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CONTENTS

A variant of anesthesia for total arthroplasty of the lower extremity joints

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Ermokhina L.V., Ermokhina N.V., Zavarzin A.Yu., Stets V.V.

Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia

Abstract. In this study we sought to optimize analgesia in total joint arthroplasty of the lower extremity and reduce the risk of arterial hypotension in patients with various degrees of obesity. The optimization contributed to the development of a new technique of spinal anesthesia. The technique leads to the epidural volume extension, as well as the decrease of local anesthetic doses administered into the subarachnoid space and saving the level of sensory block.

The aim of the study was to study the effect of the spinal anesthesia with the epidural volume extension technique on the level of sensory block and hemodynamics in patients with various degrees of obesity during total arthroplasty of the lower extremity joints for III stage osteoarthritis. The prospective single-center study included 103 patients (79 men (76.7%), mean age 59±11 years, range from 33 to 74 years) who were treated in the Department of Traumatology and Orthopedics from September 2019 to May 2020. Anthropometric parameters, levels of sensory and motor blocks, level of pain syndrome, sympathetic block, duration of surgery and anesthesia were analyzed. To assess the impact of all factors on the outcome, methods of one-dimensional analysis with the calculation of relative risk (RR) were used. All patients were divided into two groups: the control group (combined spinal-epidural anesthesia was used) and the main group (spinal anesthesia with epidural volume extension was used). The average upper level of the sensor block (Th-segment) at 15 minutes after spinal anesthesia did not significantly differ in the groups (p=0.95). Differences in the frequency of hypotension in the groups were not statistically significant (p>0.05). RR: 1.17 [95% CI: 0.794; 1.726].

Reducing the dose of a local anesthetic by 25% to provide adequate spinal anesthesia with the epidural volume extension in patients with a high body mass index achieves the same result when assessing sensory, motor and sympathetic blockages when compared with the traditional method of anesthesia.

Keywords: spinal anesthesia with the epidural volume extension, combined spinal-epidural anesthesia, hypotension, total joint arthroplasty of the lower extremity.

Introduction. Total arthroplasty of the hip (THA) and knee (TKA) joints is currently considered routine surgical intervention, the aim of which is the functional rehabilitation of patients suffering from osteoarthritis or a femoral neck fracture [1]. Both general and regional anesthesia are used for anesthetic support in the arthroplasty of large joints of the lower extremity [2].

Regional anesthesia methods have their advantages and disadvantages. The positive qualities of spinal anesthesia (SAB) are technical simplicity, rapid effect of anesthesia, high efficiency of antinociceptive protection, but its duration depends on the dose of the local anesthetic used. The advantages of epidural anesthesia include the possibility of fractional administration of anesthetics, no time limit, and effective postoperative anesthesia. However, among the disadvantages of SAB so far are intraoperative hypotension and coronary steal syndrome due to uncontrollable sympathetic block, which is dangerous in patients with concomitant coronary heart disease [3].

At the beginning of the XXI century, the technique of combining spinal and epidural anesthesia in the form of combined spinal-epidural anesthesia (CSE) began to develop [3]. Further development of CSE led to the emergence of a new technique, spinal anesthesia with the expansion of the epidural space, which was initially carried out by epidural administration of local anesthesia after SAB in order to increase the level of the sensory block, if its level was insufficient. In recent years, a saline solution without the addition of a local anesthetic has been used to expand the volume of the epidural space [4].

Thus, the technique of spinal anesthesia with the expansion of the epidural space is currently performed with 0.5% bupivacaine solution, followed by the introduction of 5 to 15 ml saline solution into the epidural space [5]. The main aim of the new anesthetic technique is to use low doses of local anesthesia injected into the subarachnoid cavity without reducing the sensory block level, which allows for the significant reduction of the hypotension risk.

In a study by Takiguchi T. and colleagues, high level of sensory block with low doses (5-7 mg) of local anesthetic was explained by its cranial spread with the expansion of the epidural space with 0.9% NaCl solution in a volume of 10 ml [6]. The study included 20 patients using myelography.

Doganci N. et al. used MRI to study changes in the volume of the dural sac in the lumbosacral area before and after epidural administration of 5, 10 and 15 ml saline solution. The authors found a significant decrease in the volume of cerebrospinal fluid in all three groups, however, when using 10 ml, the decrease in the volume of the dural sac was maximal and amounted to about 25% [4]. Applying the SAB technique with the expansion of the epidural space in orthopedic and vascular operations, Doganci N. et al did not find a relationship between the upper level of the block and the volume of saline injected into the epidural space [4].

Similar results were obtained in a prospective study of Higuchi H. et al, who noted a significant decrease in the volume of the cerebrospinal fluid and the maximum narrowing of the dural sac by 25% when 15 ml of saline solution was injected into the epidural space [7].

The search for new ways of optimizing anesthetic support for total arthroplasty (TA) of large joints of the lower extremity contributed to the implementation of the CA technique with the expansion of the epidural space.

Aim of the study. To study the effect of the SAB technique with the expansion of the epidural space on the sensory block level and hemodynamics in patients with obesity of varying degrees during planned primary TA surgeries of large joints (hip and knee) of the lower extremity for stage III osteoarthritis.

Materials and methods. A prospective single-center study of 103 patients was conducted, including 79 (76.7%) men aged 33–74 years (average age 59±11 years) who were treated in the Department of Traumatology and Orthopedics of the Burdenko Main Military Clinical Hospital from September 2019 to May 2020.

All patients underwent primary TA surgeries of hip and knee joints. Inclusion criteria: patients aged 20 to 74 years with stage III coxarthrosis or stage III gonarthrosis, who were scheduled to undergo arthroplasty of large joints of the lower extremity. Exclusion criteria: absolute contraindications to neuroaxial blockades [3], residual effects of acute cerebral circulatory disorders, immobilization of the patient, a history of severe neurological and cardiovascular pathology, diabetes

The search for new ways of optimizing anesthetic support for total arthroplasty (TA) of large joints of the lower extremity contributed to the implementation of the CA technique with the expansion of the epidural space

Table 1. Descriptive characteristic of patients

Parameters	Control group, n=42	Main group, n=61	p-value*
Medical and demographic characteristics			
Sex (m/w)	31/11	48/13	1,000
Age, years	58,4±12,1 (61,5 [IQR: 52.0–68.5, from 30.0 to 75.0])	58,4±9,7 (61 [IQR: 51.0–65.0, from 33.0 to 74.0])	1,000
BMI, kg/m²	29,62±4,48 (28,4 [IQR: 26.67–32.21, from 23.85 to 44.9])	30,22±3,98 (29,36 [IQR: 27,17–32,42, from 23,53 to 40,82])	0,92
THA	29 (7 females and 22 males)	32 (4 females and 28 males)	1,000
TKA	13 (4 females and 9 males)	29 (9 females and 20 males)	1,000
Sensory block level, Th segment	7,7±1,23 (8,0 [IQR: 7,0–8,75, from 5,0 to 10,0])	7,6±1,26 (8,0 [IQR: 6,0–9,0, from 5,0 to 11,0])	0,95
Th segment			
THA	N=29, 73±16,1 (75,0 [IQR: 60,0–80,0, from 35 to 100])	N=31, 67,2±19,9 (60,0 [IQR: 52,5–85,0, from 40,0 to 110,0])	0,35
TKA	N=13, 92±22,9 (90,0 [IQR: 73,75–96,25, from 60 to 145])	N=30, 89,1±24,2 82,5 [IQR: 75,0-95,0, from 60,0 to 155,0]	0,93
Duration of anesthesia, min			
THA	N=29, 101,7±17,5 (104,0 [IQR: 90,0–112,0, from 60,0 to 142,0])	N=31, 96,1±19,9 (92,5 [IQR: 82,25-107,75, from 69,0 to 135,0])	0,83
TKA	N=13, 115,9±21,2 (114,0 [IQR: 105,0–125,0, from 90,0 to 169,0])	N=30, 119,6±23,3 (115 [IQR: 104,0–125,0, from 87,0 to 182,0]	0,91
Volume of blood loss, ml			
THA	N=29, 230,0±69,0 (200,0 [IQR: 200,0–300,0])	N=31, 265,9±83,6 (275,0 [IQR: 200,0–300,0])	0,74
TKA	N=13, 255,0±65,0 (300,0 [IQR: 150,0–300,0])	N=30, 246,0±69,4 (300,0 [IQR: 100,0–300,0])	0,93

*The differences are statistically insignificant. Arithmetic mean ± standard deviation (median [IQR - interquartile range]).

mellitus, chronic kidney disease and liver failure, increased intracranial pressure, violation of the study protocol (or if the block was ineffective, a solution of local anesthetic was added to the epidural space) or refusal of patients to participate in the study. Informed consent to participate in the study was read and signed by each patient.

The authors analyzed anthropometric indicators (height, weight, body mass index (BMI)) and physical condition on the ASA scale. The levels of sensory and motor blocks, the level of pain syndrome were assessed according to the 10-point digital pain rating scale Numeric rating Scale for pain (NRS) [1]. Sympathetic blockade (indicators of the cardiovascular system), duration of surgery and anesthesia were also evaluated.

All patients were divided into two groups: control (using the traditional combined CSE technique) and main (using the studied technique — SAB with the expansion of the epidural space). Each group was further divided into subgroups depending on the degree of obesity according to BMI, which was later taken into account when calculating the dose of local anesthetic. The protocol of the anesthetic aid in obese patients is identical, with the exception of the method of dosing local anesthetic.

In the 1st (control) group, the calculation of the local anesthetic dose was carried out according to the Zharkov method I.P. et al. (PatentRF No. 2351370) [8]. The calculation of the dose of 0.5% isobaric bupivacaine solution by height was carried out as follows: with the height of up to 150 cm, the dose of local anesthetic was 8 mg, with the height of 150 cm — 10 mg, 0.1 mg local anesthetic was added for every 0.5 cm over 150 cm (up to 160 cm), with the height of 160 cm — 12 mg, 0.075 mg local anesthetic was added for every 0.5 cm over 160 cm (up to 180 cm), with the height of 180 cm and over, 15 mg 0.5% bupivacaine solution is needed for SAB. Then the patient's BMI was determined and the difference between the patient's BMI and BMI equal to 25 kg/m2 was calculated. The obtained value was multiplied by 2, followed by the conversion of the result into a percents, and by subtracting the result from 100% (the dose of local anesthetic calculated by height is taken as 100%), the dose of local anesthetic required by this patient for spinal anesthesia was determined as a percent. Using arithmetic proportion, the dose of local anesthetic for SAB was calculated in milligrams.

In the 2nd (main) group, the dose of local anesthetic was corrected taking into account the methodology by Zharkov I.P. et al., then the received dose was reduced by 25% according to the studies by Dognaci N. et al [4]. The expansion of the epidural space was carried out in a volume of 10 ml of saline solution, which was injected through a catheter into the epidural space exclusively in 5 minutes after SAB was performed.

First, a puncture of the epidural space at the L III–L IV level with an 18G Tuohy needle (B. Braun Medical Inc., Germany) was performed with a median access in a lying position on a healthy side under local anesthesia with lidocaine solution (2%, 4 ml). The epidural space was idedntified by losing the resistance of the air bubble. The second stage was performed by SAB: a spinal needle 27G of the Spinocan type was inserted through the bore of the epidural needle. After verification of the cerebrospinal fluid, a 0.5% solution of isobaric bupivacaine was injected into the needle hub, the dose of which was calculated by height and corrected in accordance with BMI [8]. At the third stage, after the subarachnoid injection, the spinal needle was removed together with the mandrel, a 20G catheter was inserted through the bore of the Tuohy needle into the epidural space to a depth of 5 cm, after which the puncture needle was removed. In the analyzed group, 10 ml saline solution was injected into the subarachnoid space through an epidural catheter within 5 minutes after the introduction of local anesthetic into the subarachnoid space. The catheter was fixed on the skin with a transparent aseptic sticker (Epi-Fix, Unomedical). The adjuvant was not used. "Preinfusion" was performed in the volume of 500 ml of 0.9% NaCl solution. Immediately after SAB, the patient was laid horizontally on his back. After subarachnoid administration of local anesthetic, all patients received "postinfusion" in the volume of 800-1000 ml of 0.9% NaCl solution and 500 ml of hydroxyethylated starch Voluven 130/0.4 (Fresenius Kabi, Germany).

In the intraoperative period, the following were performed: ECG registration, assessment of heart rate, SPO2, pain level according to NRS, as well as visual assessment of the condition of the skin and visible mucous membranes, non-invasive measurement of blood pressure (BP) every 5 minutes. At the beginning of the surgery, the upper level of sensory block was determined (by pin-prick methods, cold test in the Zakharin-Ged zones) [2] and the degree of the motor block (according to the Bromage Ph.R. scale, 1978) [9].

To assess the severity of arterial hypotension with SAB, the Ngan Kee classification was used W.D. et al. [10]: 1) normotension; 2) hypotension I (moderate) — a decrease in systolic blood pressure (SBP) within 10–24% of the baseline; 3) hypotension II (pronounced) — a decrease in SBP from the baseline by 25% or more.

The primary endpoint of the study was determined by the severity of arterial hypotension, secondary endpoints — the upper level of the sensory block, the level of pain syndrome.

Statistical data processing was carried out using the software packages "SPSS® softwareversion 21" and "MedCalc® Statistical Softwareversion 19.5.6". Quantitative variables were given using the mean value and standard deviation, and in the case of a distribution other than normal, in the form of Me [IQR], where Me is the median, IQR is the interquartile range. Categorical variables were described using proportions (frequency) and percentages. To study the relationship between the frequency of arterial hypotension and the dosage of local anesthetic, a univariate analysis was used. The relative risk (RR) and its 95% confidence interval (CI) were calculated in a univariate analysis. Reliability of "p" it was evaluated using a single-sample t-Student coefficient, the value of $p<0.05$ was considered statistically significant

Results and discussion. The degree of obesity was assessed using BMI in accordance with the WHO classification (1997). Normal BMI was in 61 (59.2%) patients, obesity of the I degree — in 31 (30.1%), II degree — in 6 (5.8%), III degree — in 5 (4.9%). The physical condition on the ASA scale in 13 (12.6%) patients corresponded to Class I, in 29 (28.2%) — to class II, in 61 (59.2%) — to class III.

In the control group of patients, large median values of the local anesthetic amount were (12.8 [IQR: 11.66–13.83, from 7.6 to 15.3] mg versus 9.4 [IQR: 8.55–9.95, from 6.8 to 11.5] mg, p=0.058), a large median duration of surgery for THA (75.0 [IQR: 60.0–80.0, from 35 to 100] minutes versus 60.0 [IQR: 52.5–85.0, from 40.0 to 110.0] minutes, p=0.35), a large median duration of surgery for TKA (90.0 [IQR: 73.75–96.25, from 60 to 145] minutes versus 82.5 [IQR: 75.0–95.0, from 60.0 to 155.0] minutes, p=0.93), as well as a large median duration of anesthesia for THA (104.0 [IQR: 90.0–112.0, from 60.0 to 142.0] minutes versus 92.5 [IQR: 82.25–107.75, from 69.0 up to 135.0] minutes, p=0.83), but less blood loss in THA (200.0 [IQR: 200.0–300.0] ml versus 275.0 [IQR: 200.0–300.0] ml, p=0.74). There were no differences in median values in the compared groups by age (61.5 [IQR: 52.0–68.5, range from 30.0 to 75.0] years versus 61 [IQR: 51.0–65.0, from 33.0 to 74.0] years, p=1.0), patient BMI, duration of anesthesia (114.0 [IQR: 105.0–125.0, from 90.0 to 169.0] minutes versus 115.0 [IQR: 104.0–125.0, from 87.0 to 182.0] minutes, p=0.12) and the volume of blood loss (300.0 [IQR: 200.0–300.0] ml, p=0.93) at TEC, the level of the sensory block (Table 1).

The amount of local anesthetic calculated according to the above method differed in each group, taking into account the patient's BMI. Statistically significant

Table 2. The distribution of patients into subgroups depending on the degree of obesity, the dose of local anesthetic and the level of the sensory block at the beginning of the surgery

Patients' trophic status	Control group, n=42			Main group, n=61			p-value*	p-value**
	n (%), BMI, kg/m²	Dose, mg	Th segment	n (%), BMI, kg/m²	Dose, mg	Th segment		
Normal body weight	n=26 (62%) 26,91±1,81	13,3±1,4	8±1,5 (min=5, max=10)	n=35 (57,4%) 27,5±1,8	9,7±0,8	7,1±1,5 (min=5, max=10)	p=0,03*	p=0,673
I degree of obesity	n=13 (31%) 32,32±1,07	12,0±1,5	7,6±1,4 (min=5, max=10)	n=18 (29,5%) 32,1±1,1	9,4±2,2	8,0±1,6 (min=5, max=10)	p=0,337	p=0,852
II degree of obesity	n=1 (2,3%) 37,5	10,3	10	n=5 (8,2%) 36,5±1,4	7,9±0,8	8,2±2,2 (min=6, max=11)	p=0,253	p=0,473
III degree of obesity	n=2 (4,7%) 43,87±1,58	7,8±0,4	6,0±1,4 (min=5, max=7)	n=3 (4,9%) 40,5±0,4	7,0±0,3	9,3±0,7 (min=9, max=10)	p=0,251	p=0,103

*The differences are statistically significant. The arithmetic mean ± standard deviation. Th-segment — the average upper level of the sensory block 15 minutes after CA; p-value1 — differences in the dose of MA; p-value2 — differences in the level of the sensory block.

differences (p=0.03) in univariate analysis were obtained only in the subgroup of patients with normal body weight, where the average dose of 0.5% Isobaric bupivacaine solution in the control group (n=26) was 13.3±1.4 mg, and in the main group (n=35) — 9,7±0.8 mg, the value of student's t-test at 2.23. In the remaining subgroups of patients, no statistically significant differences in the doses of local anesthetic were detected (Table 2).

The average upper level of sensory block (Th-segment) 15 minutes after SAB in the control group was 7.7±1,23 (median of 8.0 [IQR: 7,0–8,75, from 5.0 to 10]), in the study group and 7.6±1,26 (median of 8.0 [IQR: 6,0–9,0 from 5.0 to 11.0] and was not significantly different in the groups (p=0.95), the value of student's t-test — 0,06. At the same time, in each subgroup, depending on the degree of obesity, in most cases the minimum level of the sensory block reached the Th-5 segment, the maximum — Th-10, the differences were statistically insignificant, p>0.05.

Our study with univariate analysis showed that the there is no significant difference in the level of sensory block using SAB technique with the expansion of the epidural space compared to traditional combined CSE (Table 2). Similar results were obtained in the Doganci N. et al study, where they noted that the previous maximum level of the sensory block when using 5, 10, 15 and 20 ml of saline solution was the same and reached Th VI-Th VII [4].

The level of motor blockade 15 minutes after anesthesia in the groups was the same and amounted to 2.8±0.7 (median 2.0 [IQR: 2.0-3.0 from 1.0 to 3.0]) points on the Bromoge scale and did not differ statistically (p >0.05), the Student's t-test was 1.708. Similar results were obtained in a study by Sitkin S.I. et al involving 24 pregnant women, where the level of motor block 20 minutes after anesthesia in the groups was the same and amounted to 1.5±0.2, 95% CI 1.0–2.0 (p<0.001) [11].

At the beginning of the operation, none of the patients in the groups noted the presence of pain syndrome, which corresponded to 0 points on the NRS. At the end of the surgical intervention, the intensity of the pain syndrome did not increase and was regarded by most patients of both groups as no more than 0-1 points. Additional administration of analgesics was not required.

Arterial hypotension was recorded in 20 (47.6%) patients of the control group and in 34 (55.7%) patients of the main group. Differences in the frequency of adverse outcomes were statistically insignificant (p0.05); RR: 1.17 [95% CI: 0.794; 1.726]. In a univariant analysis, the dosage of 0.5% isobaric bupivacaine did not affect the risk of arterial hypotension in patients in both the study and control groups. Similar results were obtained in the study by Doganci N. study et al, where the incidence of hypotension ranged from 10 to 26% and did not depend on the volume of expansion of the epidural space [4].

No adrenomimetics were used. The average volume of infusion therapy during surgery in the groups did not significantly differ and amounted to 1275±175 ml, p>0.05.

Thus, the results obtained in this study showed how the new SAB technique with a low dose of local anesthetic and the expansion of the epidural space compares with traditional combined CSE in terms of the anesthesia effectiveness and safety (differences in the frequency of intraoperative hypotension in the groups are insignificant). In addition, the authors obtained positive results. The effectiveness of using a lower dose of local anesthetic did not differ compared to the usual dose of local anesthetic by episodes of adverse outcome (intraoperative hypotension, insufficient degree of anesthesia or sensory block level, motor block was not reached).

Conclusion. The results of the study confirm the effectiveness of analgesia when using the method of spinal anesthesia with the expansion of the epidural space, which is accompanied by high patient satisfaction. Reducing the dose of local anesthetic by 25% to ensure adequate spinal anesthesia with the expansion of the epidural space in patients with a high body mass index gives the same result in terms of sensory, motor and sympathetic blockages compared with the traditional method of anesthesia.

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Information about the authors:

Lyubov V. Ermokhina — MD, anesthesiologist-resuscitator, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia — **responsible for contacts, ermokhina_92@mail.ru**, ORCID ID: 0000-0002-0891-4937; eLibrary SPIN: 2210-5238; Researcher ID: AAQ-4769-2021

Nadezhda V. Ermokhina — MD, anesthesiologist-resuscitator, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

Alexey Yu. Zavarzin — MD, PhD, anesthesiologist-resuscitator, Head of the Department of Anesthesiology and Intensive Care, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

Valery V. Stets — MD, anesthesiologist-resuscitator, Honored Doctor of the Russian Federation, Head of the Center of Anesthesiology and Intensive Care, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

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Trigger electromyography in endoscopic transnasal surgery of the skull base tumors

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Shkarubo A.N.[1], Chernov I.V.[1], Ogurtsova A.A.[1], Chernov V.E.[2]

[1] National Medical Research Center for Neurosurgery named after academician N.N. Burdenko of the Ministry of Health of the Russian Federation, Moscow, Russia
[2] Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia

Abstract. Preserving anatomical integrity and functions of cranial nerves when removing skull base tumors is one of the significant problems of endoscopic endonasal surgery. For this purpose, it is possible to use intraoperative mapping and cranial nerves identification.
The aim of the study was to evaluate the effectiveness of trigger electromyography (T-EMG) used to prevent iatrogenic damage to the cranial nerves intraoperatively. Twenty-one patients with different skull base tumors were included in the study. Mapping and identification of cranial nerves were carried out during tumor excision, using endoscopic endonasal access. Surgeries were performed on large skull-based chordomas, neuromas of the trigeminal nerve in the cavernous sinus region, pituitary adenomas, meningiomas in the clivus and a skull-based cholesteatoma. Mapping and identification of cranial nerves were carried out using electromyography in trigger mode using bipolar and monopolar electrodes. Functional activity of cranial nerves was evaluated both before and after the operation. The effectiveness of the technique was compared with that of the control group (41 patients). In the course of surgical interventions using T-EMG in the main group of patients, 40 nerves were analyzed. In the course of the study, III, V, VI, VII, XII cranial nerves were identified intraoperatively. In 4 patients in the main group and in 13 patients in the control group, a postoperative deficit of cranial nerves was observed. We did not receive statistically reliable data that the intraoperative identification of cranial nerves using T-EMG reduces the frequency of postoperative complications in the form of a deficiency of cranial nerves (p=0.11), but the ratio of chances (0.26) testifies in favor of rarely occurring complications in main group. Trigger electromyography allows us to estimate the functional state of the cranial nerves during endoscopic endonasal operations. The method of using T-EMG is promising and requires further research.

Keywords: trigger electromyography, intraoperative identification of cranial brain nerves, endoscopic endonasal access, surgery of base skull tumors.

Introduction. Microsurgical transsphenoidal access has been used for the last 30 years to remove median tumors of the base of the skull [19–22], but with the development of endoscopic technologies, endoscopic endonasal transsphenoidal access has become the gold standard [23–27].

During any operation on the base of the skull, there is a potential risk of damage to neurovascular structures, such as the internal carotid artery, anterior cerebral arteries, and CN, which causes temporary or permanent neurological deficit [8, 9].

The frequency of iatrogenic CN injuries in skull base surgery using various intraoperative identification techniques ranges from 2 to 47% [28–31], without neurophysiological identification — from 14 to 68% [29, 32]. Neurological complications in the form of functional CN deficiency can be predicted and prevented using intraoperative neurophysiological monitoring [2, 9–13].

Two main techniques are used to identify the CN: free-run electromyography (f-EMG) and trigger electromyography (T-EMG). F-EMG has a lower sensitivity in detecting CN deficiency during endoscopic endonasal surgery of skull base tumors, since EMG activity is observed after mechanical or electrical (using coagulation) exposure to CN [14, 15].

In T-EMG, changes occur after electrical stimulation of the CN with a monopolar or bipolar electrode, which leads to the formation of a compound muscle action potential (CMAP) [6, 11].

Thus, T-EMG makes it possible to determine the location of the CN before coming into direct contact with it and, accordingly, reduce the risk of iatrogenic damage during all stages of tumor removal [15].

In this regard, the task of intraoperative identification of CN during transnasal endoscopic operations is significant.

Aim of the study. To evaluate the effectiveness of T-EMG used to prevent iatrogenic damage to the CN during surgery.

Materials and methods. The main group of the study included 21 patients (14 women and 7 men) aged 26–72 years (average age 52.8 years) operated on at the N. N. Burdenko National Medical Research Center of Neurosurgery in the period from 2013 to 2017. Surgical interventions were performed for large chordomas of the base of the skull [11], trigeminal neurinoma [5] of the cavernous sinus region, pituitary adenomas [2], meningioma of the stingray region [2] and cholesteatoma of the base of the skull [1]. During all surgeries, mapping and neurophysiological identification of CN in trigger mode were performed in the main group of patients.

The criteria for inclusion of patients in the main group were: age from 18 to 75 years, intradural spread of the skull base tumor, the spread of the tumor in the CN area of the passage, neurophysiological identification of at least one CN intraoperatively.

Table 1. Distribution of patients by nosology

Nosology	Main group (n=21)	Control group (n=41)
Chordoma	11	24
Neurinoma	5	0
Meningioma	2	2
Pituitary adenoma	2	11
Cholesteatoma	1	0
Plasmocytoma	0	2
Chondroma	0	1
Osteosarcoma	0	1

We described in detail the technique of intraoperative identification of CN used by us in a previously published paper [33]. Needle electrodes are installed in the muscles innervated by the corresponding nerves for identification. Rhythmic electrical stimulation with single pulses with a frequency of 4.7 Hz and a stimulus duration of 0.1 ms is used to map and identify CN. The current varies from 2 to 16 mA. Registration of motor muscle responses is carried out in the trigger mode of EMG with an analysis epoch of 20 ms and a sensitivity of 50 mv/ div. TIVA technology (total intravenous anesthesia) is used as an anesthetic aid. For tracheal intubation, a muscle relaxant of medium duration of action is used — 0.6 mg/kg rocuronium.

In our study, the received M-responses were classified as weak and strong. To simplify data processing, weak M-responses were represented as "0", strong ones — as "1". Weak M-responses served as a reason for careful removal of tumor tissues by the surgeon, so that they could show the existing damage to the nerve trunk or its relative proximity.

To assess the effectiveness of the technique, a comparison was made with a control group, which included 41 patients (23 men and 18 women) aged 16–73 years (average age 46.3 years).

All patients were operated on in the skull base area at the N. N. Burdenko National Medical Research Center of Neurosurgery. The distribution of patients by nosology in the control and main groups is shown in Table 1.

The neurological status and functional activity of the patients' CN were assessed before and on the 1st day after surgery, as well as during a catamnestic examination.

Control group had similar inclusion criteria except for the identification of CN intraoperatively.

Table 2. Surgery information

Number of patients and current parameters	Cranial nerves				
	III	V	VI	VII	XII
Number of patients who underwent monitoring	8	5	17	2	1
Number of mapped nerves	10	5	22	2	1
Average current strength	4–6 mA	4–10 mA	4–10 mA	4–10 mA	4–10 mA

The degree of radicality of the performed surgeries was assessed on the basis of the radicality scale proposed by Frank G., Pasquini E. (2002):

1. Radical removal when there are no signs of tumor on the control CT and/or MRI scans.

2. Subtotal removal when the remaining part of the tumor was less than 20% of the original size.

3. Partial removal when the remaining part was less than 50% of the original tumor size.

4. Insufficient removal when the remaining part of the tumor was 50% or more of the original size.

When assessing the radicality, CT and/or MRI data were compared directly at the time of discharge with the data from control studies after 3 and 6 months.

Results. From 2013 to 2017, 21 patients of the main and 41 patients of the control group were operated on. All operations were performed using endoscopic endonasal transsphenoidal access.

The results of surgical treatment were obtained on the basis of control CT, spiral CT and/or MRI scans. In the main group, 10/11 chordomas were removed totally, 1 — subtotally, 5 neurinomas — totally, 2 meningiomas — subtotally, 2 pituitary adenomas — totally, 1 cholesteatoma — subtotally.

Thus, total removal of the tumor was achieved in 81% of cases, subtotal — in 19%. In the control group, total tumor removal was achieved in 65.9% of cases (27/41), subtotal — in 19.5% (8/41), partial — in 14.6% (6/41).

CN, including III, V, VI, VII, XII nerves, were identified intraoperatively in all of the patients from the main group. Information about the nature of the surgery depending on the location of the tumor, the initial neurological status, postoperative complications, as well as the number of mapped nerves is presented in Table 2.

The incidence of complications in the form of a deficiency of one or another CN in the main group was 19% (4 patients). In 1 case, paresis of an intraoperatively unidentified nerve developed: the VI nerve was not identified intraoperatively in a patient with trigeminal neurinoma of the right cavernous sinus. In the early postoperative period, the paresis was observed, which regressed 3 months after the operation. In 3 cases, paresis of intraoperatively identified nerves developed. In the first case, paresis of the III nerve grew in a patient with neurinoma of the right cavernous sinus, which did not regress for 3 months (before the operation, paresis was less pronounced). In the second case, paresis of the VI nerve grew in a patient with a giant cholesteatoma of the base of the skull, which also did not regress for 3 months (there was no paresis before the operation). In the latter case, paresis of the VI nerve grew in a patient with giant meningioma of petroclival localization (there was no paresis before the operation).

The incidence of complications in the form of a deficiency of one or another CN in the control group was 31.7% (13 patients). In most cases (8/13), there was the appearance of a new or deepening of the existing paresis of the abductor nerve before the operation. In 6/13 cases, there was also the appearance of a new or deepening of an existing oculomotor CN paresis before surgery. 1 patient developed block nerve paresis.

Data analysis using Fisher's exact test showed differences between groups with a significance level of p-value 0.11, which is higher than the generally accepted level of alpha = 0.05 and does not allow us to reject the null hypothesis that the identification of the CN significantly reduces the risk of developing postoperative deficiency of the identified CN, and shows statistically significant differences between the groups. However, the odds ratio was 0.26 (95% confidence interval 0.025–1.36), which indicates in favor of a rarer occurrence of complications in the main group.

Discussion. Due to the close connection of the skull base formations with neurovascular structures (internal carotid artery, anterior cerebral artery and CN III to XII), even minimally invasive endoscopic endonasal approaches carry a potential risk of their damage [35–37]. In this regard, monitoring of the CN functional safety during endoscopic endonasal operations is of great interest [38].

We used T-EMG for intraoperative mapping and identification of CN in endoscopic endonasal surgery of skull base tumors. Published studies have shown that the use of T-EMG in the removal of various tumors of the base of the skull can reduce the risk of postoperative neurological complications in the form of functional deficiency of CN [15–18].

Trigger electromyography makes it possible to assess the functional state of the cranial nerves during endoscopic endonasal interventions for various neoplasms of the base of the skull. To confirm or refute the significance of using the technique to reduce the frequency of postoperative complications in the form of cranial nerve deficiency, further studies with a set of larger groups of patients are needed

The absence of M-responses when the pulse is applied to the CN may be a sign of complete damage to the nerve trunk. However, if M-responses can be obtained only with increased current strength, this indicates partial nerve damage and may become a predictor of postoperative deficiency [34]. In our study, in 3 cases, there was a postoperative deficiency of those nerves that were identified intraoperatively, while the current strength for their identification was not increased. The development of a deficit of identified CN at this stage of the study does not allow us to talk about the prognostic significance of the use of T-EMG.

Intraoperatively, we examined the functional safety of III, V, VI, VII, XII CN. In surgery of tumors spreading into the cavernous sinus, the upper orbital fissure and the petroclival region, the functional and structural integrity of extraocular CN is most at risk [1, 4, 5]. Diplopia after intraoperative trauma of extraocular CN can have a serious impact on the patient's life, as there is a loss of stereoscopic and the establishment of monocular vision, which is associated with the risk of narrowing of the visual fields, secondary amblyopia and even functional blindness [6, 7]. A functional disorder of the IV nerve leads to a less significant defect in eye movement than disorder of the III and VI nerves [39]. In our observations (in the main group), postoperative deficiency of the VI nerve most often increased (3 cases), which corresponds to the literature review data [3, 7]. The expansion of endoscopic endonasal accesses to the stingray area also necessitates monitoring of the caudal CN group [13, 40]. In one clinical case (giant cholesteatoma of the base of the skull), we mapped and identified the XII CN.

In our study, intraoperative mapping and CN identification did not reduce the radicality of operations, but allowed it to increase (81% in the main group versus 65.9% in the control group).

We have not received statistically reliable data that intraoperative identification of CN using T-EMG reduces the frequency of postoperative complications in the form of CN deficiency (p=0.11). However, the odds ratio (0.26) indicates in favor of a rarer occurrence of complications in the main group. Statistically significant results can be obtained by increasing the sample size.

Conclusion. Trigger electromyography makes it possible to assess the functional state of the cranial nerves during endoscopic endonasal interventions for various neoplasms of the base of the skull. To confirm or refute the significance of using the technique to reduce the frequency of postoperative complications in the form of cranial nerve deficiency, further studies with a set of larger groups of patients are needed.

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Information about the authors:

Alexey N. Shkarubo — MD, DSc, Leading Researcher of the 8th Neurosurgical Department (Basal tumors), National Medical Research Center for Neurosurgery named after academician N.N. Burdenko of the Ministry of Health of the Russian Federation, Moscow, Russia.

Ilya V. Chernov — MD, Neurosurgeon of the 8th Neurosurgical Department (Basal tumors), National Medical Research Center for Neurosurgery named after academician N.N. Burdenko of the Ministry of Health of the Russian Federation, Moscow, Russia.

Anna A. Ogurtsova — MD, PhD, Physiologist of the Neurophysiology Laboratory, National Medical Research Center for Neurosurgery named after academician N.N. Burdenko of the Ministry of Health of the Russian Federation, Moscow, Russia.

Valery E. Chernov — MD, PhD, Head of the 22th Neurosurgical Department (with wards for patients with brain and spinal cord lesions accompanied by paralysis (paresis) of the lower (or upper and lower) limbs and pelvic organ dysfunction) of the Neurosurgical Center, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia — **responsible for contacts, beduinum@rambler.ru**, ORCID ID: 0000-0003-4882-2444.

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Characteristics of medical implants 3D-printing

Budoragin E.S.[1], Gorshenev V.N.[2], Akopyan V.B.[3, 4], Bambura M.V.[5], Budoragin I.E.[1]

[1] *Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia*
[2] *Science Institute of Biochemical Physics named after N.M. Emanuel of the Russian Academy of Sciences, Moscow, Russia*
[3] *Moscow State Technical University named after N.E. Bauman, Moscow, Russia*
[4] *All-Russia Research Institute of Agricultural Biotechnology, Moscow, Russia*
[5] *Federal Institute of Industrial Property, Moscow, Russia*

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Abstract. Development of new materials suitable for the formation of implants via 3D-printing, as well as stimulating biological tissues regeneration, is an urgent problem in traumatology, neurosurgery, andrology and urology. The article discusses the possibilities of improving the quality of 3D-printed implants by using paste-like thermoplastic compositions, as well as using ultrasound and a rotating magnetic field to prevent changes in viscosity in extruders for 3D-printers.

Keywords: 3D-printing, implants, extruder, viscosity, thixotropy.

Introduction. A powerful impetus to was The use of syringe-like extruders in 3D printing devices for so-called inks (starting substances, usually gels characterized by thixotropy, or paste-like suspensions that thicken in the absence of mechanical influences that ensure the appearance of mixing flows in them) gave a powerful impulse to the development of technologies for making replacement implants that stimulate the regeneration of biological tissue in reconstructive surgery. Flows in the liquid inside the syringe-injector can be excited in various ways, the simplest of which is stirring using a body in the syringe that rotates under the influence of a magnetic field, or by acoustic flows initiated by ultrasound.

The creation of new biomedical materials to replace and stimulate the regeneration of biological tissues, the development of technologies for obtaining these materials and methods of their practical application remains an urgent problem in traumatology, neurosurgery, andrology, urology and other areas of medicine [1].

Numerous developments of such biomaterials and products indicate an active search for compositions with a set of specified properties. Special attention should be paid to the production methods of biomaterials suitable for volumetric or 3D prototyping in order to manufacture biological implants of complex individual shape, as well as techniques for using new biomaterials with thixotropic properties.

A promising direction for the creation of implants for regenerative medicine is shown in journal publications, as well as in patent literature [2].

It should be noted that the use of a number of biomaterials for 3D printing is associated with a problem related to their thixotropic properties. There are several approaches to its solution, but the most promising one should be recognized as the ultrasonic method of controlled reduction of the viscosity of thixotropic substances [3].

In medicine, the use of 3D printing in building implants for replacing tissue (including bone) defects, involves the use of specific "ink" — liquid, but hardening under the influence of substances that are dosed during printing in accordance with the given program. Often these "inks" are thixotropic liquids with spontaneously increasing viscosity in the absence of sufficiently intensive mechanical mixing. If such a phenomenon occurs in a syringe-extruder feeding "ink", then the feeding mode becomes more complicated or disrupted, which ultimately affects the quality of the end product.

Methods. OOne of the possible technical solutions for regulating the viscosity of a substance intended for 3D printing is to place a body of magnetic material inside the syringe barrel (between the plunger and the tip). This body is driven into rotation by a rotating magnetic field created around the syringe barrel (Fig. 1).

The device is a variant of a miniature magnetic mixer [4], which, due to the mechanical impact on the liquid inside the syringe, reduces the viscosity of the thixotropic liquid, thereby facilitating the controlled supply of thixotropic substances for 3D printing, which reduces the likelihood of error and improves the quality of the finished product.

Another simple design (Fig. 2) is an ultrasonic syringe developed earlier, made of a standard disposable 20 ml syringe and a standard ultrasonic emitter IUT 0.88–1.03 F, using a set of therapeutic ultrasound apparatus UZT-1.01 F, or a similar one, providing radiation intensity up to 2 W/cm^2.

To build such an ultrasonic syringe, it is required to remove the plunger from a standard 20 ml syringe (1), replace it with an ultrasonic source IUT 0.88-1.03 F (2) with a silicone rubber sealing ring-cuff attached to the source (3), and connect the source to the generator UZT-1.01 F with a cable (4), which allows changing both the intensity of radiation and the mode of pulse action on the liquid inside the syringe.

The study of the effect of mechanical impact or ultrasound on the viscosity of a thixotropic liquid varying over a wide range was carried out using a simple capillary viscometer (Fig. 3) consisting of a syringe barrel (1), a capillary (2) and a spring (3). To measure the viscosity, the spring is compressed, the capillary at the inlet of the

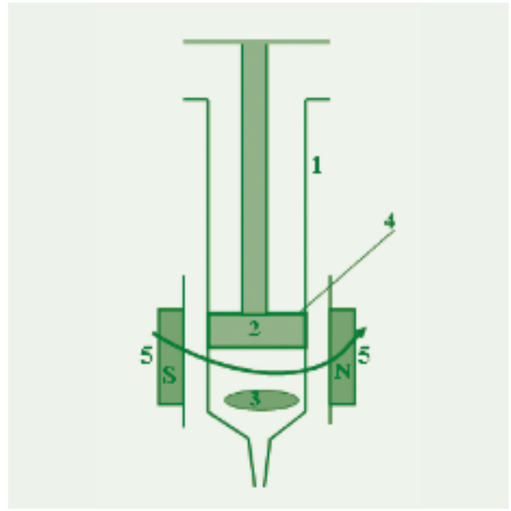

Fig. 1. Structure of the device: S, N — magnet poles; 1 — syringe barrel; 2 — plunger; 3 — body made of magnetic material; 4 — magnetic field; 5 — permanent magnets rotating around the syringe barrel

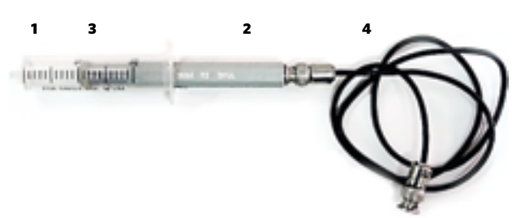

Fig. 2. Structure of ultrasound syringe using standard medical devices: 1 — syringe body; 2 — ultrasonic source IUT 0.88–1.03 F; 3 — sealing ring-cuff; 4 — cable for connecting the emitter with a medical ultrasound generator UZT-1.01 F

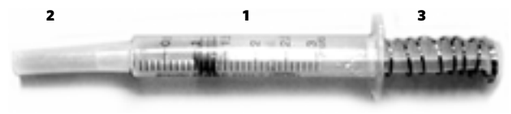

Fig. 3. Structure ofa simple capillary viscometer: 1 — body of the measuring device; 2 — capillary; 3 — spring

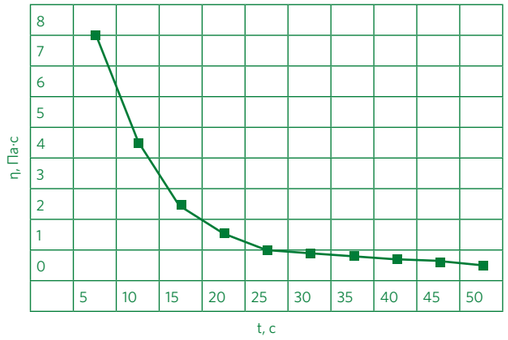

Fig. 4. Dependence of the gel dynamic viscosity of the thixotropic model fluid on the time of exposure to ultrasound

syringe is lowered into the liquid under study and the time during which the liquid is drawn into the syringe is determined due to the force of the spring, which provides equal conditions for measuring the viscosity of different liquids due to equal volumes of the substance sucked in through the capillary. It is obvious that the viscosity of liquids under these conditions is proportional to the time of filling the internal volume of the viscometer body with the liquid under study, due to the standardized spring force.

Glycerin solutions with known viscosity values were used to calibrate the capillary viscometer. Comparative results obtained on the Contraves Rheomat 108 rotary viscometer showed that the accuracy of measurements on this capillary viscometer is sufficient to evaluate experimental data.

On the model with a thixotropic liquid, it was demonstrated that when exposed to ultrasound (0.5 W/cm3), the viscosity of the gel decreases in accordance with the pattern shown on Fig. 4.

The viscosity under mechanical stress on the gel quickly drops to values at which cavitation is possible (with ultrasound parameters used), after which shock waves accompanying cavitation and intense micro-flows accelerate the process [5].

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Information about the authors:

Evgeniy S. Budoragin — MD, urologist, Head of the Urodynamic Research Office, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

Vladimir N. Gorshenev — PhD in Physical and Mathemaical Sciences, Senior Researcher of the Science Institute of Biochemical Physics named after N.M. Emanuel of the Russian Academy of Sciences, Moscow, Russia

Valentine B. Akopyan — DSc in Biology, Professor of the Moscow State Technical University named after N.E. Bauman, Senior Researcher of the All-Russia Research Institute of Agricultural Biotechnology, Moscow, Russia — **responsible for contacts, akopyan1941@mail.ru,** eLibrary SPIN: 3265-5827, Researcher ID: A-9159-2014

Maria V. Bambura — PhD in Biology, state expert on intellectual property of the 2nd category, Federal Institute of Industrial Property, Moscow, Russia.

Ivan E. Budoragin — MD, pulmonologist, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

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Tendon-muscle transposition in severe irreversible damage to the radial nerve: surgical technique and clinical practice

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Isengaliev I.N., Besedin V.D., Khrapov Yu.V.

Federal state budgetary institution "413th military hospital", Ministry of Defense, Volgograd, Russia

Abstract. Early results of tendon-muscle transposition in severe irreversible damage of the radial nerve were evaluated. The study included 11 patients with paralysis of the hand and fingers extensors due to various injuries of the radial nerve. Treatment results were assessed after 6–12 months using Moussavi et al. classification. The range of motion of extension of the hand, fingers, abduction and extension of the thumb were taken into account. The following data were obtained: excellent results were observed in 4 patients, good — in 7 patients. There were no satisfactory or bad results. Tendon-muscular transposition in the absence of clinical and electrophysiological recovery of radial nerve is a highly effective method of orthopedic correction that helps restore hand function and return functionality to patients.

Keywords: radial nerve palsy, tendon-muscle transposition.

Introduction. Among all peripheral nerve injuries, radial nerve injuries are noted in 13% of cases, and the number therapeutic failures in this patient group reaches more than 20% [1, 2]. Despite all the advancements in modern neurosurgery, a certain number of patients have a significant impairment of the hand functions after microsurgical restoration of the radial nerve. This is associated with the peculiarities of the anatomy of the radial nerve, slow regeneration (1 mm/day), muscle fibrosis, the development of contractures [3]. It leads to an increase in the recovery period, significantly lengthens the period of disability and sometimes causes lifelong disability, which entails adverse economic and social consequences [4]. Repeated reconstructive interventions in these cases are technically difficult due to the pronounced local scar-adhesive process, altered anatomy in this area and involutive changes in nervous tissue, while the tactical approach remains controversial. In addition, the chances of a successful outcome with multiple surgeries are much lower. In these conditions, tendon transposition is a real chance for the patient to restore hand function [5].

Aim of the study. Evaluation of the clinical efficacy of tendon-muscle transposition in patients with severe irreversible damage to the radial nerve, accompanied by paralysis of the hand and fingers' extensors.

Materials and methods. In the period from 2015 to 2020, we have operated on 11 patients (8 men and 3 women) aged 21 to 46 years. The patients were treated in the neurosurgery inpatient unit. The average follow-up

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period was 9 months (6-12 months). Surgery time ranged from 95 min to 210 min. No perioperative complications were observed.

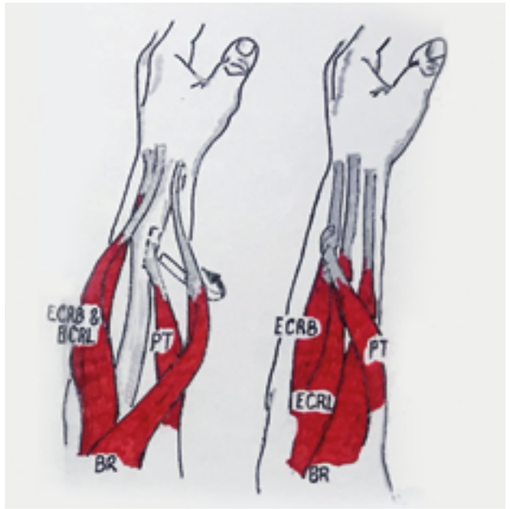
By the time of hospitalization, all patients had previously undergone reconstructive nerve surgery (neurolysis, suture of a damaged nerve, excision of post-traumatic neuromas followed by autoplasty with a calf nerve). There were no clinical and electrophysiological signs of nerve restoration for 6 months after surgical treatment.

Surgical technique. Surgical equipment used: a set of general surgical instruments, a bipolar coagulation apparatus, absorbable and non-absorbable suture materials — 6/0-2/0 prolene, 4/0-6/0 vicril or their analogues.

Surgical treatment included 3 stages:

1. **Restoration of the hand extension.** An S-shaped 12–15 cm incision of the skin, subcutaneous tissue and fascia is made along the extensor surface of the middle and lower thirds of the forearm in the projection of the m. extensor carpi radialis brevis tendon (innervated by n. radialis) and the place of attachment of the m. pronator teres tendon (innervated by n. medianus). The tendon of the latter is isolated along the entire length and with the help of a tendon stripper is separated from the radius with the obligatory inclusion of the periosteum, which gives additional length. Then the donor tendon with the periosteum is moved to the m. extensor carpi radialis brevis and fixed using the Pulvertaft tendon suture with additional adapting sutures under conditions of back extension of the hand at an angle of 45° degrees (Fig. 1). Using m. extensor carpi radialis longus as a recipient (innervated by n. radialis) may cause excessive radial deviation of the wrist.
2. **Restoration of finger extension.** An additional layered linear 4–5 cm incision is performed along the flexor surface of the lower third of the forearm with a length, projected in the middle between m. p almaris longus (innervated by n. medianus) and m. flexor carpi radialis (innervated by n. medianus). Isolated m. flexor carpi radialis tendon is cut off from the base of the second metacarpal bone, which is carried out using a tendon guide subcutaneously through the radial edge of the forearm to its extensor surface and fixed to the m. extensor digitorum communis tendon(innervated by n. radialis) proximal to the extensor retainer, thus creating a more direct line of tension. Tendon anastomosis is performed with the back extension of the hand and fingers at an angle of 45° and at maximum tension m. flexor carpi radialis (Fig. 2).

The use of m. flexor carpi ulnaris as a donor (innervated by n. ulnaris) can lead to a significant weakening of the hand flexion, loss of the possibility of using a hammer and similar movements. Due to m. flexor carpi ulnaris tendon being short, significant



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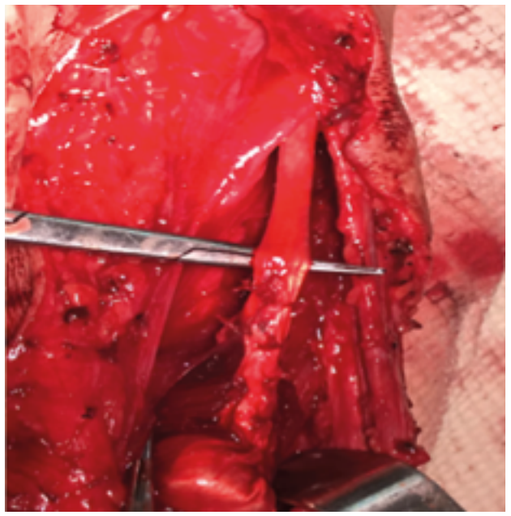

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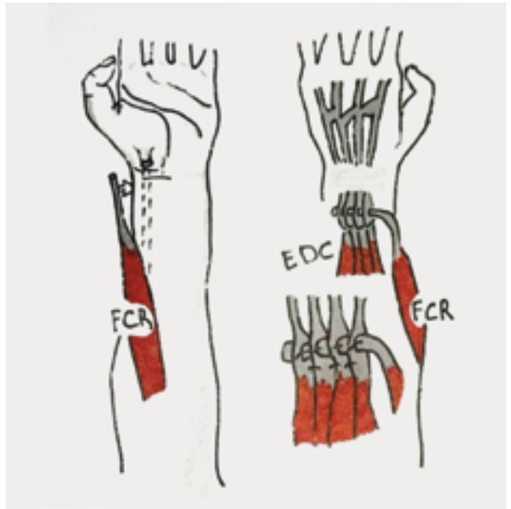
Fig. 1. Diagram and intraoperative photograph of the transposition of the m. pronator teres tendon to the m. extensor carpi radialis brevis tendon.
PT — pronator teres; ECRB — extensor carpi radialis brevis; ECRL — extensor carpi radialis longus; BR — brachioradialis



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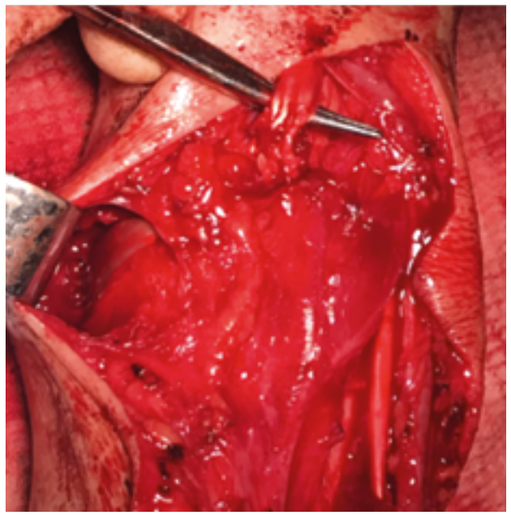

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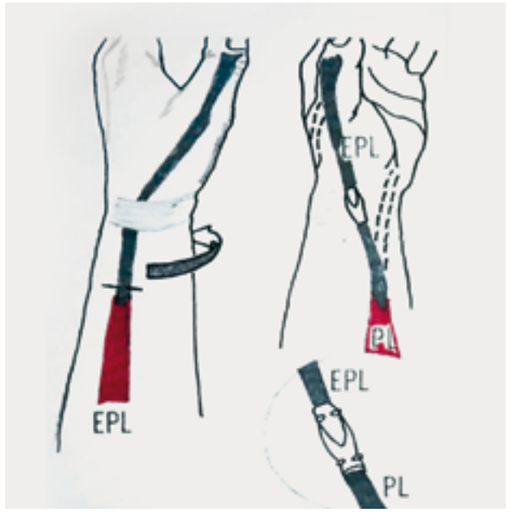
Fig. 2. Diagram and intraoperative photograph of the transposition of m. flexor carpi radialis tendon to m. extensor digitorum communis tendons.
FCR — flexor carpi radialis; EDC — extensor digitorum communis



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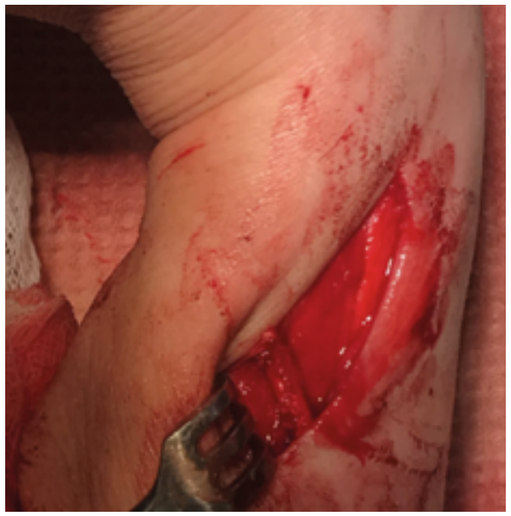

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Fig. 3. Diagram and intraoperative photograph of the transposition of the m. p. almaris longus tendon to the m. extensor pollicis longus tendon. PL — palmaris longus; EPL — m. extensor pollicis longus

Table 1. Criteria for the range of motion in the hand joint, fingers according to Moussavi et al.

	Excellent	Good	Satisfactory	Poor
Hand extension	0–80°	0	45° restriction of movements	70° restriction of movements
Finger extension	0–10°	0	45° restriction of movements	90° restriction of movements
Flexion and extension of the thumb	80–99°	60–80°	30–59°	0–29°
Hand flexion	full	0–20°	0°	dorsiflexia

Table 2. Clinical and demographic data of patients and functional results

	Sex, male/ female	Age, y.o.	Trauma mechanism	Surgery time, minutes	Hand extension	Finger extension	Flexion and extension	Hand flexion
1	male	21	incised	95	good	good	good	excellent
2	female	42	fracture	115	good	good	good	excellent
3	male	28	incised	150	good	excellent	good	good
4	male	36	traction	180	excellent	excellent	excellent	excellent
5	female	46	iatrogeny	165	good	good	good	satisfactory
6	male	25	fracture	210	excellent	excellent	excellent	excellent
7	male	43	incised	125	good	good	good	excellent
8	male	27	incised	140	excellent	good	excellent	excellent
9	female	31	incised	160	good	satisfactory	good	good
10	male	51	incised	120	excellent	excellent	excellent	excellent
11	male	28	fracture	130	good	excellent	good	good

proximal mobilization is required, which increases the traumatic nature of surgical treatment, and since this is the only elbow deviator of the hand, its use leads to radial deviation, and therefore m. flexor carpi ulnaris is not recommended for use.

3. Restoration of extension and flexion of the thumb. The next stage mobilizes m. p almaris longus (innervated by n. medianus) which is separated as distally as possible from palmar aponeurosis. Then it moves through the radial side and is fixed to the m. extensor pollicis longus (innervated by n. radialis) using a tendon suture (Fig. 3).

The surgeries were performed with patients on their backs, under general or conductive anesthesia with additional intravenous sedation.

In order to prevent the failure of tendon sutures and to preserve the achieved correction, a plaster splint was applied along the flexor surface of the forearm with the fixation of the hand and II–V fingers in the position of the back extension at an angle of 45-50°, the I finger — in the position of extension and flexion.

From the 2nd week, the training of the transposed muscles began under the supervision of a rehabilitation specialist. After 3 weeks, the plaster splint was removed, and a course of rehabilitation therapy was carried out, including massage, physical therapy, physiotherapy.

The use of tendon-muscle transposition in cases of severe irreversible damage to the radial nerve without signs of clinical and electrophysiological recovery after 5–6 months after surgical and restorative complex treatment is an effective method that contributes to a fairly rapid restoration of the functions of the hand

Treatment results were evaluated after 3 months using the Moussavi et al classification. (table. 1) taking into account the volume of movements of the extension of the hand, fingers, as well as flexion and extension of the thumb [6].

Results and discussion. No perioperative complications were observed in all 11 patients: excellent results were found in 4 patients, good results in 7 patients (Table 2). All patients subjectively noted a significant improvement in the function of the hand. In the postoperative period, 3 patients developed an unexpressed extensor contracture, which required the expansion of rehabilitation measures. No patient complaints about the weakness of the flexion of the hand were received. Forearm pronation was preserved in all patients. There was also no significant radial deviation of the hand.

Thus, tendon-muscle transposition with severe irreversible damage to the radial nerve in all cases allowed to restore the functions of the hand and improve patients' quality of life. Nevertheless, many specialists avoid using this method of treatment in their practice due to the fact that irreversible nerve damage and its consequences are at the junction of neurosurgery, traumatology-orthopedics, neurology and require a multidisciplinary approach to treatment. Moreover, in Russian literature, the issues and technical aspects of tendon-muscle transpositions in nerve damage are poorly covered, which leads to low awareness of doctors about the effectiveness of this surgery, confirmed by research and literature review.

Conclusion. The use of tendon-muscle transposition in cases of severe irreversible damage to the radial nerve without signs of clinical and electrophysiological recovery after 5–6 months after surgical and restorative complex treatment is an effective method that contributes to a fairly rapid restoration of the functions of the hand.

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Information about the authors:

Ilyas N. Isengaliev — MD, Neurosurgeon of the Neurosurgical Department, "413th military hospital", Ministry of Defense, Volgograd, Russia — **responsible for contacts, iisengaliev@mail.ru**, ORCID ID: 0000-0002-6444-4757

Vladimir D. Besedin — MD, Senior resident of the Trauma Department, "413th military hospital", Ministry of Defense, Volgograd, Russia.

Yuri V. Khrapov — MD, Head of the Neurosurgical Department, "413th military hospital", Ministry of Defense, Volgograd, Russia.

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Analysis of the duration and intensity of the humoral immune response in medical workers after COVID-19

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Kazakov S.P.[1,2], Davydova N.V.[1], Putkov S.B.[1], Reshetnyak D.V.[1], Aristarchova I.V.[1]

[1] Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia
[2] Russian Medical Academy of Continuous Professional Education of the Ministry of Healthcare of the Russian Federation, Moscow, Russia

Abstract. The article presents data on the duration and intensity of the humoral immune response in medical workers who had COVID-19 in the first wave of the pandemic. The response was analyzed based on the production of immunoglobulin M (IgM) and G (IgG) antibodies to SARS-CoV-2. Using ELISA immunoassay systems manufactured by «Vector-Best» (Novosibirsk, RF) and foreign test systems based on immunofluorescence analysis by Abbott (USA), a comparative assessment of the production of antibodies to SARS-CoV-2 was carried out. The presented semi-quantitative and quantitative data on IgM and IgG antibodies to SARS-CoV-2 in dynamics for the period from May 2020 to May 2021 in medical workers who had had COVID-19. The difference in the antibodies' detection and the dynamics of their decrease depending on the type of antibodies detected are shown. Data on the frequency of occurrence of IgM antibodies to SARS-CoV-2 in medical workers who had had COVID-19 during the observed period are presented, with the assumption of reinfection or persistence of the virus. Data are presented on the number of IgG antibodies expressed in international units (BAU/ml) and the relative number of patients who managed to maintain different (150/300/590 BAU/ml) protective levels of antibodies to SARS-CoV-2 over the observed period, including those with a minimum level of protection by the minimum titer of neutralizing antibodies.

Keywords: COVID-19, medical workers, immune response, humoral response, immunochemical methods, IgG, IgM, SARS-CoV-2.

Introduction. On January 30, 2020, the World Health Organization (WHO) declared the outbreak of the new coronavirus infection (COVID-19) in Wuhan (People's Republic of China) an emergency of international significance in the field of public health, and on March 11, 2020, due to the rapid spread of infection around the world, this process was recognized by WHO as a pandemic — a global epidemic [3, 5].

As of October 10, 2021, more than 237.7 million cases of the disease have been registered worldwide, more than 4.8 million deaths have been confirmed [3], which makes the pandemic one of the deadliest in history. In the Russian Federation, the first case of the disease was recorded on January 31, 2020 [2].

Medical workers, including the ones in Russia, were among the first to encounter the new virus. At the Burdenko Main Military Clinical Hospital (hereinafter referred to as the hospital), medical staff received the first patients with COVID-19 in the infection center. In the shortest possible time, methodological recommendations were developed, according to which patients' treatment was carried out [4, 7]. However, taking into account the airborne path of transmission of the disease, the high density of working medical workers in the hospital, the need to provide assistance for other nosologies, the lack of protective equipment, the lack of vaccine prophylaxis at that time, despite the measures taken to limit the spread of the virus in the hospital, 36.5% of medical staff were infected in the "first wave" of COVID-19.

The timely established system in the immunology department of the Center for Clinical laboratory diagnostics (detection of the SARS-CoV-2 virus in April 2020, and subsequently detection of antibodies to the SARS-CoV-2 virus in May 2020), the organization of the necessary laboratory tests (ferritin, LDH, procalcitonin and other tests used for the management of patients with COVID-19) in the department of express diagnostics, made it possible to organize the diagnosis of patients in intensive care and departments of the infectious center at the proper level.

The examination of COVID-19 medical workers in the hospital was put on a planned dynamic basis, the main purpose of which is to assess the duration and intensity of humoral (antibody) protective immunity. At the same time, it was not possible to conduct comparative studies earlier, since there were not enough test kits, and the spectrum of production of antibodies to various SARS-CoV-2 antigens is still studied at the present time [1, 6].

Until today, medical professionals, including in those the field of laboratory diagnostics, have questions about which immunochemical test system to investigate the antibody response, what level of antibodies is protective and to which antigens, which test kits to use when monitoring the disease and evaluating the post-vaccination response.

Aim of the study. To study the duration and intensity of humoral (antibody) immunity by evaluating the production of IgM, IgG immunoglobulins to SARS-CoV-2 in hospital medical workers using immunochemical test systems in dynamics.

Materials and methods. The study included 39 hospital medical workers of various profiles aged from 31 to 68 years who had had a new coronavirus infection of varying severity in April-May 2020, who were not directly involved in treating COVID-19 patients and were observed for one year. It is also characteristic that these recovered medical workers, after recovery, continued to provide medical care at their workplaces in 2020-2021, that is, they could have had repeated contact with SARS-CoV-2.

The duration of production and the level of IgM and IgG antibodies to SARS-CoV-2 were evaluated from samples of patients' blood serum collected in tubes in 1, 3, 6, 9 and 12 months after recovery from COVID-19.

We analyzed the samples on "Vector-Best" test kits (Novosibirsk, Russia) using the method of enzyme immunoassay for the detection of IgM and IgG with a semi-quantitative assessment of the signal/cut-off (S/CO) ratio expressed in arbitrary units (AU) immediately after sampling. These test kits allowed us to detect IgM antibodies to the receptor-binding domain (RBD) of S-protein and to N-protein ("SARS-CoV-2-IgM-EIA-BEST D-5502" ("Vector-Best", Novosibirsk)), as well as IgG class antibodies to the full-format trimerized S-protein of the SARS-CoV-2 virus ("SARS-CoV-2-IgG-EIA-BEST D-5501" ("Vector-Best Best", Novosibirsk)). The level of antibodies was estimated using a semi-quantitative method based on the S/CO ratio, which was calculated according to the kit's instructions as the ratio of the optical density of the sample to the optical density of the critical parameter calculated from the sum of the negative control and the estimated coefficient specified in the kit.

Patients' serum was frozen at the temperature of minus 80 °C.

In July 2021, these samples were tested using the kits developed for the quantitative tests for IgG class antibodies using chemiluminescent analysis on paramagnetic particles on the Architecti 1000SR automatic analyzer with the calculation of the results in AU/ml and subsequent conversion into international BAU/ml units (Bidingantibodyunit). Quantitative analysis performed on this test kit detected IgG class antibodies only to the RBD of the S1 protein of the SARS-CoV-2 virus, which, according to many authors, are associated up to 80% with neutralizing antibodies.

The results were statistically processed using Microsoft Office Excel 2007.

Table 1. Results of the quantitative tests for IgM, IgG antibodies ("Vector-Best" test kit) in dynamics in medical workers who underwent COVID-19

No	Sampling stages, number of patients, n	Class of immunoglobulins	Percentage of positive tests, %	Average S/CO ratio	Spread of parameters
1.	Quantity of antibodies after 1 month, n-39	IgM	59	3,12	0,14–15,28
		IgG	100	10,29	1,26–16,98
2.	Quantity of antibodies after 3 months, n-19	IgM	0	0,19	0,07–0,42
		IgG	100	14,79	4,1–17,88
3.	Quantity of antibodies after 6 months, n-20	IgM	20	1,1	0,1–5,2
			100	14,98	4,57–18,53
4.	Quantity of antibodies after 9 months, n-21	IgM	24	0,95	0,2–3,88
		IgG	100	13,69	2,23–18,02
5.	Quantity of antibodies after 12 months, n-21	IgM	38	1,85	0,2–9,80
			100	12,87	2,1–18,90

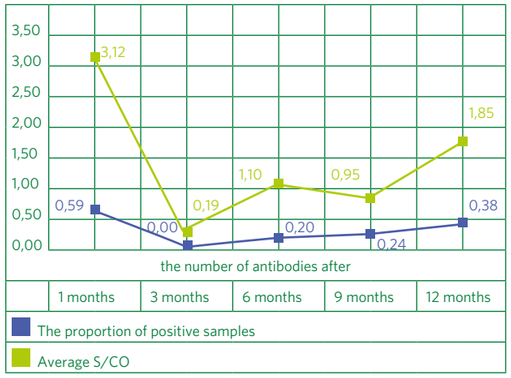

Fig. 1. Dynamics of the average number of IgM class antibodies to SARS-CoV-2 in hospital medical workers analyzed using "Vector-Best" test kit

Results and discussion. About 60% of medical workers tested positive for IgM antibodies to SARS-CoV-2 1 month after the virus was detected, which indicates the presence of an active phase of the COVID-19 infection process (Table 1).

Blood serum analysis in the group of the hospital medical workers 3 months after COVID-19 did not show IgM antibodies in any sample. The serological examination of this group of patients after 6 months showed positive results in 20% of the subjects. The average S/CO ration in this group was 1.1 AU with the range of indicators from 0.1 to 5.2 AU. The analysis for IgM class antibodies to SARS-CoV-2 in medical workers shows a slight increase in the proportion of positive results in the group to 0.24 (24%) (Fig. 1) with an overall slight decrease in the quantity of antibodies of this class to the average values in the group of 0.9 AU and a narrower data spread corridor from 0.2 to 3.88 AU.

Analysis of IgM class antibodies to SARS-CoV-2 12 months after COVID-19 showed an increase in the proportion of positive samples to 0.38 (38%), while higher average S/CO ratio values were noted, amounting to 1.85 AU with a wider data spread from 0.2 to 9.80 AU. Analysis of the material from the examined medical staff showed that, starting from the 6th month, there was a relative and absolute increase in the number of employees who detected IgM antibodies to SARS-CoV-2 with an increase in the quantitative level of antibodies. At the same time, in the period from the 6th to 12th months, IgM antibodies to SARS-CoV-2 were detected in different employees and at least 50% of them maintained this level of antibodies during the period under review.

Such dynamics of the appearance of IgM class immunoglobulins to SARS-CoV-2 in some of the hospital medical staff (an increase in the number of positive samples, S/CO ratio and the average spread of data on this parameter) allows us to consider possibly unfavorable epidemiological working conditions of the examined group, the influence of the epidemiological situation in the form of "waves" of morbidity not only in the hospital, but also in Moscow and in Russia as a whole, and also does not exclude the possible persistence of the SARS-CoV-2 virus in patients who had COVID-19 infection. The latter assumption requires careful verification and a more methodologically complex analysis of not only laboratory tests, but also a more accurate collection of data based on clinical material.

Analysis of the data on the semi-quantitative detection of IgG class immunoglobulins to SARS-CoV-2 showed the presence of antibodies to coronavirus in 100% of the medical staff included in our sample throughout the entire examination period (Table 1).

During the examination of this contingent, there was an increase in the level of S/CO ratios starting from the 1st and up to the 6th month of the examination period (Fig. 2).

The S/CO ratio level of IgG class immunoglobulins to SARS-CoV-2 was 14.79 AU with a data spread ranging from 4.1 to 17.88 AU in the 3rd month after the disease and 14.98 AU with a data spread from 4.57 to 18.53 AU after the 6th month after COVID-19 disease. The dynamics of the humoral (antibody) response in the examined group of medical staff after the 6th month shows a slight drop in both S/CO ratio and the average spread of data. The results of S/CO ratio and the average spread of data in this group of subjects during the 9th and 12th months were 13.69 AU (2.23-18.02) and 12.87 AU (2.1–18.90), respectively.

Such dynamics of IgG class immunoglobulin antibodies to SARS-CoV-2 (Fig. 2) shows that the maximum level of antibodies to S1-S2 subunits of SARS-CoV-2 proteins reaches a peak by the 6th month after the disease, followed by a slight decrease in S/CO ratio level by the 12th month of the follow-up period. Semi-quantitative analysis methods of enzyme immunoassay have a number of limitations: they are not able to accurately show the upper range of antibodies due to the design features of this method, and therefore technologically the detection of IgG class antibodies is preferably carried out by quantitative methods using chemiluminescent analysis.

A comparative study conducted in the group of hospital medical staff to assess the dynamics and level of postinfectious humoral immune response by chemiluminescent analysis on paramagnetic particles to determine IgG class immunoglobulin antibodies to the S1-protein RBD domain gave excellent results for this parameter and a more accurate calculation, primarily of the high number of antibodies (Fig. 3).

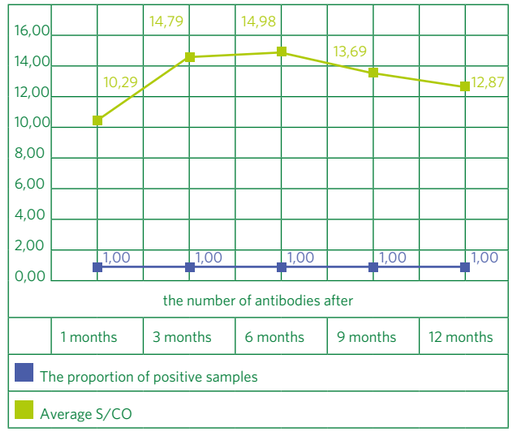

Fig. 2. Dynamics of the average number of IgG class antibodies to SARS-CoV-2 in hospital medical workers analyzed using "Vector-Best" test kit

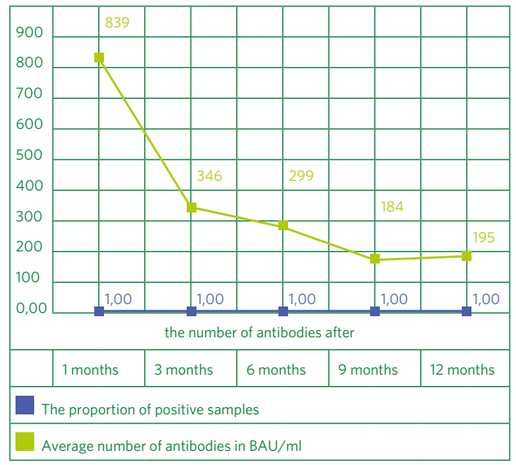

Fig. 3. Dynamics of the average number of IgG class antibodies to SARS-CoV-2 in hospital medical workers analyzed using foreign test kit

Table 2. The results of the study of the number of IgG class antibodies in dynamics in medical workers who had COVID-19 on a foreign test system

No	Sampling stages, number of patients, n	Class of immunoglobulins	Percentage of positive tests, %	Average quantity of antibodies,		Spread of parameters	
				AU/ml	BAU/ml	AU/ml	BAU/ml
1.	Quantity of antibodies after 1 month, n-21	IgG	100%	5905,6	839	183–28299	26–4018
2.	Quantity of antibodies after 3 months, n-19	IgG	100%	2435.8	346	225–7408	32–1052
3.	Quantity of antibodies after 6 months, n-21	IgG	100%	1613,3	229	240–6961	34–988
4.	Quantity of antibodies after 9 months, n-19	IgG	100%	1295,9	184	167–6147	24–873
5.	Quantity of antibodies after 12 months, n-20	IgG	100%	1374,1	195	151–6671	21–947

It was found (Table. 2) that the maximum average level of IgG class antibodies to SARS-CoV-2 was determined in the 1st month after the disease and was 839 BAU/ml.

At the same time, the spread of this parameter ranged from 26 to 4018 BAU/ml. When examining the sera of medical staff after 3 months, the average level of IgG class antibodies to SARS-CoV-2 decreased by 2.4 times and amounted to 346 BAU/ml, the indicators ranged from 32 to 1052 BAU/ml. The quantity of IgG class antibodies to SARS-CoV-2 detected by this test kit continued to decrease by the 6th and 9th months and amounted to 229 BAU/ml (34-988 BAU/ml) and 184 BAU/ml (24-873 BAU/ml), respectively. Further dynamics of IgG class antibodies to SARS-CoV-2 in the group 12 months after COVID-19 shows that the level of IgG class antibodies to SARS-CoV-2 at this point was 195 BAU/ml (21-947 BAU/ml).

We also noted in some patients a significant increase (several times) in the number of IgG class antibodies to SARS-CoV-2 in comparison with the baseline level: in 1 patient — after 3 months and in 2 patients — after 12 months. This dynamic can be explained by the possible reinfection of these employees or the persistence of the virus in the body of those who have been ill.

Currently, discussions are continuing in the scientific community on which IgG class antibodies — a pool of antibodies to full-format trimerized S-protein or to S1-protein RBD — is a more reliable indicator of the level of post-infectious humoral immunity. Our comparative data show different dynamics of IgG class antibodies to SARS-CoV-2 and require further analysis to identify neutralizing antibodies with the calculation of a more accurate correlation with the type of the detected antibody.

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Table 3. The number of employees who had COVID-19, with a protective titer of IgG-class antibodies in dynamics on a foreign test kit

No	Sampling stages	Antibody level in BAU/ml			
		7,1–150	Protective antibody level in BAU/ml		
			150–590	590 and above	Total
1.	Percentage of patients after 1 month. Absolute quantity	19%	38%	43%	81%
2.	Percentage of patients after 3 months. Absolute quantity	19%	38%	43%	81%
3.	Percentage of patients after 6 months. Absolute quantity	37%	47%	16%	63%
4.	Percentage of patients after 9 months. Absolute quantity	52%	43%	5%	48%
5.	Percentage of patients after 12 months. Absolute quantity	63%	26%	11%	37%

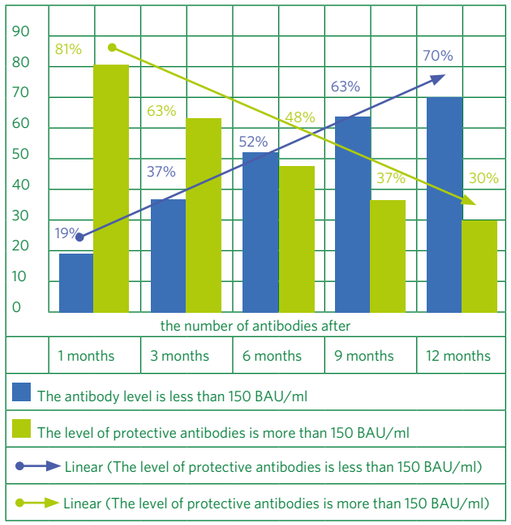

Fig. 4. Dynamics of the average number of IgG class antibodies to SARS-CoV-2 in hospital medical workers analyzed using foreign test kit

There is also a lot of information in the literature about the correlation of IgG class immunoglobulins to the S1-protein RBD domain with a high titer of neutralizing antibodies [9].

There is more and more data in the literature on the number of IgG-class antibodies to the S1-protein RBD domain which make it possible to neutralize the virus itself. Thus, according to a number of different studies [9, 10], the quantity of IgG-class antibodies to the RBD domain of the S1 protein, sufficient for protection, ranges from 150 to 590 BAU/ml. Thus, based on data from different studies and having conducted our own analysis of the results of a quantitative study of antibodies of the IgG class to the RBD domain of the SARS-CoV-2 protein, we can inform that in the group of examined hospital medical staff after 1 month 81% had a minimum protective level (150 BAU/ml) of antibodies, after 3 months — 63%, after 6 months — 48%, after 9 and 12 months — 37 and 30%, respectively (Table 3).

In the period 6 months after the disease, we observe a "cross" of the decrease in the minimum level of protective antibodies (Fig. 4) in our group of examined medical staff, which justifies the need for vaccination six months after the SARS-CoV-2 infection.

In cases where the protective level of IgG antibodies is determined as 300 BAU/590 ml or BAU/ml, the relative number of medical staff after 1 month was 62 and 43%, respectively, after 3 months — 42 and 16%, respectively, significantly decreasing to 6-th month — 25 and 5%, respectively, with average and high level metrics defined by antibodies.

Conclusions. Detection of IgM class antibodies makes it possible to detect the acute stage of the disease, possible recurrent asymptomatic disease, monitor the dynamics of recovery and monitor the persistence of the virus. We identified an increase in the quantity of positive IgM in a certain percentage of hospital medical staff during the examination period without any symptoms, which requires more careful study.

The analysis of hospital medical workers who had been ill for 1 year after suffering COVID-19 by different immunochemical methods showed similar trends in the level of IgG antibodies — first an increase, and then a subsequent decrease. There was a significant variation of values in different patients in the study conducted using two methods. We see a large difference when comparing the average number of antibodies in the 1-3 months after the disease using different methods — enzyme immunoassay and chemiluminescent. The minimum level of protective antibodies showed that the largest number of employees with such a level of protective antibodies (81%) occurred on the 1st month after the disease, and a sufficiently large number of employees have the number of

minimum protective antibodies (48 and 37%, respectively) preserved by the 6th and 9th months after the disease. In cases with a threshold level of protective antibodies up to 300 BAU/ml, the relative number of medical workers decreased to 42% by the 3rd month.

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Information about the authors:

Sergey P. Kazakov — MD, DSc, docent, Head of the Department of Medical Biochemistry and Immunopathology, Russian Medical Academy of Continuous Professional Education of the Ministry of Healthcare of the Russian Federation; Head of the Center for Clinical Laboratory Diagnostics — Chief Laboratory Assistant, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia — **responsible for contacts, gvkg.ckld@mail.ru**, ORCID ID: 0000-0001-6528-1059, eLibrary SPIN: 5560-3931; Researcher ID: C-6644-2018, Scopus ID – 57211351588.

Natalia V. Davydova — MD, doctor of the CDL of the Department of Clinical Infectious and Immunological Research of the Center for Clinical Laboratory Diagnostics, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

Stanislav B. Putkov — MD, Head of the Laboratory of the Department of Clinical Infectious and Immunological Research of the Center for Clinical Laboratory Diagnostics, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

Dmitry V. Reshetnyak — MD, PhD, doctor of the CDL of the Department of Clinical Infectious and Immunological Research of the Center for Clinical Laboratory Diagnostics, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

Irina V. Aristarchova — medical technologist of the Department of Clinical Infectious and Immunological Research of the Center for Clinical Laboratory Diagnostics, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

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Aspects of stem cell autotransplantation treatment in patients with multiple myeloma

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Kostroma I.I.[1], Sidorova Zh.Yu.[1], Semenova N.Yu.[1], Stepchenkova E.I.[2,3], Gritsaev S.V.[1]

[1] *Russian Research Institute of Hematology and Transfusiology, Saint Petersburg, Russia*
[2] *Saint Petersburg State University, Saint Petersburg, Russia*
[3] *N.I. Vavilov Institute of General Genetics, Saint Petersburg branch, Saint Petersburg, Russia*

Abstract. The effectiveness of multiple myeloma (MM) patients' treatment is dependent in particular on the depth of response after autologous stem cell transplantation (autoHSCT). The importance of predictors associated with the quality of response after autoHSCT is due to the possibility of changing the intensity of some stage of transplantation. The aim of the study was to determine the incidence of cases without the improvement of response depth after autoHSCT and to evaluate the distribution of genotype of a number of genes and status of hemopoietic niche cells as a possible predictor of autoHSCT effectiveness in MM patients.

Retrospective analysis of 84 MM patient's data was carried out. Total number of transplants performed was 112 including 84 first and 28 second transplants. The response was determined according to IWG criteria. Status of hemopoietic niche cells was evaluated by histological, immunohistochemistry and morphometric methods.

Improvment of the response depth after the first autoHSCT was recorded in 29 (54.7%) patients. Similar events were higher in the patients with previous VGPR: 57.9% vs 18.2% in patients with PR; p=0.005. There was no difference in other clinical and hematologic parameters between the groups. After the second autoHSCT the variant of response did not change in 4 out of 6 patients. The deepening of response occurred significantly more often in cases with more cells localized on endost; p=0.038.

The results of bone marrow trepanobiopsy can be considered as predictors of a possible improvement in the quality of response or lack thereof in patients with MM after performing autoHSCT.

Keywords: multiple myeloma, autologous stem cell transplantation, response, hemopoietic niche.

Introduction. Multiple myeloma (MM) is a disease that, despite the increasing list of new drugs and their combinations, still remains incurable. The reason for this is the significant variability of molecular genetic aberrations and damage to the hematopoietic microenvironment, which are transformed into plasma cells resistance to specific therapy and clonal evolution, which usually ends in patient's death [1–5].

The main goal in treating MM patients is currently recognized as the achievement of the so-called negative status of minimal residual disease (MRD) based on the results of the study of bone marrow by flow cytometry or next-generation sequencing. This partly explains the expediency of high-dose chemotherapy with the support of hematopoietic stem cells or, in other words, autologous hematopoietic stem cell transplantation (autoHSCT), the implementation of which is associated with further improvement in the quality of the response, including obtaining a MRD-negative status. At the same time, it is impossible to exclude such a scenario when intravenous administration of high-dose melphalan in monotherapy or in combination with other anti-myeloma drugs is not accompanied by a change in the response option to a more favorable one [6–9].

Aim of the study. Assessment of the frequency of cases where MM patients without a complete response (CR) in the pretransplantation period do not show its improvement after autoHSCT. It was also planned to identify changes in the hematopoietic microenvironment characteristic of this clinical situation.

Material and methods. A retrospective analysis of the data of 84 MM patients who underwent autoHSCT was performed.

As a mode of pretransplantation preparation (conditioning regimen), patients were injected with 200 or 140 mg/m2 melphalan on its own or in combination with thiotepa or carfilzomib [10, 11].

The response option according to the IWG criteria [13, 14] was established based on the results of a control examination at the clinic or at the place of residence of patients. The examination period is 60–100 days after autoHSCT.

Status of hemopoietic niche cells was evaluated by histological, immunohistochemistry and morphometric methods. Trepanobioptates of bone marrow were fixed in 10% buffered formalin, decalcified in EDTA solution. Dehydration and paraffin impregnation were performed according to a standardized technique in an automatic histological processor Vip5Jr (Sakura, Japan) in a ready-made solution of IsoPREP and a paraffin medium HISTOMIX (Biovitrum, Russia). Using a rotary microtome (Sakura, Japan), sections with a thickness of 3 microns were made, which were subsequently stained with hematoxylin-eosin and azur-II-eosin. The area of microvessels of the bone marrow vascular niche was immunohistochemically determined using monoclonal antibodies CD34 cl.II (Dako, USA).

The results were processed according to the exact Fischer method, using the "odds ratio" indicator with a 95% confidence interval (CI >confidence interval) and a p-value. To identify the differences in the number of cells on the endost, the Student's t-criterion was used. The statistical significance of the differences was assumed at the value of $p<0.05$.

Results. At the time of transplantation, CR, VGPR and PR were obtained from 31 (36,9%), 19 (22,6%) and 33 (39.3%) patients, respectively. Stabilization of the disease was verified in 1 (1.2%) patient.

According to the results of autoHSCT, an improvement in the quality of response was recorded in 29 patients, which was 54.7% of 53 patients with less than CR. Of these, in 11 patients with previous VGPR and 6 patients with PR, complete response was achieved. A very good partial response was found in 11 patients with previously established PR. In a patient with stabilization of the disease, a decrease in the production of pathological protein by more than 50% was regarded as an achievement of PR.

Thus, an improvement in the quality of response after autoHSCT occurred in 11 (57.9%) of 19 patients with VGPR and in 17 (51.5%) of 33 patients with PR. Despite the almost identical efficacy, the frequency of PR was significantly higher in patients with previous VGPR than in patients with PR: 57.9 and 18.2%, respectively; p=0.005; OR=6.19, 95% CI [1.7-22]. The clinical and hematological indicators of patients with improved response quality after autoHSCT and without it are presented in Table 1.

According to statistical analysis, there were no significant differences between the groups based on the presented indicators. At the same time, the number of patients receiving medications other than bortezomib and lenalidomide in the pretransplantation period was higher in the group with no response: 29.2 versus 13.8% in the group with a response. Also in this group, a smaller number of patients were administered a dose of 200 mg/m2melphalan: 66.6% vs. 79.3%.

The analysis of the morphological features of the bone marrow microenvironment based on trepanobioptates was carried out in 11 patients with improvement and in 7 patients without improvement in the quality of response after autoHSCT.

Differences in the number of cells on the endost were revealed: in the group with improved response quality, there were significantly more of them (2.7±0.3 cells per unit length of the trabecula) than in patients without improvement (1.9±0.2 cells per unit length of the trabecula); p=0.038 (according to the Student's t-criterion). In the group with improved response, morphologically marked places with active osteoblasts and active stromal cells, next to which locally recorded an increased number of microvessels.

Table 1. Clinical and hematological indicators of MM patients with and without improvement in response quality after autologous hematopoietic stem cell transplantation

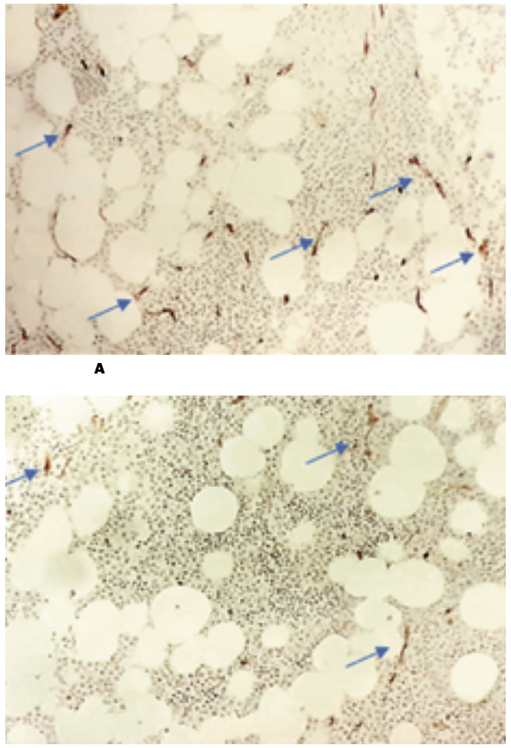
Indicators	Response quality improvement after autoHSCT	
	Yes	No
Number of patients, n	29 (54,7%)	24 (45,3%)
Median age (range), years	56 (38–67)	51,5 (46–68)
Immunochemical variants of MM		
IgG	19 (65,5%)	19 (79,1%)
IgA	9 (31,1%)	4 (16,7%)
BJ	1 (3,4%)	1 (4,2%)
Previous therapy		
bortezomib	29 (100%)	23 (95,8%)
lenalidomide	14 (48,3%)	11 (45,8%)
other	4 (13,8%)	7 (29,2%)
Number of regimens in the previous period		
median	2	2
≤2	23 (79,33%)	17 (70,8%)
≥3	6 (20,7%)	7 (29,2%)
Conditioning regimen		
Mel200	23 (79,3%)	16 (66,6%)
Mel140	3 (10,3%)	4 (16,7%)
other	3 (10,3%)	4 (16,7%)

There were no significant differences in the vessel area. However, in patients with the improvement of the quality of the response, vessel area of up to 9% in the field of view (figure comparable to the area of vessels in healthy bone marrow) were almost twice as likely (Fig. 1) than the compare group: 72.7 and 42.8%, respectively; p=0.33; OR=3.2 mm, 95% CI [0.33–40.3]. In the group with no changes in response quality, 57% of patients had increased vascular density and an increase in the number of adipocytes, especially near bone beams and endosteal zones. The indicators have no statistical significance due to the small sample of patients in the group.

Discussion. The analysis shows that the implementation of autoHSCT is accompanied by an improvement in the quality of response in slightly less than 60% of MM patients who were diagnosed with PR or VGPR in the pretransplantation period. The data obtained correspond to the literature review data [6–8].

The interest in the problem of improving the quality of the response is quite understandable: the achievement of VGPR or PR is almost always one of the indicators, the presence of which is associated with an improvement in the survival rates of MM patients [7, 8, 15]. So, according to M. Cavo et al. [7], CR or nearly CR along with performing tandem autoHSCT, platelet count >150×109/l, hemoglobin >100 g/l at the onset of disease and age younger than 55 years is associated with improved progression-free and event-free survival rate, and in combination with base hemoglobin >100 g/l and serum creatinine less than 177 mol/l >with improved overall survival rate.

Despite the contradictory opinions [16–18], an important condition for improving the quality of the response is the dose of melphalan as part of the conditioning regimen. For example, A. Brioli et al. [16] reported a significant increase in the frequency of ≥VGPR when prescribing melphalan in a dose of 200 mg/m2 compared with a smaller dose: 93% and 76%, respectively; p<0.001. Thus, it is possible that in some patients in our study, the lack of improvement in the quality of the response could be the result of a reduction in the intensity of pretransplantation preparation. However, this factor probably becomes of fundamental importance only when there is a need for a regular change of medications to achieve one of the response options, which may partly indicate the resistance of myeloma cells to therapy, which can be overcome by prescribing the maximum allowable dose of melphalan or a combination of the latter with other drugs.



A

B

Fig. 1. Microcirculation vessels in bone marrow trepanobioptates in patients: A — without response improvement: an increased number ≥9%, B — with response improvement ≤9% (blue arrows). Immunohistochemical reaction with antibodies to CD34cl.II. ×100

At the same time, both our own data and data from other authors suggests the importance of indicators other than the achievement of CR associated with the effectiveness of high-dose consolidation therapy [20, 21]. These undoubtedly include molecular genetic aberrations detected during the MM diagnosis or arising in the natural course of the disease, and the MRD status, which should be considered as another surrogate marker of the myeloma cells sensitivity to treatment [3, 22]. At the same time, the inclusion of new drugs in the induction reginmens, along with the transfer of a number of "back-up" drugs to the first line of therapy and the tendency to prescribe combinations of 4 drugs with different mechanisms of action [1], can reduce or even remove the prognostic potential of the standard indicators used and require the development of prognostic scales with the manipulation of new predictors [23, 24].

According to the study, the findings revealed during the analysis of histological bone marrow preparations may be informative: the density of microcirculation vessels and morphofunctional characteristics of cells on the endost [28–30]. Thus, the association of excessive angiogenesis with the decrease in the survival rate of MM patients after autoHSCT was previously demonstrated [28, 30].

Our own data indicate that histological findings in a bone marrow biopsy should be considered as potential predictors of the effectiveness of autoHSCT in MM patients. Thus, it seems justified to use drugs that inhibit excessive angiogenesis for the treatment of MM patients in whom the ineffectiveness of high-dose melphalan is associated with excessive vascular density in histological bone marrow preparations

Conclusion. Performing up-front autoHSCT, that is, in the first line after achieving one of the response options for induction therapy, primarily involves improving the quality of the response in the post-transplantion period, which, as the study showed, happens not in all cases. A possible solution to this problem may be further intensification of the pretransplantation preparation regime, conducting tandem transplantation and/or consolidating courses in the posttransplantation period. A necessary condition for the personalization of the treatment aid and, accordingly, modification of the treatment algorithm before, during and / or after autoHSCT is a scale that allows us to predict the effectiveness of transplantation based on the results of a comprehensive examination performed after the completion of individual stages. Our own data indicate that histological findings in a bone marrow biopsy should be considered as potential predictors of the effectiveness of autoHSCT in MM patients. Thus, it seems justified to use drugs that inhibit excessive angiogenesis for the treatment of MM patients in whom the ineffectiveness of high-dose melphalan is associated with excessive vascular density in histological bone marrow preparations.

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Information about the authors:

Ivan I. Kostroma — MD, PhD, Senior Researcher of the Republican Center for Bone Marrow Transplantation, Russian Research Institute of Hematology and Transfusiology of the FMBA of Russia, St. Petersburg, Russia — **responsible for contacts**, **obex@rambler.ru**, ORCID ID: 0000-0003-3768-0831; eLibrary SPIN: 781916 1520-6784; Researcher ID: ABE-9298-2021

Zhanna Yu. Sidorova — PhD in Biology, Senior Researcher, Russian Research Institute of Hematology and Transfusiology of the FMBA of Russia, St. Petersburg, Russia.

Natalya Yu. Semenova — PhD in Biology, Senior Researcher, Russian Research Institute of Hematology and Transfusiology of the FMBA of Russia, St. Petersburg, Russia.

Elena I. Stepchenkova — PhD in Biology, Head of the Laboratory of Mutagenesis and Genetic Toxicology, St. Petersburg Branch of the N.I. Vavilov Institute of General Genetics of the Russian Academy of Sciences, St. Petersburg, Russia.

Sergei V. Gritsaev — MD, DSc, Head of the Republican Bone Marrow Transplantation Center, Russian Research Institute of Hematology and Transfusiology of the FMBA of Russia, St. Petersburg, Russia.

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Ultrasound-guided intra-articular injection of hyaluronic acid for osteoarthritis of the carpometacarpal joint of the thumb

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Grechukhin D.A., Kerimov A.A., Naida D.A.

Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia

Abstract. Osteoarthritis (OA) is the most common disease in orthopedic practice, which is characterized by chronic pain in the joints and joint dysfunction. OA of the carpometacarpal joint (CMCJ) of the thumb is the most common type of hand osteoarthritis.
The aim of the work was to evaluate the effect of ultrasound-guided intraarticular injection of hyaluronic acid (HA) for osteoarthritis of the CMCJ of the thumb (stage II–III Kellgren–Lawrence) in patients with persistent pain syndrome for 3 months and with failure of NSAIDs therapy.
The study included 18 patients with stage II–III CMCJ OA who received intraarticular injection of HA drugs with a mass of 2400,000 kDa in the volume of 1.0 ml twice with an interval of 10 days. Demographic characteristics, body mass index, stage of osteoarthritis (CMCJ), severity of pain syndrome according to visual analog scale (VAS) and upper limb function assessed with the DASH questionnaire (disabilities of the arm, shoulder, and hand) were evaluated. Data was collected at the start of the study and in 1, 3 and 6 months after the first injection. DASH and VAS scores were compared using a variance analysis of repeated measurements. The non-parametric Friedman criteria was used to check the differences in proportions. The value of $p<0.05$ was considered statistically significant.
There was a significant improvement in DASH values in 1, 3 and 6 months after injection. There were statistically significant differences between DASH values at the start of treatment and 6 months after therapy: $\chi^2=45.7$; df 3, $p<0.001$. There was also a significant decrease in the average VAS score during the study in 1, 3 and 6 months after the first injection. The differences in VAS score at the start of treatment and in 6 months reached statistical significance: $\chi^2=47.1$; df 3, $p<0.001$. Improvement occurred after 1 month after first injection and persisted throughout the entire follow-up period for 6 months.
HA injections provide pain relief and improve upper limb function in patients who are resistant to analgesics and physiotherapy. A significant decrease in pain was observed as early as 1 month after the first intra-articular injection of GNC. The obtained results already allow us to recommend the use of HA drugs for CMCJ OA.

Keywords: CMCJ, osteoarthritis, hyaluronic acid, glucocorticoids.

Introduction. Osteoarthritis (OA) is the most common disease in orthopedic practice. It is characterized by chronic joint pain and joint function impairment. According to the definition, osteoarthritis combines a heterogeneous group of diseases of various etiologies with similar biological, morphological, clinical manifestations and outcomes, which stem from damage to all joint elements: cartilage, subchondral bone, synovial membrane, ligaments, capsules, periarticular muscles. Currently, the incidence of osteoarthritis is growing rapidly, which is explained by the increase in life expectancy [1, 2].

Both conservative and surgical methods are used to slow the disease progression. According to the current guidelines of societies dedicated to OA research, its treatment includes the use of non-pharmacological methods (physical therapy, physiotherapy), nonsteroidal anti-inflammatory drugs (NSAIDs), symptomatic slow-acting drugs (Symptomatic Slow-acting Drugs for Osteoarthritis — SYSADOA, formerly known as "chondroprotective agents") and intra-articular administration of drugs.

In recent years, there has been more and more data on the effectiveness of hyaluronic acid (HA) in OA treatment, but its role is still not clearly defined. Some recommendations for OA treatment note that HA drugs are used in cases when the symptoms persist despite the use of NSAIDs [1, 2]. At the same time, Osteoarthritis Research Society International (OARSI) does not give clear-cut recommendations on the use of HA drugs for OA treatment and suggests their use only after assessing the risks, comorbidities, disease phenotype, localization of the primary lesion, as well as patient's preferences.

There is a steady trend towards a comprehensive personalized approach to OA therapy (that is, in relation to a specific patient), using not only HA drugs, but also systemic drugs. Most associations and societies recommend oral administration of the SYSADOA drug group as the first step in the drug treatment. This drug group is characterized by slow onset of effect and the need for long-term administration. To obtain an effect in a shorter period of time or if oral therapy is ineffective, injectable drugs of the SYSADOA group are actively used. I.e., in the multicenter open-label study PRIMULA with the use of glycosaminoglycan-peptide complex (Rumalon®) in the treatment of patients with OA in the absence of the effect of previous oral therapy, a high efficiency of parenteral course was noted with respect to reducing pain and the need for painkillers [3]. Rumalon® has been studied in long-term controlled studies in OA of the knee and hip joints. The effect on the symptoms of OA of the joints of the hand can be assumed only on the basis of these data.

With regard to the effect of drugs of the SYSADOA group on the OA of the hand joints, there is data on the effectiveness of diacerein, an anti-inflammatory drug whose mechanism of action is based on the suppression of the activity of interleukin-1β — one of the most significant cytokines in the pathogenesis of OA. The results of the study showed that, compared with oral chondroitin sulfate, diacerein (Diaflex (Rompharm)) showed a faster (2–4 weeks) clinical effect on the symptoms of OA, including cases with damage to small joints of the hand, which is probably due to the peculiarities of the mechanism of action of the drug. Also, when using Diaflex, a more pronounced aftereffect was observed [4].

Osteoarthritis of the first carpal-metacarpal joint (risarthrosis) is the most common type of OA that occurs when the joints of the hand are affected, and its incidence is steadily increasing [12, 14]. Risarthrosis is accompanied by pain, a decrease in the strength of the hand grip, stiffness, limited amplitude of movements, which affects the function of the hand and, thus, reduces the patient's quality of life. Currently there is no gold standard in the treatment of risarthrosis [11]. Conservative treatment aims to relieve pain and preserve the functionality of the thumb, including its stability, mobility and strength. Glucocorticosteroids (GCS) which can be used to treat synovitis immune to conservative therapy are most often administered as intra-articular injections in the treatment of this OA type. However, the benefits of this treatment are debatable, since frequent use of GCS can have pronounced side effects, including calcification of the periarticular structures, degeneration of tendons and ligaments, as well as deterioration and loss of elasticity of articular cartilage [5, 8]. High-level evidence data (IIb) has been published, indicating that HA could be a safe alternative to corticosteroids in the treatment of risarthrosis [15]. From a technical point of view, the introduction of HA preparations into the joint cavity presents a certain challenge, since this joint is small, and in the absence of proper experience, it is possible to damage the articular surfaces with a needle. Some authors recommend using ultrasound navigation during the HA introduction to facilitate intra-articular insertion and minimize unwanted side-effects [11]. We have studied the effectiveness of intra-articular administration of the HA preparation in the treatment of risarthrosis.

Materials and methods. The study included 18 patients with risarthrosis. Inclusion criteria: age over 40 years, lack of positive dynamics after NSAID therapy during the month before the start of the study, persistent pain syndrome during the last 3 months. Exclusion criteria: severe concomitant diseases (including neurological, systemic or autoimmune) and the history of injuries and operations on the first carpocarpal joint, as well as intra-articular administration of GCS and HA drugs.

The study involved patients with stage II-III OA of the first carpocarpal joint according to the Kellgren–Lawrence classification (Fig. 1).

Patients' mean age in the study group was 58.1 years (41-73) (Fig. 2).

The average duration of pain at the time of inclusion in the study was 4.89 months (median 5.0 months), the median body mass index was 24.0±2.45 in the sample.

Drug administration technique. The wrist was placed on the back surface, while the ultrasound sensor was oriented parallel to the first metacarpal bone. Then the sensor was slowly moved proximally or distally until the hypoechoic gap was revealed, defining the base of the first metacarpal bone of the thumb and the distal end of the trapezoid bone. The injection site was disinfected with povidone-iodine and alcohol. The injection was performed using a simple "free hand" technique under the control of the ultrasound sensor. Access to the joint cavity was provided by a 25G needle. For intra-articular administration, an HA preparation with a molecular weight of 2.4 million kDa (Hyalurom) was used, the volume of administration was 1.0 ml. After 10 days, the procedure was repeated.

The DASH questionnaire (disabilities of the arm, shoulder, and hand) was used as a subjective assessment of the hand function and the effectiveness of the treatment [6]. The dynamics of the pain syndrome was assessed using a visual-analog scale (VAS). Data collection was carried out before the start of the study and in 1, 3 and 6 months after the first injection.

The DASH questionnaire allows you to characterize the health status of patients and the presence of symptoms (impaired hand function) during the previous week. The questionnaire includes 30 items in which the patient assesses the degree of restriction when exercising upper limb movement (21 items), the severity of pain at rest and pain associated with activity, tingling, weakness and stiffness (5 items), as well as the impact on social activities, work, sleep and self-esteem (4 item). Each item has 5 response options reflecting the severity of a particular symptom, and the number of points for the response options is directly proportional to the severity of the impairement. The obtained results are summarized and used to calculate the total DASH value in the range from 0 (no violations) to 100 (severe disability, inability to use the upper limb).

VAS is an 11-point scale ranging from 0 ("no pain") to 10 ("the strongest possible pain"). A successful result is defined as an improvement in VAS score by more than 50% from the original one.

DASH and VAS estimates were obtained at the times indicated above and compared using a variance analysis of repeated measurements. The nonparametric Friedman criterion was used to check the differences in

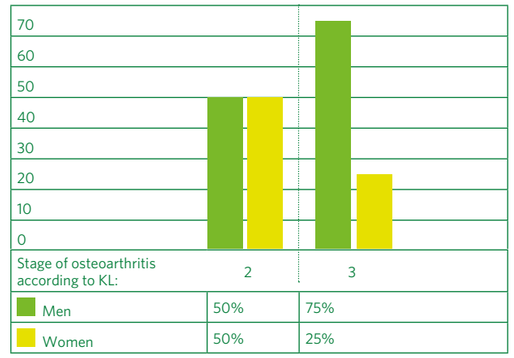

Fig. 1. Distribution of patients depending on gender and stage of osteoarthritis according to Kellgren-Lawrence

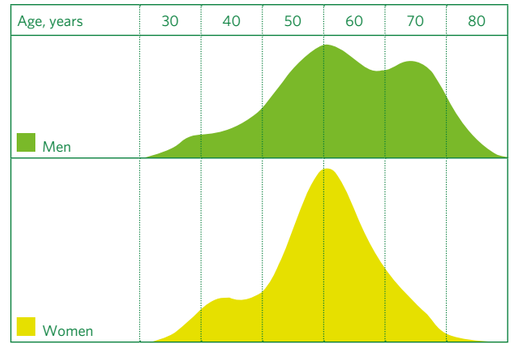

Fig. 2. Distribution of patients by gender and age

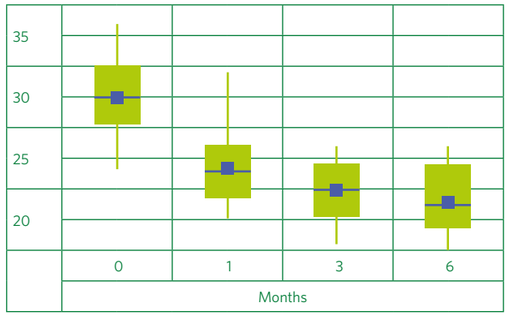

Fig. 3. DASH questionnaire scores in dynamics before the introduction of HA and 1, 3 and 6 months after

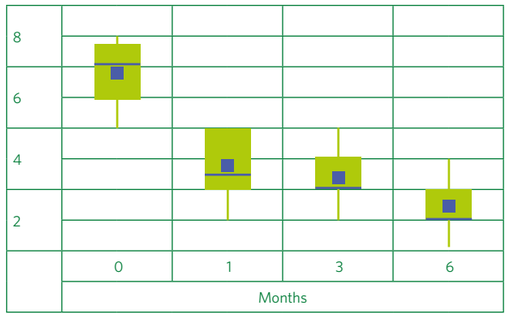

Fig. 4. VAS values in dynamics before the introduction of HA and 1, 3 and 6 months after

In the course of the study, we found that HA injection provided pain relief and improved upper limb function in patients with resistance to analgesics and physiotherapy

proportions. Statistical analysis was carried out using the Jamovi statistical package (version 2.2.2). The value of $p<0.05$ was considered statistically significant

Results. There was a significant improvement in DASH in 1, 3 and 6 months after the injection. When using the nonparametric Friedman criterion, statistically significant differences were obtained between DASH values before treatment and 6 months after therapy: $\chi2=45.7$; df 3, $p<0.001$ (Fig. 3). Pairwise analysis using the Darbin-Connover criterion demonstrated a significant improvement in results (a decrease in the DASH score) already 1 month after the start of treatment ($p<0.001$). Moreover, the differences remained valid at each control time point.

There was a significant decrease in the average VAS score in 1, 3 and 6 months after the first injection. The differences in VAS scores before the start of treatment and 6 months after it reached statistical significance: $\chi2=47.1$; df 3, $p<0.001$ (Fig. 4).

Improvement occurred as early as 1 month after the start of treatment and persisted throughout the follow-up period for 6 months.

Discussion. In the course of the study, we found that HA injection provided pain relief and improved upper limb function in patients with resistance to analgesics and physiotherapy. A significant decrease in pain was observed as early as 1 month after the first intra-articular injection of the HA preparation of our choice (Hyalurom). The obtained results allow us to recommend the use of HA drugs for risarthrosis, however, repeated studies are necessary 12 months or more after the introduction of HA to assess the long-term results.

Hyaluronic acid is one of the main components of synovial fluid, it provides hemostasis of articular fluid, acts as a lubricant, is able to absorb part of the impact, thereby reducing the load on the articular cartilage. It is known that the concentration of HA in the articular fluid decreases with osteoarthritis [13], which determines the relevance of intra-articular administration of the preparation. In routine practice, GCS drugs are most often used as injections into the joint for pain syndrome in OA, which can lead to long-term unwanted side-effects. According to published data, the use of HA preparations could provide the same effective reduction of pain syndrome and improvement of limb function as GCS drugs, however, it has a satisfactory safety profile [5, 7, 9-11].

Conclusion. It is important to note that a comprehensive approach showed the most successful results of osteoarthritis treatment. The combined use of basic SYSADOA therapy, short courses of NSAIDs and orthosis of the affected joint with intra-articular injection of HA allows for the drastic increase of the remission period and improve patient's quality of life.

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Information about the author:

Dmitry A. Grechukhin — MD, orthopedic traumatologist, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia — **responsible for contacts, dr.grechukhin@gmail.com**, ORCID ID: 0000-0001-7163-7744.

Artur A. Kerimov — MD, doctor of the highest category, Head of the Trauma Department of the CTiO, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

Daria A. Naida — surgeon of the Trauma Department of the CTiO, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

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Resection of the chest wall with Codubix alloplasty polymer material for treating recurrent sarcoma

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Vasiukevich A.G., Fedosyuk A.M., Puchkov S.N., Fokin A.V.

Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia

Abstract. A 77-year-old patient was operated on for local recurrence of pleomorphic sarcoma of the left half of the chest wall with the involvement of three ribs in the tumor process. Successful extensive resection of the chest wall with Codubix plastic material made it possible to preserve the skeleton. Periodic accumulation of uninfected exudate can be considered as reactive plervritis, which required periodic evacuation of the contents of the left pleural cavity.

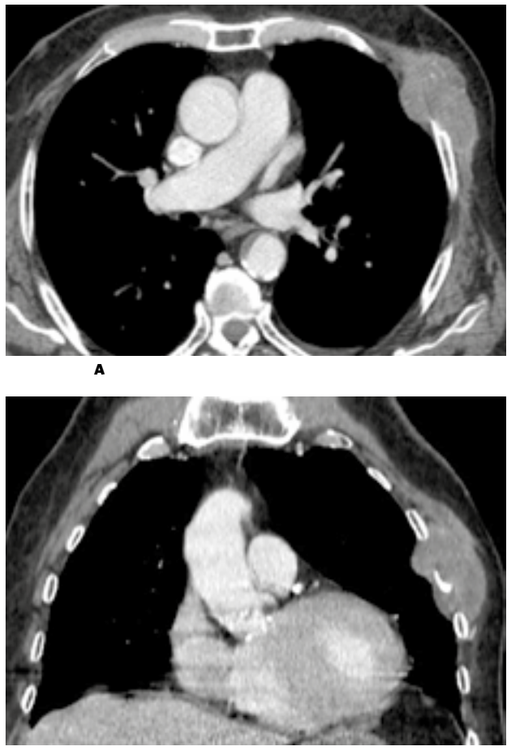
Keywords: chest wall surgery, chest wall sarcoma.

Introduction. Soft tissue sarcomas often recur [1–7], and when localized on the chest wall, a recurrent tumor can grow into the ribs and sternum [6]. After curative resection of the chest wall, there is almost always a need for plastic surgery of fairly large in terms of area defects. The main requirement for the methods of such surgeries is the preservation of the skeleton function, which ensures adequate breathing. Numerous methods of defect restoration are usually associated with the use of some rigid biological or synthetic material and advanced tissue flaps of the patient [5]. Such clinical cases are quite rare in the practice of thoracic surgery departments and are of interest in terms of the use of various reconstructive techniques, taking into account the localization of the tumor, its size and histological shape.

Clinical case. Patient P., 77 years old, in November 2017 noticed the appearance of a tumor on the anterolateral surface of the chest, in the projection of the left pectoralis major muscle. The tumor slowly increased in size and by the time the patient sought medical help by November 2018 reached the size of 7.0×6.0×4.0 cm. He was hospitalized at the Burdenko Main Military Clinical Hospital.

Histological examination of the tumor material obtained by trepanobiopsy: histological picture and immunophenotype of pleomorphic cell sarcoma of high malignancy with muscle differentiation (expression of Myo D1). No distant tumor metastases were detected.

On 19.12.2018 the patient underwent surgery. The intraoperative revision revealed that the tumor was located in the external parts of the large and small pectoral muscles and grew into the dentate muscles. A wide excision of the tumor was performed with the removal of the nipple-areolar complex on the left, resection of the large and small pectoral, dentate muscles and removal of axillary tissue. Resection was performed within



A

B

Fig. 1. Recurrent tumor at the level of IV, V, VI ribs on the left

pathologically unchanged tissues, retreating from the edge of the tumor from 2.0 to 4.0 cm.

There were no complications in the postoperative period. Based on the planned histological examination of the removed material, which was consistent with the histological structure determined by the results of the preoperative examination of the biopsy material, the diagnosis was "Undifferentiated pleomorphic sarcoma of the soft tissues of the chest wall on the left pT2bN0M0G3". No tumor tissue was detected in the edges of the resected material. Chemoradiotherapy was not performed. The wound healed by primary intention healing. The patient was discharged in good condition.

In October 2019, the progression of the disease was discovered, which manifested by a pathological fracture of the V rib on the left on 10/25/2019. When coughing, he started experiencing pain in the chest on the left. The patient sought medical care at the 1472 Military-Navy clinical hospital. When examined locally: the postoperative scar tissue on the anterolateral surface of the breast on the left was loose. Under the scar tissue,

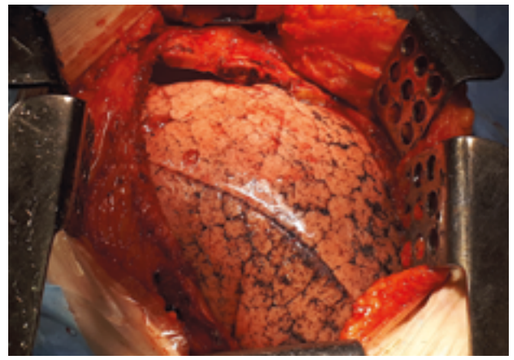


Fig. 2. Chest wall defect after resection

in the projection of the IV–VI ribs, a mass lesion of up to 100 mm in the largest dimension is found. The tumor is fixed and moderately painful on palpation. Computed tomography (CT) of 29.10.2019 (Fig. 1) showyв a solid pathological mass on the anterior chest wall on the left, at the level of the IV, V and VI ribs, between the midclavicular and anterior axillary lines, measuring 100×63×40 mm, with a nodular contour and a pathological fracture of the V rib.

For further treatment, the patient was hospitalized at the Burdenko Main Military Clinical Hospital. At the tumor conference on 11.11.2019, a decision was made to proceed with surgical treatment in the volume of chest wall resection on the left with combined plastic surgery. In order to assess surgical risks, ultrasound duplex scanning of brachiocephalic arteries was performed. The patient was diagnosed with stenosing atherosclerosis of the carotid arteries on both sides with a predominant lesion of the left carotid artery — narrowing of the lumen up to 80%. Taking into account anamnestic data on three episodes of acute cerebrovascular accident in 2008, December 2018 and January 2019 with the formation of intracerebral post-ischemic cysts, hemianopsia, reflex upper right-sided hemiparesis, as well as dyscirculatory encephalopathy of the II degree, an eversion carotid endarterectomy on the left was performed on 04.12.2019.

On the 12.12.2019, chest wall resection (IV, V and VI ribs) with alloplasty with synthetic Codubix material was performed. The operation was started with a wide arcuate incision of soft tissues in the projection of the VI rib. The flap, including the skin and subcutaneous tissue, is mobilized in the cranial direction to the armpit. The tumor had clear contours with its size corresponding to the CT data. The tumor involved the V rib and the muscles of the adjacent intercostal spaces. Chest wall resection was performed (including IV, V and VI ribs) as a single block with the tumor (Fig. 2). The distance

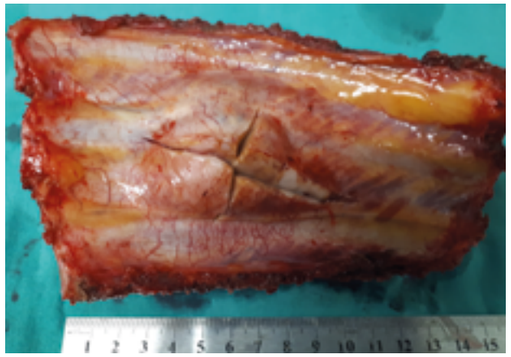


Fig. 3. Resected part of the chest wall with the tumor

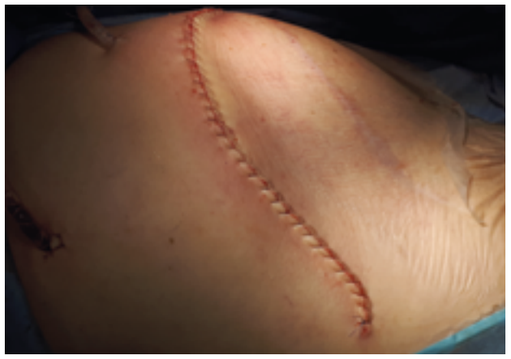
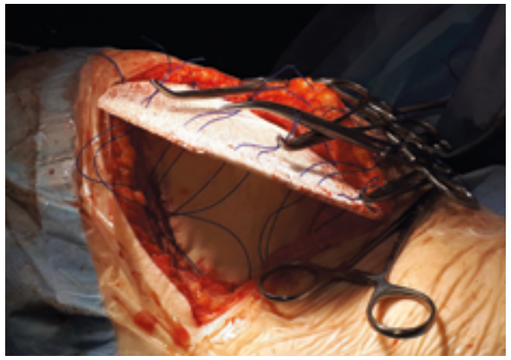
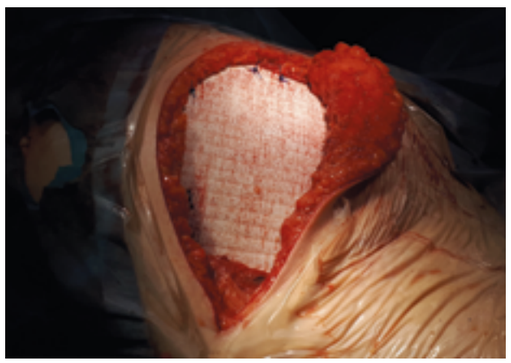


Fig. 5. View after suturing the wound



A



B

Fig. 4. Stages of replacement of the chest wall defect with synthetic Codubix material

from the edge of the tumor to the resection line is from 3.5 to 5.5 cm (Fig. 3).

With the help of special scissors, an allograft from the Codubix plate was cut out according to patterns from a rigid polyethylene film, exceeding the size of the chest wall defect by 2.5 cm along each edge. The allograft is fixed to the anterior and posterior segments of the resected ribs, as well as to the III and VII ribs by U-shaped prolenic sutures (Fig. 4).

Silicone drainage tubes were installed into the pleural cavity and the space between the graft and subcutaneous tissue. The allograft was covered with a pre-formed flap of skin and subcutaneous tissue, the wound was sewn in layers (Fig. 5). There were no complications in the postoperative period. During histological examination of the removed material, the histological form of the recurrent tumor does not differ from the primary one. According to the decision of the postoperative tumor conference, the patient was recommended to undergo adjuvant chemotherapy with anthracyclines. At the beginning of September 2020, the patient given a generally satisfactory condition had a swelling in the area of the surgery on the chest wall. According to CT data, fluid was detected both in the left pleural cavity and above the allograft. Exudate with a total volume of up to 2 liters was punctually evacuated at the patient's place of residence.

On 28.10.2020, the patient was hospitalized in the Department of thoracic surgery of the Burdenko Main Military Clinical Hospital. According to ultrasound examination and CT from 03.11.2020 (Fig. 6), there was no fluid over the allograft, which is in the previous adequate position, in the left pleural cavity — about 700 ml of exudate.

On 03.11.2020 silicone drainage was installed in the left pleural cavity, the exudate was evacuated, after four days the drainage was removed. In the next five

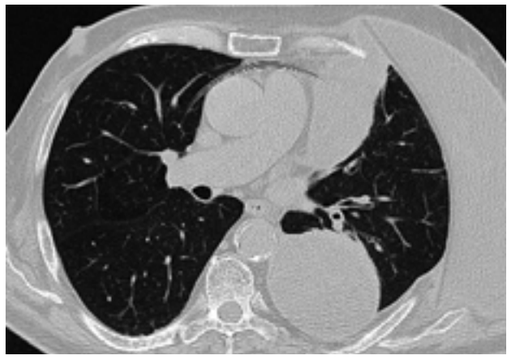
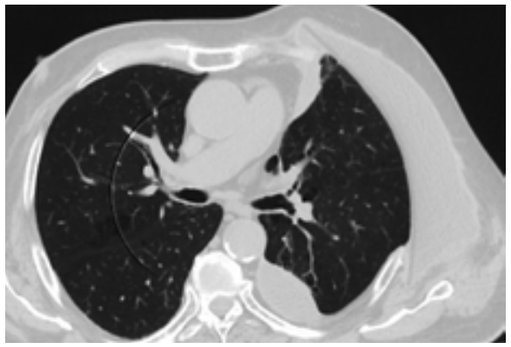


Fig. 6. Exudate in the left pleural cavity and above the allograft



B

Fig. 7. The position of the Codubix allograft is stable

Thus, the presented clinical case shows the possibility of replacing extensive chest wall defects in recurrent sarcoma with the new synthetic Codubix material with a good functional result. At the same time, when using this plastic material, there is a side effect—recurrent reactive pleurisy, accompanied also by the accumulation of exudate over the allograft, which requires periodic removal of fluid from the pleural cavity. In such cases it is advisable to perform examination of the patient, control ultrasound of the pleural cavity and chest wall at least once every 3 months or in case of characteristic complaints

days, no accumulation of exudate was observed during control ultrasound. The patient was discharged in good condition.

The last hospitalization of the patient on 01.07.2021 in the Burdenko Main Military Clinical Hospital was also associated with the accumulation of exudate in the left pleural cavity (350 ml) and over the allograft (450 ml) (Fig. 7). The fluid from the left pleural cavity was removed using a plastic catheter, and fluid located above the allograft was punctured. Bacterioscopy and culture of the removed exudate performed during the last two hospitalizations did not show any pathological microflora. No tumor cells were detected during cytological examination either. There is currently no progression of the tumor process.

Conclusion. Thus, the presented clinical case shows the possibility of replacing extensive chest wall defects in recurrent sarcoma with the new synthetic Codubix material with a good functional result. At the same time, when using this plastic material, there is a side effect — recurrent reactive pleurisy, accompanied also by the accumulation of exudate over the allograft, which requires periodic removal of fluid from the pleural cavity. In such cases it is advisable to perform examination of the patient, control ultrasound of the pleural cavity and chest wall at least once every 3 months or in case of characteristic complaints.

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Information about the authors:

Andrey G. Vasiukevich — MD, PhD, Head of Thoracic surgery department, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia — **responsible for contacts, agvasiukevich@mail.ru**, ORCID ID:0000-0003-1167-9592

Andrey M. Fedosyuk — MD, oncologist surgeon, plastic surgeon, head of department No. 33 of the Radiological Center, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

Sergey N. Puchkov— MD, PhD, oncologist surgeon of the Radiological Center, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

Alexander V. Fokin — MD, resident of the Department of thoracic surgery, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

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Asymptomatic bacteriuria

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Vasechko E.S., Pavlov M.Yu.

Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia

Abstract. Understanding asymptomatic bacteriuria can help clinicians in selecting rational antimicrobial therapy and improve disease outcomes.

Keywords: bacteriuria, urinary tract infections, asymptomatic bacteriuria, infectious complications, antimicrobial therapy, «sterile» leukocyturia, urethral pain syndrome in women.

The concept of asymptomatic bacteriuria could help physicians in matters of rational aintimicrobial therapy (AMT) of urinary tract infections and improve treatment outcomes. The detection of bacteria, WBC and RBC in the urine is a diagnostic sign of urinary tract infection (UTI). The concept of "significant" bacteriuria (SB) was introduced to distinguish the microorganisms introduced through contamination from living and reproducing bacteria in the urine and urinary tract (UT) when collecting material [1]. Interpretation of SB, asymptomatic bacteriuria (AB), "sterile" leukocyturia (SL) in combination with clinical information helps to make the optimal decision. "Significant" bacteriuria is characterized by the presence and growth of one or more bacterial species in the urine and UT in the titer, depending on the "masking" factors (Table. 1), biological features of the disease, microorganisms and contamination exceeding the threshold. The term implies the true presence and growth of bladder bacteria and (or) bacteria originating in the bladder from infected tissues in the urine, and it is also numerically expressed by urine bacterial count (UBC), that is, the quantity of bacterial cells per 1 ml of urine, and is measured in CFU/ml.

Urine sampling technique affects the probability and degree of material contamination, which is reflected in the UBC values:

- suprapubic puncture and simultaneous catheterization of the urinary tract — $>10^3$ CFU/ml;
- on the first day in the presence of a permanent urinary catheter — $>10^3$ CFU/ml, starting from the second day — $>10^5$ CFU/ml.

For "slow-growing" microorganisms (coagulase-negative staphylococci, Mycobacterium tuberculosis, fungi Blastomyces dermatitidis, Histoplasma capsulatum, Cryptococcus neoformans, Coccidioides immitis, C. Posadasii, Haemophilus influenzae) any UBC is significant. In patients with UTI, bacteria are detected in a quantity exceeding 10^5 CFU/ml. UBC in the range of 10^3–10^4 CFU/ml can be detected in healthy people. On the other hand, the "standard" titer ($>10^5$ CFU /ml) should be reduced

in the presence of factors "masking" bacteriuria. Table 1 shows the factors that "mask" the SB titer.

The presence of any of these factors reduces the diagnostic threshold of UBC. In uncomplicated infections, as a rule, one type of microorganism is plated. In patients with prolonged catheterization, it is sometimes possible to plate 4 or more different types of microorganisms. The microbial count of individual co-existing species is often $<10^5$ CFU/ml, which is probably explained by the competition in the colony, the dynamic balance of antimicrobial protection and virulence factors [1]. Table 2 shows the diagnostic thresholds of the microbial count for certain categories of patients.

Urethral pain syndrome in women is defined as the presence of periodic dysuria (stranguria localized in the urethra, usually during urination, daytime, nighttime pollakiuria) in the absence of UTIs or other pathologies [2]. The syndrome is most often found in women, less often in men and children [3]. Urethral pain syndrome significantly reduces patients' quality of life, accompanied by increased irritability, anxiety, dysphoria and depression [4].

Urethral pain syndrome is a disease of ambiguous etiology. Diagnosis is largely based on symptoms, and research is aimed at excluding other conditions affecting the lower UT. The absence of a generally accepted and evidence-based treatment scheme leads to the use of many different methods that depend on the doctor's practices and beliefs [5]. Despite the fact that the criterion of UPS is the absence of a proven infection, in about 2/3 of cases treatment begins with local or systemic antibacterial therapy (ABT) [6]. To date, the paradigm of understanding the role of ABT in UPS has changed, starting with the assessment of the impact of such therapy and up to the question of its expediency.

Bergman A. (1989) noted that with tetracycline therapy, the success rate is not higher than with placebo [7]. Burkhard F.C. (2004) and his colleagues suggest that treatment with doxycycline is justified, since 70% of the studied population actually benefited from treatment [8]. Kaur H. (2007) and colleagues claim that antibiotics (azithromycin or doxycycline) as the first line of therapy, followed by low doses to prevent relapse (nitrofurantoin 50 mg per day, ofloxacin 200 mg per day) and prevent recurrent UTIs are necessary [9]. Modern studies, for example, Swamy S. (2018), Sinha S. (2019), confirm the effectiveness of long-term ABT for UPS [10, 11].

Recurrent uncomplicated lower urinary tract infection (rUTI) in women is characterized by the occurrence of two or more symptomatic episodes of UTI within 6 months or three within a year [12]. Recurrent uncomplicated lower urinary tract infection significantly reduces the quality of life (more than 50% have 6 episodes of UTI per year, 15% — about 12 episodes per year) [13]. Members of the Enterobacteriaceae family, including E. coli, recognized as etiological factors of rUTI [14], which are symbionts of almost all biotopes of the macroorganism [15], under certain conditions initiate an infectious inflammatory process.

Table 1. Factors "masking" the bacterial count

Factors
High diuresis with frequent urination
On the first day after the installation of a permanent catheter
Early stages of "urethral syndrome" in women
Slow-growing microorganisms
Sampling urine during therapy
Tuberculosis
Systemic mycoses
Obtaining culture material by suprapubic puncture

Recurrence of a UTI is associated in more than 2/3 of cases with a previously detected strain of E. coli. Activation of genotype-determined virulence factors leads to regular relapses and symbiotic existence of a bacteria colony in the UT in a relapse-free period [16].

Leukocyturia accompanied about a quarter of cases of bacteriuria in titer $<10^2$ CFU/ml, in other rUTI cases, AB was observed, which was sufficient for another recurrence of UTI [17]. Significant bacteriuria reaches the diagnostic level with 10^2 CFU/ml, and in combination with monitoring of the average number of WBC (more than 1.5 times the baseline level) can be considered a diagnostic marker for detecting the transition to the active phase of inflammation and UTI recurrence [18].

The diagnostic significance of UBC in patients with manifesting UTI is secondary, the diagnostic hypothesis is confirmed by the clinical picture, data from laboratory and instrumental examinations. Cultures are necessary to clarify the etiology of the process and determine the possibility of treatment correction if necessary.

Asymptomatic bacteriuria is a "significant" bacteriuria, regardless of the level of leukocyturia, characterized by the absence of clinical manifestations associated with a UTI. The incidence of AB reaches 15% and is higher in women and men aged 65 to 80 years, after 80 it reaches 40-50%. Most patients with AB will never develop symptomatic UTI and there will be no side effects. For some categories of patients, AB initiates a high probability of systemic infection and infectious complications (IC), affecting the course and outcome of the disease. AB cannot be considered an infection as long as there are no signs of inflammation of UT organs.

Table 2. Diagnostic thresholds of microbial count

Patient categories	Microbial count, CFU/ml	Additional requirements
Outpatients	$>10^5$	
Asymptomatic women	$>10^5$	3 cultures — same species microorganisms or 1 culture + nitrin test
Asymptomatic men	$\geq10^4$	2 cultures — same species microorganisms or 1 culture + nitrin test
Patients with clinical manifestations:		
women with urethral pain syndrome (UPS);	$\geq10^3$ (in the present time)	The microbial count has lost its significance* as a factor in SB
acute uncomplicated infections;	$\geq10^4$	1 culture + leukocyturia (≥20)
recurrent uncomplicated UTIs in women;	$\geq10^2$–10^3	
chronic complicated infections*	$\geq10^5$	Not required

*Criterion (>105 CFU/ml) was widely used in screening and epidemiological studies. In the presence of factors "masking" bacteriuria, the threshold of UBC decreases to >10>2-104 CFU/ml.

Table 3. Categories of patients who are indicated for antibacterial therapy of asymptomatic bacteriuria

Patient	Comments
Pregnant women	Therapy duration — 4–7 days
Endourological interventions	A short targeted (not empirical) course is 1–2 doses; the first one can be administered 30–60 minutes before the procedure

The prevalence of bacteriuria increases with age. In women over 60 years old, the frequency of AB is 10%, increasing with age up to 20–30%. In men over 70 years old, the prevalence of AB is 5–10%. To diagnose AB in elderly men, a single detection of bacteriuria in the quantity of $>10^5$/ml is sufficient. In women, a two-time isolation of one microorganism type in the quantity of $>10^5$ cfu/ml is required. *P. mirabilis* AB is particularly dangerous. In the absence of treatment, struvite stones often develop in such cases. P.mirabilis AB should not be left untreated in diabetics, pregnant women and compromised patients, since their risk of developing a complicated infection is significantly higher [1]. Normal urine is usually sterile. Table 3 shows the categories of patients for whom ABT of AB is indicated (based on the clinical recommendations of the American Society of Infectious Diseases for the Treatment of AB, 2019) [19].

The lack of AB treatment in pregnant women can lead to premature birth, pyelonephritis, and the child's insufficient weight. Screening of bacteriuria in pregnant women is performed in the early stages, at the first visit to the women's clinic. The optimal duration of the ABT course varies in the range of 4–7 days (depending on the antibacterial drug). The shortest effective course should be used.

Endourological interventions with possible injury to the UT mucosa in conditions of varying degrees of

Asymptomatic bacteriuria is a "significant" bacteriuria, regardless of the level of leukocyturia, characterized by the absence of clinical manifestations associated with a UTI. The incidence of AB reaches 15% and is higher in women and men aged 65 to 80 years, after 80 it reaches 40–50%

Table 4. Categories of patients who are not indicated for antibacterial therapy of asymptomatic bacteriuria

Categories	
Infants and children	In elderly patients with delirium ABT for AB is performed after a diagnostic search for other causes of neurocognitive disorder
Healthy adults	
Non-pregnant women in pre- and postmenopause	
Patients with diabetes mellitus	
Patients with permanent urinary catheters and spinal cord injuries	
Kidney recipients 1–3 months after transplantation (terms vary in different sources)	

Table 5. Causes of "sterile" leukocyturia

No.	Causes
1.	Contamination during urine sampling:
	vaginal contents;
	prepucial content
2.	Non-communicable diseases
	tubulointerstitial nephritis (analgesic nephropathy, beta-lactam antibiotics);
	stones and foreign bodies;
	the use of cyclophosphamide;
	genitourinary injury;
	tumors of the bladder or kidney;
	glomerulonephritis;
	rejection of a kidney transplant
3.	Infectious diseases
	chlamydial or gonococcal urethritis;
	tuberculosis and fungal infections;
	systemic fungal lesions;
	viral cystitis (herpes, adenoviruses, varicella-zoster);
	leptospirosis, Haemophylus influenza;
	bilgarciosis;
	infections of adjacent areas;
	appendicitis;
	diverticulitis;
	prostatitis

wound contamination (clean, conditionally clean, dirty) differ in the frequency of systemic IC. A short surgical course (according to urine culture), aimed at reducing the degree of contamination of UT in AB, reduces the frequency of systemic infectious complications.

Antibacterial therapy in a number of patients with AB does not improve outcomes, delays the period of hospitalization, increasing treatment costs, antimicrobial resistance, and the frequency of Cl. Difficile infection.

Table 4 shows the categories of patients with AB for whom it is advisable to refrain from ABT (based on the clinical recommendations of the American Society of Infectious Diseases for the Treatment of AB, 2019) [19].

UT infections are one of the most common reasons for prescribing antimicrobials. Treatment of AB without convincing reasons does not benefit most patients and could be harmful [20].

"Sterile" leukocyturia without bacteriuria is not the dominant feature in the diagnosis of UTIs, requires a differentiated assessment and should not be attributed to infection without sufficient grounds. The causes of SL can be infectious, non-communicable diseases, infections of adjacent areas. SL may persist for some time after a UTI. Table 5 shows the conditions associated with "sterile" leukocyturia.

Conclusion. Prevention of urinary tract infections is a complex problem. Since 2008, numerous studies have described the treatment of AB in patients for whom the American Society of Infectious Diseases did not recommend treatment (grade D recommendation) [21]. Current recommendations, in our opinion, do not fully reflect the possible variants of clinical scenarios of asymptomatic bacteriuria, which requires further research in this area.

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Information about the authors:

Evgeniy S. Vasechko — MD, senior urologist of the Emergency Urology Department, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia — **responsible for contacts, urology@vk.com**, ORCID ID: 0000-0001-7349-3844; Researcher ID: AAX-8840-2021.

Michael Yu. Pavlov — Head of the Emergency Urology Department, Main Military Clinical Hospital named after academician N.N. Burdenko Russian Defense Ministry, Moscow, Russia.

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