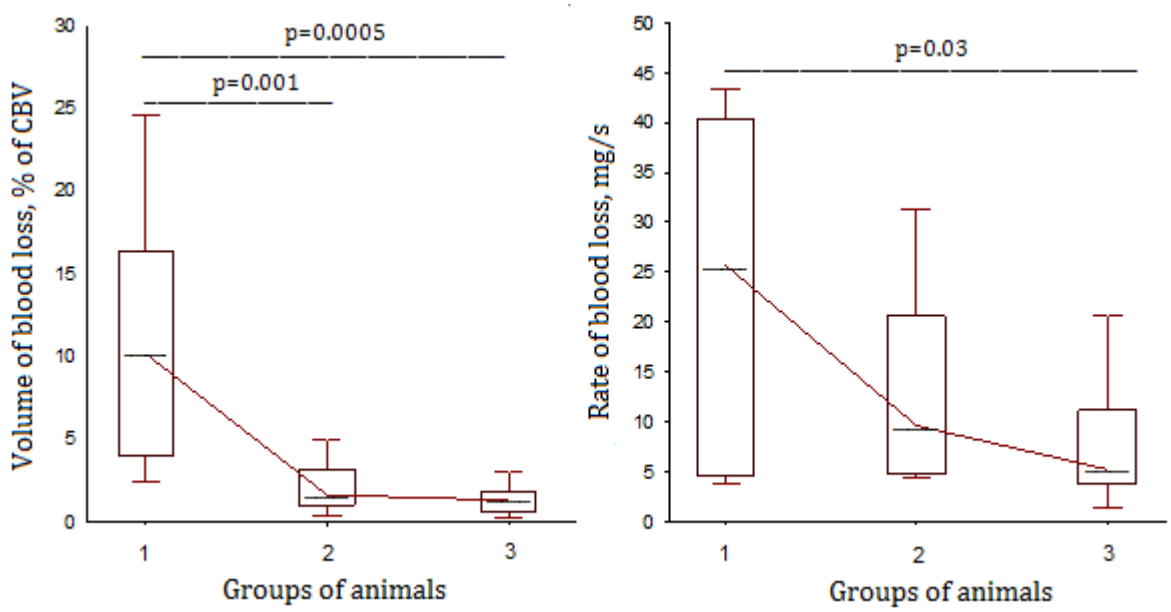

Figure 2. Comparative analysis of blood loss parameters in experimental animals after dosed liver injury.

In the study of hemostasis indicators in animals, we have not found any significant decrease in the number of platelets and fibrinogen concentration (before and after injection) in all compared groups (Table 1). Along with this, the relationship between the dose of the injected FM and the level of D-dimer in blood plasma (F=6.37; p<0.001) was established by the method of dispersion analysis. Table 2 shows that the increase in the level of this marker by 7.0 times (p=0.002) was observed after the application of FM at a dose of 2.5 mg/kg.

Table 1

Indicators of hemostasis system in animals with placebo and received fibrin-monomer at different doses

Indicators	Group No. 1		Group No. 2		Group No. 3	
	before (0)	after (1)	before (2)	after (3)	before (4)	after (5)
Platelets, ×10⁹/L	617.0 [456.0÷760.5]	524.0 [480.5÷686.5]	526.0 [464.3÷602.8]	524.0 [452.0÷600.5]	551.5 [437.3÷600.5]	479.0 [403.5÷568.3]
		p_{0-1}>0.05		p_{2-3}>0.05		p_{4-5}>0.05
Fibrinogen, g/L	3.30 [2.80÷4.40]	3.70 [2.80÷4.50]	3.75 [2.80÷4.45]	3.40 [2.80÷4.80]	3.25 [2.59÷3.93]	3.20 [2.60÷3.35]
		p_{0-1}>0.05		p_{2-3}>0.05		p_{4-5}>0.05
D-dimer, ng/ml	100.0 [100.0÷100.0]	100.0 [100.0÷175.0]	100.0 [100.0÷175.0]	100.0 [100.0÷200.0]	100.0 [100.0÷200.0]	700.0 [500.0÷800.0] (Δ + 7.0 times)
		p_{0-1}>0.05		p_{2-3}>0.05		p_{4-5}=0.002

Notes: the results are presented in the form of Me [25÷75], where Me is the median in the sampling population; [25÷75] – the 25th and 75th percentile; p – the level of statistical significance of differences of compared indicators; n – the number of individuals in the group; "before" – indicators before the introduction of FM or placebo, "after" – indicators an hour after the introduction of FM or placebo; Δ – statistically significant difference of the studied indicator before and after introduction of FM or placebo.

Systemic action of FM at different doses had a hemostatic effect without significant increase in the generation of blood plasma thrombin in experimental animals in the test of calibrated thrombography by Hemker (Table 2).

Table 2

Indicators of thrombin generation test (calibrated thrombography by Hemker) in animals with placebo and received fibrin-monomer at different doses

Indicators	Group No. 1		Group No. 2		Group No. 3	
	before (0)	after (1)	before (2)	after (3)	before (4)	after (5)
Lag time, min	2.0 [2.0÷2.7]	2.0 [1.8÷2.7]	2.3 [2.0÷2.4]	2.0 [2.0÷2.7]	1.9 [1.7÷2.3]	1.9 [1.8÷2.5]
		p_{0-1}>0.05		p_{2-3}>0.05		p_{4-5}>0.05
ETP, nmol×min	373.9 [338.7÷500.4]	484.8 [360.6÷622.5]	421.8 [406.4÷461.5]	423.4 [380.5÷451.9]	394.7 [368.5÷461.9]	415.3 [382.8÷467.3]
		p_{0-1}>0.05		p_{2-3}>0.05		p_{4-5}>0.05
Peak thrombin, nmol/L	76.2 [40.7÷90.9]	81.7 [34.3÷138.8]	78.3 [55.2÷103.9]	73.1 [58.5÷91.2]	64.3 [51.0÷95.8]	80.7 [51.7÷93.0]
		p_{0-1}>0.05		p_{2-3}>0.05		p_{4-5}>0.05
ttPeak, min	5.8 [5.0÷7.3]	5.4 [4.6÷6.3]	4.9 [4.5÷6.3]	5.8 [4.6÷7.3]	5.1 [4.0÷5.8]	5.2 [4.1÷5.7]
		p_{0-1}>0.05		p_{2-3}>0.05		p_{4-5}>0.05

Note: the results are presented in the same way as Table 1.

In macroscopic study of the liver injury site in animals of group No. 1, thin, smooth, shiny, pinkish thrombotic overlays were determined (Figure 3). In microscopic study, thrombotic masses consisted of a large number of unchanged red blood cells and thin tender fibrin strands. Thickness of thrombotic masses averaged 79.5±8.3 μm.

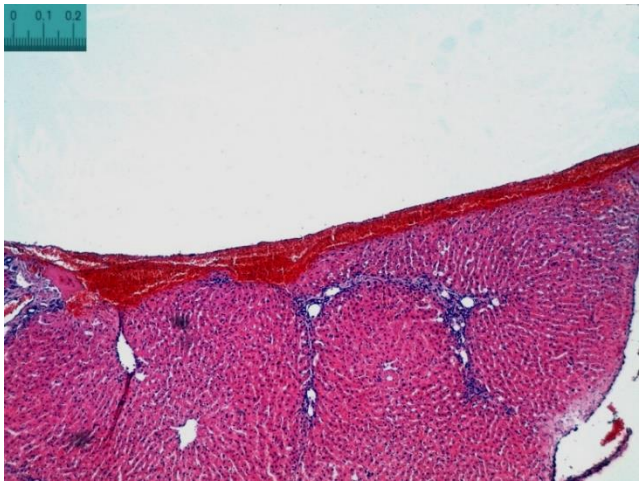

Figure 3. Thin thrombotic overlays consisting of red blood cells and thin fibrin strands in group No. 1. Coloring with haematoxylin and eosin. Zoom x40.

In animals of group No. 2, there was a completely different morphological picture at the site of liver injury compared to group No. 1 (Figure 4). Macroscopically, massive, thick, bosselated, brown thrombotic overlays were detected at the site of liver injury. In microscopy, thrombotic masses consisted of a large number of unchanged and hemolyzed red blood cells, as well as thick branching gross fibrin strands. Thrombotic overlays averaged 324.4±22.8 μm, exceeding the size of those in group No. 1 by 4 times (p=0.0000001).

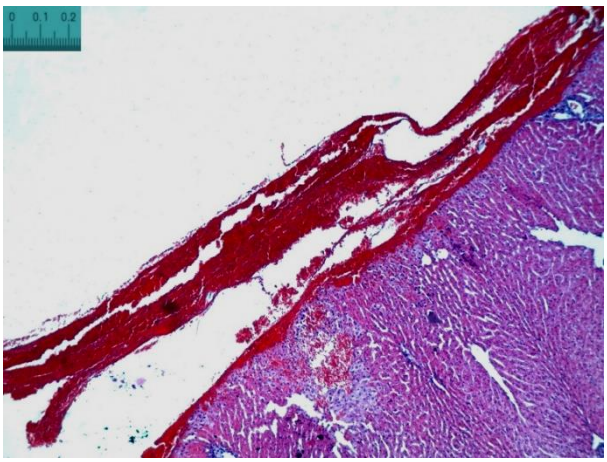

Figure 4. Massive thrombotic overlays consisting of unchanged and hemolyzed red blood cells and thick branching fibrin strands in group No. 2. Coloring with haematoxylin and eosin. Zoom x40.

In animals of group No. 3, the morphological picture of the site of liver injury was similar to that in animals of group No. 2 (Figure 5). Macroscopically, at the site of damage, massive, bosselated, brownish thrombotic overlays were also determined. In microscopic study, thrombotic masses consisted of a large number of hemolyzed red blood cells and thick, gross fibrin strands. Thrombotic overlays averaged 319.5±8.8 μm, exceeding the size of those in group No. 1 by 4 times (p=0.0000001). It should be noted that the

thickness of thrombotic overlays in groups No. 2 and No. 3 did not differ (p=0.8).

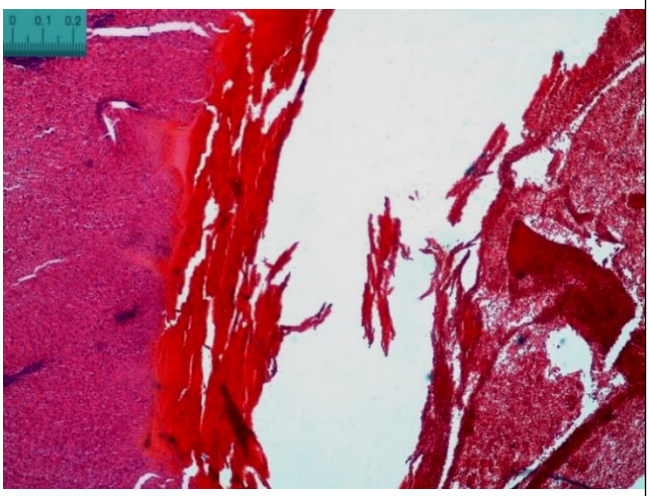

Figure 5. Massive thrombotic overlays consisting of hemolyzed red blood cells and thick fibrin strands in group No. 3. Coloring with haematoxylin and eosin. Zoom x40.

Thus, the results of experiments "in vivo" with systemic administration of FM at different doses (0.25 and 2.5 mg/kg) an hour before the injury of the parenchymatous organ showed a significant decrease in the volume of post-injury blood loss. At the same time, dose-dependent hemostatic action was traced both in terms of the volume of lost blood and the rate of blood loss. We should note that the high applied dose of FM (2.5 mg/kg) led to intravascular thrombus formation, which was manifested by a sevenfold increase in the level of D-dimer in blood plasma. The mechanism of this prothrombotic effect of the high dose of FM can be explained due to the fact that soluble products of thrombin action on fibrinogen (desAABB-fibrinogen) in sufficient concentrations in blood plasma represent the classical basis for fibrin formation and thrombus formation. And this could be related to their ability to reduce blood loss in dosed liver injury in this case. However, the fact of decrease in the volume of blood lost in the application of 10–20 times a lower dose of FM (0.25 mg/kg), not accompanied by platelet consumption and an increase in D-dimer level, can be considered as a phenomenon that has yet to be explored. It is also noteworthy that both doses of FM did not contribute to a change in the level of endogenous thrombin potential of blood plasma in animals, which suggests the possible presence of other mechanisms of fibrin formation at the site of injury. At the same time, it should be said that the morphological picture of the wound surface indicates the inclusion of fibrin in the mechanism of stopping parenchymatous bleeding. Thus, the presence of massive thrombotic overlays containing thick fibrin strands and hemolyzed red blood cells at the site of liver injury in animals receiving FM, firstly, confirms the fibrin mechanism, and secondly, raises the question for researchers: what mechanisms are the basis for initiating of fibrin formation by FM in the microcirculation zone without changing plasma thrombin generation.

It may also be taken into account that after i.v. injection of FM at a dose of 0.25 mg/kg its calculated concentration in blood plasma is about 0.007 g/L, while the concentration of own fibrinogen in experimental animals range from 3.40 to 3.75 g/L by median (Table 1). Comparing the levels of these proteins (1:470–1:530) in blood plasma, it can be argued that the introduced FM (at a dose of 0.25 mg/kg) is not able to independently form the fibrin clots and the hemostatic effect induced by it has a nature different from classical representations.

Conclusions

1. Systematic injection of fibrin-monomer at a low dose (0.25 mg/kg) an hour before injury is manifested by a pronounced hemostatic effect.
2. The hemostatic effect of a low dose of fibrin-monomer is realized without signs of systemic thrombin and thrombus formation.
3. The morphological pattern of the injured surface after stopping bleeding indicates a fibrin hemostatic mechanism, the nature of which has not yet been studied.
4. The systemic hemostatic effect of fibrin-monomer observed in the experiment can serve as a prerequisite for the creation of a new generation of hemostatic drugs in the future.

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Conflict of interest. The authors declare that there is no conflict of interest.

References:

1. Rossaint R, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernández-Mondéjar E, Filipescu D, Hunt BJ, Komadina R, Nardi G, Neugebauer EA, Ozier Y, Riddez L, Schultz A, Vincent JL, Spahn DR. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. *Crit Care*. 2016; 12 (20): 100. DOI: 10.1186/s13054-016-1265-x.
2. Levi M. Management of bleeding in patients treated with direct oral anticoagulants.

Crit Care. 2016; 20: 249. DOI: 10.1186/s13054-016-1413-3.

3. Damage Control Resuscitation at Level IIb/III Treatment Facilities. *Joint Theater Trauma System Clinical Practice Guideline*. 2013.

4. Zubairov D.M. *Molecular bases of blood clotting and thrombus formation*. Kazan: FEN; 2000: 368.

5. Kuznik B.I. *Cell and molecular mechanisms of regulation of hemostasis system in norm and pathology*. Chita: Express-izdatelstvo; 2010: 832.

6. Park KJ, Kwon EH, Kim HJ, Kim SH. Evaluation of the diagnostic performance of fibrin monomer in disseminated intravascular coagulation. *Korean J. Lab. Med*. 2011; 31 (3): 143–7. DOI: 10.3343/kjlm.2011.31.3.143, PMID: 21779185.

7. Vdovin V.M., Momot A.P., Orekhov D.A., Tolstokorov I.G., Shevchenko V.O., Krasyukova V.O., Shakhmatov I.I., Lycheva N.A., Belozerskaya G.G. Time-dependent systemic hemostatic effects of fibrin monomer in controlled liver injury in the experiment. *Kazan Medical Journal*. 2019; 2(100): 257–263. DOI: 10.17816/KMJ2019-257.

8. *Guidelines for experimental (preclinical) study of new pharmacological substances*. Ed. R.Yu. Khabriev. M.: Medicine publishing house; 2005: 832.

9. *Guidelines for conducting preclinical trials of drugs. Part One*. Ed. A.N. Mironov. M.: Grif and K; 2012: 944.

10. *European convention for the protection of vertebrate animals used for experimental and other scientific purposes*. Strasburg: Council of Europe, 1986: 11.

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RETROSPECTIVE ANALYSIS OF PATHOMORPHOLOGICAL CHANGES IN THE LUNGS OF PEOPLE WHO DIED OF FATAL HYPOTHERMIA

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The article presents a retrospective analysis of pathomorphological changes in the lungs of people who died of fatal hypothermia. A total of 181 forensic medical protocols were studied. It is shown that morphological changes in lungs depended on the rate of dying, which was significantly influenced by ambient temperatures at the site of detection of the corpse. At a slow rate of dying (n=103) (t=+16°C to –10°C), there were more often found mucous secretion in the bronchi, emphysema and spasm of the bronchi, deposition of mucous secretion in the glands of the submucous base of the bronchi, and the "calorific" effect of capillaries of conductive parts of the lungs; at a rapid rate of cooling (n=78) (t=–11°C to –30°C), alveolar edema, stasis in vessels of microcirculation, hemorrhage in alveoli, desquamation of the bronchial epithelium were more often revealed; these changes may indicate the failure of compensatory adaptive processes in the lungs.

Key words: *hypothermia, rate of dying, compensatory adaptive reactions, retrospective analysis.*

Modern pathomorphology is increasingly moving from the standpoint of descriptive discipline to functional one, studying morphological equivalent of adaptive compensatory reactions [1, 2, 3, 4, 5, 6, 7, 8, 9]. These reactions occur in almost any acute pathological process and play an important role in adaptive organ restructuring in response to external adverse factors [10, 11, 12].

Hypothermia is one of the most powerful environmental factors affecting the human body. Pulmonary tissue has a wide range of adaptive compensatory reactions to the effect of hypothermia. All these adaptive compensatory reactions occurring in the lungs are aimed at providing temperature homeostasis. Thus, spasm of bronchi and bronchioles creates an obstacle to the flow of cold air and reduces the area of contact with the cover epithelium, and the "calorific" effect, which is manifested in the congestion of the vessels in peribronchial tissue, promotes warming of air. Compensatory emphysema usually occurs on the periphery of spasmed bronchi [13, 14]. The "deposition" of mucous secretion in goblet cells prevents the cooling of epithelium. According to Shapovalenko N.S. et al. (2011) [15], mucus production is the essential stage of adaptation of bronchial mucous membranes to the cold factor impact.

Other morphological equivalents of hypothermia, such as pronounced dystelectasis, stasis in vessels of microcirculation, fibrination, alveolar edema and hemorrhage in alveoli, are expressions of failure adaptive compensatory processes in the respiratory system.

Diagnosis of the rate of dying can be based on an assessment of the duration of exposure to low temperature, the state of the body, and the conditions in which it is found. Pathomorphological criteria of the rate of dying from hypothermia in the lungs were investigated in single works only [16].

The work objective was a retrospective analysis of pathomorphological changes in the lungs of people who died of fatal hypothermia, with determination of compensatory adaptive criteria depending on the rate of dying.

Materials and methods

The retrospective analysis included 181 people who died of fatal hypothermia in the period from 2014 to 2016 in Barnaul. The data were obtained from the analysis of forensic autopsy protocols, as well as partly from the protocols of forensic histological studies.

The age of the victims ranged from 1 to 95 years and averaged 52.8±1.2 years. There were 142 males (78.45%) and 39 females (21.55%). The ambient temperature at the detection of the corpse fluctuated from +16 to –30°C and averaged –7±0.8°C. Ethyl alcohol in the blood was detected in 34% of cases. Its concentration ranged from 0.7 to 4.9 ppm and averaged 0.9±0.1 ppm. Pathology of the cardiovascular system was found in 35% of cases, pathology of the respiratory system was detected in 14% of cases.

The frequency of occurrence of 11 hypothermia pathomorphological markers was investigated: mucous secretion in bronchi, pulmonary emphysema, spasm of the bronchi, desquamation of the bronchial epithelium, deposition of mucous secretion in the glands of the submucous base of the bronchi, height of the epithelial layer in bronchi, spasm of vessels, calorific effect of capillaries of conductive parts of the lungs (pronounced congestion of capillaries of the bronchi), pulmonary edema, stasis in vessels, and hemorrhage in alveoli. We also matched pathomorphological changes in the respiratory system with one of the most important factors of the rate of dying: the ambient temperature. To do this, the victims of hypothermia were divided into 2 groups depending on the ambient temperature: the first group (slow rate of dying) included 103 dead found at temperatures ranging from +16 to –10°C; the second group (fast rate of dying) included 78 dead found at temperatures from –11 to –30°C, and a comparative analysis of pathomorphological changes in the study groups was carried out as a percentage.

Statistical processing of the obtained data was carried out using the Statistica 10.0. statistical programs package and the statistical analysis package of the MS EXCEL 2010 program.

Results and discussion

The results of the retrospective analysis showed that the mucous secretion in the bronchi generally, without separation of the victims into groups depending on the rate of cooling, was found in 44.35% of cases. In the first group of the study (slow rate of dying), the mucous secret was detected in 54.5% of cases, and in the second group (fast rate of dying), in 33.3% of cases (Figure 1a; Table 1).

In total, emphysema was detected in 91% of cases. In the first group of the study, emphysema was detected in 93% of cases, and in the second group, in 89% of cases (Figure 1b; Table 1).

Table 1

Pathomorphological changes in the respiratory system at death from hypothermia depending on the rate of dying

Pathomorphological indicators	Slow rate of dying (%)	Fast rate of dying (%)
Mucous secretion in the bronchi	54.5	33.3
Pulmonary emphysema	93	89
Spasm of the bronchi	91.3	72.5
Desquamation of the bronchial epithelium	49	60.9
Deposition of mucous secretion in the glands of the submucous base of the bronchi	81.8	48.1
Increase in the height of the epithelial layer in bronchi	72	25.4
Calorific effect of capillaries of conductive parts of the lungs	63.4	93.2
Spasm of vessels	60.3	63.6
Pulmonary edema	45.2	63.6
Stasis in vessels	38.3	40
Hemorrhage in alveoli	19.2	61.8

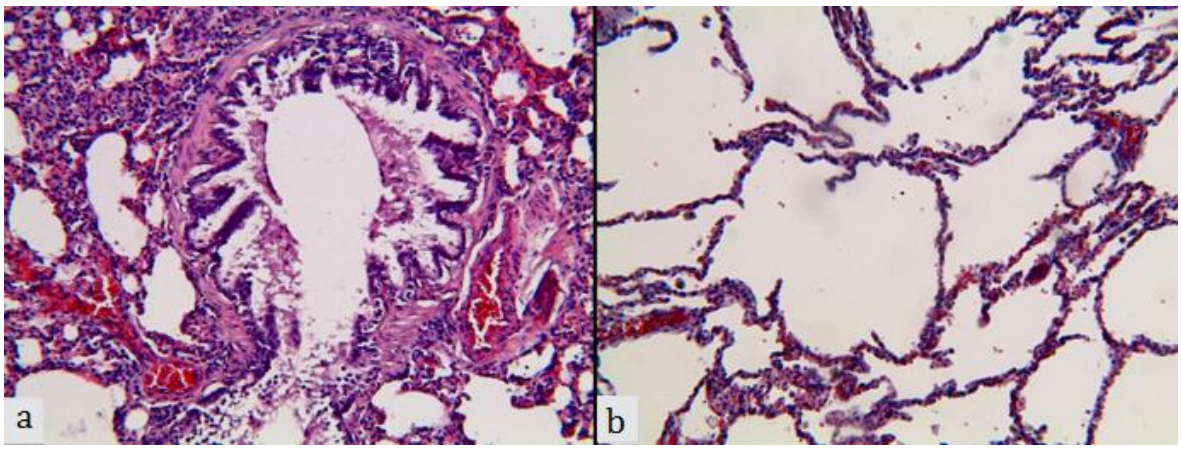

Figure 1. Pathomorphology of pulmonary tissue in fatal hypothermia: a – accumulation of mucous secret in the bronchus; b – pronounced emphysema. Coloring with haematoxylin and eosin. Zoom x100.

In total, spasm of the bronchi was detected in 82.4% of cases. In the first group of the study, bronchospasm was found in 91.3% of cases, and in the second group, in 72.5% of cases (Figure 2a; Table 1). It should be noted that concomitant bronchospasm with the formation of typical high figures of "ears" were detected only at very low temperatures (–30°C) in 0.8% of cases.

Desquamation of the bronchial epithelium was generally found in 42.7% of cases. In the first group of the study, epithelial desquamation was detected in 49% of cases, and in the second group, in 60.9% of cases (Figure 2b; Table 1).

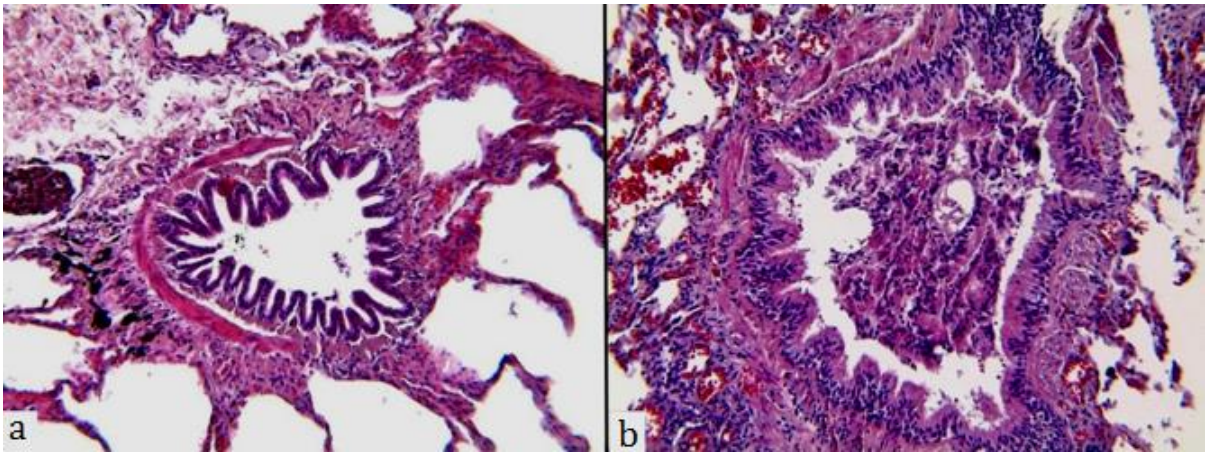

Figure 2. Pathomorphology of pulmonary tissue in fatal hypothermia: a – spasm of the bronchus; b – desquamated epithelium in the lumen of the bronchus. Coloring with haematoxylin and eosin. Zoom x100.

The deposition of secretion in the glands in general was revealed in 39.7% of cases. In the first group of the study, the deposition of secretion in the glands was found in 81.8% of cases, and in the second group, in 48.1% of cases (Figure 3a; Table 1).

Increase in the height of bronchial epithelium in general was revealed in 54% of cases. In the first group of the study, the increase in the height of the epithelium was found in 72% of cases, and in the second group, in 25.4% of cases (Figure 3b; Table 1).

"Calorific" effect of capillaries of conductive parts of the lungs (pronounced congestion of capillaries of the bronchi) was generally found in 63.4% of cases. In the first group of the study, the calorific effect was detected in 93.2% of cases, and in the second group, in 26.5% of cases (Figure 3b; Table 1).

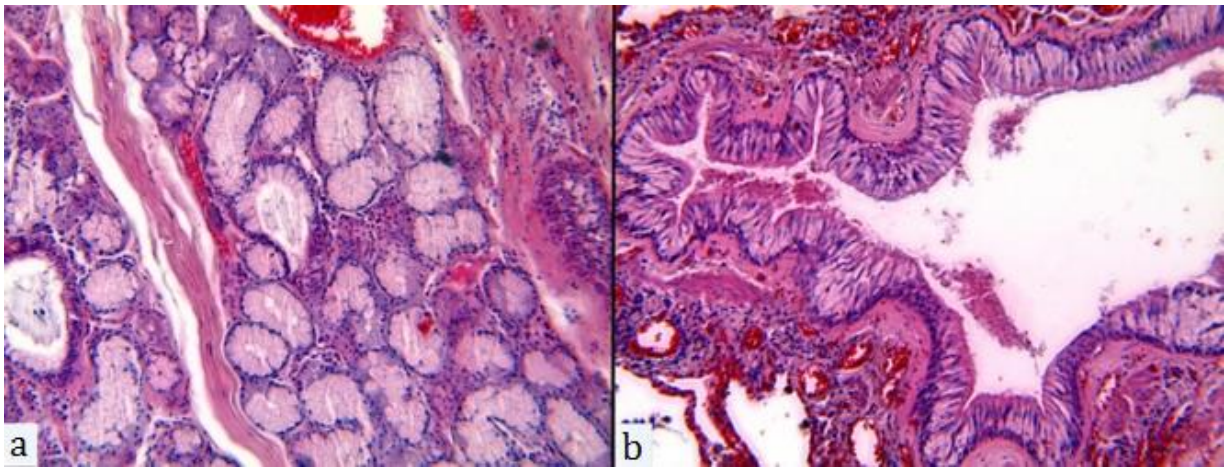

Figure 3. Pathomorphology of pulmonary tissue in fatal hypothermia: a – deposition of mucous secretion in the glands of the submucous base of the bronchi; b – high epithelium lining the bronchus and the calorific effect of capillaries (pronounced congestion of capillaries of the bronchi). Coloring with haematoxylin and eosin. Zoom x100.

Angiospasm was generally detected in 37.6% of cases. In the first group of the study, spasm of the vessels was detected in 60.3% of cases, and in the second group, in 63.6% of cases (Figure 4a; Table 1).

Pulmonary edema was generally detected in 52.6% of cases. In the first group of the study, pulmonary edema was found in 45.2% of cases, and in the second group, in 63.6% of cases (Figure 4b; Table 1).

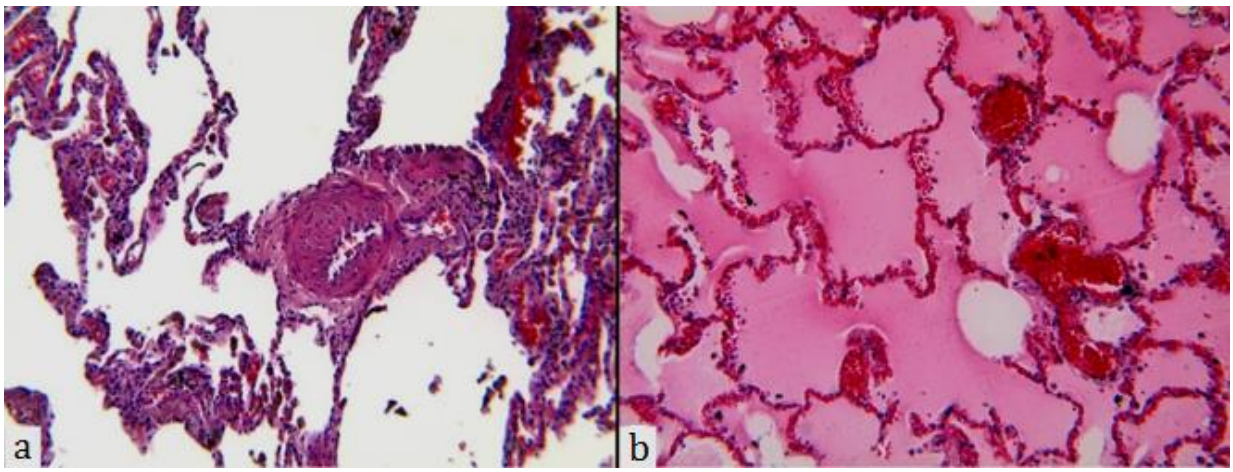

Figure 4. Pathomorphology of pulmonary tissue in fatal hypothermia: a – angiospasm; b – pulmonary edema. Coloring with haematoxylin and eosin. Zoom x100.

Stasis in vessels of microcirculation in general was revealed in 47.4% of cases. In the first group of the study, stasis in vessels was found in 38.3% of cases, and in the second group, in 40% of cases (Figure 5a; Table 1).

Hemorrhage in alveoli was generally detected in 42.7% of cases. In the first group of the study, hemorrhage in alveoli was found in 19.2% of cases, and in the second group, in 61.8% of cases (Figure 5b; Table 1).

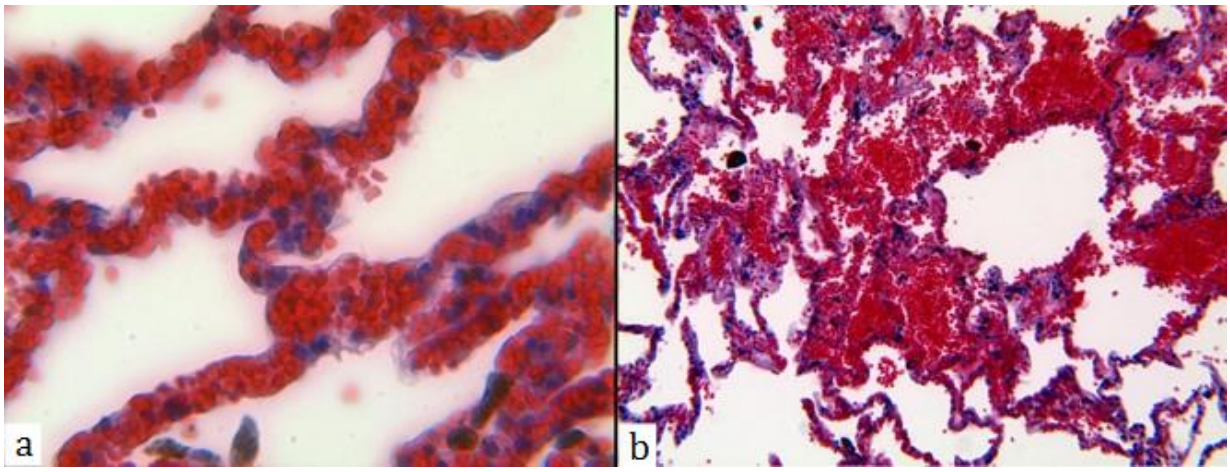

Figure 5. Pathomorphology of pulmonary tissue in fatal hypothermia: a – pronounced stasis in capillaries of interalveolar septums; b – hemorrhage in alveoli. Coloring with haematoxylin and eosin. Zoom x400; 100.

Conclusion

Thus, the results obtained by us coincide with the data of literature [11, 12, 17]. The results of the retrospective analysis showed that pathologic anatomical changes of the lungs of people who died of fatal hypothermia were caused by adaptive compensatory processes. With that, these changes were more pronounced at a slow rate of dying than at a fast rate. At a slow rate of dying, the mucous secretion in the bronchi, pulmonary emphysema, spasm of the bronchi, deposition of mucous secretion in the glands of the submucous base of the bronchi, and "calorific" effect of capillaries of conductive parts of the lungs were most often found. At a fast rate of dying, alveolar edema, stasis in vessels of microcirculation, hemorrhage in alveoli, desquamation of the bronchial epithelium were more often found, which may indicate failure of adaptive processes. At the same time, death from hypothermia often occurred in the presence of background pathology, which imposed a significant imprint on the morphology of hypothermia. The pathomorphological picture was imposed by changes arising from the pathology of the cardiovascular and respiratory systems. In particular, the pronounced fibrosis of vessels and bronchi in some cases did not allow to diagnose the phenomenon of spasm. With severe chronic bronchitis accompanied by massive inflammation in the bronchial wall, contractility of the bronchus was significantly reduced. Emphysema was often present in obstructive bronchitis. Also compensatory emphysema was present in the border zone with areas of pneumosclerosis, pneumonia, and tumor processes. The "calorific" effect of congestion of

bronchial vessels in chronic bronchitis could often be confused with the morphological manifestation of inflammation. Consequently, in death from fatal hypothermia in cases of background pathological processes, the level of severity of pathomorphological indicators characteristic of death from hypothermia decreased, it depended on the nature, severity, and prevalence of the pathological process.

Conflict of interest. The authors declare that there is no conflict of interest.

References:

1. Viter V.I., Stepanyan Yu.S. Concept of "adaptation" at hypothermia. *Problems of examination in medicine.* 2007;1:22-24.

2. Lycheva N.A., Shakhmatov I.I., Kiselev V.I., Bobrov I.P., Lepilov A.V., Dolgatov A.Yu. Pathomorphology of skeletal musculator and microcirculatory vascular bed in experimental hypothermism. *Forensic medicine. Science. Practice. Education.* 2017; 2: 12-16.

3. Dolgatov A.Yu., Bobrov I.P., Lepilov A.V., Kryuchkova N.G., Alymova A.A., Lushnikova E.L., Molodykh O.P. Morphofunctional characteristics of the mast cell population of the liver of white rats by deep immersion hypothermia (experimental research). *Bulletin of Medical Science.* 2018; 3: 24-28.

4. Bobrov I.P., Lycheva N.A., Kryuchkova N.G., Lepilov A.V., Shakhmatov I.I., Dolgatov A.Yu., Osipova A.V., Krasova A.A. Morphofunctional characteristics of nucleolar organizer regions of hepatic cells at the experimental cold stress and in the post hypothermic period. *Modern Problems of Science and Education.* 2018;1:54.

5. Bobrov I.P., Lepilov A.V., Dolgatov A.Yu., Kryuchkova N.G., Fominykh S.A., Shakhmatov I.I., Goryaeva M.V., Alymova E.E. Morphofunctional activity of nucleolar organizers and exchange of ribonucleoproteins in liver cells of white rats under experimental cold stress. *Bulletin of Scientific Conferences.* 2018; 2-1: 13-15.

6. Bobrov I.P., Lepilov A.V., Dolgatov A.Yu., Kryuchkova N.G., Fominykh S.A., Shakhmatov I.I., Goryaeva M.V., Alymova E.E. Mast cells of skeletal musculature of white rats in deep experimental hypothermia. *Bulletin of Scientific Conferences.* 2018; 2-1: 15-17.

7. Bobrov I.P., Lepilov A.V., Guldaeva Z.N., Dolgatov A.Yu., Alymova E.E., Kryuchkova N.G., Lushnikova E.L., Molodykh O.P. The mast cell infiltration of the rats lungs after hypothermia. *Modern Problems of Science and Education.* 2019; 1:8.

8. Bobrov I.P., Lepilov A.V., Dolgatov A.Yu., Kryuchkova N.G., Bakarev M.A., Molodykh O.P. Influence of cooling environment on ploidometric parameters of hepatocytes of white rats. *Bulletin of Experimental Biology and Medicine.* 2019; 2: 163-168.

9. Bobrov I.P., Lepilov A.V., Guldaeva Z.N., Dolgatov A.Yu., Alymova E.E., Sosedova M.N., Kryuchkova N.G., Orlova O.V., Lushnikova E.L., Bakarev M.A., Molodykh O.P. Morphofunctional characteristics of the mast cell population in the lungs of rats after an once and repeated deep immersion hypothermia. *Modern Problems of Science and Education.* 2019; 2:162.

10. Os'minkin V.A. On forensic medical assessment of adaptation processes in the respiratory system at the action of low temperatures. *Informational letter 1211/01-05 dated 16.10.2000.*

11. Os'minkin V.A., Os'minkin S.V. The compensatory and adaptive reactions of the respiratory system as the diagnostic criteria for histological studies in forensic medicine. *Forensic Medical Expertise.* 2015; 3: 12-16.

12. Viter V.I., Pugovkin V.V., Yurasov V.V., Kulbitsky B.N., Pokotilenko V.G., Filippenkova E.N. *Morphological diagnostics of cold trauma*. M.: Korina-ofset; 2012: 96.

13. Os'minkin V.A. Pathomorphology of the lungs at death from hypothermia. *Forensic Medical Expertise.* 1987; 3: 44-47.

14. Os'minkin V.A. Histomorphological changes of lung tissue at death from hypothermia. *Forensic Medical Expertise.* 1988; 3: 27-28.

15. Shapovalenko N.S., Dorovskikh V.A., Tseluyko S.S., Slastin S.S., Zhou X.D., Li Q. Morphofunctional changes in rats trachea at cold stress against reamberin and eleutherococcus introduction. *Bulletin Physiology and Pathology of Respiration*. 2011; 39: 33-39.

16. Os'minkin V.A. Some morphological features of pulmonary tissue characterizing the rate of hypothermia. *Forensic Medical Expertise.* 1990; 3: 13-15.

17. Chudakov A.Yu. Compensatory changes of lung tissues in acute general deep overcooling. *Morphology.* 1999; 3: 18-21.

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RADIOFREQUENCY ABLATION AND TRADITIONAL PHLEBECTOMY IN PATIENTS WITH PRIMARY VENOUS DISEASE

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The aim of the study was to compare clinical features of patients with primary venous disease (varicose disease) in surgical treatment with the use of radiofrequency ablation of the great saphenous and small saphenous veins and different variants of traditional phlebectomy. The retrospective study included 308 patients of different clinical classes of venous disease: varicose disease. Patients were divided into 2 groups depending on the use of the endovascular (radiofrequency ablation) or the traditional method of eliminating reflux on the great saphenous vein. It is shown that in surgical treatment of varicose disease the use of various surgical technologies of venous reflux elimination should be individualized.

Key words: *varicose disease, crossectomy, stripping, radiofrequency ablation of the great saphenous vein.*

Primary venous disease (varicose disease – VD) affects 25% of the adult population of developed countries [1]. Crossectomy in combination with the great saphenous vein (GSV) stripping remains the main method of treatment of this disease [2]. However, the "open" surgical technique is aggressive and requires long recovery. Since the 1990s, endovascular methods have been introduced into clinical practice, they are performed from the vein lumen without anatomical dissection of veins. The radiofrequency technique uses a radiofrequency catheter with ultrasonic navigation. The catheter heats the vein wall, and the increased temperature causes the destruction of intima and media with contraction, thickening, and damage of collagen. This leads to temporary occlusion of the vein lumen. The technique uses tumescent local anesthesia for additional vein compression, which enhances the effects of radiofrequency ablation (RFA) [3]. Until 2006, the first generation catheter (ClosurePlus) was used, which provided heating of tissue up to 85°C. The second generation catheter (ClosureFAST) heats the tissue up to 120°C and produces more heat. With its use, the procedure includes segmental ablation with 20-second cycles.

Comparison of results of treatment of patients with the use of the traditional technique and RFA was carried out on precisely selected groups of patients, usually with the low class of venous disease according to CEAP [6]. Hence, in the European and Russian clinical recommendations with relevant amendments, endovascular methods (RFA) are preferred [4, 5]. Therefore, the aim of the study was to compare clinical features of patients with VD in surgical treatment with the use of RFA of the great saphenous and small saphenous veins and different variants of traditional phlebectomy.

Materials and methods

The work is based on the data of a retrospective study, which includes 308 patients (308 limbs) with varicose disease. Patients were operated in the KSBHI "Altai Regional Cardiologic Dispensary", the clinical base of the Department of Faculty Surgery named after Professor I.I. Neimark and Hospital Surgery with the course of FVE. Patients were divided into 2 groups. In the first group (96 patients; 31.2%), the reflux elimination on the GSV using the RFA technology was carried out. In the second group (212 patients; 68.8%), crossectomy and stripping of the GSV were performed with the use of traditional surgery technologies (Figure 1).

The technique of operation of traditional phlebectomy consisted of high ligation and removal (stripping) of the GSV using the Bebkokk probe. Depending on the preoperative ultrasound data, the short (to the upper third of the crus) or the long (to the ankle) stripping was performed.

The technique of RFA consisted in preoperative mapping of the GSV or the small saphenous vein (SSV), determining its location. Further, in the upper third of the crus under ultrasound control, a puncture of the GSV was carried out, and through the introducer, the ClosureFAST catheter was inserted to saphenofemoral or saphenopopliteal anastomosis. Then, after tumescent anesthesia, ablation of the GSV or SSV was carried out. Varicose tributaries to the crus and thigh were removed using the open technique or "microphlebectomy" with Müller hooks.

The data of the study are represented by mean values and absolute numbers. Frequency of a trait between groups was compared using tests of fourfold tables.

There were no differences by sex and age in the groups of operated patients (Table 1). The mean age was more than 50 years; more than 60% of

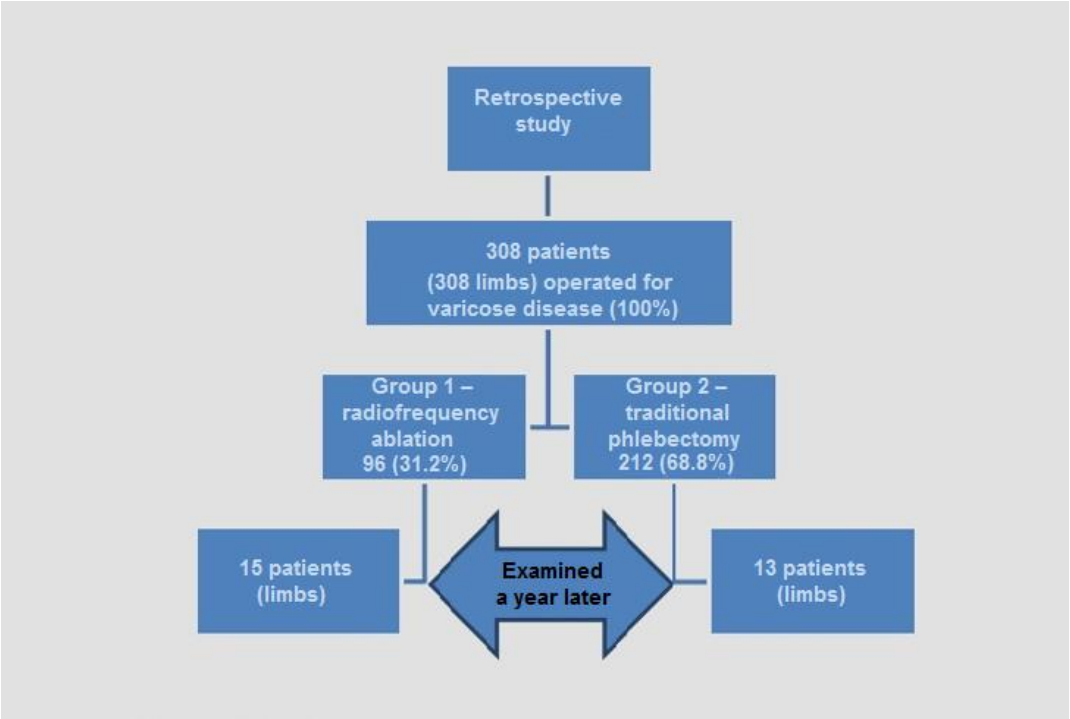

Figure 1. Scheme of retrospective study.

patients in both groups were women. The types of surgery are presented in Table 2. As can be seen from the table, after the elimination of reflux on the GSV, additional removal of tributaries was carried out. The technique of microphlebectomy was used more often, it allowed to achieve the best cosmetic result and accelerate rehabilitation of patients. In patients with traditional phlebectomy, the long stripping was often used.

Table 1

Characteristics of operated patients

Trait	Groups of patients				p
	The first one		The second one		
	abs number	%	abs number	%	
Sex					
male	30	31.2	68	32.1	0.612
female	66	68.8	144	67.9	
Total	96	100.0	212	100.0	
Mean age (years)	50.0±13.9		54.9±13.5		0.602

Table 2

Types of surgery in groups of operated patients

"Target" veins under removal	Groups of patients				p
	The first one		The second one		
	abs number	%	abs number	%	
GSV + "open" removal of tributaries	10	10.4	174 Short stripping – 48 Long stripping – 125	82.1 22.6 59.0	0.00001
GSV + microphlebectomy	80	83.3	19	9.0	0.00001
SSV	6	6.2	19	9.0	0.742
Total	96	100.0	212	100.0	

Results and discussion

The study of clinical features of patients with different variants of reflux elimination techniques for the GSV was carried out taking into account clinical classes of venous disease according to CEAP classification [6]. The first group of patients with clinical class C_{2-3} contained 19.1% (p=0.001) more than the second group (Table 3). Clinical class C_4 among patients of the first group was found by 15% less frequently (p=0.036).

Table 3

Frequency of types of surgery in groups of analyzed patients with different classes of venous disease

Clinical classes of venous disease, CEAP, 2004 [1]	Groups of operated patients				p
	The first one		The second one		
	abs number	%	abs number	%	
C_{2-3}	80	83.3	137	64.6	0.001
C_4	10	10.4	53	25.0	0.036
C_{5-6}	6	6.2	22	10.4	0.372
Total	96	100.0	212	100.0	

In patients with primary (C_{2-3}) classes of venous disease, RFA was more often performed. These are patients with varicose veins and limb edema who do not have pronounced chronic venous insufficiency (CVI) and a long history of varicose disease. Technically, RFA in these patients was justified by a number of reasons, the main of which was the clinical class. In higher classes of lesion (C_4), traditional phlebectomy was more often used in patients with trophic disorders. These were patients with a more severe degree of CVI. In patients with epithelized or healed trophic ulcer (class C_{5-6}), there was no difference in the frequency of surgery. This is due to the fact that in severe forms of CVI in patients with severe cardiac pathology, RFA was performed as a faster and minimally invasive procedure.

In domestic and foreign literature, considerable attention is paid to the issues of comparative evaluations of RFA and traditional surgery. For this purpose, based on the design of the study (Figure 1), remote results of surgery after a year were selected to be studied using the VCSS scale (Venous Clinical Severity Score), proposed by the research group of the American Venous Forum [7]. The average VCSS score before and after surgery did not have a statistically significant difference in the groups of analyzed patients (Table 4). Therefore, the method of eliminating the pathological reflux on the GSV did not affect the long-term results.

Table 4

Remote results of radiofrequency ablation and traditional surgery in patients with varicose disease

Indicator	Sample of group 1 (n=15)		Sample of group 2 (n=13)		p_{1-3}	p_{2-4}
	1	2	3	4		
	Before surgery	After surgery	Before surgery	After surgery		
VCSS (X±n)	1.31±0.31	0.51±0.27	1.42±0.34	0.64±0.28	0.132	0.241

Note: VCSS – Venous Clinical Severity Score.

In the recently published works, there were no differences in relapses of the disease, recanalization, neovascularization, technical errors and the need for repeated operations, indicators of quality of life (questionnaires CIVIQ2, SF-36, CEAP — VCSS), and duration of stay in the in-patient hospital [8, 9]. In the Cochrane review published by Nesbitt C, 2014 [10], there was no difference in early and late postoperative complications. Such data are given in the domestic work by Burleva E.P., published in 2018 [11]. In fact, there is no difference in major clinical evaluations between RFA and traditional phlebectomy, except for faster rehabilitation. The choice between surgical intervention and minimally invasive methods is limited in terms of efficiency or safety, so the relative cost of treatment becomes one of the decisive factors. High quality evidence, randomized clinical trials are needed to confirm and further communicate the results [12].

Thus, the widespread introduction of endovascular technologies (RFA) in the treatment of VD is justified. However, research show that the use of the method is preferable for patients with

primary classes of venous disease with mild CVI. With more severe venous lesions, traditional surgery remains a method of choice.

Conclusions

1. In surgical treatment of VD, the use of various surgical technologies of venous reflux elimination should be individualized.

2. Of all patients with VD with different clinical classes of the disease, 31.2% of patients can carry out endovascular treatment (RFA).

Conflict of interest. The authors declare that there is no conflict of interest.

References:

1. Evans CJ, Allan PL, Lee AJ, et al. Prevalence of venous reflux in the general population on duplex scanning: the Edinburgh Vein Study. *J Vasc Surg.* 1998;28:767-76.

2. Zolotukhin I.A., Bogachev V.Yu., Kuznetsov A.N. Stem phlebectomy in varicose disease. *Flebologiya*. 2007;1:8-14.

3. Perrin M. Traitement chirurgical endovasculaire des varices des membresinférieurs. Techniques etrésultats. *Tech Chir Chir Vasc.* 2007;43(161 C). doi:10.1016/S0246-0459(07)43331-7.

4. Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg.* 2015;49:678-737. doi: 10.1016/j.ejvs.2015.02.007

5. Russian clinical recommendations for diagnosis and treatment of chronic vein diseases. *Flebologiya*. 2018;3:1-96.

6. Eklöf B, Rutherford RB, Bergan JJ, Carpentier PH, Gloviczki P, Kistner RL, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. *J Vasc Surg*. 2004;40(6):1248-52.

7. Vasquez MA, Rabe E, McLafferty RB, Shortell CK, Marston WA, Gillespie D, et al. Revision of the venous clinical severity score: Venous outcomes consensus statement: Special communication of the American Venous Forum Ad Hoc Outcomes Working Group. *J Vasc Surg*. 2010;52(5):1387-96. doi: 10.1016/j.jvs.2010.06.161

8. Rasmussen LH, Lawaetz M, Bjoern L, Vennits B, Blemings A, Eklof B. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins. *Br J Surg*. 2011;98(8):1079-87. doi: 10.1002/bjs.7555.

9. Lurie F, Creton D, Eklof B, Kabnick LS, Kistner RL, Pichot O, et al. Reprinted article "Prospective randomised study of endovenous radiofrequency obliteration (closure) versus ligation and vein stripping (EVOLVeS): two-year follow-up". *Eur J Vasc Endovasc Surg*. 2011;42 Suppl 1:S107-13. doi: 10.1016/j.ejvs.2011.06.019.

10. Nesbitt C, Bedenis R, Bhattacharya V, Stansby G. Endovenous ablation (radiofrequency and laser) and foam sclerotherapy versus open surgery for great saphenous vein varices. *Cochrane Database Syst Rev*. 2014;(7):CD005624. doi: 10.1002/14651858.CD005624.pub3.

11. Burleva EP, Tyurin SA, Smirnov OA, Faskhiev RR. Comparative 3-year results of phlebectomyand thermal ablation for lower limb varicose veins. *Angiol Sosud Khir*. 2018;24(2): 82-91.

12. Van der Velden SK, Lawaetz M, De Maeseneer MG, Hollestein L, Nijsten T, van den Bos RR; Members of the Predictors of Endovenous Thermal Ablation Group. Predictors of Recanalization of the Great Saphenous Vein in Randomized Controlled Trials 1 Year After Endovenous Thermal Ablation. *Eur J Vasc Endovasc Surg*. 2016;52(2):234-41. doi: 10.1016/j.ejvs.2016.01.021.

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ASSESSMENT OF PERINATAL RISK IN PREGNANT WOMEN WITH A UTERINE SCAR

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The relative risk of adverse perinatal outcome (RR) was assessed in 200 women with singlet pregnancy and a uterine scar after a single caesarean section.
Statistically significant factors of perinatal risk in the presence of a uterine scar were established: maternal age of 30 years and more (RR=1.53; 95% CI 1.02–2.29, p=0.042), chronic nicotine dependence (RR=1.86; 95% CI 1.18–2.91, p=0.007), intergestational interval of 2 years or less (RR=1.81; 95% CI 1.21–2.72, p=0.004), presence of three or more abortions in the history (RR=1.98; 95% CI 1.28–3.06, p=0.002). The uncomplicated course of this pregnancy significantly reduced the perinatal risk (RR=0.34; 95% CI 0.12–1.0, p=0.05).
Verification of perinatal risk factors in combination with ultrasonic markers of the state of the fetoplacental system can be used in choosing the method of delivery in pregnant women with a uterine scar after a single caesarean section.
Key words: *pregnancy, uterine scar, perinatal risk factors.*

Despite a large number of scientific studies and practical recommendations for the management of pregnancy and childbirth in women with a uterine scar after caesarean section, such aspect of the problem as the impact of the uterine scar on perinatal outcomes is not sufficiently reflected in the literature. Considering the caesarean section as a gentle method of delivery for the fetus, it should be remembered that the course of the prenatal period is significantly determined by the state of health of the woman, including the state of her reproductive organs, and the uterus after caesarean section is an anatomically deficient organ. It is known that perinatal risk factors are numerous and diverse, reliable prediction of perinatal outcomes for the choice of delivery method requires not only clinical assessment, but also determination of predictors of placental dysfunction [1, 2, 3]. However, at the present stage of the development of obstetrics, to justify the possibility of vaginal delivery in women after the previous caesarean section, clinical and ultrasonic criteria of scar consistency are mainly evaluated [4, 5]. At the same time, in order to choose the method of delivery in the interests of the fetus, it is advisable to conduct an in-depth assessment of perinatal risk in pregnant women with a uterine scar.

The aim of the study was to assess the perinatal risk in women with a uterine scar after a single caesarean section in the lower uterine segment.

Materials and methods

The analysis of the course and outcome of pregnancy in 200 women with a uterine scar after a single caesarean section in the lower uterine segment was conducted; women were separated into two groups depending on the condition of newborns. Group I (n=68) consisted of women with adverse perinatal outcomes: antenatal fetal death, premature birth, birth of full-term babies with the intrauterine growth retardation syndrome of hypotrophic or hypoplastic type, diseases of posthypoxic genesis (or their combination). Group II (n=132) included women who gave birth to healthy full-term babies. Only cases of singlet pregnancy in women without decompensated somatic diseases were included in the study. The age of pregnant women was from 20 to 42 years. All women were examined in full in accordance with the order of the Ministry of Health of the Russian Federation No. 572n "On approval of the procedure for delivery of health-care services on the profile "obstetrics and gynecology (except for the use of assisted reproductive technologies)" and were delivered in the "Perinatal Center (Clinical) of Altai Krai" during 2017-2018.

Statistical processing of the results was carried out using the computer program MedCalc 9.1.0.1. The results are presented in the form of M values (arithmetic mean value) ±σ (mean square deviation). The critical level of significance was taken ≤0.05. The assessment of risk factors for adverse perinatal outcome in uterine scar was based on the analysis of more than 50 potential predictors and was carried out using the MedCalc 9.1.0.1 program through fourfold conjugation tables, where one of the indicators was the case of adverse perinatal outcome. The effect of each particular factor was assessed by the relative risk (RR). To demonstrate the connection strength, 95% confidence interval (CI) for RR was calculated.

Results and discussion

The reason for the division of patients into clinical groups was the analysis of the condition of newborns, which allowed us to establish that premature births took place in 23 cases (11.5% of the total number of observations) in the framework of our study. Intrauterine growth retardation (estimated by G.M. Dementieva and E.V. Korotkova, 1981) of hypotrophic type was registered in 21 newborns, of hypoplastic type in 6 children, including one newborn with intrauterine growth retardation of degree II and one child with degree III of severity. Anthropometric indicators of full-term children of group I were significantly lower: the average body weight was 2973.3±436.7 g (in group II: 3438.1±373.4 g, p<0.0001), the average body length 50.3±2.4 cm and 52.2±1.9 cm (p<0.0001). In group I of women, the number of newborns with a body weight of 4000 g or more was 1.5% (one child), in group II – 3.8% (5 children, p=0.642). In our study, one case of perinatal mortality (antenatal fetal death at week 29 of pregnancy) occurred. The Apgar scale of the state of newborns for the first minute after birth showed that only half of the children (35 newborns, or 52.2%) in group I and all 132 children in group II (100%, p<0.0001) had a satisfactory functional condition and were evaluated by 7–9 points. The average score on the Apgar scale in group I was 6.2±1.3 points, in group II: 8.2±0.5 points (p<0.0001). The dominant nosological form determining the morbidity of newborns in group I was the hypoxic ischemic central nervous system damage, which was registered in 42 (62.7%) newborns. Respiratory disorders with respiratory failure of I-II degree were observed in 28 children (41.8%), including 23 pre-term newborns with respiratory distress syndrome and 5 full-term children with transient tachypnea. In addition, 6 children (9.0%) of group I had intrauterine pneumonia. 35 children (52.2%) were transferred to the second stage of treatment.

The assessment of perinatal risk factors revealed a number of social and clinical anamnestic features of women with a uterine scar, who gave birth to sick children: age characteristics, features of their social status, obstetric parity, and obstetrical and gynecological history. The average age of pregnant women of group I was 31.6±5.4 years, women of group II – 30.3±4.5 years (p=0.056), in group I, the majority were women aged 30 years and more (63.2% and 47.7%, p=0.05). When assessing the social status, an increase in the proportion of housewives in the group of women with unfavorable perinatal outcomes was found (51.5% and 35.6%, p=0.044), while the number of females of vocational profession (32.4% and 39.4%, p=0.406) and employees (16.2% and 25.0%, p=0.214) were comparable.

49 patients of group I (72.1%) and 111 pregnant of group II (84.1% p=0.068) were in registered marriage, 12 and 16 patients respectively (17.6% and 12.1%, p=0.397) in actual marriage, 7 women of group I and 5 pregnant women of group II (10.3% and 3.8% respectively, p=0.129) gestated pregnancy out of wedlock.

The number of women with chronic nicotine dependence was significantly higher in group I (10 patients, which is 14.7%) than in group II (7 women, i.e. 5.3%, p=0.047).

Analysis of somatic burden did not reveal significant differences in the compared groups. Chronic infectious and inflammatory diseases of the urinary tract were registered in 20.5% of patients of group I and 19.7% of group II (p=0.958), chronic arterial hypertension in 7.4% and 6.8% (p=0.182) respectively, thyroid diseases in 8.8% and 10.6% (p=0.878), periconceptional obesity in 10.3% and 20.5% (p=0.105), chronic infectious and inflammatory diseases of ENT-organs and respiratory organs – in 14.7% and 7.6% (p=0.182). The undifferentiated connective tissue dysplasia syndrome (according to criteria of T.Yu. Smolnova et al., 2003) [6] was revealed in 16.2% of pregnant women of group I and 9.8% of women of group II (p=0.275). The proportion of somatically healthy women in the compared groups was 19.2% and 26.5% respectively (p=0.332).

This pregnancy was the second in 29 women of group I (42.6%) and in 72 patients of group II (54.5%, p=0.148), the third in 18 (26.5%) and in 31 (23.5%, p=0.769) patients, the fourth and more in 21 (30.0%) and in 29 (22.0%) women respectively (p=0.229). A history of 26 patients of group I (38.2%) and 47 women of group II (35.6%, p=0.836) suffered from induced abortions. Spontaneous miscarriages were also recorded in comparison groups with the same frequency (25.0% and 26.5%, p=0.953). At the same time, the proportion of women with three or more abortions in the history (both induced and spontaneous) was significantly higher in the group of patients with adverse perinatal outcomes and amounted to 14.7% (in group II 4.5%, p=0.025). The proportion of women with spontaneous births in the history of the compared groups was comparable (19.1% and 13.6%, p=0.416), but premature births (20.6% and 10.6%, p=0.086) and perinatal losses in the history (10.3% and 7.6%, p=0.704) were slightly more common in pregnant women of group I.

The gynecological history of women of the compared groups was characterized by a comparable proportion of hormone-dependent diseases (uterine fibroid, endometriosis, menstrual disorders), which were detected in 15 patients of group I (22.6%) and in 23 women of group II (17.4%, p=0.540), and chronic infectious and inflammatory diseases of the genitals (5.9% and

7.6% respectively, p=0.878).

The intergestational interval after the first caesarean section was from one to 14 years (on the average, 5.1±4.5 years in group I and 5.4±3.5 years in group II, p=0.804). The interval of up to two years was observed in 15 women of group I (22.1%) and 12 patients of group II (9.1%, p=0.019), from 3 to 5 years – in 26 (38.2%) and 64 pregnant women 48.5%, p=0.216) respectively, from 6 to 9 years – in 14 pregnant women of the first group (20.6%) and in 34 of the second group (25.8%, p=0.522), 10 years and more – in 13 (19.1%) and in 22 (16.6%) patients respectively (p=0.807). In the previous pregnancy, 40 patients (58.8%) of group I and 84 women (63.6%) of group II were delivered in emergency order; 28 (41.2%) and 48 (36.4%) women (p=0.611) respectively on a regular basis. Indications for operative delivery did not differ significantly in the compared groups (Table 1).

Table 1

Indications for caesarean section in women with a uterine scar with the previous pregnancy

Indications	Perinatal outcomes				p
	Adverse (n=68)		Favorable (n=132)		
	Abs.	%	Abs.	%	
Anomalies of labor activity	20	29.4	48	36.4	0.405
Pelvic presentation	13	19.1	25	18.9	0.876
Intrauterine hypoxia of the fetus	9	13.3	21	15.9	0.781
Preeclampsia and eclampsia	8	11.8	15	11.4	0.881
Premature detachment of a normally positioned placenta (PDNPP)	6	8.8	6	4.5	0.367

Analysis of the course of gestation showed that uncomplicated pregnancy was much more common in women who gave birth to healthy children (4.4% and 15.9%, p=0.032). The frequency of gestational complications, such as threatened abortions (32.4% and 23.5%, p=0.237), threatening premature birth (29.4% and 24.2%, p=0.532), and moderate preeclampsia (8.8% and 3.0%, p=0.149), was slightly higher in group I of women. Anemia was recorded in 12 (17.6%) women of group I and in 36 women of group II (27.3%, p=0.178), hypertension without proteinuria caused by pregnancy was detected with identical frequency (11.8% and 10.6%, p=0.985).

The most significant differences were found in assessing the condition of the fetoplacental system according to the results of Doppler velocimetry in the II and III trimesters of pregnancy: placental dysfunction with hemodynamic disorders in the "mother–placenta–fetus" system was detected in 32 (47.0%) women of group I and in 44 (33.3%) pregnant of group II (p=0.082). In both groups, disorders of uteroplacental circulation prevailed (38.2% and 28.0%, p=0.189), but the specific weight of disorders of fetoplacental circulation was higher in pregnant women of group I (Table 2). In addition, in women of group I, intrauterine growth restriction was more often recorded by ultrasound results (14.7% and 0.8%, p=0.0002), as well as intrauterine hypoxia of the fetus according to the results of cardiotocography (8.8% and 0%, p=0.0025).

Table 2

Specific weight of signs of placental dysfunction in women with a uterine scar depending on the perinatal outcome

Signs	Perinatal outcomes				p
	Adverse (n=68)		Favorable (n=132)		
	Abs.	%	Abs.	%	
Decrease in uteroplacental blood flow	26	38.2	37	28.0	0.189
Decrease in fetoplacental blood flow	6	8.8	7	5.3	0.516
Intrauterine growth restriction by ultrasound results	10	14.7	1	0.8	0.0002
Intrauterine hypoxia of the fetus	6	8.8	0	0	0.0025
Polyhydramnios	9	13.2	18	13.6	0.888
Oligohydramnios	7	10.3	6	4.5	0.202

43 women of group I (63.2%) were delivered by operative means, planned caesarean section was performed in 31 pregnant women (45.6%), emergency one – in 12 (17.6%). 25 (36.8%) women of group I and 32 (24.2%) of group II (p=0.088) had vaginal delivery. In group II, caesarean section was performed in 100 (75.8%) women, among them, 86 pregnant women (65.2%) in the planned order (p=0.012 compared to group I). Thus, in the framework of our study, it was found that in the group of women who gave birth to healthy children, planned caesarean section was more frequent.

In 10 pregnant women of group I (14.7%) and 14 in group II (10.6%, p=0.538), there was an outflow of amniotic fluid before the beginning of labor activity, which in some cases served as an indication for emergency operative delivery. In three cases, the indication for emergency caesarean section in pregnant women of group I was suspected failure of a uterine scar according to the results of ultrasound, although no clinical signs of scar failure (local soreness, blood discharges) were registered in any of the observations.

In general, the attempt of vaginal delivery was made in women of group I significantly more often (30 pregnant women, or 44.1%) than in pregnant women of group II (34 patients, i.e. 25.8%, p=0.014). Analysis of vaginal delivery of patients with a uterine scar (n=64) showed that the deviations from the normal course of childbirth had decisive importance in choosing an operative method of delivery in emergency order: premature rupture of membranes and absence of spontaneous labor activity during 6–12 hours of observation, abnormalities of labor activity, intranatal fetal stress.

The data obtained in our study show that many clinical and anamnestic factors influence the perinatal risk in the presence of a uterine scar. The factors moderately influencing the increase in risk are the 4th or more current pregnancy (RR=1.34; 95% CI 0.89–2.01, p=0.154), perinatal losses in the history (R=1.24; 95% CI 0.89–2.26, p=0.493), and a number of somatic diseases. The presence of chronic somatic infectious and inflammatory diseases (diseases of the urinary system, ENT-organs and respiratory organs) increased the perinatal risk by 1.3 times (RR=1.27; 95% CI 0.86–1.89, p=0.231), the undifferentiated connective tissue dysplasia syndrome – by 1.4 times (RR=1.41; 95% CI 0.87–2.29, p=0.160). At the same time, the absence of extragenital pathology in the mother moderately increased the probability of birth of a healthy child (RR=1.14; 95% CI 0.93–1.41, p=0.213). In addition, almost all gestational complications led to an increase in perinatal risk: threatened abortion (RR=1.33; 95% CI 0.89–1.98, p=0.166), threatening premature birth (RR=1.18; 95% CI 0.78–1.79, p=0.421), hypertensive disorders during pregnancy (RR=1.59; 95% CI 1.03–2.45, p=0.034). In the absence of gestational complications during this pregnancy, a significant reduction in perinatal risk was observed (RR=0.34; 95% CI 0.12–1.0, p=0.05). Statistically significant perinatal risk factors in the presence of a uterine scar are presented in Table 3.

Table 3

Perinatal risk factors in women with a uterine scar

Sign	RR	95% CI	p
Maternal age 30 years and more	1.53	1.02–2.29	0.042
Housewife	1.53	1.04–2.24	0.031
Chronic nicotine dependence	1.86	1.18–2.91	0.007
Intergestational interval of 2 years or less	1.81	1.21–2.72	0.004
3 or more abortions in the history	1.98	1.28–3.06	0.002
Premature birth in the history	1.59	1.03–2.45	0.034
Complications of a current pregnancy, total	2.95	1.01–8.66	0.048
Including:			
Early toxicosis	1.97	1.21–3.22	0.007
Hypertensive disorders during pregnancy, total	1.59	1.03–2.45	0.034
Moderate preeclampsia	1.84	1.07–3.17	0.029
Intrauterine growth restriction by ultrasound results	2.96	2.29–3.94	<0.0001
Hemodynamic disorders in the “mother–placenta–fetus” system	1.48	1.01–2.17	0.046

As can be seen from the table, a reliable connection of perinatal risk is established with the maternal age of 30 years and more, short intergestational intervals, smoking, and the presence of three or more abortions (both spontaneous and induced) in the history. The meaningful perinatal risk factors were early toxicosis (the risk doubled) and moderate

preeclampsia: the relative risk of an adverse perinatal outcome in the presence of this complication increased by 1.9 times. In addition to gestational complications, the perinatal risk was largely associated with factors such as the detection of intrauterine growth restriction by ultrasound diagnosis and hemodynamic disorders in the "mother–placenta–fetus" system; these factors increased the relative risk of the birth of a sick child by 3 and 1.5 times respectively.

The results obtained in the course of the study showed that the perinatal risk increases due to not only antenatal, but also intranatal factors. The risk of adverse pregnancy outcome for the fetus and the newborn increased moderately with premature (prenatal) outflow of amniotic fluid (RR=1.26; 95% CI 0.75–2.12, p=0.375) and was associated with vaginal delivery in the presence of a uterine scar: the perinatal risk increased by 1.5 times (RR=1.46; 95% CI 0.98–2.15, p=0.055).

The presented analysis allows us to conclude that adverse perinatal outcomes in women with a uterine scar were associated with various and numerous anamnestic and clinical risk factors, which is consistent with the literature data [1, 7].

Our study also found that 47 pregnant women in group I (69.1%) had a combination of two or more statistically significant perinatal risk factors. This fact suggests that the conduction of vaginal delivery in these women, even in the presence of a consistent uterine scar, maximizes the risk of the birth of a sick child and determines the expediency of performing repeated caesarean section in the planned order.

Conclusion

Currently, the problem of vaginal delivery in women with a uterine scar is far from being resolved. The choice of optimal timing and methods of delivery in patients with a uterine scar after caesarean section presents significant difficulties and should be made individually in each case. Verification of perinatal risk factors can help in choosing the method of delivery of a pregnant woman with a uterine scar, which should be determined by both the consistency of the scar and the risk of vaginal delivery for the fetus.

The main clinical and anamnestic factors of perinatal risk in the presence of a uterine scar are the maternal age of 30 years and more, intergestational interval of 2 years or less, presence of three or more abortions (both spontaneous and induced) in the history, smoking, complicated course of the current pregnancy.

Verification of perinatal risk factors in combination with ultrasonic markers of the state of the fetoplacental system can be used in choosing the method of delivery of a pregnant woman with a uterine scar after a single caesarean section.

Conflict of interest. The authors declare that there is no conflict of interest.

References:

1. Radzinsky V.E., Knyazev S.A., Kostin I.N. *Obstetric risk: Maximum information – minimum danger for mother and baby*. Moscow: Eksmo; 2009: 288.

2. Igitova M.B. *Prediction, diagnosis and treatment of gestational complications in women with high perinatal risk*: author's abstract of dissertation... of the Doctor of Medical Sciences. Moscow; 2010.

3. Igitova M.B., Dmitrienko K.V. Prediction of adverse perinatal outcomes based on determination of placenta growth factor. *Mother and Baby in Kuzbass*. 2014; 4(59):38-41.

4. Bolotova O.V. *Improvement of diagnosis of uterine scar condition after caesarean section*: author's abstract of dissertation... of the Candidate of Medical Sciences. Moscow; 2011.

5. Sinitsyna S.S., Kravchenko E.N., Rubleva G.F., Vladimirova M.P., Kuklina L.V. Natural delivery in women with a scar on the uterus. *Mother and Baby in Kuzbass*. 2018;1(72):64-67.

6. Smolnova T.Yu., Buyanova S.N., Savelyeva S.V. et al. Phenotypic symptom complex of connective tissue dysplasia in women. *Clinical medicine*. 2003;8:42–48.

7. Igitova M.B. *High risk pregnancy (clinical and pathogenetic aspects).* Barnaul: Regional Reference and Information Pharmaceutical Center; 2013: 124.

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SOCIAL ASPECTS AND CLINICAL CHARACTERISTICS OF COMMUNITY-ACQUIRED PNEUMONIA IN CHILDREN OF ALTAI KRAI

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The clinical and social characteristics of 172 children with community-acquired pneumonia aged from 6 months to 17 years are given. The analysis of premorbid social and obstetric perinatal risk factors in children with pneumonia was carried out. 70 children were diagnosed with uncomplicated pneumonia, 102 patients were diagnosed with pneumonia with pulmonary and pleural complications. In the structure of pulmonary and pleural complications, pleuritis took the first place, it was revealed in 56.9% of patients, destruction of the lung was noted in 33.3% of patients, pneumothorax was diagnosed in 11.7% of patients, pyothorax was found in 9.8% of patients. In some children, combined pulmonary and pleural complications were revealed. Patients with complicated pneumonia in the clinic were dominated by toxic syndrome, and more pronounced inflammatory changes were noted in blood tests.
It was found that pneumonia with pulmonary and pleural complications was more likely to be acquired by children under artificial feeding, with concomitant atopic and/or allergic diseases, with unfavorable social conditions, having mothers with extragenital pathology and/or pregnancy pathology.
Key words: *community-acquired pneumonia in children, premorbid factors, clinical characteristic, pulmonary and pleural complications.*

Inflammatory lung diseases in children are one of the topical problems of modern pulmonology and pediatrics in general. The urgency of the problem is due to the fact that the bronchopulmonary system diseases occupy one of the leading places in the pathology of childhood, and the course of the disease is characterized by clinical features, as well as by a high risk of complications and adverse outcomes [1, 2, 3]. According to statistical data, the pneumonia morbidity remains quite high in Altai Krai and the Siberian Federal District [4]. Lung diseases largely determine the mortality structure in different age groups, especially in newborns and children of the first year of life [1, 2, 4, 5, 12]. Community-acquired pneumonia requires the appointment of complex and antibacterial therapy, and pneumonia with pulmonary and pleural complications is included in the group of high thrombogenic risk, as part of the patients with complicated pneumonia reveal various disorders of various links of the hemostasis system, the severity of which depends on the degree of activity of the disease [5, 6, 7, 8].

The risk groups for the development of pyoinflammatory complications in community-acquired pneumonia in children are patients with low immune function as a result of various predisposing and premorbid factors [10, 11]. Risk factors can be divided into two groups: firstly, it is the state of health of the mother (early and/or late toxicosis of pregnancy, threats of termination of pregnancy, intrauterine infections and bacterial infections, anemia and/or other somatic diseases of the mother during pregnancy, social and financial situation of parents). Secondly, it is the presence of concomitant background diseases and the somatic status of the child (asphyxia and morphofunctional immaturity at birth, anemia of various severity, rachitis, hypotrophy, atopic diseases, early transfer to artificial feeding) [3, 5, 9, 10, 11, 12]. The presence of a variety of social and/or premorbid factors in children with pneumonia, as well as other somatic diseases, contributes to a more severe course of community-acquired pneumonia in children with possibility of development of pulmonary and extrapulmonary complications [5, 7, 10, 11].

Pyoinflammatory complications in lung diseases in children occur at different periods of the disease. This leads to the need to identify and analyze possible predisposing social and premorbid factors, as well as to identify other background somatic diseases that may increase the risk of development of pulmonary and/or extrapulmonary complications in pneumonia, especially in young children [3, 5, 7, 10].

The research objective was to identify and analyze predisposing social, obstetric, perinatal and other premorbid risk factors in children of Altai Krai with community-acquired pneumonia, as well as to assess the possible impact of these factors on the severity of the disease.

Inclusion criteria are the following**:** 1) children with pneumonia aged from 6 months to 17 years; 2) the study was carried out in a prospective mode

with the written consent of parents for examination and treatment of children with community-acquired pneumonia.

Exclusion criteria are the following: 1**)** presence of congenital malformations of the bronchopulmonary system and/or intercurrent diseases; 2) refusal of patient's parents from examination and treatment.

Materials and methods

In order to achieve the study objective, we examined 172 children aged from 1 to 17 years, including 92 (53.5%) boys and 80 (46.5%) girls. All patients were treated in the departments of Pulmonology, Pediatric Surgery and Resuscitation of the KSBHI "Altai Regional Clinical Children's Hospital" and the KSBHI "Children's City Clinical Hospital No. 7 of the city of Barnaul" during 2010–2017.

All patients with community-acquired pneumonia were examined, the survey included: examination of the patient; collection of history of life and history of the disease; identification of features of obstetric and social history; general and biochemical blood tests; chest X-ray in direct and side projection. In order to study the social status, we used data from the family history (survey) of parents. Statistical data were processed using the StatSoft Statistica 5.0 application program package.

In the general group of the examined (172 children), there was a predominance of right-sided pneumonia, which was revealed in 107 (62.2%) children. We diagnosed left-sided pneumonia only in 48 (28%) patients. Only 17 (9.8%) children had the bilateral lung disease. In the general group of patients with pneumonia, the average age was 3.6±0.48 years, the distribution by age groups was as follows: from 1 to 3 years – 106 (61.7%) children, from 4 to 6 years – 28 (16.2%) children, from 7 to 17 – 38 (22.1%) patients.

In our work, we used the international classification of diseases of the tenth revision. According to the results of the study, we formed two groups of patients: the first group included 70 children diagnosed with uncomplicated pneumonia, which accounted for 40.6% of the total number of surveyed. The second group consisted of 102 children who had pneumonia with pulmonary and pleural complications, accounting for 59.4% of the total number of patients.

In the group of patients with uncomplicated pneumonia, the average age was 3.31±0.32 years. Of these, 47% were boys and 53% were girls. The distribution by age groups was as follows: from 1 to 3 years – 46 (65.7%) patients, from 4 to 6 years – 14 (20%) children, from 7 to 17 – 10 (14.3%) patients.

Boys dominated the group of children with complicated pneumonia: boys – 57%, girls – 43%. The distribution by age was the following: from 1 to 3 years – 54 (52.9%) children, from 4 to 6 years – 18 (17.6%) children, from 7 to 17 years – 30 (29.5%) patients. In both the first and second groups of patients with community-acquired pneumonia, children aged 1 to 3 years (65.7% and 52.9% respectively) prevailed.

Results and discussion

We conducted a comparative analysis of data of history, clinical and laboratory data, obstetric and perinatal, as well as social risk factors in all children with community-acquired pneumonia. It was revealed that in the group of patients with uncomplicated pneumonia, urban residents prevailed: 63 (90%) children, while in the group of children with complicated pneumonia, the majority of surveyed were rural residents: 71 children (69.6%). The proportion of the urban population with complications was only 30.4%. Thus, pulmonary and pleural complications were twice more often diagnosed in rural residents.

When analyzing the social status, we paid attention to the family members, lifestyle, the presence of work and bad habits of parents. Upon that, we found that among patients with complicated pneumonia, with pulmonary and pleural complications (group 2), both parents had jobs in only 25% of patients, and the number of unemployed families was 32%, which was significantly different from the data of the first group (with uncomplicated pneumonia), where we have not identified unemployed families, and the share of families where both parents have jobs was 48% ($p<0.01$), which indicates the difference in the material wealth of the families of the first and second groups of patients. We noted that the majority (91%) of children with uncomplicated pneumonia were from two-parent families. We found that in the group of children with pulmonary and pleural complications, the proportion of two-parent families was 52%, and the number of children from single-parent families (when the child was raised by one parent) was 48% ($p<0.01$). We analyzed the frequency of smoking parents in both groups of children with community-acquired pneumonia. The negative effects of nicotine on the fetus and the physical development of the child are known for a fact. Nicotine also has an adverse effect on the course of pneumonia, and in some children, the course of pneumonia may be complicated by bronchial obstruction syndrome. During the examination, we found that more than 2/3 of children with complicated pneumonia were passive smokers, while in children with uncomplicated pneumonia, the share of smoking parents was only 25%. Thus, we have identified significant differences in social status and material wealth from the place of

residence of children (city, village) with different course of community-acquired pneumonia.

In comparing the data of obstetric and gynecological history of mothers of both groups of patients, we also noted significant differences. Thus, in mothers of the second group of patients (with pulmonary and pleural complications), obstetric and perinatal risk factors (pathology of pregnancy, early and late toxicosis, threatened miscarriages, intrauterine infections and bacterial infections during pregnancy), as well as other somatic diseases of the mother (chronic pyelonephritis, anemia, VVD, etc.) occurred significantly more frequently in 82% cases. At the same time, mothers of patients with uncomplicated pneumonia (group 1) had obstetric and perinatal risk factors and other somatic diseases in only 32% of cases ($p<0.01$).

The clinical course of diseases in children is influenced by the nature of feeding and the presence of concomitant background diseases. When collecting the history of life and disease, we noted significant differences in the nature of feeding children with community-acquired pneumonia. Children of the first group with uncomplicated pneumonia were naturally fed for 7.2±1.3 months, while in patients with pulmonary and pleural complications (group 2), the duration of breastfeeding averaged 3.6±0.6 months, which significantly differed from the duration of breastfeeding in patients with uncomplicated pneumonia ($p<0.01$). According to literature data, the presence of allergies and/or atopic diseases is one of the aggravating factors contributing to the development of severe complications in various somatic diseases in children [5, 10, 11]. During the examination of children with community-acquired pneumonia, we noted significant differences in the presence of food and/or drug allergies, as well as various atopic diseases between the first and second groups of patients. Allergy to medicines, food products and/or atopic diseases were observed in 18% of patients with uncomplicated pneumonia, while in patients with complicated pneumonia, this pathology was detected in 56% of cases ($p<0.01$). In our opinion, the pathology of pregnancy and childbirth, concomitant somatic diseases, presence of allergies and atopic diseases, as well as the nature of feeding, are one of the factors influencing the formation of immunity. Thus, children with low immune function, from families with low social status, who were previously artificially fed, with a severe obstetric history, and the presence of concomitant atopic or other background diseases were more likely to suffer from pneumonia.

Clinical characteristics of the first group of patients. Analysis of the clinical course of uncomplicated pneumonia revealed that more than 75% of children examined were admitted to hospital with suspected pneumonia with catarrhal and/or toxic syndromes. In the first three days of the disease, pneumonia was diagnosed in 97% of patients in the first group. Nasopharynx catarrhal phenomena and cough were observed in all patients, in 2/3 of patients, the toxic syndrome was one of the main clinical implications of uncomplicated pneumonia. The increase in temperature was observed in 98% of children, with that, febrile temperature was registered in 70% of patients, increase in body temperature to subfebrile figures was noted in 28% of the examined. In physical examination, shortening of percussion sound and/or weakening of breathing was revealed in 72% of patients of the first group. During auscultation, hard breathing was observed in 96% of the patients surveyed, the presence of small-bubble rales in 45% of children, medium-bubble rales in 25% of patients, crepitations in 16% of patients. Thus, local, percussion and auscultatory symptoms typical for pneumonia were observed in 80% of children of the first group without significant differences between sex and age subgroups.

The conducted X-ray examination in two projections allowed us to diagnose focal pneumonia in 56% of patients of the first group, focal confluent – in 31% of patients, segmental – in 3%, and polysegmental pneumonia – in 10% of those surveyed. By localization, in 91% of cases, there was a one-sided character of the process, bilateral process was diagnosed only in 9% of patients. Bilateral localization of the process was more common in young children ($p<0.01$).

Thus, the clinical course of uncomplicated pneumonia in the patients examined was accompanied by catarrhal phenomena, fever, and symptoms of intoxication. Local physical changes in the lungs were observed in only 80% of patients. According to chest radiography, inflammatory infiltration was mainly focal, with right-sided localization in most of the examined.

Clinical characteristics of the second group of patients (with the presence of pulmonary and pleural complications). Analysis of the course of the disease in these patients allowed to establish that 77 (75.5%) children were admitted to specialized departments on the 4–7 day from the onset of the disease. From the history, it was established that in a significant part of children (70%) nasopharynx catarrhal phenomena prevailed in the disease onset. Pneumonia was diagnosed in the first three days in only 41 (40.2%) patients. In the remaining patients (59.8%), the diagnosis of pneumonia was made later; in the group of patients with complicated pneumonia, residents of rural areas prevailed. As we found, the late request for qualified medical care was the

reason for the untimely diagnosis of the disease.

At admission to hospital, the main clinical implications of pneumonia with pulmonary and pleural complications in children were: the toxic syndrome, which is registered in all children of the second group, and cough, which is also detected in 100% of patients. The course of complicated pneumonia was accompanied by dyspnea in 93% of patients; dyspnea was observed much more often in children of early age compared to children of school age. We observed an increase in temperature in 98% of patients with pulmonary and pleural complications. At the same time, febrile fever was established in 73% of the examined, the increase in body temperature to subfebrile figures was observed in 25% of patients.

During the lung X-ray in two projections, most patients with pulmonary and pleural complications revealed right-sided pneumonia. In the structure of pulmonary complications, pleuritis took the first place, it was detected in 58 (56.9%) of 102 children, lung destruction was detected in 34 (33.3%) patients, pneumothorax was diagnosed in 12 (11.7%) patients, pyothorax was detected in 10 (9.8%) of 102 patients. It should be noted that some patients found a combination of various pulmonary and extrapulmonary complications. Shortening of percussion sound and weakened breathing were observed in 100% of patients with complicated pneumonia. By auscultation, small-bubble rales were heard in 53% of patients, medium-bubble rales – in 28% of children, the presence of crepitation was established in 22% of patients, and only 16% of patients had dry rales. Some patients in the dynamics of the disease revealed assorted wet and/or dry rales. Clinically, the combination of local percussion and auscultatory symptoms was observed in 100% of patients with pulmonary and pleural complications. In most of the patients examined, the course of complicated pneumonia was characterized by fever, symptoms of intoxication with respiratory failure, characteristic auscultatory data, and inflammatory changes in the general blood test.

We conducted a comparative analysis of laboratory indicators in children with different course of community-acquired pneumonia. One of the markers of inflammatory reaction in pneumonia is the level of C-reactive protein, the increase of which is caused by the current acute inflammatory process. We found that the level of CRP (16.44±0.26 mg/ml) in children with complicated pneumonia was significantly higher ($p \leq 0.05$) than in uncomplicated pneumonia (5.53±0.17 mg/ml). When interpreting the laboratory data, we revealed reliable differences in the indicators of the general blood test in different groups of patients with community-acquired pneumonia. So, peripheral blood indicators were inflammatory only in 2/3 of patients with uncomplicated pneumonia (group 1). In children (group 1), leukocytosis was registered in 57% of cases, neutrophilia – in 53% of patients, leukopenia was revealed in 17% of children, lymphocytosis was noted in 5% of the examined patients. Increased ESR (20.2±4.2 mm/h) was detected in 52 (74.3%) of 70 patients, mild anemia (Hb 101.4±6.2 g/L) was diagnosed in 8 (11.4%) of 70 patients, more often iron deficiency anemia (IDA) was detected in young children.

Most patients with pulmonary and pleural complications (group 2) showed more pronounced inflammatory changes in the general blood test. Leukocytosis was detected in 65% of patients, left-shift neutrophilia was observed in 92% of cases, leukopenia was detected in 5% of those surveyed. Of 102 patients with complicated pneumonia, 92 (90.2%) showed an acceleration of ESR (32.3±3.6 ml/h), which was more typical for bacterial pneumonia**.** We diagnosed iron deficiency anemia in 60 (58.8%) of 102 patients with complicated pneumonia. This includes: IDA of mild severity (Hb 98.4±3.2 g/L) was detected in 38 (37.2%) patients; IDA of moderate severity (Hb 80.4±4.3 g/L) was diagnosed in 19 (18.6%) patients; severe anemia (Hb 64.4±2.2 g/L) was detected in 3 (2.9%) of 102 surveyed.

In the analysis of the obtained data, it was established that the severity of inflammatory changes in blood and the presence of IDA in the patients examined depended on the severity of the course of pneumonia, the presence or absence of pulmonary and pleural complications. Thus, the level of CRP in pulmonary and pleural complications was three times higher than this indicator in children with uncomplicated pneumonia (16.44±0.26 mg/ml and 5.53±0.17 mg/ml respectively) ($p<0.01$). Indicators of ESR were also significantly different, acceleration of this indicator was found in 74.3% of patients with no complications and in 90.2% of patients (20.2±4.2 mm/h and 32.3±3.6 ml/h respectively) with pulmonary and pleural complications ($p<0.01$). The presence of iron deficiency anemia is a background disease and worsens the course of pneumonia, it is also significantly more often detected in the group of children with pulmonary and pleural complications than in the group of patients without complications (in 58.8% and 11.4% of patients respectively) ($p \leq 0.01$).

A clinical examination of patients with community-acquired pneumonia has revealed that pneumonia with pulmonary and pleural complications is more likely to occur in children with the low immune function, who were previously artificially fed, from families living in rural areas, with low and/or unfavorable social and living conditions, children with anemia, rachitis,

atopic and/or allergic diseases, whose mothers had a somatic and/or extragenital pathology, whose pregnancy had various obstetric and perinatal risk factors. The presence of concomitant background diseases in children with community-acquired pneumonia, as well as the above predisposing social and/or premorbid factors increases the risk of lung diseases and contributes to the more severe course of pneumonia with the possible development of pulmonary and pleural complications.

Conflict of interest. The authors declare that there is no conflict of interest.

References:

1. Sorokina E.V., Ilyina E.S., Mizernitsky Yu.L. et al. Analysis of fatal cases from respiratory diseases in children. *Pulmonology of childhood. Problems and solutions*. 2003;3:33-35.

2. Lyutina E.I., Manerov F.K. Morbidity and mortality of community-acquired pneumonia in children and adolescents living in Kuzbass region. *Pediatria.* 2015;2:203-206.

3. Dorokhov N.A. *Clinical and laboratory characteristics of uncomplicated and complicated pneumonia in children*: dissertation ... of the Candidate of Medical Sciences. Barnaul; 2017.

4. *The main indicators of health of the population and health care of the Siberian Federal District in 2013. Collected volume of statistical and analytical materials. Issue 13.* Ed. O.V. Strelchenko. Novosibirsk; 2014: 298.

5. Li T.S., Lobanov Yu.F., Vykhodtseva G.I. et al. *Pneumonia in children. Pulmonary and extrapulmonary complications*. Barnaul; 2009: 121.

6. Volkova Yu.V., Sidorenkova N.B., Terskikh S.M. Analysis of antibacterial therapy of community-acquired pneumonia in children at the outpatient stage. *Medical Review. Science and Practice*. 2015;Appl.3:20-21.

7. Skudarnov E.V., Dorokhov N.A., Malyuga O.M., Seroklinov V.N., Mironenko I.I. Factors of thrombogenic risk in children with community-acquired pneumonia. *Tromboz, gemostaz i Reologia*. 2018;2(74):36-40.

8. Dorokhov N.A., Skudarnov E.V., Antropov D.A. Features of reaction of coagulation hemostasis system in children with pneumonia. *Bulletin of the East Siberian Scientific Center of the Siberian Branch of the Russian Academy of Medical Sciences*. 2016;1(1):12-15.

9. Mashina N.S., Galaktionova M.Yu. Influence of breastfeeding of children of the first year of life on formation of health (experimental study). *Postgraduate Doctor*. 2014;66(5):194-198.

10. Dorokhov N.A., Skudarnov E.V., Antropov D.A., Boyko A.V., Dauletova Ya.A. Effect of premorbid factors on the clinical course of community-acquired pneumonia in children. *Mother and Baby in Kuzbass*. 2016;1(64):45-49.

11. Skudarnov E.V., Dorokhov N.A., Malyuga O.M., Seroklinov V.N. Social and clinical aspects of community-acquired pneumonia in children. *Pediatric Bulletin of the South Ural.* 2017;1:67-71.

12. Cherkasova T.M., Remneva O.V., Nesterov Yu.N., Chugunova T.N., Nevskaya O.V. Obstetric and perinatal risk factors of intrauterine pneumonias. *Russian Pediatric Journal*. 2008;3:11-13.

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PROGRESSIVE EXTRAUTERINE PREGNANCY OF 40.4 WEEKS AFTER RUPTURE OF THE RUDIMENTARY UTERINE HORN WITH EXIT OF THE FETUS INTO THE ABDOMINAL CAVITY: CASE OF CLINICAL OBSERVATION

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Ectopic pregnancy is a life-threatening complication of the gestational process. Diagnosis of rare forms of ectopic pregnancy has certain difficulties, so every clinical case is of interest to obstetrician-gynecologists. The case of proper observation of progressive extrauterine pregnancy of 40.4 weeks after rupture of the rudimentary uterine horn with exit of the gestational sac into the abdominal cavity is presented. The operation and tactical approaches to the management of this case are described.
Key words: *ectopic pregnancy, extrauterine pregnancy, pregnancy in the rudimentary horn, abnormality of uterus development.*

According to modern statistics, every 10th patient (9.5%) admitted to the gynecological hospital has extrauterine (ectopic) pregnancy, which in the vast majority of cases (96.5–98.5%) is represented by pregnancy of tubal localization [1, 2].

Rare varieties of this pathology include ovarian, abdominal pregnancy and pregnancy in the rudimentary (embryonal) uterine horn, the frequency of which does not exceed 0.1–0.9% [1, 3].

During ontogenesis, the uterus and the vagina develop as a result of fusing of two Müllerian ducts. In case of delay of development of one of them, formation of the unicornuate uterus with an underdeveloped (rudimentary) horn occurs. The embryonal horn usually does not have cavitary anatomical communication with the main uterus, it is connected with it by means of a solid muscular peduncle, detaching from the uterus at the level of the bottom or the internal orifice [1, 4].

Compared to other localizations of ectopic pregnancy, in the rudimentary uterine horn, there are more favorable conditions for implantation of a gestational sac due to the fact that the mucous membrane of the embryonal horn is more complete than, for example, in a tube. On the other hand, the lack of a well-developed vascular network and the predominance of connective tissue over the muscular one significantly limit the possibility of long-lasting pregnancy prolongation. As a result of progressive growth of the gestational sac, there is a gradual perforation of the muscle layer with chorionic villi, thinning of the wall, and rupture of the embryo invagination at the short term of pregnancy (most often in 8–16 weeks) [1, 2, 5]. Diagnosis of pregnancy localized in the rudimentary horn most often occurs during surgery after the development of intraabdominal bleeding. At the same time, the literature describes isolated cases of progression of ectopic pregnancy before the term of physiological maturity of the fetus [6].

Taking into account the low prevalence of this nosology, the difficulties of diagnosis and the high numbers of maternal mortality in such localization of the gestational sac (7-8 times higher than in tubular, and 90 times higher than in the uterine) [7], each clinical case of pregnancy development in the rudimentary uterine horn is of considerable practical interest.

Clinical case (proper observation):

Pregnant Z., 32 years old. The current pregnancy is II, upcoming childbirth is I. In the history, there is I uncomplicated medical abortion in 2012. Z. considers herself somatically healthy, vegetarian. In 2012, she once appealed to a gynecologist with complaints of minor pain in the lower abdomen, conservative therapy was carried out for ovarian cyst on the left. The menstrual function is not disturbed, there are no symptoms of algodismenorrhea. The last menstruation was from 10.06.16 to 14.06.16.

During the current pregnancy, Z. was not subjected to regular medical check-up, ultrasound was not carried out. According to oral information provided, the pregnancy proceeded without complications, there were no pathological secretions from the genital tract. She went to the obstetrician-gynecologist of the private clinical and diagnostic center of Barnaul on the 20 of March 2017 for the first time in connection with the absence of labor activity in a full-term pregnancy. During ultrasound, central placental presentation

with pronounced morphological changes (the true placenta in-growth and trophoblastic disease cannot be excluded), absolute oligohydramnios were diagnosed.

20.03.17 at 17:30 in an urgent order, she was delivered by the emergency medical service team to KSBHI "Perinatal Center (Clinical) of Altai Krai" from an outpatient visit. When admitted, she complained about moderate discomfort and pain feelings in the abdomen with active fetus movements. The characteristics are: height 162 cm, weight 73.6 kg, belly of the spherical shape, AC – 105 cm, FH – 35 cm, transverse lie of the fetus, head of the fetus on the left. During the external examination, parts of the fetus are well palpable, attention is drawn by active (subcutaneous) fetus movement. The fetal heartbeat is listened, rhythmic, 140 bpm.

According to ultrasound: transverse lie of the fetus, EFW – 4045 grams, placenta completely fulfills the lower segment, large in area, sharply thickened (up to 100 mm), myometrium in the lower segment of the uterus is not determined clearly due to sharply enlarged vessels and vascular lacunas performing the projection of the lesser pelvis. The uterine cervix is not differentiated, it is a conglomerate of sharply enlarged vessels. The muscular tissue in the uterine body area is located indistinctly (the presence of only serosal layer cannot be excluded), amniotic fluid is not present. Conclusion: A full-term pregnancy. Big fetus. Central placental presentation with signs of placenta percreta (the presence of vascular invasion as a result of trophoblastic disease is possible). Abdominal pregnancy is not excluded.

According to Doppler velocimetry and CTG data, the functional state of the fetus is compensated. The laboratory examination revealed signs of moderate severity anemia (Hb – 87 g/L). Taking into account the suspicion of trophoblastic disease, a blood test for HCG was taken (the level corresponds to a full-term pregnancy).

With the results of the survey, the pregnant woman was examined in consultation. During the discussion, the presence of central placental presentation in the patient with signs of placenta percreta and invasion in the uterine cervix was recognized to be the most probable obstetric pathology. Taking into account the high risk of massive obstetric blood loss, it was decided to carry out operative delivery on a regular basis on 21.03.17. Estimated volume of operation: bottom caesarean section followed by total hysterectomy.

On 21.03.17, under the conditions of the Cell Saver 5+ device, the lower midline incision was performed. In the abdominal cavity, there is no liquid blood and pathological effusions. The free space of the abdominal cavity is occupied by a safe fetal bladder with a live, full-term fetus in a transverse position. Fetal membranes are sharply thickened, cloudy, of greenish color. There is little amniotic fluid (about 400 ml); in the amnion cavity, there is a large amount of thick meconium (Figure 1, 2).

In the course of the umbilical cord, it was found that the placenta is located in the lower pole of the fetal bladder, thick (about 6 cm) and has an area of attachment with a diameter of 15 cm.

After careful removal of the safe fetal bladder with the fetus from the abdominal cavity, it was found that the embryo invagination is connected with a non-pregnant uterus (located in the lesser pelvis and enlarged to 8 weeks) by means of muscular band 3*3*1.5 cm, departing from the left tubal angle (probably, rudimentary uterine horn) (Figure 3). Left appendages are flattened along the lower pole of the fetal bladder and are not separate anatomical formations. Unaltered right appendages depart from the right tubal angle of the non-pregnant uterus. There are single planar adhesions of the greater omentum with the body of the non-pregnant uterus.

Outside the operative wound, the fetal membranes were opened instrumentally, a live full-term girl weighing 4160 grams, 56 cm long, was extracted, with an assessment on the Apgar score of 4/8 points.

Figure 1. Safe fetal bladder with a full-term fetus.

Figure 2. Little amniotic fluid (about 400 ml); a large amount of thick meconium in the amnion cavity.

Figure 3. Connection of the embryo invagination with a non-pregnant uterus by means of muscular band 3*3*1.5 cm, departing from the left tubal angle.

After ligation and crossing of round and IP ligaments on the left, counter clamps were applied on the muscular peduncle. Embryo invagination together with the inseparable placenta and left appendages were cut off sharply. In the left angle area, there were no penetrating defects of muscle tissue and additional stroke in the non-pregnant uterus. On the left border of uterus, a pronounced vascular network was determined by the type of malformation. The stump of the muscular peduncle was stitched with separate vicryl sutures. When sewing, the uterus tissue was cut, abundantly diffusely bled. Full hemostasis was achieved after ligation of the uterine artery ascending branch on the left and local hemostasis with applying absorbable hemostatic tightly woven tissue from oxidised regenerated cellulose (Figure 4). Total blood loss was 900 ml.

Figure 4. Ligation of the uterine artery ascending branch on the left and local hemostasis with applying absorbable hemostatic tightly woven tissue from oxidised regenerated cellulose.

Gross specimen: embryo invagination (probably, rudimentary uterine horn) with placenta, membranes, and the uterine tube. The placenta was tightly attached to the wall of the lower pole, it was tearing when trying to separate (there might be villi in-growth).

During histological examination: the wall of the embryo invagination was is represented by dense tissue consisting of necrotic chorionic villi of all generations (stem, supporting, intermediate, terminal), embedded into massive deposits of fibrinoid and fibrin with lime deposits. In a more detailed study, the connection was found between the necrotic placenta tissue and a very narrow muscle layer in which fibrinoid deposits and thophoblast invasion were determined. There was no decidual membrane. The presence of fragments of muscle tissue in the wall of the embryo invagination was a confirmation of the existing rudimentary uterine horn.

Thus, in retrospective understanding of the fact of intraoperative discovery, it is possible to assert that in pregnant Z. 32 years old there was a congenital anomaly of development of genital organs in the form of the rudimentary uterine horn without anatomical communication with the main uterus. Morphological structural inferiority of tissues of the rudimentary horn led to its hyperextension with subsequent violation of the integrity of the embryo invagination, the exit of the gestational sac into the abdominal cavity with the formation of secondary abdominal pregnancy.

The uniqueness of this case is determined not only by the full development of the fetus outside the uterus before the full-term pregnancy, but also by the absence of massive intraabdominal bleeding at rupture of the rudimentary uterine horn, most likely associated with the tamponade of the resulting defect by the tissues of the greater omentum. During the repeated detailed collection of the history, it was established that in the period of pregnancy about 12 weeks the patient noted short-term spastic pains in the abdomen, irradiating to the right supraclavicular region, which indicates signs of irritation of the diaphragm nerve due to intra-abdominal distress.

P.S. When conducting ultrasound of the genital organs and the lesser pelvis in 1 month, the ultrasound picture corresponded to the norm of the postpartum period. There were no deviations in the development and health of the newborn.

Conflict of interest. The authors declare that there is no conflict of interest.

References:

1. Makarov R.R. *Extrauterine pregnancy*. Leningrad: Medgiz; 1958: 128.

2. Radzinsky V.E. *Obstetric aggression*. M.: Mediabureau StatusPraesens; 2017: 250.

3. Satybaldina B.A., Espaeva R.N., Iskakova A.M., Sagalbaeva U.E., Zhaksylykova M.A. Clinical cases of rare forms of ectopic pregnancy. *Vestnik KazNMU*. 2016;1: 20-23.

4. Radzinsky V.E., Fuks A.M. *Gynecology*. M.: GEOTAR-Media; 2014: 708-731.

5. Kurtser M.A. *Emergency conditions in obstetrics and gynecology. Diagnosis and treatment*. M.: Binom. Laboratory of Knowledge; 2009: 57-63.

6. Liskovich V.A., Egorova T.Yu., Naumov I.A. Full-term pregnancy in the rudimentary uterine horn: case of clinical observation. *Journal of the Grodno State Medical University*. 2005;1:71-74.

7. Volgina V.F., Volkovitskaya V.V. Ectopic pregnancy as a cause of maternal mortality. *Russian Bulletin of Obstetrician-Gynecologist*. 1997;2: 23-25.

8. Buyanova S.N., Shchukina N.A., Chechneva M.A. Abdominal pregnancy. *Russian Bulletin of Obstetrician-Gynecologist*. 2014;5:71-74.

9. Demidov V.N., Sarkisov S.E., Demidov A.V. Abdominal pregnancy: Clinical picture, diagnosis, outcomes. *Obstetrics and Gynecology*. 2014;12:94-99.

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CHROMOSOMAL ANALYSIS OF BLOOD LYMPHOCYTES IN PATIENTS WITH MIXED INFECTION OF TICK-BORNE ENCEPHALITIS AND HUMAN GRANULOCYTIC ANAPLASMOSIS

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The aim of the study was to assess the cytogenetic effects of mixed infection of tick-borne encephalitis and human granulocytic anaplasmosis compared to the corresponding mono-infections.
Materials and methods. In total, 46 patients were examined: 12 with mixed infection, 10 with human granulocytic anaplasmosis, and 24 with tick-borne encephalitis. The age of patients varied from 22 to 46 years. In the examination, a standard method of chromosomal analysis of blood lymphocytes was applied.
Results. It was found that tick-borne infections are accompanied by a statistically significant increase in the level of cytogenetic disorders during the first three months after clinical recovery. Normalization of levels of cytogenetic disorders in patients with mixed infection and mono-infection of tick-borne encephalitis was observed 6 months after clinical recovery. In patients with human granulocytic anaplasmosis mono-infection, it occurred 1 month after hospitalization. It is shown that a particularly high level of cytogenetic disorders was observed in the initial period of the disease. Most of the aneuploid cells were hypoploid. The most frequently missing chromosomes are those of groups D and G. Chromatid breaks were the predominant type of structural disorders of chromosomes.
Key words: *chromosome aberrations, tick-borne encephalitis, human granulocytic anaplasmosis, mixed infection.*

In recent decades, tick-borne infections have become one of the most urgent infectious diseases in almost all regions of the Russian Federation. The consequences of these natural focal infections for Siberia are particularly serious. In our previous studies [1], for the first time in our country, it was found that the virulent strain of tick-borne encephalitis virus can induce in vitro a significant increase in the number of aneuploid cells and cells with chromosome aberrations. If radiation and chemical mutagens are studied fairly well, the mutagenic effects of infections are studied only sporadically. For this reason, there is no clear understanding of mechanisms of their mutagenic effects. In addition, the effects of this cytogenetic instability in a person who has suffered an infectious disease have not been studied, making it difficult for any scientifically based medicogenetic forecast.

Currently available information on the cytogenetic consequences of tick-borne infections does not allow to answer the question that arises in the process of rehabilitation of the patient: how quickly and in what time occurs the restoration of cytogenetic homeostasis of the body in a sick person.

The aim of the study was to assess in the dynamics the cytogenetic effects in patients with mixed infection of tick-borne encephalitis and human granulocytic anaplasmosis compared to the corresponding mono-infections.

Materials and methods

A total of 46 patients were examined, including 12 patients with mixed infection, 10 with mono-infection of human granulocytic anaplasmosis, and 24 with tick-borne encephalitis. The age of patients varied from 22 to 46 years. Blood was taken from the basilic vein immediately after hospitalization. Besides, 30, 60 and 180 days after discharge from the hospital, blood was taken again from the same persons. Patients did not receive medication before hospitalization and were not subjected to X-ray examination methods. Diagnosis was established on the basis of positive results of serological tests (enzyme immunoassay), characteristic clinical picture, and epidemiological data. Previously, each surveyed had the informed consent to conduct a cytogenetic study, approved by the ethical committee of the Siberian State Medical University of the Ministry of Health of the Russian Federation. The study conformed to the requirements of the Declaration of Helsinki of the World Association "Ethical Principles for Medical Research Involving Human Subjects" as amended in 2013 and "Rules of Clinical Practice in the Russian Federation", approved by the Order of the Ministry of Health of the Russian Federation of 19.06.2003 No. 266. As a control, a chromosomal test was carried out in 14 healthy blood transfusion donors comparable to the major groups by age and sex. Cultivation of blood leukocytes, preparation of materials for analysis was carried out by standard generally accepted method. Metaphase plates were analyzed using the PrimoStar microscope (Zeiss, Germany)

with zoom of 15×90. At least 100 cells were studied in each patient. All the materials were pre-encrypted. Statistical processing was carried out using the Statistica v. 6.0 software package. The frequency of observed karyopathologies was calculated in The EH Software Program, Rockefeller University, NY (USA). All quantitative indicators of the study were processed using the Student's t-test for independent samples, since testing of distribution law using the Kolmogorov–Smirnov test did not reveal differences from normal. Differences of the compared results (M±m, where M is the sample arithmetic mean, m is the error of the arithmetic mean) were considered valid at the reached significance level $p<0.05$.

Results and discussion

It was found that in patients with mixed infection at the beginning of the disease (1-2 days of hospitalization) the number of cells with cytogenetic disorders was 5.6 times higher than in the group of healthy donors (12.2±2.3% and 2.18±0.49% at $p<0.001$), and in patients with tick-borne encephalitis, it was 3.9 times higher than in control (8.46±1.82 and 2.18±0.49% at $p<0.001$ respectively). In patients with human anaplasmosis, the increase in the number of cells with chromosomal disorders was the smallest compared to control: 1.8 times (3.92±0.22% at $p=0.032$). In all cases, a significant increase in the number of aneuploid and polyploid cells, as well as cells with structural chromosomal disorders is shown. Most of the aneuploid cells were hypoploid. In patients with tick-borne encephalitis and in patients with mixed infection, chromosomes from groups D and G were naturally often missing. Polyploid cells were mostly tetraploid. In control, they could be met very rarely.

In patients with tick-borne encephalitis and in patients with mixed infection, more than half of all chromosome aberrations were chromatid breaks. Chromosome breaks were observed only in some patients. In patients with tick-borne encephalitis and in patients with mixed infection, chromosome 2 was most often affected. Deficiency in the number of violations was observed in chromosomes of groups C, D and E, with no structural chromosome problems in groups F and G at all. An increased number of breaks was found in telomeric areas of long arms of chromosomes of groups A, B, C, and D. In all these cases, the differences between the expected frequency of violations and the observed frequency are true ($p<0.001$). In short arms of most chromosomes, violations were not revealed. A repeated examination of patients with tick-borne encephalitis and patients with mixed infection, conducted 1 month after discharge from the hospital, did not reveal a significant decrease in the number of cells with cytogenetic violations. After 3 months, the majority of those who have been ill begin the process of normalization of levels of cytogenetic disorders compared to control. However, the number of cells with chromatid exchange and aneuploidy in convalescents remains significantly increased ($p=0.014$, $p=0.027$, $p=0.041$ respectively). After 6 months, the frequency of cells with cytogenetic disorders in all groups normalizes to the control level ($p>0.05$). In patients with human anaplasmosis, normalization of karyotype was noted 1 month after hospitalization.

The data show that tick-borne infections, as well as some other infectious diseases, increase the number of cells with chromosomal disorders. Viruses are known to induce the formation of aneuploid and polyploid cells [2]. In patients with tick-borne encephalitis, in hypoploid cells, there were no chromosomes of groups D and G belonging to nucleolus organizer chromosomes. It is shown that chemical and infectious agents inhibiting the decomposition of the nucleus during cell division can influence the processes of divergence of these chromosomes in mitosis [1, 3]. In leukocytes of patients, breaks were localized mainly in telomeric and near-centromeric regions, which are known to be formed by heterochromatin. The obtained data correspond to the generally accepted idea that heterochromatic areas are most sensitive to the effect of most mutagenic factors [2]. This uniformity of observed lesions of chromosomes induced by various infectious agents suggests the presence of some common mechanisms in their occurrence.

In this regard, the most tested hypothesis is the one related to the activity of the immune system, one of the functions of which is the elimination of genetically modified cells from the body [4, 5], thus, normalization of the number of cytogenetically modified cells in the body of a sick person should be expected when restoring the ability of the immune system to support cytogenetic homeostasis of the body.

Conclusion

Tick-borne infections are accompanied by a significant increase in the level of cytogenetic disorders during the first three months after clinical recovery. It was found that tick-borne infections are accompanied by a statistically significant increase in the level of cytogenetic disorders during the first three months after clinical recovery. Normalization of levels of cytogenetic disorders in patients with mixed infection and mono-infection of tick-borne encephalitis was observed 6 months after clinical recovery. In patients with human granulocytic anaplasmosis mono-infection, it occurred 1 month

after hospitalization. It is shown that a particularly high level of cytogenetic disorders was observed in the initial period of the disease. Most of the aneuploid cells were hypoploid. The most frequently missing chromosomes are those of groups D and G. Chromatid breaks were the predominant type of structural disorders of chromosomes.

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References:

1. Ilyinskikh N.N., Ksents A.S., Ilyinskikh E.N. *Micronucleus analysis in the assessment of cytogenetic instability*. Tomsk: Tomsk Pedagogical University, 2011: 312.

2. Ilyinskikh N.N., Ilyinskikh I.N. Effect of tick-borne encephalitis virus on the chromosomes of human cells. *Cytology and Genetics*. 1976;10(4): 331-333.

3. Ilyinskikh NN, Ilyinskikh IN, Ilyinskikh EN. *Infectious mutagenesis (Cytogenetic effects in human and animal cells as well as immunoreactivity induced by viruses, bacteria and helminthes)*. Saarbrucken (Germany): LAP LAMBERT Academic Publishing; 2012: 218.

4. Sullivan KE, Stiehm ER. *Stiehm's immune deficiencies*. Amsterdam: Academic Press (an imprint of Elsevier); 2014: 456.

5. Tsuda YL, Mori Y, Abe T. Nucleolar protein B23 interacts with Japanese encephalitis virus core protein and participates in viral replication. *Microbiol. Immunol*. 2006; 50(3): 225-234.

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DYSPEPSIA SYNDROME AND PATHOLOGICAL CHANGES OF THE UPPER GASTROINTESTINAL MUCOSA IN PATIENTS WITH ACUTE VIRAL HEPATITIS A AND B

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In patients with acute viral hepatitis A and B in clinical practice, the state of the mucosa of the gastroduodenal zone is rarely assessed, despite the presence of a risk of developing acute erosion and ulcers of the upper gastrointestinal mucosa.

Key words: *acute viral hepatitis A, acute viral hepatitis B, mucosa of the gastroduodenal zone, acute erosion and ulcers, dyspepsia.*

Acute viral hepatitis A and B (AVHA and AVHB) are considered to be "amenable" infections. However, under a number of conditions (human-made disasters, military operations, reduction of vaccination and sanitary conditions), they occupy a leading position among infectious diseases [1, 2, 5]. At the same time, an important task of the medical service is to achieve convalescence in patients as soon as possible [9, 10].

The main criteria of convalescence include normalization of the general state, disappearance of dyspeptic manifestations and jaundice, restoration of liver functions according to laboratory parameters. However, a number of factors can lead to a slowdown of clinical and laboratory convalescence, which are rarely taken into account in the clinic of infectious diseases. It is well known that the presence of erosive ulcerative defects of the upper gastrointestinal mucosa in patients with both infectious and non-infectious diseases burdens the course of the main disease and often requires urgent pathogenetic and symptomatic therapy [3, 4, 6, 7, 8, 11]. The development of acute erosions and ulcers is also possible in patients with acute viral hepatitis A against the background of reduced detoxification function of the liver and the development of hypergastrin- and hyperhistaminemia [3, 12].

The study objective was to compare the etiological features of dyspepsia syndrome and pathological changes of the upper gastrointestinal mucosa in patients with AVHA and AVHB.

Materials and methods

126 patients were examined: 82 patients with acute viral hepatitis A and 44 patients with acute viral hepatitis B. The underlying disease was diagnosed on the basis of typical clinical, epidemiological and laboratory data, including marker diagnostics of viral hepatitis. According to the "inclusion/exclusion" criteria, patients without complications and serious concomitant diseases are included in the study.

AVHA proceeded in light and moderate form (45% and 55%), AVHB – in light, moderate and heavy form (29.6%, 38.6%, 31.8% respectively).

During the first days of hospitalization (first 3–10 days from the onset of the disease), all patients after signing the informed consent, except for the standard clinical and laboratory examination, were performed fiberoptic esophagogastroduodenoscopy with a fiberscope of Japanese firm PENTAX model FG-29H with straight optics arrangement according to the standard method.

Calculations were carried out on a DELL 500 portable multimedia computer using a statistical section in the Microsoft Office Excel 2007 for Windows XP spreadsheet and Biostatistica program. For quantitative parameters having a normal distribution, the following indicators were calculated: M as the arithmetic mean, m as the average error of the arithmetic mean. To compare average values, we used the Student's t-test. When working with non-parametric indicators, the χ^2 criterion was used, the analysis of small samples was carried out using the Fisher's exact test. The results were considered statistically significant at the values of the achieved significance level (p) less than 0.05.

Results and discussion

The structure of dyspepsia syndrome in patients with AVHA and AVHB was analyzed in accordance with the Rome II criteria (1998). There were no differences in the structure of dyspepsia syndrome depending on the etiology. Such dyspeptic symptoms as epigastric pain, nausea, vomiting, decreased appetite were revealed with the same frequency both in patients with AVHA and in patients with AVHB (86.6% and 79.6% of patients respectively, χ^2=0.601, p>0.05).

Regardless of the presence or absence of dyspeptic complaints in patients with acute viral

hepatitis A and acute viral hepatitis B, during endoscopic examination, various pathological changes of the mucous membrane of the gastroduodenal zone were revealed in the midst of the disease. In 37.8% of patients with AVHA and 38.6% of patients with AVHB, erosive ulcerative defects of the mucous membrane were revealed on the background of inflammatory phenomena in the stomach and duodenum, the remaining patients had endoscopic signs of superficial, focal gastritis/gastroduodenitis.

The frequency of detection of erosive ulcerative lesions (EUL) of the upper gastrointestinal mucosa was not caused by the etiology and severity of the course of acute viral hepatitis.

In both groups in the first 9 days from the onset of the disease, erosive ulcerative lesions of the mucous membrane were diagnosed more frequently than in the following days. Thus, among 29 patients with AVHA examined in the first 9 days from the onset of the disease, erosive ulcerative defects of the mucous membrane of the gastroduodenal zone (MM of the GDZ) were diagnosed in 16 (55.2%), among 53 patients examined later – in 15 (23.8%), χ^2=4.67, p<0.05. The same pattern was observed in patients with AVHB: in the first 9 days of the disease, EUL of the mucous membrane of the GDZ were diagnosed 2.4 times more often than in the following days. Thus, among 8 patients surveyed in the first 9 days, EUL of the MM of the GDZ were revealed in 6 (75%), among 36 patients surveyed later – in 11 (30.5%), χ^2=3.74, p<0.05.

In the course of the study, we have determined a reliable relationship between the functional state of the liver and the nature of changes of the MM of the GDZ among patients with AVHA and AVHB.

In particular, in AVHA in patients with combined erosive ulcerative pathology, in the midst of the disease, there was a double increase in the level of AST in comparison with patients with isolated erosive ulcerative pathology defects of the duodenal bulb. A significantly lower prothrombin index (PI) was also found in patients with combined gastric and duodenal EUL compared to patients with gastritis/gastroduodenitis (Table 1).

Table 1

The main laboratory indicators in patients with AVHA depending on the localization of erosive ulcerative defects of the mucous membrane of the gastroduodenal zone, M±m

Indicators / Groups		Gastric EUL n=8 I	Duodenal EUL n=16 II	Combined localization EUL n=7 III	P_{I-II}	P_{II-III}	P_{I-III}
AST IU/l	midst	907.2±285.5	579.1±144.2	1381±400.5	p>0.05	p>0.05	p>0.05
	7–10 day	52±34.19	255±142.1	154.6±58.99	p>0.05	p>0.05	p>0.05
	discharge	54.17±8.8	63.75±13.89	108.9±14.25	p>0.05	p<0.05	p<0.01
PI	midst	0.8±0.03	0.87±0.02	0.73±0.03	p>0.05	p<0.001	p>0.05
	7–10 day	0.89±0.03	0.87±0.04	0.81±0.05	p>0.05	p>0.05	p>0.05
	discharge	0.83±0.03	0.88±0.02	0.82±0.04	p>0.05	p>0.05	p>0.05

Thus, a large area of erosive ulcerative lesion of the MM of the GDZ in patients with acute viral hepatitis A is associated with more pronounced AST indicators and a low level of prothrombin index.

Higher rates of ALT activity were found among patients with AVHB with erosive ulcerative pathology than in patients with gastritis/gastroduodenitis, while the mean values of prothrombin index were the same regardless of the presence or absence of erosions and ulcers of the MM of the GDZ (Table 2).

It should be noted that in patients with acute viral hepatitis A and B, the development of acute erosive ulcerative lesions often took place without dyspeptic symptoms. Thus, with acute viral hepatitis A in the presence of dyspeptic complaints, EUL of the upper gastrointestinal mucosa were revealed in 36.6% of patients, in the absence of dyspepsia syndrome – in 45,5% of patients. A similar pattern was observed in patients with AVHB: in the presence of dyspeptic symptoms, erosive ulcerative pathology of the gastroduodenal mucosa was diagnosed in 37.1%, which did not differ significantly from the frequency of detection of EUL of the upper gastrointestinal mucosa in patients without dyspeptic disorders – 44.4%.

Conclusions

1. Patients with acute viral hepatitis A and B experience dyspeptic complaints with approximately the same frequency.
2. Regardless of the presence of dyspepsia syndrome, in a third of patients with AVHA and AVHB, various pathological changes of the upper

Table 2

The main laboratory indicators in patients with AVHB with various pathology of the upper gastrointestinal mucosa, M±m

Indicators / Groups		Erosive ulcerative pathology n=17 I	Gastritis/ gastroduodenitis n=27 II	P_{I-II}
ALT, IU/l	midst	2210±368.4	1233±208.5	p<0.05
	7–10 day	735.4±161.1	568.2±109.4	p>0.05
	discharge	256.9±48.76	204.5±31.36	p>0.05
PI	midst	0.78±0.03	0.82±0.03	p>0.05
	7–10 day	0.84±0.02	0.88±0.02	p>0.05
	discharge	0.85±0.02	0.89±0.02	p>0.05

gastrointestinal mucosa are identified, they have acute character, more often diagnosed in the first 9 days from the onset of the disease, with predominant localization in the duodenum.

3. The overall rate of erosive ulcerative lesions of the gastroduodenal mucosa does not depend on the etiology of acute viral hepatitis, the severity of the underlying disease, the presence or absence of dyspeptic syndrome, which complicates timely diagnosis and emphasizes the crucial role of endoscopic examination in the complex diagnosis of pathology of the upper gastrointestinal tract in such patients.

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References:

1. Lyalyukova E.A., Vershinina M.V., Budarina N.A., Yarkov A.N. *Viral hepatitis*. Ed. G.I. Nechaeva, Yu.V. Belan. - Rostov-on-Don: Fenix; 2007: 125.

2. Zhdanov K.V., Lobzin Yu.V., Gusev D.A., Kozlov K.V. *Viral hepatitis*. St. Petersburg: FOLIANT; 2011: 304.

3. Gubergrits N.B., Lukashevich G.M., Zagorenko Yu.A. Hepatogenic gastropathy and hepatogenic ulcers: an old history that remains new forever. *Art of Treatment*. 2005; 19(3):12-18.

4. Kalinin A.V., Loginov A.F. Symptomatic gastroduodenal ulcers. *Pharmateca*. 2010;2:38-45.

5. Karetkina G.N., Yushchuk N.D. Hepatitis A. *Infectious diseases. National guide*. Ed. N.D. Yushchuk, Yu.Ya. Vengerov. M.: GEOTAR – Media; 2009: 601-613.

6. Kotaev A.Yu. Acute erosions and ulcers of the upper gastrointestinal tract, complicated by bleeding. *Russian Medical Journal*. 2006;14(6): 501-504.

7. Mayer K.-P. *Hepatitis and consequences of hepatitis*. M.: GEOTAR MEDICINE; 1999: 432.

8. Maleev V.V., Martynov V.A., Klochkov I.N. Clinical and endoscopic characteristics of acute erosive ulcerative pathology of the upper gastrointestinal tract in patients with hemorrhagic fever with renal syndrome, leptospirosis and tularemia. *I.P. Pavlov Russian Medical Biological Herald*. 2014;3: 48-55.

9. Podymova S.D. Liver diseases. M.: Medicine; 1998: 704.

10. Yushchuk N.D., Klimova E.A., Znoiko O.O., Karetkina G.N., Maksimov S.L., Martynov Yu.V. et al. Protocol of diagnosis and treatment of patient with viral hepatitis B and C. *Russian Journal of Gastroenterology, Hepatology, Coloproctology*. 2010;20(6): 4-60.

11. Khanevich M.D., Koshevoi A.P. Treatment of bleeding from stomach ulcers and duodenal ulcers in patients with liver pathology. *Grekov's Bulletin of Surgery*. 2003;162(5):109-113.

12. Portincasa P, Moschetta A, Di Ciaula A, Palmieri VO, Milella M, Pastore G, Palasciano G. Changes of gallbladder and gastric dynamics in patients with acute viral hepatitis A. *Eur. J. clin. Invest*. 2001; 31(7): 617-622.

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THE LEVEL OF AWARENESS OF ORTHOPEDIC DENTISTS ABOUT THE METHODS OF OPTIMIZATION OF THE ADAPTATION PROCESS IN PATIENTS TO REMOVABLE DENTAL PROSTHESES

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The article presents the analysis of the results of questionnaires of orthopedic dentists about the methods of optimization of the adaptation process to removable dental prostheses.
Key words: *adaptation, optimization, removable dentures.*

Despite the progressive development and improvement of methods of treatment and technologies used in dentistry, the need of the population for orthopedic care is gradually increasing in recent years. At the same time, the use of removable dentures also increases in relation to the total volume of manufactured orthopedic structures, which is explained by various factors. Due to this trend, the interest in this direction increases, as well as the number of patents for inventions aimed at improving the process of adaptation of patients to removable dental prostheses [2, 3].

However, as experience shows, a large number of patients still refuse to use the manufactured prostheses for one reason or another [1, 4]. In this regard, we have got interested to find out the level of awareness of orthopedic dentists about possible ways of optimizing adaptation to removable dental prostheses.

The work objective was to analyze the results of questionnaires of orthopedic dentists in order to determine their level of knowledge about the methods of optimization of the adaptation process in patients to removable dental prostheses.

Research tasks:

1. To identify the most popular among orthopedic dentists ways to improve the effectiveness of adaptation of patients to removable dental prostheses.
2. To determine the ways of adaptation of patients to removable dentures, the use of which orthopedic dentists eliminate in their practice.

Results and discussion

We conducted a survey of 80 orthopedic dentists of private and outpatient practice in the city of Barnaul. The questionnaire includes nine questions, two of which are grid.

It turned out that all the doctors interviewed recommend adhesives to patients to fix removable dentures. Of these, 76% of orthopedic dentists appoint them, as it should, only in adverse anatomical and physiological conditions, 21% in complete absence of teeth, and 3% always, regardless of the clinical situation.

The most popular forms of adhesive agents are gels and creams (77%). 17% of respondents believe that the properties of adhesive agents do not depend on their form of release. The rest prescribe inserts and powders (6%).

More than half of doctors (56%) do not prescribe physiotherapy treatment in their practice to patients using removable dentures. 19% refuse because of the absence of such a department in the clinic. 22% prescribe the mentioned treatment only in the presence of pathology of the mucous membrane of the prosthetic bed, 3% use it frequently.

48% of orthopedic dentists do not use two-layer bases (bases with elastic back) in their practice, 37% use only in unfavorable anatomical and physiological conditions, 9% at the patient's complaints of pain under the prosthesis basis, 6% as a stage of prosthesis on implants.

The most popular means for hygienic care of prostheses are: cleaning (fast-dissolving) tablets (76%), ultrasonic baths (9%), good polishing of the structure surface (3%). 9% of respondents do not assign anything except standard means and hygiene items (toothpaste and brush).

Most doctors (43%) do not prescribe drugs of systemic action (stress-protective, antioxidant), considering them ineffective. 29% of respondents are of the opinion that their patients will not take them, therefore do not prescribe. 28% appoint them after consultation with the patient's therapist.

Locally, i.e. in the form of applications, drugs are prescribed by doctors in the presence of pathology of the mucous membrane (62%). 25% believe that correction of removable prosthesis will be sufficient. 13% prescribe them both in pathology and for prevention.

The most popular among the drugs of local use, which are prescribed by orthopedic dentists, are: those containing chlorhexidine (40%), keratoplasties (25%), those containing vitamins (11%), combined gels (7%), herbal decoctions (2%),

NSAIDs (2%). 13% of respondents do not conduct any local treatment.

According to the majority of respondents, a significant role in the adaptation process is played directly by the patient (94%). Only 6% of respondents believe that the main role in this process is played by a doctor and a dentist.

Conclusions

1. Most often, to accelerate the process of adaptation of patients to removable dentures, orthopedic dentists recommend the use of adhesives (100%) and preparations of local anti-inflammatory action (75%), among which those containing chlorhexidine (40%), vitamins (11%), and keratoplasties (25%) are preferable.
2. For hygienic care of removable dentures, in addition to toothbrushes and pastes, cleaning, fast-dissolving tablets (76%) are mainly prescribed.
3. Most respondents refuse to use oral drugs, two-layer bases, and physiotherapeutic procedures in their clinical practice to improve adaptation of patients to removable dentures.

Conflict of interest. The authors declare that there is no conflict of interest.

References:

1. Grokhotov I.O.*Optimization of adaptation of elderly people to removable laminar dentures*: author's abstract ... of the Candidate of Medical Sciences. Yekaterinburg; 2015: 26.
2. Zholudev S.E. Features of prosthesis with complete removable dentures and adaptation to them in elderly and senile people. *Ural Medical Journal*. 2012;8:25-31.
3. Zholudev S.E. *Adhesive agents in prosthetic dentistry.* M.: Medical book; 2007: 94.
4. Oreshaka O.V., Ganisik A.V., Grokhotov I.O., Nikulin D.D. Adaptation to removable dental prostheses and ways of its optimization. Barnaul: ASMU; 2014: 25-35.

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