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Бариатрическая хирургия у пациентов пожилого возраста
Bariatric surgery in elderly patients

Анестезиологический мониторинг ЭЭГ у гериатрических пациентов в ЛОР-хирургии
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Peroneus longus tendon autograft for anterior cruciate ligament reconstruction: a systematic review

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The endoscopy room of the Federal State Budgetary Institution Federal Scientific and Clinical Center of the Federal Medical and Biological Agency of Russia. Head of the endoscopy department, PhD D.V. Sazonov (right) and endoscopist, doctor of medical sciences, honored doctor of the Russian Federation S.L. Khankin (on the left) perform an examination of the gastrointestinal tract.

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BARIATRIC SURGERY IN ELDERLY PATIENTS

A.V. Smirnov[1], V.R. Stankevich[1], E.S. Danilina[1], V.I. Sychev[1], E.M. Voronets[1], Vl.I. Sharobaro[2], N.A. Solovyev[1], Yu.V. Ivanov[1], R.I. Khabazov[1]

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ABSTRACT

BACKGROUND: *Bariatric surgery is indicated to patients with morbid obesity and aged 18–60 years. In older aged patients, such surgery can also be taken into consideration, however, the procedure of selecting the patients is not included into the clinical recommendations, which determines the topicality of the research.* ***AIM:*** *To establish a protocol for surgical treatment of morbid obesity in patients older than 60 years.* ***METHODS:*** *The research included 800 patients operated during the period of 2018–2023 at the Federal State Budgetary Institution "Federal Scientific and Clinical Center" of the Federal Medical-Biological Agency of Russia due to the presence of morbid obesity, of which 38 had an age of 61 and older. All the patients underwent only two types of surgery — laparoscopic longitudinal resection and laparoscopic Roux gastric bypass surgery. All the patients of the older age group underwent personalized selection for surgical treatment, screening procedures were arranged in order to detect the senile asthenia syndrome and, retrospectively, to stratify them using the GeriBari prognostic scale. During one year of follow-up, the remote results were assessed in all the patients along with the quality of life.* ***RESULTS:*** *There were no postoperative complications in the older age group, the 30-day mortality was 2.6% (1 patient has died from the complications of the coronaviral infection). The weight loss was found to be significantly less in the older age group (61 and older) comparing to the main group of patients (18–60 years): for laparoscopic longitudinal resection — 55.5% versus 73%, respectively (p=0.01), for laparoscopic Roux gastric bypass surgery — 58% versus 77.5% (p=0.0008). The remission of type 2 diabetes was achieved in 70.6% of the patients of the older age group. The quality of life among the patients of the older age group, even with the slight decrease of the excess body weight, was significantly better 12 months after surgery.* ***CONCLUSION:*** *Among the elderly patients with morbid obesity, it is possible to perform bariatry surgeries safely and effectively when following the proposed protocol.*

Keywords: *bariatric surgery; gastric bypass; longitudinal gastrectomy; obesity; old age; frailty.*

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BACKGROUND

Bariatric surgery, according to clinical recommendations issued by the Ministry of Health of the Russian Federation (ID:28), is indicated to patients aged 18–60 years with morbid obesity, in which conservative procedures had no effect. The comments specify that, in the other age groups, surgical treatment can also be taken into account, however, the procedure for selecting the patients was not established [1]. The number of the elderly population irreversibly grows world-wide. According to official data from the Federal State Statistics Service, in Russia as of the 1st of January 2023, there were a total of 29.38 million people aged older than 60, or approximately 20% of all the citizens[1]. With this, the maximal occurrence of obesity is reported specifically in the age group of 60–70 years and, according to some estimates, reaches 57.76% in men and 80.99% in women [2].

Physiological changes occurring with aging can affect the efficiency of metabolic and bariatric surgery, the rate of postoperative complications and the ability of elderly patients to restore after surgery [3–5]. Just a while ago, the majority of clinical recommendations worldwide concerning the treatment of obesity in the elderly age, have prioritized conservative procedures [6], however, in the last 10 years, a steady growth was reported in the number of trials on the efficiency and safety of bariatry surgeries in patients aged over 60–65 years. The treatment results were positive, while the risk of complications and lethal outcomes was more related with the presence of severe concomitant diseases, smoking, cognitive disorders and senile asthenia syndrome [7]. In 2022,

[1] Federal State Statistics Service [Internet]. Distribution of population by age groups. Access mode: https://rosstat.gov.ru/folder/12781.

БАРИАТРИЧЕСКАЯ ХИРУРГИЯ У ПАЦИЕНТОВ ПОЖИЛОГО ВОЗРАСТА

А.В. Смирнов[1], В.Р. Станкевич[1], Е.С. Данилина[1], В.И. Сычев[1], Е.М. Воронец[1], Вл.И. Шаробаро[2], Н.А. Соловьев[1], Ю.В. Иванов[1], Р.И. Хабазов[1]

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АННОТАЦИЯ

Обоснование. *Бариатрическая операция показана больным морбидным ожирением в возрасте 18–60 лет. В более старшем возрасте такая операция также может рассматриваться, однако порядок отбора пациентов в клинических рекомендациях не оговорён, что и обусловливает актуальность исследования.* ***Цель исследования*** *— разработать протокол хирургического лечения морбидного ожирения у пациентов старше 60 лет.* ***Методы.*** *В исследование включено 800 пациентов, прооперированных в период 2018–2023 годов в ФГБУ ФНКЦ ФМБА России по поводу морбидного ожирения, из них 38 были в возрасте 61 года и старше. Всем пациентам выполнялось только два вида операций — лапароскопическая продольная резекция и лапароскопическое гастрошунтирование по Ру. Все пациенты старшей возрастной группы прошли персонифицированный отбор на хирургическое лечение, проводились скрининг на синдром старческой астении и ретроспективно стратификация по прогностической шкале GeriBari. В течение года наблюдения у всех пациентов оценивали отдалённый результат и качество жизни.* ***Результаты.*** *Послеоперационных осложнений в старшей возрастной группе не было, 30-дневная летальность составила 2,6% (погиб 1 пациент от осложнений коронавирусной инфекции). Потеря веса оказалась значимо меньше в старшей возрастной группе (61 год и старше) в сравнении с основной группой пациентов (18–60 лет): при лапароскопической продольной резекции — 55,5% против 73% соответственно (p=0,01), при лапароскопическом гастрошунтировании по Ру — 58% против 77,5% (p=0,0008). Ремиссия сахарного диабета 2-го типа достигнута у 70,6% пациентов старшей возрастной группы. Качество жизни пациентов старшей возрастной группы даже при небольшой потере избытка массы тела статистически значимо улучшилось в течение 12 месяцев после операции.* ***Заключение.*** *У пожилых больных морбидным ожирением возможно безопасное и эффективное выполнение бариатрических операций при соблюдении предлагаемого протокола.*

Ключевые слова: *бариатрическая операция; гастрошунтирование; продольная резекция желудка; ожирение; пожилой возраст; старческая астения.*

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the recommendations from the American Society for Metabolic & Bariatric Surgery (ASMBS) and from the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) have stated that the age itself cannot be the contraindication for undergoing surgery, however, thorough selection is recommended among the aged patients, including the tests for senile asthenia syndrome [8]. Senile asthenia is the central geriatric syndrome, including the age-associated decrease of the physiological reserves and of the functions in the organism, which makes it more vulnerable for the effects from the internal and external factors, which determined the high risk of unfavorable events [9]. For the purpose of screening evaluation of senile asthenia, multiple scales were proposed, however, in Russia, only the “Age is not a drawback” questionnaire was validated, approved by the clinical recommendations on “Senile asthenia” (approved by the Ministry of Health of the Russian Federation, ID: 613) [10].

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In the accessible national literature, we could not find any research works with the assessment of senile asthenia among the bariatric surgery patients. Thus, the conduct of national research aimed at developing the protocol for selecting patients from the older age group for bariatric surgery, is still topical.

Research aim — to develop a protocol for surgical treatment of morbid obesity in patients older than 60 years.

METHODS

Research design

A retrospective comparative single-center research was arranged with the evaluation of the direct and remote results of surgical treatment of morbid obesity in two groups of patients — 18–60 years inclusive (the main group) and aged 61 and older (the elderly group). The medical aid for the patients with morbid obesity was provided in accordance with the "Obesity" clinical recommendations from the Ministry of Health of the Russian Federation (ID: 28).

Conformity Criteria

Inclusion criteria: body mass index over 40 kg/m^2; body mass index ranging from 35 to 40 kg/m^2 with the presence of diseases associated with obesity and requiring constant therapy (type 2 diabetes, hypertensive disease, chronic cardiac insufficiency, sleep apnea syndrome).

Non-inclusion criteria: presence of oncological diseases with currently under treatment or follow-up; acute myocardial infarction; acute disorders of cerebral circulation; thromboembolic complications of cardio-vascular diseases in the last 2 months; terminal stages of renal injury; decompensated state of the organs or systems; presence of depression or psychiatric disorders.

Research facilities

The research was carried out within the premises of the Federal State Budgetary Institution "Federal Scientific and Clinical Centre for Specialized Types of Medical Care and Medical Technologies of the Federal Medical-Biological Agency" (FSBI Federal Scientific and Clinical Center of the Federal Medical-Biological Agency of Russia), where during the time period from 2018 until 2023, a total of 800 bariatry surgeries were conducted in morbid obesity patients.

Medical Procedure Description

All the patients were treated with strict following the protocol of perioperative management and performing the bariatric manipulations, which was previously described by the authors of the present article [11]. Additionally, patients aged from 61 and older had a screening assessment for the presence of senile asthenia syndrome using the "Age is not a drawback" questionnaire (table 1). With the result of 0–4 points, no additional procedures were conducted, while when having 5 points and higher, the patient was referred to the geriatrician and the further tactics was defined together during the consilium. Special attention was paid to the consultation by the Psychiatrist, with the presence of depression or psychiatric disorders being considered a contraindication for surgical treatment.

Table 1

The "Age is not a drawback" questionnaire

Did you lose 5 kg and more during the last 6 months?*	Yes/No
Do you experience any restrictions in everyday life due to decreased vision or hearing?	Yes/No
During the last year, did you have any injuries caused by falling, or episodes of falling without traumas?	Yes/No
Did you feel depressed, sad or anxious within the last weeks?	Yes/No
Do you have problems related to memory, orientation or planning abilities?	Yes/No
Do you suffer from urine incontinence?	Yes/No
Do you have difficulties moving around the house or outdoors (walking up to 100 m or climbing a single staircase)?	Yes/No
For each positive answer, 1 point is scored. Legend (interpretation): ≤2 points — no senile asthenia, 3–4 points — probable pre-asthenia, 5–7 points — probable senile asthenia.	

Note. * Meaning unintentional weight loss. If the patient was losing weight voluntarily (by following the special diet or regular physical activity), the point is not scored.

The first surgery in the patient aged older than 60 years was carried out after accumulating the experience of 100 bariatric interventions in other age categories. The surgeries in patients older than 61 were carried out by a single surgeon with the assistants being the physicians having an experience of not less than 100 episodes of assisting during the bariatric surgeries (no trainees were allowed to participate in the surgical team). Anesthesiological aid was performed by the anesthesiologists trained on the specific features of anesthetic support in bariatry patients and having an employment experience of not less than 5 years in the same occupation.

Two types of bariatry surgeries were used — the laparoscopic gastric bypass (GB) and the laparoscopic longitudinal gastric resection (LGR). The surgery technique in all the patients was the standard one with its description provided in earlier publications from the authors [11].

Methods for registration of outcomes

Retrospective assessment was used to evaluate the risk of bariatric surgery based on the GeriBari prognostic scale (table 2), developed based on the analysis of the data bases of The Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program in the USA (40,199 operated geriatric patients) [12]. Partially dependent functional status was reported in case of the necessity of the aid of another person during the everyday activities.

During the postoperative period, the rates of postoperative complications (classification by Clavien-Dindo, 2004), of repeated hospitalizations and of the mortality within the nearest 90 days from the surgery were evaluated.

After 12 months, the evaluated parameters included the percentage of excess weight loss, the rates of type 2 diabetes remission, as well as the cases of developing thromboembolic complications, acute myocardial infarction or acute disorders of the cerebral circulation along with the mortality.

The percentage of excess body mass index loss (%EBL) was calculated as the ratio of weight loss to the baseline excessive body weight. In order to calculate the excessive body weight, the ideal body weight was subtracted from the body weight value before surgery (body length in centimeters – 100). For example, if the person having a body height of 170 cm had a body weight of 120 kg before surgery, and after 1 year his weight has decreased to 80 kg, the %EBL equals 80%: 100×(120–80)/(120–(170–100))=100×40/50.

The remission of diabetes type 2 was defined as the level of glycosylated hemoglobin (HbA1c) being less than 6.5% for not less than 3 months in the absence of sugar-reducing therapy.

Separate evaluations in patients of the older age group were performed to define the quality of life in accordance with non-specific SF-36 questionnaire (Short Form-36) before bariatric surgery and after 12 months.

Table 2

GeriBari Prognostic scale [12]

Parameter	Points
Roux gastric bypass (comparing to longitudinal gastric resection)	6
Partially dependent functional status	6
Intake of anticoagulants	5
Chronic kidney disease	5
Oxygen dependence	4
Myocardial infarction in the past	4
Chronic venous insufficiency	4
Venous thromboembolic complications	3
“Major” heart surgeries in the past	3
Chronic obstructive pulmonary disease	3
Gastroesophageal reflux disease	2
Surgery time	2 for each hour
Interpretation	
Low risk (less than 6% of serious complications)	≤14
High risk of (more than 6% of serious complications)	>14

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Ethical review

All the research participants have signed the voluntary informed consent for treatment and surgery. The conduct of the research was approved by the local Ethics Committee of the Federal State Budgetary Institution "Federal Scientific and Clinical Center" of the Federal Medical-Biological Agency of Russia (protocol No. 11, dated November 11, 2019).

Statistical analysis

The sample size was not preliminarily calculated.

During the statistical analysis, the nonparametric methods were used. The data were presented as the median with defining the upper and lower quartiles (Me [Q1; Q3]). The differences between quantitative characteristics were calculated using the Mann-Whitney test. The comparison of qualitative characteristics was done using the $\chi 2$ (chi-square) method. The software used was IBM SPSS 27. The obtained differences were considered statistically significant in case when the *p* value was <0.05 (95% of confidence).

RESULTS

Research sample (participants)

During the research period, the in-patient examination procedures for the purpose of defining the indications for bariatric surgery at the Federal State Budgetary Institution Federal State Budgetary Institution "Federal Scientific and Clinical Center" of the Federal Medical-Biological Agency of Russia were arranged for 74 individuals older than 60 years (64 years [62.5; 65.5]). The bariatric surgery was approved for 38 (51.35%) individuals aged 64 years [62.5; 67] with maximum age of 74 years. There was no significant difference in the age of the patients between the operated ones and those assigned for conservative treatment tactics (p=0.08). In all the cases, the decision of excluding the patient from the bariatric surgery group was made individually during the multidisciplinary consilium and it was based on the evaluation of the surgery risk due to the somatic status, the presence of senile asthenia syndrome, as well as the subjective factors, such as the patient's compliance and the readiness of strict following the recommendations, as well as the need for social-household aid and care. The characteristics of the research participants are provided in table 3.

When analyzing the data in the group of operated patients, it was found that only in 2 (5.3%) cases, the results of using the "Age is not a drawback" screening questionnaire were 0 points, 1 point was scored by 3 (7.9%) patients, 2 points — by 16 (42.1%), 3 points — by 15 (39.5%) and 4 points — by 2 (5.3%). In 23 (60.5%) patients, senile asthenia syndrome was not found, while 15 (39.5%) were diagnosed with pre-asthenia. Thirty-six out of 38 (94.7%) operated patients had mobility difficulties, 16 (42.1%) have reported problems with memory, orientation and planning abilities, 15 (39.5%) cases were associated with restrictions caused by diminished hearing and vision, 13 (34.2%) patients felt depressed and sad, other 13 (34.2%) had episodes of falling within 1 year and 6 (15.7%) had urinary incontinence-related problems. Constant intake of 5 and more medicinal products was reported for 9 (23.7%) patients; 8 (21%) had chronic pain syndrome; 8 (21%) have informed about living alone.

Table 3

Characteristics of the patients

Parameter	Older group *n*=38	Main group *n*=762	*p*
Males, *n* (%)	8 (21)	214 (28)	>0.05
Females, *n* (%)	30 (79)	548 (72)	>0.05
Age, years	64 [62; 66]	42 [35; 50]	-
Baseline body mass index, kg/m^2	45 [62.5; 67]	42 [35; 50]	>0.05
Type 2 diabetes, *n* (%)	17 (44.7)	318 (41.7)	>0.05
Laparoscopic Roux gastric bypass, *n* (%)	21 (55.3)	381 (50)	>0.05
Laparoscopic longitudinal gastric resection, *n* (%)	17 (44.7)	299 (39.2)	>0.05
Post-operative complications, Clavien-Dindo I–II, *n* (%)	0	6 (0.8)	>0.05
Post-operative complications, Clavien-Dindo III–IV, *n* (%)	0	20 (2.6)	>0.05
Mortality within 90 days from surgery, *n* (%)	1 (2.6)	1 (0.1)*	>0.05
%EBL in 12 months	56.5 [45; 69.5]	75 [66.5; 82.25]	<0.00001

Note. * Cause of death — traffic accident.

The assessment of elderly patients using the GeriBari prognostic scale has shown high surgery risk only for 5 (13.2%) patients (table 4).

Primary findings

None of the patients of the older age group had surgical complications in the perioperative period. The postoperative bed day count did not differ from that in the main group (3–4 days). During the next 90 days after surgery, there were 2 hospitalizations caused by heart rhythm disorder and by hypertensive crisis. One female patient (2.6%) aged 66 has died on day 14 after LGR with the cause being the multi-organ insufficiency and multisegmental pneumonia with a background of diagnosed coronaviral infection, with this background, there were no any signs of surgical complications found.

The remote results were accessible for evaluation in all the patients.

A man aged 65 has died 11 months after laparoscopic gastric shunting due to acute cardiovascular insufficiency.

The numbers of the loss of excess body weight after 12 months are provided in Fig. 1. Twelve months later, the %EBL after the LGR was 55.5% [39.15; 69.75], after GB — 58% [54.5; 69]. Three patients after LGR had the %EBL values not exceeding 1/3 (17%, 20% and 28%, respectively). The maximal %EBL value after LGR was 93%; the minimal %EBL after GB was 40% with the maximal being 102%, however, the statistical differences between two types of surgeries were insignificant (p=0.43). In the main group, the %EBL was significantly higher both for LGR (73% [61; 80], p=0.01) and for the GB (77.5% [67; 85], p=0.0008).

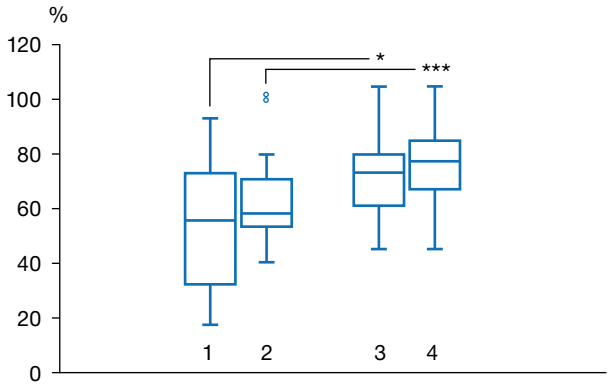

Fig. 1. Loss of excess body weight in 12 months after bariatric surgery: 1 — laparoscopic longitudinal gastric resection (older age group), 2 — laparoscopic gastric bypass surgery (older age group), 3 — laparoscopic longitudinal gastric resection (main group), 4 — laparoscopic gastric bypass surgery (main group). The differences were statistically significant: p <0.05 (*) and p <0.001 (***).

Before surgery, type 2 diabetes, requiring sugar-reducing therapy, was diagnosed in 17 persons, with two of them receiving insulin therapy, while the other 15 were taking tableted medicines. In 12 months, 16 (94%) of patients had clinical improvement. Complete remission was achieved in 12 cases (70.6% of the

Table 4

Characteristics of the patients in accordance with the GeriBari scale

Parameter	Patients *n*=38 (%)
Roux gastric bypass (comparing to longitudinal gastric resection)	21 (55.3)
Partially dependent functional status	15 (39.5)
Intake of anticoagulants	4 (10.5)
Chronic kidney disease	2 (5.3)
Oxygen dependence	0
Myocardial infarction in the past	3 (7.9)
Chronic venous insufficiency	4(10.5)
Venous thromboembolic complications in the past	1 (2.6)
“Major” heart surgeries in the past	0
Chronic obstructive pulmonary disease	1 (2.6)
Gastroesophageal reflux disease	6 (15.8)
Surgery time, min	110 [70; 160]
Interpretation	
Low risk (≤14)	33 (86.8)
High risk of (>14)	5 (13.2)

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total number of diabetes patients and 80% of the total number of patients taking only tableted drugs). Both patients receiving (before surgery) insulin therapy were switched to taking only tableted medicines. Two patients had achieved a decrease in the dosage of the tableted antihyperglycemic drugs. Only 1 (6%) patient aged 64 years after GB had his diabetes course characteristics at the same level.

The quality of life of the patients in the older age group has significantly increased (Fig. 2), with this, we did not note any relation between the parameters of the quality of life and the extent of losing excess body weight. Even in patients with insignificant weight loss (%EBL 17–28%), significant improvement was reported in the quality of life.

DISCUSSION

Over the past decades, the developed countries were showing an increase in the duration of life along with the simultaneous growth of the occurrence of obesity. The percentage of adipose tissue increases with age, while the muscle/bone mass decreases as a result of lower levels of basal metabolism, decreased production of anabolic hormones, as well as due to the decreased reactivity to thyroid hormones and leptin. If younger individuals have a muscle mass of approximately 40%, to the age of 75 it corresponds to about 25% of the whole body volume. Shortening of the volume of skeletal muscles results in a decrease in the rate of basic metabolism after the age of 20 years by 2–3% a year, and after the age of 50 — by 4% every year [13].

The advances in medical technologies have provided a possibility of performing bariatric interventions in elderly patients with a sufficient level of safety, which is why we can see a progressive growth in the number of publications in this issue. Some authors suppose that bariatric surgery gives comparable results in younger and elderly patients, while the other trials have proved a longer postoperative bed day count and lesser excess body weight loss among the patients older than 60 years [14, 15].

The recent systematic review and meta-analysis conducted by J. Kapała et al. [16] and including the operated patients older than 70 years (*n*=3923), has shown that, in one year after surgery, the mean loss of excessive body weight was 54.66%, the improvement of the diabetes course was reported in 50% of observations, arterial hypertension — in 36%, reflux-esophagitis — in 50%, sleep apnea — in 36% and hyperlipidemia — in 25%. The rate of postoperative complications was ~2% with the fatal outcomes showing 1%.

P. Gerber et al. [17], based on the analysis of the Swedish register involving 57,215 operated patients, inform that patients older than 60 years have strong

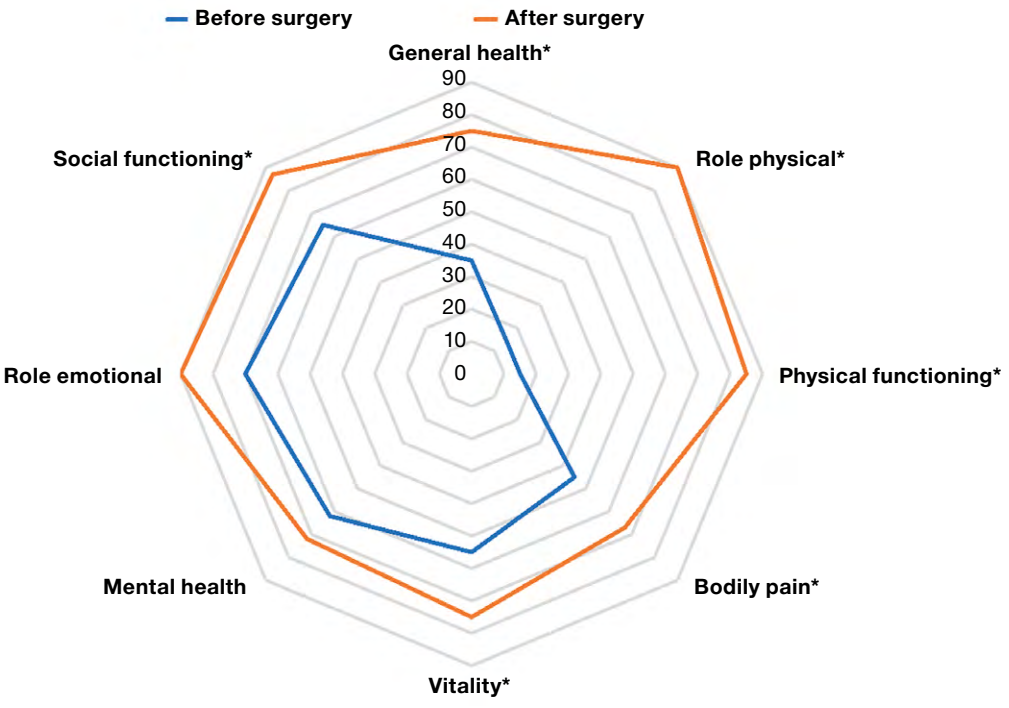

Fig. 2. Changes in the quality of life among the morbid obesity patients of the older age group after bariatric surgery (* marks the parameters with the statistically significant differences).

and stable improvements of the physical and obesity-related quality of life even 5 years after bariatric surgery. As for the metabolic results, the conducted trials confirm the efficiency of bariatric surgery in terms of treating diabetes. However, longer duration of diabetes causes irreversible loss of beta-cells, which is why the metabolic mechanism of GB and LGR is predictably less effective in the older age comparing to younger patients. A number of research works has shown the absence of differences in the efficiency of the LGR and GB in terms of diabetes in elderly patients, which is also confirmed by our results [18, 19].

Despite the already accumulated vast data on bariatric surgeries in elderly patients, there are controversial opinions on the postoperative complications. Thus, according to data from USA registries, the mortality after bariatry surgeries among the elderly is 0.27% (3 times higher than in younger cohort) [12]. Upon analyzing the Scandinavian obesity register, the similar mortality value was observed among the elderly — 0.27%, while the total mortality was at the level of 0.03% [20]. However, according to data from the national register of the Netherlands, the 30-days mortality after bariatric surgery did not differ in the younger and older cohorts, being 0.2% [21]. In a recent review by N.Ç. Başaran [22] it was reported that the mortality after bariatric surgery among the elderly in various trials is within the ranges of 0–0.34%, and this level is comparable to the mortality data for cholecystectomy (0.2–6%).

The investigators have no unified opinion on the best variant of bariatric surgery in elderly from the point of view of the risks and results, but only two options of standard surgical interventions were considered — the LGR and the Roux GB. LGR is the most commonly conducted bariatric surgery world-wide. A meta-analysis by S. Giordano et al. [23] involving 2259 patients after laparoscopic LGR from 11 research works, has shown comparable results from the point of view of safety and resolving the associated diseases among the elderly and the younger patients, even though in the patients of the older age group, lower weight loss was noted. A randomized multicenter research has shown that, in patients older than 65 years, GB comparing to LGR is associated with better loss of excess body weight (68% versus 60%, respectively; p=0.044) and higher rates of diabetes remission (85.7% versus 46.15%, respectively; p=0.27) [24]. According to data from M. Kermansaravi et al. [25], obtained as a result of the systematic review and "umbrella" meta-analysis (6 meta-analyses), the elderly persons undergoing LGR had lower (comparing to GB) mortality parameters, the same was shown for the early and late complications (by 55%, 55% and 41%, respectively), however, the noted findings also included lower efficiency in terms of the results related to weight loss and to the recurrences of obesity-related disease. The research by J.S. Frieder et al. [26] has analyzed the largest single-center experience of bariatric surgery among the elderly patients (LGR and GB were carried out in 2486 morbid obesity patients) and has shown that the number of complications was significantly higher in the GB group comparing to LGR (27.7% versus 9.4%; p <0.01). In general, the majority of research works note that LGR in elderly patients is a safer surgery comparing to the GB.

The principles of selecting older patients for bariatric surgery are still not clearly developed, while in practice they often involve individualized decisions by the consilium of physicians. The IFSO recommendations (2022) state that one of the objective criteria for patient assessment could be the presence of senile asthenia syndrome [8]. This recommendation is based on the research by A.B. Gondal et al. [7], involving 21,426 patients aged from 60 years and older, in which it was shown that the weakness evaluation scale could be used as a method for stratifying the risks for patients before bariatric surgery. In the research performed by the group headed by R. Sebastian [27], based on the analysis of the treatment results from 650,882 patients (72% LGR, 28% GB), the authors came to the conclusion that the presence of senile asthenia syndrome is associated with higher surgery risks, which is related to the "cumulative deficit" (when the cumulative effect from the number of pre-existing concomitant diseases is higher than in cases of their separate assessment).

J.T. Dang et al. [12], based on the analysis of the data on the results of GB and LGR in 40,199 geriatric patients, have developed the GeriBari prognostic scale, showing a sensitivity of 46.0% and the specificity of 100%, which was used in our retrospective research. The fact that high risk was detected only in 13% of our patients, indirectly confirms the efficiency of the scale. The benefit of the scale is its controllability: in case of the patients having significant diseases and conditions, refusing to perform GB in favor of LGR allows leaving the patient in the low risk group. However, this scale does not take into account the presence of senile asthenia syndrome, and in our research, none of the participants had senile asthenia. During the present trial, for selecting the patients for bariatric surgery, we have used the only screening questionnaire validated in our country on the

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presence of senile asthenia syndrome "The Age is not a drawback". This questionnaire is generally similar to the ones used by the authors of the abovementioned trials. According to our opinion, the combined use of the "Age is not a drawback" screening questionnaire and the GeriBari scale can allow for determining the category of patients older than 60 years, in which performing bariatric surgery is safe.

We have obtained the data similar to the global ones, indicating the safety of bariatry surgeries among the elderly patients with the condition of following a number of principles:

1) individual selection of patients, including the use of screening questionnaire for the purpose of ruling out senile asthenia;
2) strict following the perioperative protocol of following the patients;
3) performing the surgery by means of an experienced surgical team;
4) justified type of surgical intervention.

CONCLUSION

Currently, the possibility of performing bariatry surgeries in patients older than 60 years in the Russian Federation is, in fact, considered being the "grey zone", for it is not clearly regulated by the clinical recommendations. The current research, according to out data, is the first in Russia.

As a result of analyzing the obtained data, the following conclusions can be drawn. In particular, bariatric surgeries in patients older than 60 years are plausible and safe, just as in younger patient, but with following a number of conditions. The efficiency of bariatric surgery in terms of decreasing the excess body weight after 60 years is significantly lower, however, the metabolic effects are at the high level, which determines higher quality of life in the patient after surgery. Patients older than 60 years, having conventional indications for bariatric surgery, should undergo additional selection procedures: it is necessary to rule out senile asthenia syndrome in them (based on using the screening questionnaire and on the conclusion by the geriatrician), to take into account the presence of surgery risk factors, as well as a number of subjective factors, such as the compliance level, the readiness to strictly follow the recommendations, the need for social-household aid and care. Currently, for the older age group, only two types of bariatry surgeries were justified — the Roux laparoscopic gastric bypass surgery and the laparoscopic longitudinal gastric resection. The protocol of perioperative managing the patient from the older age group should be strictly followed, while the surgery itself shall be performed solely by an experienced surgical team (with an experience of more than 100 bariatry surgeries).

ADDITIONAL INFORMATION

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Authors' contribution. *A.V. Smirnov* — general concept, search and analytical work, processing and discussion of the study results, writing the article, participating in performing operations and patient care; *V.R. Stankevich, E.S. Danilina, V.I. Sychev, E.M. Voronets* — participating in performing surgical operations on patients, patient care, collecting results; *Vl.I. Sharobaro* — participating in patient care, search and analytical work, discussing the study results; *N.A. Solovyev, Yu.V. Ivanov, R.I. Khabazov* — general concept, managing patient treatment and discussing the study results, editing the text. The authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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THE FUNCTIONAL INSTRUMENTAL TEST OF FLEXION-EXTENSION MOTION IN THE RADIOCARPAL JOINT: REFERENCE PARAMETERS

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ABSTRACT

BACKGROUND: *The stroke represents a significant medical-social problem due to its high morbidity and mortality with a tendency towards increasing the overall occurrence rates. A total 80% of the patients show persisting impaired functions of the upper limb. The current approaches, such as Clinical scales and Questionnaires, are being criticized for subjectivity and insufficient precision. It is necessary to develop an instrumental method for evaluating the functions of the upper limb, the method that is applicable in the clinical settings.* ***AIM:*** *To develop a functional test for the objective diagnostics of the wrist joint functions, applicable in the clinical settings.* ***METHODS:*** *A functional test was proposed for evaluating the biomechanics of the radiocarpal joint by means of using the inertial sensors. The research sample was a group of 15 healthy volunteers (5 males and 10 females aged from 23 to 33 years), not having any joint diseases or neurological disorders. The research was carried out within a period of one year (2022–2023). The primary endpoint was the determination of the amplitude, the time and the motion trajectory in the wrist joint when performing two tests — the "Wrist-0" and "Wrist-flex". An assessment was done of the duration of the motion cycle, of the motion maximal amplitude and phase.* ***RESULTS:*** *The evaluation of the upper limb functions using the clinical scales (ARAT, FMA-UE, MRC) has demonstrated, that the parameters correspond to the ones in healthy individuals. When using the "Wrist-0" test, the motion amplitude was significantly lower than in the «Wrist-flex» test ($p < 0.05$). No statistically significant differences were found in the motion amplitude between the right and left limbs determined using both tests ($p > 0.05$). The maximal flexion phase for the "Wrist-0" tests occurs significantly earlier than for the "Wrist-flex" test for the right hand ($p < 0.05$). The duration of the motion cycle did not significantly differ between the tests for the right hand ($p > 0.05$) and was significantly higher for the "Wrist-flex" test in the left hand ($p < 0.05$).* ***CONCLUSION:*** *A set of reference values was established for the functional tests. Insignificant differences were reported for the functions of the right and left radiocarpal joints. The test proposed requires insignificant time for its implementation and it can be used for objective diagnostics of the radiocarpal joint functions in patients.*

Keywords: *cerebral stroke; upper limb; wrist joint; function; kinematics.*

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BACKGROUND

The stroke represents an important medical-social problem due to its high morbidity and mortality rates. In Russia, the annual registered number of cases reaches 170–380 cases per 100 000 of population with a total number of stroke cases being ~380 000 a year. The World Health Organization predicts an increase in the numbers of acute cerebrovascular event cases by 30% within a period until year 2025 [1].

The stroke causes the development of disorders in the motor, sensory, visual, affective, cognitive and speech aspects. About 80% of ischemic stroke survivors have persisting impaired functions of the upper limb, despite the conducted rehabilitation activities [2].

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ФУНКЦИОНАЛЬНАЯ ИНСТРУМЕНТАЛЬНАЯ ПРОБА ДВИЖЕНИЙ СГИБАНИЯ-РАЗГИБАНИЯ ЛУЧЕЗАПЯСТНОГО СУСТАВА: НОРМАТИВНЫЕ ПАРАМЕТРЫ

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АННОТАЦИЯ

Обоснование. *Инсульт представляет собой значимую медико-социальную проблему из-за высокой заболеваемости и смертности с тенденцией к увеличению общего числа заболевших. У 80% пациентов сохраняются нарушения функции верхней конечности. Существующие подходы, такие как клинические шкалы и опросники, критикуются за субъективность и недостаточную точность. Необходима разработка инструментального метода оценки функции верхней конечности, применимого в клинических условиях.* ***Цель исследования*** *— разработать функциональную пробу для объективной диагностики функции лучезапястного сустава, применимую в клинических условиях.* ***Методы.*** *Предложена функциональная проба для оценки биомеханики лучезапястного сустава с использованием инерционных сенсоров. Объектом исследования стали 15 здоровых добровольцев (5 мужчин и 10 женщин в возрасте от 23 до 33 лет), не имеющих заболеваний суставов и неврологических нарушений. Исследование проводилось в течение одного года (2022–2023). Первичной конечной точкой было определение амплитуды, времени и траектории движений лучезапястного сустава при выполнении двух тестов — «Кисть-0» и «Кисть-Сгиб». Проводилась оценка длительности цикла движения, максимальной амплитуды и фазы движения.* ***Результаты.*** *Оценка функции верхней конечности с помощью клинических шкал (ARAT, FMA-UE, MRC) показала, что параметры соответствуют показателям здоровых людей. В тесте «Кисть-0» амплитуда движений была достоверно ниже, чем в тесте «Кисть-сгиб» ($p < 0,05$). Не найдено статистически значимых различий в амплитуде движений между правой и левой конечностями в обоих тестах ($p > 0,05$). Фаза максимального сгибания в тесте «Кисть-0» наступает достоверно раньше, чем в тесте «Кисть-сгиб» для правой руки ($p < 0,05$). Длительность цикла движения не отличалась достоверно между тестами для правой руки ($p > 0,05$) и была достоверно выше в тесте «Кисть-сгиб» для левой руки ($p < 0,05$).* ***Заключение.*** *Установлены нормативные параметры для функциональной пробы сгибания-разгибания лучезапястного сустава. Предложенная проба требует незначительного времени для проведения и может быть использована для объективной диагностики функции лучезапястного сустава у больных.*

Ключевые слова: *церебральный инсульт; верхняя конечность; лучезапястный сустав; функция; кинематика.*

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When assessing the functions of the upper limb, special attention is paid to the active extension in the radiocarpal joint, for this motion is required for grasping [3, 4] and for fulfilling the basic household activities [5, 6]; the active extension of the wrist is also the predictor of restoring the upper limb functions [7].

The main methods for the diagnostics of the upper limb functions are still the clinical scales and questionnaires. Such an approach is often criticized due to its low accuracy and high degree of subjectivity. The objective diagnostics methods are being actively researched by the scientific community, but the

information on the real functioning of the upper limb is still lacking [8].

The important aspect of rehabilitation after a cerebrovascular stroke is the instrumental evaluation of the motor activity and dynamic registration of the rehabilitation using objective methods. An example of the objectivization of the upper limb movements is the video-analysis method [9–11]. Despite the high accuracy of motion capture systems, this method is relatively more costly, requiring significant amount of time for obtaining and processing the results, with the data evaluation performed only in the settings of a specialized laboratory.

As an objectivization instrument, myography can also be used. In the research by I.S. Hwang et al. [12], when using this method, it was found that the synkinesia level in the arm after a cerebrovascular stroke is related to its functionality. Despite the fact that electromyography is an important diagnostic tool for evaluating the muscle functions, the method only provides information on the electric activity of the muscles and does not allow for receiving information on the limb motion, not to mention such parameters as the motion amplitude and coordination.

The effective tool for motion registration is the goniometry method, often used during an evaluation of the motion amplitude in various joints of the upper and lower limbs [13], however, it is important to note that, as of today, the method of manual measuring the motion amplitude using the goniometer should be considered obsolete. Besides, the goniometry method allows for obtaining information about the maximal motion amplitude, but not about the motion process itself.

The inertial sensors used in the strap down navigation technology are a new generation of devices, showing high automatization degree and measurement accuracy [14, 15]. The inertial sensors were shown to be beneficial comparing to the motion video analysis method, for their use, not supposing the presence of special laboratory settings for collecting the information, requires significantly less time when preparing for testing. Recent trials have demonstrated that inertial sensors provide sufficient measurement accuracy comparing to the motion video analysis systems [16].

There are also other methods of objectivization of the upper limb functions, such as electrogoniometry and videoradiography, however, they are complex in terms of reproducibility and they are accompanied with large numbers of internal errors when performing the tests [17, 18].

Despite the significant number of high-accuracy instruments available for the evaluation of the wrist functions, there is no unified methods established at the present moment. For example, in the research by Y. Li et al. [19], a diagnostic protocol was compiled, consisting of 11 test movements for the upper limb, with the movements taken from the Fugl-Meyer Assessment scale (FMA), however, in clinical practice, its use is quite labour-intensive due to the large amount of information obtained from various sources.

During the course of their research work, C.I. Renner et al. [7], when evaluating the dynamic parameters and strength parameters of the upper limb in patients after a cerebrovascular stroke using the dynamometry and inertial sensors with its further comparison to the clinical scales, have accented the importance of dynamic parameters in the evaluation of restoring the upper limb functions, but the authors were not using the analysis of motion trajectory.

In the research by S.I. Lee et al. [20], small autonomous inertial sensors were used for evaluating the regularity of using the right and left palms in everyday household activity among healthy subjects. The proposed method, though it can be used for the evaluation of the motor functions of the upper limbs with determining multiple parameters, is more intended for quantitative evaluation of the motor functions. In turn, such parameters as amplitude, time and trajectory can be the key ones when compiling and adjusting the programs of rehabilitation activities in patients with impaired upper limb functions, nevertheless, the possibility of registering the household motions within a long-term period is very attractive.

Thus, the existing methods used for evaluating the upper limb functions, including the clinical scales and questionnaires, are criticized for their subjectivity, fragmentarity and often doubtful results, while the objective diagnostics methods include, for example, kinematic parameters, functional electromyography and motion dynamics parameters. The application of the whole set of biomechanical analysis tests appear to be a complex technical and methodical problem. Besides, the majority of devices capable of performing such a biomechanical analysis, are limited in terms of its use in the clinical settings. On the other hand, such technologies as inertial sensors allow for registering the previously inaccessible parameters, including the settings that were not previously even considered (for example, daily household activities).

The biggest problem, however, is that there is yet no unified and all-purpose method developed for

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evaluating the functions of the radiocarpal joint, while the existing methods are difficult to reproduce [21]. Upon designing such a test, it is important to keep in mind the specific features of muscle functioning and, in particular, the fact that the muscle can demonstrate significant force characteristics in the position of maximal tension [22]. Creating the all-purpose method for objective diagnostics, accessible for use in the settings of an average physician's office, could significantly promote to spreading the use of instrumental evaluation methods in private offices, in-patient departments and medical rehabilitation units.

Research aim — to develop a functional test for registering the flexion-extension motions in the radiocarpal joint with the possibility of using it in the clinical settings.

METHODS

Research design

Experimental, longitudinal, pilot research.

Conformity Criteria

Inclusion criteria: healthy volunteers without the locomotor system diseases or neurological disorders; aged from 23 to 33 years; absence of joint injuries or diseases in the past medical history; presence of written informed consent for participation in the research.

Non-inclusion criteria: presence of chronic joint diseases or neurological disorders; presence of injuries or recent traumas which may affect the functions of the upper limbs; intake of medicinal products, which may affect the motor function or kinematics; presence of cognitive disorders, which may hamper the implementation of the research protocols.

Exclusion criteria: incompliance of the research protocols or follow-up requirements; developing complications or adverse effects during the research.

Research Duration

The research was carried out during the time period from 2022 until 2023 at the laboratory of the Scientific-Research Center for Medical Rehabilitation under the Federal State Budgetary Institution "Federal Center of Brain Research and Neurotechnologies", subdivision of the Federal Medical-biological Agency of Russia.

Medical Procedure Description

Biomechanical evaluation method. For evaluating the functions of the radiocarpal joint, a functional test was developed, consisting of two tests, which include isolated wrist joint movements. For the purpose of performing the test, two inertial sensors were used, which are a part of "Stadis-Kinematika" set (Neurosoft, Russia) with attaching them to the human body using elastic bands with Velcro fasteners (Hook-and-loop), along with a personal computer with standard software installed and a writing desk with a chair.

When performing the test, the subject was positioned sitting on a chair touching the back of the chair with his trunk, with the legs bent at 90 degrees angle, with the feet firmly touching the floor surface. The writing desk was positioned on the test limb side. The forearm of the test limb was positioned on the desk at the pronated position (palm down). The sensors must be attached to the upper limb with their base facing the patient in the following way: sensor № 1 should be attached to the lateral surface and in the proximal part of the forearm (Fig. 1), sensor № 2 — to the edge of the palm. The test proposed consists of two kinematic tests — the "Wrist-0" and the "Wrist-flex".

The "Wrist-0" test should be performed at a limited amplitude and includes the extension of the wrist joint from the 0 degrees position. At the beginning of test, the wrist and the forearm of the patient are positioned on the surface of the writing desk (pronated), while the shoulder is abducted by ~20–30 degrees. Upon receiving the "Start" order, the patient needs to perform, at least, 3 (maximum -10) extension movements in the radiocarpal joint, reaching the maximum angle and following the rate chosen by the patient. The testing procedure shall be ceased upon receiving the "Stop" order.

The "Wrist-flex" test should be performed at the wrist flexion position (with the wrist freely hanging from the desk) and using the full amplitude. At the beginning of the test, the patient's forearm is positioned on the surface of writing desk at the pronated position, with the shoulder being abducted by ~20–30 degrees, the wrist is positioned at the flexing position (freely hanging from the desk). Upon receiving the "Start" order, the patient needs to perform the same number of movements as during the "Wrist-0" test, at a rate convenient for the patient. The testing procedure shall be ceased upon receiving the "Stop" order (see Fig. 1).

The software provides the following information: duration of the complete movement cycle (from the beginning of extension until returning to starting position) in seconds; the mean movement goniogram (the amplitude-time function) of the performed movement cycles; the maximal mean motion amplitude in degrees; the mean maximal amplitude phase (the time of maximal amplitude onset during the

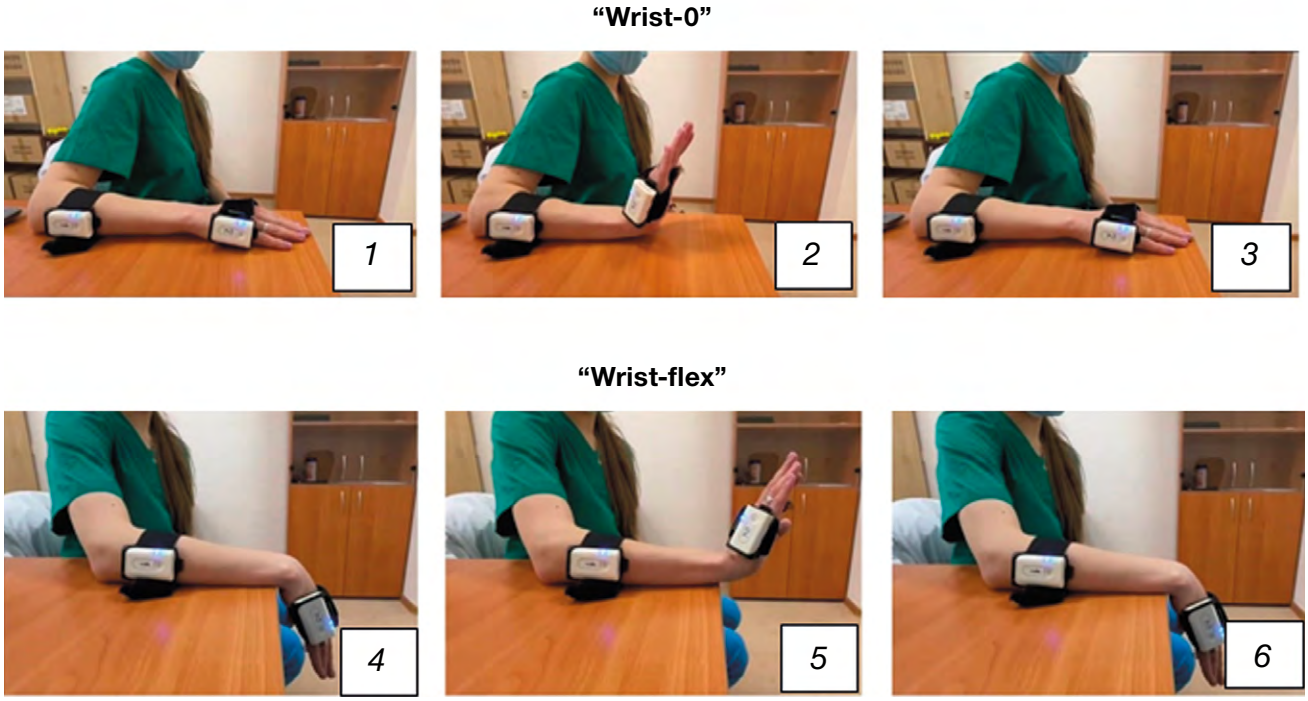

Fig. 1. The attachment of the sensors to the upper limb: "Wrist-0" test (*1* — positioning of the upper limb before the movement initiation; *2* — positioning with wrist extension; *3* — upper limb position at the end of the motion cycle) and the "Wrist-flex" test (*4* — positioning of the upper limb before the movement initiation; *5* — maximal wrist extension position; *6* — positioning of the upper limb at the end of motion cycle).

motion cycle) as a percentage (%) of the whole motion cycle time (Fig. 2).

Having two variants of the test allows for receiving more information on the functioning of the upper limb in a patient, as well as for evaluating the minimal, but conscious movements made by the patient at the position of maximal tension of wrist extensor muscles due to the effects of the palm's own weight ("Wrist-flex").

Research outcomes

The main research outcome. The obtained data include the biomechanical functional parameters of the radiocarpal joint, evaluated using two functional tests ("Wrist-0" and "Wrist-flex"). The key parameters are the motion amplitude, the maximal flexion phase and the duration of motion cycle. These parameters are necessary for achieving the research aim, for they allow for performing an objective evaluation of the efficiency of the functional tests proposed.

Additional research outcomes. Insignificant differences were found in the functions on the left and right sides.

Ethical review

The conduction of the research was approved by the local ethics committee of the Federal State Budgetary Institution "Federal Scientific and Clinical Centre for Specialized Types of Medical Care and Medical Technologies" under the Federal Medical-Biological Agency of Russia (protocol No. 11/25-04-22 dated 25.04.2022).

Statistical analysis

The processing of the obtained results was carried out using standard methods of descriptive variation statistics with calculating the median, the 25% and 75% quartiles. The "Statistica 12" software pack was

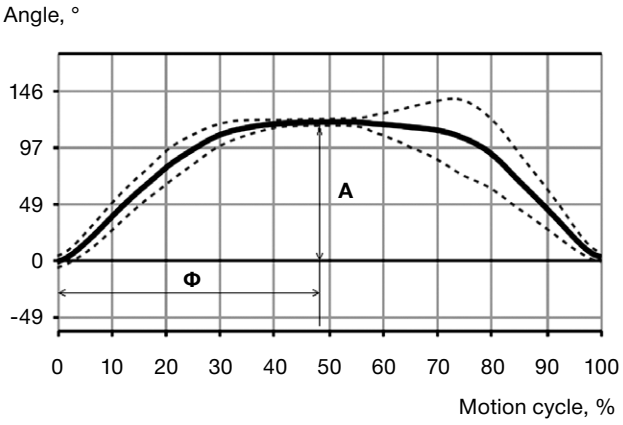

Fig. 2. Goniogram: A — motion amplitude; Φ — maximal angle phase of the flexion (within the complete motion cycle).

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used. The evaluation of the significance of differences was done using the Wilcoxon test with the p <0.05. Comparative evaluation was performed for similar parameters of the left and the right wrists, as well as for the "Wrist-0" and "Wrist-flex" tests.

RESULTS

Research sample (participants)

The research included a total of 15 practically healthy volunteers, not having a past medical history of injuries or diseases of the locomotor system, of which 10 were females and 5 were males; the mean age was 26.5±3.5 (23–33) years. The informed consent was obtained from all the subjects before the research initiation. The healthy subjects did not have any diseases of the joints and did not have neurological disorders or injuries. Before the conduction of the research, all the participants had an assessment of the functions of the upper limbs using the following clinical scales: muscle strength assessment (Medical Research Council, MRC), Fugl-Meyer Assessment of Upper Extremity (FMA-UE), an assessment of motor possibilities in the upper limb (Action Research Arm Test, ARAT).

Primary findings

The results obtained when using the evaluation by means of the clinical scales are provided in table 1. As expected, they correspond to the parameters of a healthy individual.

The results for the tested parameters are provided in table 2. The motion amplitude registered when performing the "Wrist-0" test was significantly lower comparing to the motion amplitude obtained when performing the "Wrist-flex" test (p <0.05). When comparing the motion amplitude in the right and left limbs, no statistically significant deviations were found for both tests (p >0.05).

The maximal flexion phase during the "Wrist-0" test was registered significantly earlier comparing to the "Wrist-flex" test for the right side (p <0.05). On the left side, the maximal flexion phase shows no significant differences (p >0.05).

The duration of motion cycle did no significantly differ between the "Wrist-0" and "Wrist-flex" tests for the right side (p >0.05), being significantly higher for the "Wrist-flex" test on the left side (p <0.05).

DISCUSSION

Based on the results of the research, all the test subjects (healthy volunteers) have demonstrated the maximal points when using the clinical scales, which was the expected result.

The amplitude parameters have demonstrated complete matching between the left and the right arms in both tests, however, some differences were found in the maximal amplitude phase and in the motion duration. In particular, the maximum extension angle phase in the "Wrist-0" test occurs significantly earlier for the right side, while on the left such differences were not detected, which can indicate the presence of asymmetry in the motion control among the right-handed subjects, which corresponds to the data on the interhemispheric differences in terms of controlling the motor skills. The duration of the motion cycle for the right hand was similar for both tests, despite the presence of almost two-fold difference in motion amplitude. For the left arm, the motion cycle duration with the "Wrist-flex" test was significantly higher, which may indicate the specific features of motor activity in the left arm of the right-handed

Table 1

Evaluation of the upper limb functions using the clinical scales

Parameter	Right	Left
ARAT, points	57	57
FMA-UE, points	126	126
MRC, points	5	5

Table 2

Tested parameters of the amplitude, phase and cycle duration for the right and the left radiocarpal joints

Parameter	Right			Left		
	Amplitude, Degrees.	Phase, %	Cycle, Sec	Amplitude, Degrees.	Phase, %	Cycle, Sec
Wrist-0	79 [67; 86]*	41 [38; 45]*	1.78 [1.53; 2.46]	80 [74; 86]*	46 [39; 48]	1.85 [1.4; 2.06]*
Wrist-flex	137 [123; 156]	47 [42; 58]	2.27 [1.7; 2.57]	138 [124; 158]	43 [39; 53]	2.07 [1.74; 2.67]

Note. * Statistically significant difference comparing to the same parameter during of the "Wrist-flex" test (p <0.05).

individuals. With this, the direct comparison of the same parameters in the right and left arms did not show significant differences: this allows for making a conclusion that the interhemispheric differences have a rather indirect type. The obtained data show that the interhemispheric differences were insignificant, which allows for supposing the possibility of compiling the general references for both limbs.

The research work by P.S. Santos et al. [23], just like our research, has employed similar positions of the hand and of the palm for evaluating the wrist functions, however, the main attention was paid to studying the tremors, not the characteristics of motion amplitude.

The research works headed by V. Costa [15] and M.A. Wirth [16], were also focused on the amplitude characteristics of wrist flexion-extension, and their results are comparable to ours: in particular, the parameters of wrist extension (~68° in the research by V. Costa [15] and 79° in our research for the "Wrist-0" test, as well as the value of ~126° in the research by M.A. Wirth [16] and 137° for the "Wrist-flex" test in our research) correspond to data obtained during these research. The pronated position of the wrist in our research could affect the muscle activity and the motion amplitude, especially in patients with neurological disorders. For example, the position in which the forearm is located at the table with the wrist protruding outside the borders of the working surface and experiencing tension, being parallel to the floor, like it was done by V. Costa [15], can be acceptable for healthy subjects, but it is associated with difficulties in patients with muscle weakness. Taking this into consideration, our research can be more applicable for patients with neurological disorders, for the position, in which the forearm muscles are initially in the relaxed state, better reflects the real motor capabilities. In the research work by M.A. Wirth [16], unlike our research, the wrist (during the evaluation process) was positioned with the thumb pointed upwards between the pronation and supination modes, while our research has employed the pronated positions. The position used by the authors, allows for practically ruling out the effects of the wrist's own weight. This difference may also significantly affect the results, especially in patients with neurological disorders, for the wrist position affects the distribution of the muscle activity and movement coordination.

The amplitude parameters obtained during the research works headed by P.S. Santos [23] and M.R. Pourahmadi [24], were also similar to our "Wrist-0" test results, however, the evaluation in theses research works was carried out using accelerometers built into a smartphone. In this case, one should take into consideration the mass-inertial characteristics of the smartphone, which may hamper the conduction of the test movement in paresis patients.

As for the comparability of the results obtained during the evaluation of the biomechanical and clinical methods, the article by S. Patel et al. [25] reports high correlation between the results of evaluating the upper limb movement quality in each functional task (Functional Ability Scale, FAS) and the data from inertial sensors. A similar result was reported in terms of the ARAT and FMA tests for the upper limb in the article by M.N. McDonnell et al. [26], which shows the comparability of the data obtained using inertial sensors and the traditional clinical assessment methods.

The comparability of the data obtained using the inertial sensors and the golden standard — the motion video analysis, was evaluated for the given localization in the research by R. Pérez et al. [27]. The authors have reported high correlation between the motion analysis system based on inertial sensors and the video-analysis of the movements, which confirms the reliability of the inertial systems. However, the difference between the signals, resulting due to specific locations of placing the sensors on the clothes of the test subjects, can be the source of errors, which accentuates the necessity of strict calibration of sensors for the purpose of increasing the measurement accuracy. These data are useful for keeping in mind when developing the protocols of future research works. With this, the inertial technology allows for conducting the measurements in real life settings, which is inaccessible for video-systems.

Thus, in the healthy test subjects, the wrist position and the effects of gravity are not significant factors that limit the motion amplitude. This fact can also be used in clinical practice.

In the research works analyzed by us, the main attention was paid to the motion amplitude parameters, while the evaluation of movement cycle duration was less frequent. However, none of them contained the examples of analyzing the maximal angle phase, which constitutes an important underestimated aspect. This parameter plays the key role in the evaluation of the movement exercise quality, for it reflects the moment of achieving the maximal amplitude during the motion cycle. Besides, the analysis of the maximal angle phase allows for indirect evaluation of the degree of

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controlling of motion by a test subject at all the phases of the exercise. In particular, the synchronicity and the precision of the phase distribution within the motion may indicate the coordination of the muscle works and the presence of interhemispheric differences, which makes this parameter especially important for the objective diagnostics of motor functions.

Based on this research, reference values were obtained for the proposed functional tests. The functional tests for the evaluation of flexion-extension in the radiocarpal joint provide more detailed quantitative and qualitative information comparing to the conventional clinical scales. The test is easy to perform, it takes only several minutes and it can be implemented in everyday clinical practice for the diagnostics and monitoring of the rehabilitation of patients, for example, with paresis due to cerebral stroke.

Research Limitations

This research had a number of limitations. First of all, the small sample size (the number of test subjects). The small sample size can also decrease the statistical power of the analysis, especially when evaluating the small differences between the right and the left hand. The important direction for further research works could be increasing the sample size, which could increase the validity of the conclusions and include a wider spectrum of variations of the motor functions of the wrist in various categories of individuals.

Another limitation is that the research did not include the use of myography methods for the evaluation of muscle activity. This could provide more detailed information on muscle coordination and its contribution to the motion characteristics. In order to further improvement of the method and its implementation into clinical practice, additional research are required with using myography, which allows for more precise evaluation of the participation of the main muscles within the movement. It is also important to note that the positions of attaching the inertial sensors and the specific features of their calibration could affect the results. The individual differences in the limb biomechanics among the participants, such as anatomic features, could also affect the data, which requires additional analysis.

We suppose the future research should pay more attention to widening the sample size with including the patients having impaired functions of the wrist for more precise evaluation of the kinematic parameters and for their comparative analysis to a group of healthy test subjects. This should allow for defining the specific features of the impairment and for more precise determining the diagnostic value for the parameters, such as the maximal angle phase, the amplitude and duration of the motion cycle.

Besides, the perspective direction is the inclusion of the functional electromyography method together with the kinematic assessment. This could help determining how the muscles work during various phases of the motion, and performing a simultaneous monitoring of the muscle activity. Such an approach should provide a more complete insight on the mechanisms of motion and it should allow for comparing the kinematic data with the muscle control, which is of special importance when detecting small differences in the movement coordination and which has a great importance when working with the patients suffering from neurological abnormalities.

CONCLUSION

The reference data were obtained for the proposed functional tests of flexion-extension motions in the radiocarpal joint. The sensitivity of biomechanical diagnostics allows for obtaining the differences between the left and the right arms, with this, the characteristics of the differences allow for applying the general reference ranges.

The proposed functional test can be used for objective evaluation of the functional status and of dynamic changes in patients with neurological disorders of the upper limb and with impaired functions of the radiocarpal joint.

ADDITIONAL INFORMATION

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Competing interests. The authors declare that they have no competing interests.

Authors' contribution. *D.V. Skvortsov* — research design, literature search and processing, manuscript writing; *D.A. Lobunko* — literature search and processing, research, statistical analysis, manuscript writing; *G.E. Ivanova* — general guidance, research design. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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NON-INVASIVE ELECTROENCEPHALOGRAM-BASED ANESTHESIOLOGICAL MONITORING IN GERIATRIC PATIENTS IN THE ENT-SURGERY

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ABSTRACT

BACKGROUND: *Demographic ageing of the society and the growing demand for medical service among the elderly citizens require perfecting the anesthesiology approaches.* ***AIM:*** *Evaluation of the efficiency of using various types of electroencephalography-based monitoring when performing general anesthesia in the settings of ENT-surgery in geriatric patients.* ***METHODS:*** *The randomized study included 99 patients (70–85 years old, ASA III–IV) who underwent surgery under general anesthesia for ENT pathology. The patients were distributed into three groups: Group A (n=33) — anesthesia controlled by CONOX — monitoring, Group B (n=33) — no cerebral monitoring, Group C (n=33) — controlled by BIS monitoring. The controlled parameters included the dosage of the medicinal products (Propofol, Fentanyl, Sevoflurane), the hemodynamics, the rates of intraoperative awakenings, postoperative nausea and vomiting, the need for additional pain medications and the parameters of the cognitive functions before and after surgery.* ***RESULTS:*** *The Propofol dosage in Group B was higher than in Groups A and C (p=0.016 and p=0.012 respectively). The concentration of Sevoflurane in Group C was lower (p=0.016), than in Groups A and B. Hemodynamic disorders and postoperative nausea/vomiting were more often observed in group B. Intraoperative awakenings were reported in 3% of the patients in Group A, in 9% for Group B and in 6% patients in Group C. Additional pain management was required in 39% of the patients in Groups A and B along with 42% in Group C, no statistical difference was found between the groups. Cognitive functions were better preserved in Group A with the duration of general anesthesia being more than 120 minutes (p=0.044).* ***CONCLUSION:*** *Anesthesiology monitoring based on electroencephalogram parameters, optimizing the dosages of the medicinal agents, decreases the rates of hemodynamic disorders, of intraoperative awakenings and of postoperative nausea and vomiting. Combined with the clinical monitoring of the electroencephalogram parameters, this accelerates rehabilitation and improves the surgery outcomes. The optimization of the dosage of opioids with controlling the anesthesia depth index (the Nociception Index, qNOX) positively affects the postoperative cognitive status of the patients.*

Keywords: *anesthesia; anesthesiology monitoring; ENT; geriatry.*

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BACKGROUND

In parallel with the development of anesthesiology, a necessity has appeared to control the efficiency of general anesthesia components (syncope or hypnosis, analgesia, neurovegetative block and myorelaxation), for both the insufficient anesthesia level, resulting in subconscious sensation of pain or anesthesia awareness, and the excessive anesthesia depth can serve as the predictors of negative consequences with increasing the neurotoxic effects of anesthetic drugs, which is especially important among the aged and elderly patients [1–3]. Inadequate level of sedation and analgesia in such patients can act as an inductor of the onset and further progression of encephalopathy. Multiple research works have correlated the development of postoperative delirium and postoperative cognitive dysfunctions with excessive sedation depth, with its duration being more than 120 minutes and with the age of the patients — older than 65 years [4–6]. Besides, possible effects of

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НЕИНВАЗИВНЫЙ АНЕСТЕЗИОЛОГИЧЕСКИЙ МОНИТОРИНГ НА ОСНОВЕ ЭЛЕКТРОЭНЦЕФАЛОГРАММЫ У ГЕРИАТРИЧЕСКИХ ПАЦИЕНТОВ В ЛОР-ХИРУРГИИ

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АННОТАЦИЯ

Обоснование. *Демографическое старение общества и растущая потребность в медицинском обслуживании пожилых граждан требуют усовершенствования анестезиологических подходов.* ***Цель исследования*** *— оценить эффективность применения различных видов мониторинга на основе электроэнцефалографии при проведении общей анестезии в ЛОР-хирургии у пациентов гериатрического профиля.* ***Методы.*** *В рандомизированное исследование включены 99 пациентов (70–85 лет, ASA III–IV), прооперированных в условиях общей анестезии по поводу ЛОР-патологии. Пациенты разделены на три группы: группа А (n=33) — анестезия под контролем монитора CONOX, группа В (n=33) — без церебрального мониторинга, группа С (n=33) — под контролем монитора BIS. Оценивались дозировки препаратов (пропофол, фентанил, севофлуран), гемодинамика, частота интраоперационных пробуждений, послеоперационная тошнота и рвота, потребность в дополнительном обезболивании и когнитивные функции до и после операции.* ***Результаты.*** *Доза пропофола в группе В была выше, чем в группах А и С (p=0,016 и p=0,012 соответственно). Концентрация севофлурана в группе С была ниже (p=0,016), чем в группах А и В. Гемодинамические нарушения и послеоперационная тошнота и рвота наблюдались чаще в группе В. Интраоперационные пробуждения отмечены у 3% пациентов группы А, у 9% — группы В, у 6% — группы С. Дополнительное обезболивание потребовалось 39% пациентов групп А и В, 42% — группы С без статистической разницы между группами. Когнитивные функции лучше сохранялись в группе А при длительности общей анестезии более 120 минут (p=0,044).* ***Заключение.*** *Анестезиологический мониторинг на основе электроэнцефалограммы, оптимизируя дозировку препаратов, снижает частоту гемодинамических нарушений, интраоперационных пробуждений и послеоперационных тошноты и рвоты. В сочетании с клиническим мониторингом электроэнцефалограммы ускоряются восстановление и улучшаются исходы операции. Оптимизация дозировки опиоидов под контролем индекса глубины анальгезии (qNOX) положительно влияет на послеоперационный когнитивный статус пациентов.*

Ключевые слова: *анестезия; анестезиологический мониторинг; ЛОР; гериатрия.*

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anesthesia were shown with regard to the manifestation and progression of the Alzheimer's disease [3].

Due to the advances in the methods of obtaining and processing the electroencephalography (EEG) signals, from 1990s, the set of tools available to anesthesiologists was supplemented with the methods to evaluate the anesthesia depth in the real time mode during surgical interventions [7]. The widely known methods of additional monitoring in anesthesiology include the EEG bispectral index (BIS) — the parameter that measures the sedation depth [8, 9]. The CONOX monitor (Fresenius-Kabi, Germany), along with the sedation depth index (quantitative consciousness index, qCON), using the frontal electroencephalography / electromyography data, also calculates the quantitative nociception index (qNOX) using the neuronal network to calculate the power ratios for various EEG frequencies (adaptive neuro-fuzzy inference system, ANFIS) and

the suppression splashes [10–12]. Both indexes — qCON and qNOX — can reflect the EEG changes in response to pain stimuli, though the qNOX reaction is more dynamic than qCON. This is due to the fact that the increase of qNOX is a consequence of developing EEG changes directly from pain stimulation, while the increase of qCON is resulted by the secondary effect of pain stimulation. The calculations of qCON and qNOX can be affected by the use of muscle relaxants [12].

Research aim — to evaluate the efficiency of various types of electroencephalography-based monitoring upon performing the general anesthesia in the settings of ENT-surgery among the geriatric patients.

METHODS

Research design

A single-centre open-label prospective randomized controlled research was arranged.

Several results of the present research were published earlier and were describing the intraoperative monitoring of sedation depth and analgesia in patients older than 70 years in the settings of ENT-surgery. The present article is the continuation of previously performed research work with the inclusion of Group C (the use of BIS-monitoring) and with summarizing the results for all the three research groups [13].

Conformity Criteria

Inclusion criteria: age from 70 years and older; patients operated due to the presence of ENT-diseases.

Non-inclusion criteria: psychiatric and neurological diseases (including chronic alcoholism or drug abuse); significant decrease in the cognitive functions (MMSE scores ≤24).

Exclusion criteria: the use of artificial ventilation during the postoperative period.

Research facilities

The research was carried out within the premises of the Federal State Budgetary Institution "National Medical Research Center for Otorhinolaryngology" of the Federal Medical-Biological Agency (FSBI NMRCO of the Russian Federal Medical-Biological Agency).

Research Duration

From January 2021 until June 2024.

Medical Procedure Description

The research included 99 patients aged 70–85 years with a grade III–IV physical status according to the surgical-anesthesiological risk scale from the American Society of Anesthesiologists (ASA) and undergoing ENT surgeries. All the patients were receiving general combined anesthesia using the endotracheal method. Intravenous induction of anesthesia — consequential administrations of Fentanyl (1–2 μg/kg) and Propofol (0.60–1.90 mg/kg). Tracheal intubation after relaxation with Rocuronium bromide (0.6–0.8 mg/kg), maintaining relaxation with the fractional dosages of 0.2–0.4 mg/kg. All the patients were receiving anesthesia with Sevoflurane using the low-flow method with the flow of air-oxygen mixture at a rate of 1 l/min. The oxygen concentration in the air mixture is 30–50%.

In all the groups, the evaluation of minute pulmonary ventilation, the respiratory capacity, the concentration of Sevoflurane and the partial pressure of carbon dioxide upon inhaling and exhaling was carried out using the anesthesia machines manufactured by General Electric (USA): GE Care Station 620, GE AVANCE CS 2, GE DATEX-OHMEDA.

The patients were divided into three groups. In Group A (n=33), general anesthesia was carried out with the controls by means of the CONOX monitor; patients of Group B (n=33) were not controlled by cerebral monitoring; patients from Group C (n=33) were receiving general anesthesia with the BIS monitoring (BIS VISTA manufactured by Medtronic, USA). All the patients were undergoing standard intraoperative monitoring (non-invasive measurements of blood pressure, heart rate, respiration rate and blood hemoglobin saturation with oxygen).

For the evaluation of the cognitive status, all the patients underwent the MMSE test (mini-mental state examination) [14]. The testing was carried out twice within 24 h — before surgery and in 24 hours after surgery. In Group A, the anesthesia tactics was based on analyzing the qCON and qNOX indexes.

After the induction of anesthesia and tracheal intubation, Sevoflurane inhalations were beginning from the concentration of 5–8% by vol. with a background of moderate hyperventilation ($etCO_2$ 30–34 mmHg). Upon achieving the minimal alveolar concentration (MAC) of 1.0, normoventilation was initiated ($etCO_2$ 34–42 mmHg), with the beginning of surgical intervention taking place with a background of decreasing the Sevoflurane concentration to 1.0–1.5% by vol. and with the MAC reduced to 0.7–0.8 (15–20 minutes after the induction with further correction of the concentration of the anesthetic agent, if necessary). Fentanyl was fractionally administered with portions of 1 μg/kg (once every 15–20 minutes). Constant registration was set for the qCON and qNOX

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indexes (every 15 minutes). During surgery, the qCON value was maintained at the level of 40–60. When the values were dropping below <40, the Sevoflurane concentration was also decreased, while in cases of elevation above >60, the concentration was increased, maintaining the qNOX value at the level of 40–60. If the qNOX index was increasing above 60, the patient was additionally receiving 1 μg/kg of Fentanyl.

In Group B, analgesia was provided by Fentanyl calculated as 1–2 μg/kg every 30–35 minutes, additional administrations of Fentanyl and/or changes in the Sevoflurane concentration in the inhaled air mixture were regulated empirically with analyzing the hemodynamic parameters (decreased or increased mean blood pressure and/or heart rate by more than 20% comparing to the baseline), the half-elimination time of the medicinal products and the intensity of the pain stimuli (depending on the stage of surgery).

In Group C, similar to Group A, the dosages of the anesthetic agents (Propofol and Sevoflurane) were adjusted based on the BIS levels. The Fentanyl dosage was taken empirically, just like in Group B. During the course of the surgery, the BIS levels were maintained at the level of 40–60. If the levels were dropping below 40, the concentration of Sevoflurane was decreased, if the levels were exceeding 60 — increased.

For the evaluation of the postoperative pain, Pain Visual Analogue Scale (VAS) was used, according to which, the score under 4 cm was classified as weak, 4–7 cm — moderate, ≥7 cm — severe pain [15]. The presence of postoperative delirium (confused consciousness) in patients was evaluated using the CAM-ICU scale (Confusion Assessment Method for Intensive Care Unit) [16].

Research outcomes

After surgery, the analyzed parameters included the total consumption of Propofol, Sevoflurane and Fentanyl; the intraoperative hemodynamical profile (blood pressure, heart rate); the cases of postoperative delirium; the rate of initial manifestations of intraoperative awakening (initial vegetative changes expressed as the acceleration of pulse, developing spontaneous respiratory movements and elevation of airway pressure were considered as being the initial manifestations of intraoperative awakening, in all the cases theses manifestations lasted for 1–3 minutes, during the postoperative period, all the patients had no memories of intraoperative awakening) as well as postoperative nausea and vomiting.

Subgroup analysis

The subgroup analysis was based on the duration of general anesthesia (<120 or >120 minutes).

Methods for registrations of outcomes

We have used the medical records and the protocols of anesthesiology aid along with the parameters recorded by CONOX and BIS monitors.

Ethical review

The conduct of the research was approved by the local Ethics Committee of the Federal State Budgetary Institution “NMRCO” of the Russian Federal Medical-Biological Agency (protocol No. 4/23, dated 27.11.2023).

Statistical analysis

Taking into consideration the research aim, the correlation between the intraoperative dosages of hypnotic and narcotic medications and the levels of sedation depth (BIS) or the depth of sedation and analgesia (CONOX), in order to calculate the sample size, we have used the significance level of 0.05 to avoid the type I error (alpha level, bilateral), and the level 0.20 to avoid the type II error (beta), using the Spearman’s correlation coefficient of 0.5. Thus, each group needed to contain not less than 32 patients [17, 18].

The statistical processing of the research results was carried out using the SPSS software (version 26, IBM, USA). For the purpose of defining the correctness of sample distributions, the Kolmogorov–Smirnov non-parametric test was used. Data were provided as absolute values (rates in percentages) or medians with the 25th and 75th percentile (Me [25%; 75%]) depending on the type of data. The analysis of differences between the groups was done using the Mann-Whitney method or the chi-square test and the Fisher’s exact test, depending on the data. The dynamic analysis of intragroup data differences was carried out using the Wilcoxon test. The correlation analysis was conducted using the Spearman’s test (rho). The direction (direct or reverse) and the strength of correlational relationships were determined by the coefficient level: in case of rho >0, the relation was considered direct, while the rho <0 was considered reverse. The strength of the relation (rho) was evaluated as weak if the value was <0.3, as moderate — if the value was 0.3≤ rho ≤0.7 and as strong for the levels of >0.7. The statistically significant level was stated for the *p* value being <0.05.

RESULTS

Research sample (participants)

The patients of three research groups did not differ in terms of clinical-demographic characteristics, the severity of surgical interventions and concomitant diseases also did not statistically differ (p >0.05). The perioperative evaluation of the patient's cognitive status (MMSE) between the groups before and after surgery did not differ (p >0.05).

Main research outcomes

Monitoring the analgesia depth (in group A) has allowed for administering lesser dosages of Fentanyl boluses (0.5–1 μg/kg every 15–20 minutes instead of 1–2 μg/kg every 30–35 minutes in Groups B and C), though more frequent (every 15–20 minutes) depending on the analgesia level, not causing any sudden changes in the hemodynamic parameters. The use of BIS in Group C has allowed for decreasing the total Sevoflurane dosage. The dosages of Propofol in Group B (where empirical calculation was used) were higher than in group A, and higher than in Group C (table 1).

The difference in the number of cases of hemodynamic disorders (p=0.240), postoperative nausea and vomiting (p=0.538), initial manifestations of intraoperative awakening (p=0.587), postoperative delirium (p=0.771) and postoperative pain (p=0.959) between Groups A, B and C was insignificant (Fig. 1).

The rate of postoperative nausea and vomiting was 18% in Group B, 9% — in Group A, 12% — in Group C, which, according to the correlation analysis data, was related to the duration of the surgical intervention [(rho)=0.472; p=0.001)], to the usage of insufficient dosages of Fentanyl

Table 1

The comparison of the dosages of the anesthetic agents and opioid analgesics between groups, Me [25%; 75%]

Drug	Group			*p*			
	A (CONOX) (*n*=33)	B (control) (*n*=33)	C (BIS) (*n*=33)	A/B	B/C	A/C	A/B/C
Propofol, mg/kg	1.6 [1.30; 1.77]	1.76 [1.54; 1.90]	0.71 [0.62; 1.14]	**0.016**	**0.012**	0.325	0.129
Fentanyl, μg/kg	1.92 [1.62; 3.13]	2.21 [1.35; 3.71]	2.07 [1.71; 2.38]	0.672	0.439	0.428	0.444
Sevoflurane, MAC	1 [1; 1]	1 [1; 1]	1 [0.80; 1.07]	0.539	0.135	0.067	**0.016**

Note. Semi-bold font indicates statistically significant parameters (p <0.05).

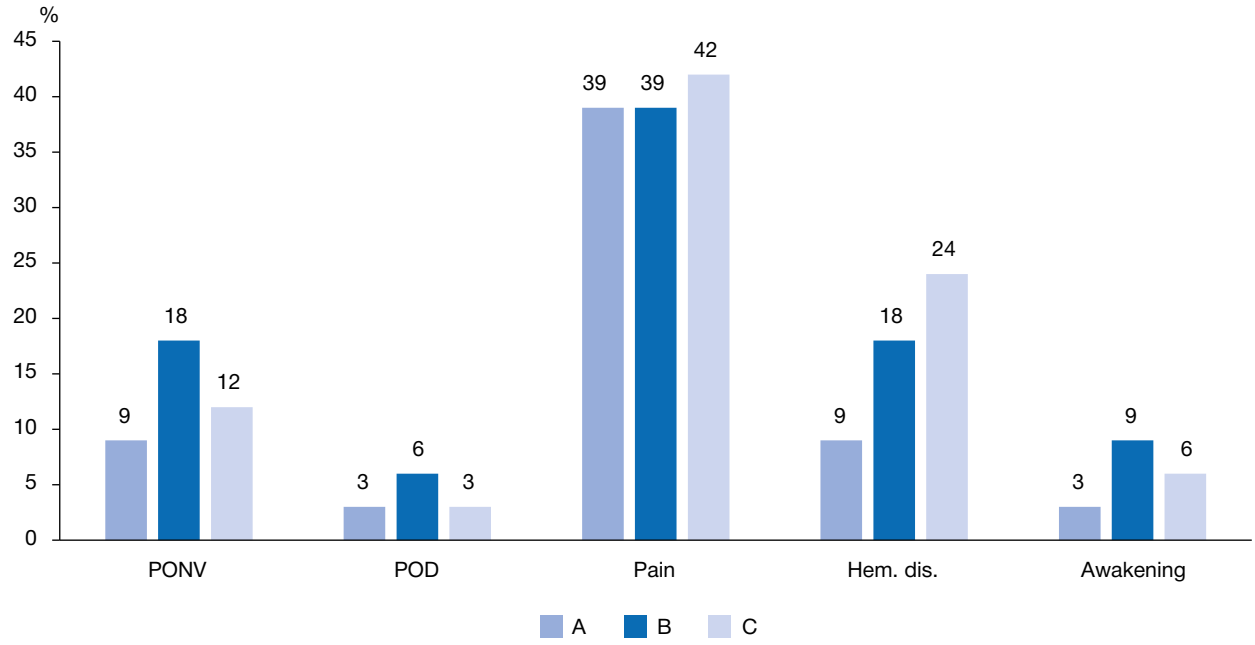

Fig. 1. The adverse effects in the peri-operational period. A, B, C — study groups; PONV — postoperative nausea and vomiting; POD — postoperative delirium; Pain — postoperative pain; Hem. Dis. — hemodynamic disorders; Awakening — initial manifestations of intraoperative awakening.

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[(rho)=-0.259; p=0.010)] and to the presence of postoperative pain [(rho)=0.411; p=0.001)].

Postoperative delirium, expressed as mild short-term disorders, has resolved with no special therapy within several hours after surgical intervention. The rates of developing postoperative delirium did not statistically differ between the groups (p >0.05) and it was showing weak correlation to the duration of surgery [(rho)=0.249; p=0.013)] or intraoperative variability of blood pressure [(rho)=0.302; p=0.002)].

Additional research outcomes

When analyzing the duration of anesthesia, it was found that Fentanyl dosage with the duration of anesthesia being <120 minutes was higher than for the duration of >120 minutes (table 2).

The MMSE cognitive status parameters after surgery were higher in Group A for the duration of surgery being >120 minutes and with lesser Fentanyl dosages, respectively (table 3); in Groups B and C, the MMSE parameters after surgery did not differ depending on the duration of general anesthesia (p=0.679 and p=0.255 respectively), though the Fentanyl dosages were different (p=0.002 and p=0.024 respectively).

The comparison of the dosages of anesthetics and analgesics inside each group depending on the duration of anesthesia has shown that Fentanyl dosages for higher duration of general anesthesia (>120 minutes) were less than in cases when general anesthesia lasted <120 minutes (table 4). In Group A, Propofol dosage was higher for long-term general anesthesia (>120 minutes), than in cases of general anesthesia lasting <120 minutes (see table 4). The Sevoflurane concentration did not differ between the groups depending on the duration of general anesthesia.

In Group A, the qNOX5 index (the parameter of analgesia depth during extubation and right after extubation) was higher for the anesthesia duration being >120 minutes comparing to the duration of <120 minutes (93.5 and 92 respectively; p=0.004), which is probably, related to relatively high dosages of Fentanyl when the surgery duration was <120 minutes. Other noted findings include a moderate positive correlation between the duration of anesthesia and the qNOX5 [(rho)=0.501; p=0.003)] along with mild negative correlation between the Fentanyl dosages and the qNOX5 [(rho)=-0.385; p=0.027)].

Undesirable phenomena

No undesirable phenomena were reported as related to using the sedation and analgesia depth monitors (CONOX) and the sedation depth monitors (BIS).

DISCUSSION

In the current anesthesiology practice, the EEG-based anesthesia monitoring methods are being used quite widely, of which, the most conventional is the BIS sedation depth monitoring [9], however, a very promising option is the possibility of monitoring not only the sedation level, but also the analgesia level. The

Table 2

The use of anesthetic agents and opioid analgesics in the groups depending on anesthesia duration, Me [25%; 75%]

Parameter	Duration, minutes		*p*
	<120	>120	
Number patients, *n* (%)	59 (59.6)	40 (40.4)	-
Propofol, mg/kg	1.36 [0.76; 1.71]	1.60 [1.03; 1.83]	0.095
Fentanyl, μg/kg per hour	2.56 [1.87; 3.75]	1.75 [1.22; 2.08]	**0.001**
Sevoflurane, MAC	1 [1; 1]	1 [0.8; 1.0]	0.276

Note. Semi-bold font indicates statistically significant parameters (p <0.05).

Table 3

The dependence of the cognitive functions on the duration of general anesthesia and dosages of opioid analgesics in Group A, Me [25%; 75%]

Parameter	Duration, minutes		*p*
	<120	>120	
Fentanyl, μg/kg per hour	2.85 [1.75; 3.56]	1.70 [1.06; 1.86]	**0.001**
MMSE after surgery	27 [27; 27]	28 [27; 29]	**0.044**

Note. Semi-bold font indicates statistically significant parameters (p <0.05).

Table 4

The use of anesthetic agents and opioid analgesics in study groups depending on anesthesia duration, Me [25%; 75%]

Parameter	Duration, minutes		*p*
	≤120	>120	
Group A			
Number of patients, *n* (%)	21 (63.6)	12 (36.4)	-
Propofol, mg/kg	1.57 [1.13; 1.68]	1.76 [1.5; 1.84]	**0.013**
Fentanyl, μg/kg per hour	2.85 [1.75; 3.56]	1.70 [1.06; 1.86]	**0.001**
Sevoflurane, MAC	1 [1; 1]	1 [0.8; 1.0]	0.058
Group B			
Number of patients, *n* (%)	19 (57.6)	14 (42.4)	-
Propofol, mg/kg	1.76 [1.40; 1.84]	1.80 [1.68; 2.00]	0.114
Fentanyl, μg/kg per hour	3.52 [1.87; 4.22]	1.59 [1.11; 2.37]	**0.002**
Sevoflurane, MAC	1 [1; 1]	1 [0.8; 1.0]	0.212
Group C			
Number of patients, *n* (%)	19 (57.6)	14 (42.4)	-
Propofol, mg/kg	0.71 [0.62; 0.97]	0.72 [0.62; 1.28]	0.815
Fentanyl, μg/kg per hour	2.22 [1.98; 2.81]	1.88 [1.55; 2.09]	**0.024**
Sevoflurane, MAC	1 [0.80; 1]	1 [0.8; 1.16]	0.304

Note. Semi-bold font indicates statistically significant parameters ($p < 0.05$).

use of extended monitoring of anesthesia depth is of special importance among the high risk group patients, which, certainly, include geriatric patients.

During the course of our research, the usage of CONOX and BIS monitors has allowed for decreasing the dosage of Propofol required for anesthesia induction (in mg/kg) in Groups A and C comparing to the dosages in the control group B (see table 1). Taking into consideration that the hypotensive effect of Propofol is dose-dependent, optimizing its dosages helps to stabilize the hemodynamics in the patient, decreasing the rates and the severity of perioperative complications, including the neurological ones [19]. Arterial hypotension often develops during the induction or in case of low intensity pain stimulus (the vegetative component of pain reaction in the organism) depending on the surgery stage, while the blood pressure increase or heart rate increase usually occurring during intubation or extubation, as well as upon untimely administration of the analgesic agent [20–22], which was more often observed in Groups B and C. The hemodynamic parameters in Group A were more stable comparing to two other research groups. This result, on the one hand, provides the justification for using auxiliary methods of EEG-based anesthesiology monitoring, on the other hand — the insufficiency of controlling only the sedation depth without monitoring the analgesia level, which was discussed in previous research works [23–25].

Due to monitoring the sedation depth in Group C (BIS), Sevoflurane concentration during the MAC was lower comparing to other research groups (see table 1), however, this was not enough for decreasing the rates of hemodynamic disorders [9, 26].

The Fentanyl dosages in cases of longer duration of general anesthesia (>120 minutes) were less than in cases of shorter general anesthesia (<120 minutes) (see table 2), which is apparently related to the pharmacokinetics of the medicinal product in the said categories of patients. Upon multiple administrations of Fentanyl, some kind of plateau was formed in terms of its concentration in tissues and blood, which was specifically decreasing the demand for additional dosages, which could eventually and positively affect the cognitive status of the patients from Group A, in which the CONOX monitor, besides sedation depth, has allowed for controlling also the analgesia level [27]. The medical literature contains data on the benefits of uninterrupted administrations of analgesics (for example, via the infusion pump with adjusting the infusion rate, if necessary) comparing to bolus administrations [28].

In Group A, the MMSE cognitive status parameters after surgery were higher with the surgery duration

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of >120 minutes (with lesser Fentanyl dosages, respectively). This phenomenon is not conflicting with the theory about the neurotoxicity of anesthetic agents, especially in elderly and aged patients [1–3]. In Group A, the qNOX5 index (analgesia level at the moment of extubation) was also higher for the general anesthesia duration being >120 minutes, where the Fentanyl dosage was lower, which indicates lesser residual concentration of Fentanyl in such patients, which shortens the time of their restoration.

The initial manifestations of intraoperative awakening in our research, followed by vegetative symptoms, such as hypertension, tachycardia, developing single spontaneous respiratory movements without remembering anything occurring during the anesthesia in the postoperative period (which, most probably, was the sign of the transition from the stage of mild surgical anesthesia grade III-2 to the stage of superficial anesthesia grade III-1) were reported (in a descending order) in Groups B, C and A. With this, the attempts to obtain deeper narcosis took 1–3 minutes [17].

Hypotension during surgery is a risk factor for postoperative delirium. According to our data, postoperative delirium has correlated to the impaired hemodynamics [(rho)=0.358; p=0.001)]. The decrease of cerebral circulation as a result of hypotension is considered a significant risk factor for postoperative delirium, especially if it is following the course of surgical intervention for a long period of time [29, 30]. Intraoperative pain is also the risk factor for developing cognitive dysfunctions, for the areas of the brain that participate in pain perception and in the cognitive functions, are interconnected [30]. The rates of postoperative nausea and vomiting may depend on the duration of the surgical intervention (in our research (rho)=0.472; p=0.001) and on using excessive /insufficient dosages of sedative and narcotic medications, as well as on the excessive anesthesia depth [31].

Research limitations

The limitations of this research were resulting from several important factors. First of all, the research was conducted in a single medical center with a limited number of participants, which limits the representativity of data and hampers its extrapolation. The use of a single research facility and the limited patient sample do not allow for ruling out the effects of local factors.

Secondly, the absence of validating the results in other medical institutions decreases the versatility of the conclusions, which is important for the practical application of the obtained data. Besides, the limited follow-up period and the absence of follow-up data complicates the evaluation of the long-term effects of using the EEG-based anesthesiology monitors, especially in patients with peri-operational adverse effects.

Thus, despite the significance of the obtained data, the said limitations embound the justification and summarizing of results.

CONCLUSION

The implementation of non-invasive anesthesiology monitoring of sedation and analgesia depth based on EEG parameters in geriatric patients within the settings of ENT-surgery allows for more precise optimizing the dosing of sedative and narcotic medications, which promotes to decreasing the rate and the severity of hemodynamic disorders, to decreasing the rates of intraoperative awakenings and postoperative complications when comparing to using the sedation depth monitors. Combined with conventional clinical monitoring, EEG-monitoring accelerates the recovery after anesthesia and improves the outcomes of surgical interventions. Besides, the optimization of the dosing of opioid analgesics with controlling the analgesia depth index (qNOX) favorably affects the cognitive functions among geriatric patients during the postoperative period. Nevertheless, EEG-based anesthesiology monitoring methods are only the valuable addition to the traditional clinical-instrumental monitoring, but they do not replace it.

ADDITIONAL INFORMATION

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Authors' contribution. *M.H. Altoufaili* — patient selection, results analysis, article writing; *T.V. Klypa* — concept development and scientific editing of the article; *I.A. Mandel* — statistical processing of the article; *M.S. Orekhova* — selection and analysis of scientific literature. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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STAGING IN THE TREATMENT OF CHRONIC CALCULOUS CHOLECYSTITIS, COMPLICATED BY CHOLEDOCHOLITHIASIS

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ABSTRACT

BACKGROUND: *Chronic calculous cholecystitis is the most widespread disease in scheduled surgery departments, which in 10–15% of observations is complicated by choledocholithiasis. As of today, the commonly acknowledged staged treatment tactics includes first an endoscopic lithoextraction, later followed by the laparoscopic cholecystectomy, with the durations of performing the latter not being defined.* ***AIM:*** *To define the optimal timings of performing the laparoscopic cholecystectomy after an endoscopic lithoextraction in cases of chronic calculous cholecystitis, complicated by choledocholithiasis.* ***METHODS:*** *The research included patients with chronic calculous cholecystitis, complicated by choledocholithiasis, which during the period of 2016–2023 years have received surgical aid at the Federal State Budgetary Institution "Federal Scientific and Clinical Center" of the Federal Medical-Biological Agency of Russia (n=87). Simultaneous endoscopic lithoextraction and laparoscopic cholecystectomy were carried out in 20 patients; 19 patients were operated within a single hospitalization with undergoing endoscopic lithoextraction and in 3 days — laparoscopic cholecystectomy (early cholecystectomy); in 48 patients laparoscopic cholecystectomy was delayed by 1–2 months after the endoscopic lithoextraction (interval cholecystectomy).* ***RESULTS:*** *When comparing the treatment results in three groups of patients, no statistically significant differences were observed, however, in the group of interval cholecystectomy, a tendency was shown for increasing the surgery duration, the conversion rate and the number of complications.* ***CONCLUSION:*** *In patients, not having signs of severe course of the disease, it is possible to perform simultaneous endoscopic lithoextraction and laparoscopic cholecystectomy. In the absence of complications, the applicable options include early (within 3 days) conducting the laparoscopic cholecystectomy, which does not worsen the results, however, it alleviates the necessity of repeated hospitalization and, probably, slightly decreases the risk of complications.*

Keywords: *cholecystectomy; choledocholithiasis; gall stone disease; chronic cholecystitis; endoscopic retrograde cholangiopancreatography.*

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BACKGROUND

Cholecystectomy caused by the presence of chronic cholecystitis is the most widespread scheduled surgery in Russia. According to data from the information-analytical bulletin "Surgical Aid in the Russian Federation", the number of cholecystectomies in 2023 was 152 220 [1]. The occurrence rate of choledocholithiasis caused by the gall stone disease, according to different estimations, varies from 5 to 30% (with a mean of 10–15%) among the total number of gall stone disease patients [2]. In the existing clinical recommendations, after endoscopic lithoextraction in cases of chronic calculous cholecystitis, complicated by choledocholithiasis, a necessity is postulated of performing laparoscopic cholecystectomy [3], however, the optimal timings of its execution are determined only in local guidelines [4]. The accumulated data indicate that, when choosing the follow-up tactics, the prognosis in the patients significantly worsens: an increase is reported in the rates of recurrences (2-fold) and in the total mortality [5].

There are three principally different tactical approaches — simultaneous surgery, early cholecystectomy, which, in turn, is divided into cholecystectomy conducted in 3, 7 and 14 days, and the interval cholecystectomy (within the periods from 14 days to several months). The option that is widely acknowledged is the interval cholecystectomy. In this case, there are no unfavorable risk factors of developing complications, such as the mechanical jaundice and local

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ЭТАПНОСТЬ В ЛЕЧЕНИИ ХРОНИЧЕСКОГО КАЛЬКУЛЁЗНОГО ХОЛЕЦИСТИТА, ОСЛОЖНЁННОГО ХОЛЕДОХОЛИТИАЗОМ

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АННОТАЦИЯ

Обоснование. *Хронический калькулёзный холецистит — наиболее распространённое заболевание в плановой хирургии, которое в 10–15% наблюдений осложняется холедохолитиазом. На сегодняшний день общепризнана поэтапная тактика лечения, когда первоначально производится эндоскопическая литоэкстракция, а затем лапароскопическая холецистэктомия, при этом сроки выполнения последней не определены.* ***Цель исследования*** *— определить оптимальные сроки выполнения лапароскопической холецистэктомии после эндоскопической литоэкстракции при хроническом калькулёзном холецистите, осложнённом холедохолитиазом.* ***Методы.*** *В исследование включены больные хроническим калькулёзным холециститом, осложнённым холедохолитиазом, которым в 2016–2023 годах оказывали хирургическую помощь в ФГБУ ФНКЦ ФМБА России (n=87). Симультанная эндоскопическая литоэкстракция и лапароскопическая холецистэктомия проведены 20 пациентам; 19 больным в рамках одной госпитализации выполнены эндоскопическая литоэкстракция и в течение 3 дней лапароскопическая холецистэктомия (ранняя холецистэктомия); 48 пациентам лапароскопическая холецистэктомия была отсрочена на 1–2 месяца после эндоскопической литоэкстракции (интервальная холецистэктомия).* ***Результаты.*** *При сравнении результатов лечения трёх групп пациентов статистически значимых отличий не получено, однако в группе интервальной холецистэктомии отмечена тенденция к увеличению длительности операции, частоты конверсий и числа осложнений.* ***Заключение.*** *У пациентов, не имеющих признаков тяжёлого течения заболевания, возможно выполнение симультанной эндоскопической литоэкстракции и лапароскопической холецистэктомии. При отсутствии осложнений целесообразно раннее (в течение 3 дней) выполнение лапароскопической холецистэктомии, которая не приводит к ухудшению результатов, однако избавляет от необходимости повторной госпитализации и, вероятно, несколько снижает риск осложнений.*

Ключевые слова: *холецистэктомия; холедохолитиаз; желчнокаменная болезнь; хронический холецистит; эндоскопическая ретроградная холангиопанкреатография.*

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inflammatory reaction resulting due to the concrement passage and endoscopic manipulations. However, in a number of research works, it was demonstrated that interval cholecystectomy is associated with the risk of iatrogenic injury of the common bile duct and of the duodenum, with larger conversion rates and higher rates of purulent-septic complications, there is also a risk of developing repeated unfavorable biliary events (repeated choledocholithiasis, acute cholecystitis, cholangitis, acute biliary pancreatitis), which even more aggravate the patient status and lead to long-term therapy. Simultaneous endoscopic retrograde cholangiopancreatography (ERCP) and cholecystectomy (hybrid surgery) allow for avoiding repeated general anesthesia and provide a possibility of shortening the treatment duration, however, they require coordination of the surgical and endoscopic teams along with the corresponding equipment required in the surgery room, which is not available in all the medical organizations. Besides, in case of developing complications, their correction can be difficult.

Due to the abovementioned, it is necessary to analyze the experience of treating the patients with chronic calculous cholecystitis combined with choledocholithiasis with further drafting specific recommendations.

Research aim — to define the optimal timings for conducting the laparoscopic cholecystectomy after

an endoscopic retrograde cholangiopancreatography with lithoextraction in cases of calculous cholecystitis combined with choledocholithiasis.

METHODS

Research design

A retrospective comparative research was carried out, which has analyzed the treatment results in three groups of patients with gall stone disease, chronic calculous cholecystitis and choledocholithiasis, which were treated using the staged treatment tactics. The groups were assigned according to the intervals of performing cholecystectomies after the endoscopic intervention: group 1 — interval cholecystectomy after ≥1 month; group 2 — early cholecystectomy within the nearest 3 days; group 3 — simultaneous cholecystectomy.

In order to provide better relevance of the research conclusions, the following conformity criteria were applied.

Conformity criteria

Inclusion criteria: clinical-instrumental signs of chronic calculous cholecystitis combined with choledocholithiasis; patients aged 18 years and older; absence of previous surgeries involving the organs of the hepatopancreatobiliary zone, as well as absence of developmental defects in the bile ducts; completed cases of using staged treatment tactics (conducted and successful endoscopic removal of concrements from the bile ducts, and cholecystectomy).

Non-inclusion criteria: class B and C mechanical jaundice (according to the classification by E.I. Galperin); signs of acute cholecystitis and/or cholangitis; signs of acute biliary pancreatitis; presence of oncological diseases during the treatment process; acute myocardial infarction, acute impairment of cerebral circulation, thromboembolic complications of cardio-vascular diseases within the last 2 months; terminal stages of kidney damage; decompensated status of the organs or systems; coagulation disorders. The non-inclusion of patients with class B or C mechanical jaundice means that, with the initial presence of complications of the disease, significantly aggravating it, namely the renal failure, the encephalopathy (hepatic failure), gastro-intestinal hemorrhages and sepsis, the patients were not included into the research.

Exclusion criteria. A total of 2 patients were excluded from the research, in which, after the ERCP, endoscopic papillosphincterotomy and lithoextraction, there was insufficient data to rule out the retroduodenal perforation due to significant quantities of free gas in the abdominal cavity, which required open-access surgical intervention at the extent of laparotomy, cholecystectomy and duodenal mobilization (The Kocher manoeuvre). Perforation was not confirmed in both cases, the patients underwent external cholangiostomy via the cystic duct, followed by draining of the abdominal cavity and of retroperitoneal space.

Research facilities

The research work was carried out within the premises of the Federal State Budgetary Institution "Federal Scientific and Clinical Centre for Specialized Types of Medical Care and Medical Technologies of the Federal Medical-Biological Agency" (FSBI Federal Scientific and Clinical Center of the Federal Medical-Biological Agency of Russia).

Research Duration

The research work was arranged within a time period from January 2016 until December, 2023 (8 years).

Medical Procedure Description

Simultaneous intervention was carried out in the following order. Initially, laparoscopic access was used to resect the gall bladder (after the ERCP, the small intestine gets expanded with gas, which complicates the course of laparoscopic cholecystectomy), then followed the carbon dioxide desufflation from the abdominal cavity, but without extracting the troacars. The next step was the endoscopic intervention, which included the ERCP, the endoscopic papillosphincterotomy and lithoextraction. According to indications, lithotripsy was also conducted (mechanical or laser-assisted) with the endoprosthetic treatment of the bile ducts. Upon the completion of the endoscopic intervention, pneumoperitoneum was applied once again with the control assessment of the surgical intervention zone. The draining was done at the discretion of the operating surgeon.

Laparoscopic cholecystectomy was conducted at the conventional manner using four ports in accordance with principles of the critical view of safety (CVS). The bladder was extracted after being put into the container via the troacar access at the umbilical area or through the epigastric troacar.

The endoscopic intervention was carried out by a single endoscopist in the settings of the general anesthesia. The detailed description of the ERCP is provided in earlier publications [6]. In all the patients,

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prophylaxis of acute post-manipulation pancreatitis was arranged by means of rectal administration of 100 mg Diclofenac directly before intervention (2 h) and intravenous drip infusion of Octreotide at a dosage of 600 μg/day.

After the ERCP, all the patients were prescribed (for 24h) control testing for blood pancreatic amylase level along with the ultrasound examinations of the abdominal cavity. Hyperamylasemia with the value exceeding 3x the upper margin of the reference ranges and the presence of infiltration in the area of the hepatoduodenal ligament was considered a contraindication to the early conduct of laparoscopic cholecystectomy.

Research findings

The assessment included direct cholecystectomy results, such as surgery time, intraoperative complications, the number and the type of postoperative complications (classification by Clavien-Dindo, 2004), the duration of stay at the In-Patient Department. The surgery duration in the simultaneous surgery group was evaluated with subtracting the endoscopic intervention time. The postoperative bed days were counted only after cholecystectomy. The remote results were followed up within not less than 1 year after surgery.

The criteria for "complex" choledocholithiasis used were the commonly acknowledged ones and they were previously described by the number of authors [7].

Ethical review

The research work was carried out in accordance with the ethical standards of the Helsinki Declaration of the World Medical Association "Ethical Principles for Medical Research Involving Human Participants" amended in 2013. All the research participants were informed about the duration and the type of research. All the patients have signed an informed voluntary consent for treatment and undergoing surgeries, as well as for using the anonymized data on their health status for scientific purposes. The research was approved by the local Ethics Committee of the Federal State Budgetary Institution "Federal Scientific and Clinical Center" of the Federal Medical-Biological Agency of Russia (protocol No. 5, dated 15.05.2024.).

Statistical analysis

The minimal required sample size included 19 participants in each group in order to have the possibility to reject the null hypothesis with 80% power at the level of α=0.05. The calculations of the sample size were done using the PS Power and Sample Size Calculations software (version 3.0.11 for MS Windows). The qualitative data were provided as absolute values and percentages, while the quantitative ones — as the mean values with standard deviations. In order to test the differences for significance, we have used the following tests: qualitative variables were analyzed using the chi-square test ($\chi 2$), the quantitative ones — using the Mann–Whitney test. The software used was IBM SPSS 27. The p value was set at the level of <0.05 for significant results.

RESULTS

Research sample (participants)

Within the time period of 2016–2023, at the Federal State Budgetary Institution "Federal Scientific and Clinical Center" of the Federal Medical-Biological Agency of Russia, a total of 1429 cholecystectomies and 278 endoscopic interventions in the biliary tracts were carried out for the reason of gall stone disease and its complications. The research included 87 patients with a combination of chronic calculous cholecystitis and choledocholithiasis (6% of the total number of cholecystectomies), which had a successful endoscopic removal of concrements from the bile ducts and laparoscopic cholecystectomy: 20 patients had simultaneous laparoscopic cholecystectomy and ERCP, 19 had received laparoscopic cholecystectomy in 3 days after ERCP within a в single hospitalization, 48 — ERCP and laparoscopic cholecystectomy, delayed by 1–6 months. The groups of patients were comparable in terms of demographic characteristics. The characteristics of the patients and the treatment results are provided in table 1.

Primary findings

In the group of interval laparoscopic cholecystectomy, there were significantly more reports of having a "complex" choledocholithiasis (18.75%) and mechanical jaundice (39.6%), however, statistical significance for these differences was not achieved (p >0.05). The duration of surgery was the highest in the group of interval laparoscopic cholecystectomy, however, the statistical significance was not shown (p >0.05). Hyperamylasemia during the first 24 hours after ERCP was reported in 10 (11.5%) cases out of 87, in 8/48 (16.6%) for the group of interval tactics and in 2/20 (10%) in the group of simultaneous intervention. In the group of early laparoscopic cholecystectomy, there were no reports of hyperamylasemia, for its presence served as a contraindication to performing

Table 1

Characteristics of the patients and treatment results

Parameter	Laparoscopic cholecystectomy		
	simultaneous *n*=20	early *n*=19	interval *n*=48
Age, years	55.4±7.2	61.6±11.2	64.5±13.7
Males, *n* (%)	9 (45)	8 (42.1)	21 (43.75)
Females, *n* (%)	11 (55)	11 (57.9)	27 (56.25)
"Complex" choledocholithiasis, *n* (%)	2 (10)	0	9 (18.75)
Mechanical jaundice, *n* (%)	5 (25)	3 (15.8)	19 (39.6)
Surgery time	52.5±23.7	60.4±24.8	72.3±30
Conversion, *n* (%)	0	0	3 (6.25)
Postoperative bed days	3.5±0.6	3.8±0.7	4.1±2.45
Complications, *n* (%)	0	0	2 (4.2)

Note. Upon the statistical analysis of data, none of parameter has shown significance of the differences (p <0.05).

laparoscopic cholecystectomy. In 4/87 (4.6%) patients hyperamylasemia was combined with signs of acute pancreatitis. None of the patients has required repeated invasive interventions or treatment at the Intensive Care Unit. There were no cases of intraoperative hemorrhages (intra-abdominal ones and the ones from the zone of the major duodenal papilla). During the laparoscopic cholecystectomy, none of the reports had iatrogenic damage of the bile ducts. No conversions were reported in the group of simultaneous and early intervention, while the group of interval laparoscopic cholecystectomy had 3/48 (6.25%) of conversions (p >0.05).

After laparoscopic cholecystectomy, the groups of simultaneous and early surgery had no reported cases of complications. In the group of interval laparoscopic cholecystectomy, there was one case of laparotomy wound suppuration (in a patient with conversion) and a single case of suture sinus in the area of the epigastric troacar access, developing in one month after surgery.

The duration of hospitalization after laparoscopic cholecystectomy was the most long-term in the group of interval approach, however, no statistical significance was demonstrated for these differences (p >0.05). In the group of interval laparoscopic cholecystectomy, repeated hospitalizations before undergoing surgery due to the recurrence of choledocholithiasis or developing acute cholecystitis were reported in 3 (6.25%) cases. There were no fatal outcomes.

DISCUSSION

The optimal surgical tactics for the complicated course of the gall stone disease, when the patient has both the chronic calculous cholecystitis and the choledocholithiasis, is still a matter of discussion. Currently, the commonly acknowledged tactics is the staged one, when the patient initially undergoes an endoscopic intervention, aimed at the sanitation of the bile ducts from the concrements, followed by cholecystectomy. A recent meta-analysis including 13 research works (n=2598), published during the period from 2002 until 2019, has shown that cholecystectomy is statistically significantly resulting in a decrease in the risk of biliary events and mortality (odds ratio, OR, 0.38; p=0.03) [8]. And, if the necessity of cholecystectomy was justified, the optimal timings of its conduct with regard to the endoscopic intervention in the biliary ducts with the presence of choledocholithiasis are not defined. The simultaneous approach, when the laparoscopic cholecystectomy and the endoscopic intervention are performed simultaneously, has shown its benefits as a significant decrease of therapy durations [9]. Besides, during the simultaneous surgery, the "rendezvous" method can be used — which is the antegrade transvesical cannulation of the bile duct, during which, the surgeon uses the vesical duct to introduce the endoscopic guide wire, which, in turn, can be extracted using the duodenoscope [10]. This method allows for successfully performing endoscopic papillosphincterotomy and endoscopic lithoextraction in case of difficult cannulation of the major duodenal papilla. However, simultaneous surgery is only possible in the settings of good coordination between the surgical and endoscopic services of the clinical institution, while the equipment level of the operating room should allow implementing a hybrid approach expressed as using the X-ray apparatus (the C-arch). Taking into consideration the highlighted organization difficulties, it is not applicable to recommend the routine implementation of simultaneous interventions.

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The passage of the concrements along the common bile duct and performing endoscopic manipulations in the bile ducts with the administration of the contrasting agent inevitably results in the development of local inflammatory reaction, the swelling of the hepatoduodenal ligament, which makes difficult performing cholecystectomies. Besides, in part of the patients, mechanical jaundice develops, which can also negatively affect the number of cholecystectomy complications. Within this context, in the routine clinical practice, the interval approach has become widespread, when cholecystectomy is delayed by 2 weeks up to several months to allow for a regress of inflammatory-infiltrative changes in hepatopancreatobiliary area. However, the inflammatory reaction can progress into tissue scarring, when the manipulations in the Calot's triangle become more complex than at the acute phase of the inflammation. In the research by E. Bergeron et al. [11], it was shown that, when sparing the gall bladder after the endoscopic treatment of choledocholithiasis, repeated biliary events (acute cholecystitis, choledocholithiasis, cholangitis, cholangiogenic liver abscesses, pancreatitis) develop in 28.5% of the cases within a median time of 34 days with a rate of 2.5% already in 1 week. As opposed to this, after cholecystectomy, biliary events were reported only in 1.9% of the patients. Patients with repeated biliary events had significantly longer hospitalization time, more long-term post-operative hospital stay and higher rates of open-access surgeries.

A.M. Beliaev et al. [12] inform that the delay of laparoscopic cholecystectomy after endoscopic lithoextraction (double-stage approach with an interval of 16 weeks) is associated with a 10-fold higher risk of serious iatrogenic damage to the biliary ducts and 3-fold higher risk of converting the laparoscopic surgery to the open-access one. With this, 23% of the patients were repeatedly hospitalized with the diagnosis of acute calculous cholecystitis or acute pancreatitis after ERCP and sphincterotomy, which indicates the necessity of performing preventive laparoscopic cholecystectomy as earlier as possible. R. Şenocak et al. [13], when comparing the patients undergoing staged interventions, came to the following conclusion: laparoscopic cholecystectomy needs to be performed 2 weeks after the ERCP, upon exceeding this time, the risk of conversion significantly increases. C. Friis et al. [14] have published a systematic review of observational and randomized trials, which allowed the authors to state that the safest option is the laparoscopic cholecystectomy within the first 24 hours after ERCP (4.2% of conversions). With the delay by 24–72 hours, the risks of conversion increase up to 7.6%, with the delay time exceeding 2 weeks — up to 14%. The systematic review and meta-analysis by N. Poprom et al. [15], including 4 randomized and 4 retrospective trials with total number of patients being 1327, has shown that, in patients undergoing cholecystectomy after ERCP at the same day or within 72 hours, the risk of complications (with insignificant but notable absolute decrease of the duration of stay at the In-Patient Department and of the surgery time) was decreased by 37–73%.

In 2022, a research was published that was headed by the Head Surgeon of the Moscow Healthcare Department, an academician of the RAS, A.V. Shabunin [4]. Within the premises of the Surgical Clinical Unit of the Botkin Hospital, an analysis was done for the treatment results of 229 patients. It was found that laparoscopic cholecystectomy, conducted simultaneously and early after the ERCP along with lithoextraction, is characterized by significantly lesser surgery duration, as well as by significantly lesser number of postoperative complications. The authors make a conclusion that, for patients with complicated gall stone disease, the most preferable is the simultaneous or earlier conduct of laparoscopic cholecystectomy after ERCP.

Our results correlated with the results from other authors: we have similar data on surgery duration, hospitalization duration and the number of conversions. The small number of complications in our research can be explained by the fact that all the surgical interventions were carried out by highly qualified surgeons.

Research limitations

As a result of analyzing the publications on the given topics, an overwhelming impression has developed that the important unfavorable events in all the trials occurred rarely, while the confidence intervals were located over a wide range. The same has also happened upon analyzing our own experience. None of the patients had iatrogenic damage of the common bile duct or duodenum, no lethal cases were registered. The obtained differences on the conversion rate and surgery duration, despite being worse in the group of interval cholecystectomy, were not supported by statistical significance due to the small sample size. It is worth noting that, after applying the non-inclusion criteria for ensuring the relevance of the results, the number of patients in our clinics was small — 87 for 8 years (or 9–11 patients per a year). However, a recent systematic review has presented only 1327 patients enlisted into the trials during the time period from 2005 until 2020 [15]. This circumstance

makes out experience significant. Arranging further multicenter research works with a unified methodology should allow for obtaining more specific answers to the question about the optimal tactics for treating this category of patients.

CONCLUSION

Modern technologies allow for providing medical aid to the patients with chronic calculous cholecystitis and choledocholithiasis at high levels of efficiency and safety. In patients not having signs of the severe course of the disease, it is possible to perform simultaneous ERCP, endoscopic papillosphincterotomy and lithoextraction along with laparoscopic cholecystectomy. In the absence of ERCP complications, the practicable option is the early (within 3 days) performing laparoscopic cholecystectomy, which does not worsen the results, however, it relieves from the necessity of repeated hospitalization and, probably, slightly decreases the risk of complications.

ADDITIONAL INFORMATION

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INTRAOPERATIVE EVALUATION OF THE INTESTINAL WALL VIABILITY

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ABSTRACT

An analysis of data from national and foreign literature was carried out in terms of intraoperative determination of the intestinal viability in cases of developing the diseases in the abdominal cavity organs, associated with impaired intestinal blood supply. The basis of this work is the analysis of the modern literature on the methods of intraoperative evaluation of mesenteric ischemia. Impaired mesenteric blood supply is often the consequence of a number of reasons of developing critical conditions (mesenteric thrombosis, acute adhesive intestinal obstruction, incarcerated hernia etc.), also representing a high risk factor for lethal outcomes. Special attention is paid to the occlusion-related pathogenetic mechanism of developing mesenteric ischemia, which is accompanied by rapid development of irreversible morphological changes in the tissues and by significant disorders in the homeostasis systems of the organism. The generally available method for visual evaluation of the intestine viability is not always valid in terms of determining the degree of intensity of the ischemic changes in the intestinal wall. The algorithm of determining the intestine viability includes the determination of the intestine color, the peristaltic motions, the pulsation and the blood filling of mesenteric vessels with dynamic evaluation of these signs after the injecting the local anesthetic drug solution into the mesenterium and after "warming" the intestine with towels soaked in warm sodium chloride solution. In the current surgical conditions, a more precise method is required for intraoperative determination of the tissue viability. For the purpose of the objective evaluation of the intestinal blood supply, the recommendations include using intraoperative ultrasonic and laser Doppler flowmetry, as well as the regional transillumination angiotensometry of the intramural vessels in the small intestine. At the same time, a number of optical spectroscopy and visualization methods show high sensitivity to changes in blood microcirculation without using exogenous contrasting, which can also be successfully used when evaluating the intestinal circulation. According to data from modern literature, there is still controversy on the efficiency of various methods for intraoperative evaluation of disorders of the regional blood microcirculation and the intestine viability, which justifies the conduct of further research works.

Keywords: *intestine; ischemia; viability; biomedical optics; perfusion.*

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INTRODUTION

According to clinical recommendations from the World Society of Emergency Surgery (WSES), acute mesenteric ischemia develops in case of sudden cessation of intestinal blood supply, leading to cell damage, necrosis of the intestinal wall and death of the patient. Intestinal ischemia can have an occlusion-related or a non-occlusive origin. The occlusion-related pathogenetical mechanism includes the embolism of the mesenteric artery (50%) and the thrombosis of the mesenteric artery (15–25%) or vein (5–15%) [1]. The prevalence of non-occlusive ischemia, according to data from J. Canceco et al. [2] from the California University, is 25%. Non-occlusive ischemic lesions

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ИНТРАОПЕРАЦИОННАЯ ОЦЕНКА ЖИЗНЕСПОСОБНОСТИ КИШЕЧНОЙ СТЕНКИ

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АННОТАЦИЯ

Проведён анализ данных отечественной и зарубежной литературы по вопросам интраоперационного определения жизнеспособности кишечника при заболеваниях органов брюшной полости, сопровождающихся нарушением кровоснабжения кишечника. Нарушение мезентериального кровоснабжения часто является следствием ряда причин критических состояний (мезентериального тромбоза, острой спаечной кишечной непроходимости, ущемлённой грыжи и др.) и фактором высокого риска летального исхода. Особое внимание уделяется окклюзионному патогенетическому механизму возникновения мезентериальной ишемии, которая сопровождается быстрым развитием необратимых морфологических изменений тканей и выраженным нарушением системы гомеостаза организма. Общедоступный метод визуальной оценки жизнеспособности кишки не всегда достоверен в определении степени выраженности ишемических изменений кишечной стенки. В алгоритм определения жизнеспособности кишки входит определение цвета кишечника, перистальтики, пульсации и кровенаполнения брыжеечных сосудов с динамической оценкой этих признаков после введения в брыжейку кишки раствора местного анестетика и «согревания» кишки салфетками, смоченными тёплым раствором хлорида натрия. В современных условиях во время хирургической операции необходим более точный интраоперационный способ определения жизнеспособности тканей. Для объективной оценки кровоснабжения кишечника рекомендуется использовать интраоперационную ультразвуковую, лазерную допплеровскую флоуметрию, регионарную трансиллюминационную ангиотензометрию внутристеночных сосудов тонкой кишки. Ряд оптических методов спектроскопии и визуализации имеет высокую чувствительность к изменению микроциркуляции крови без использования экзогенного контрастирования, что также может быть успешно использовано в оценке кровотока кишечника. Отсутствие однозначных рекомендаций в отношении эффективности различных методов интраоперационной оценки нарушений регионарной гемомикроциркуляции и жизнеспособности кишки обусловливает необходимость проведения дальнейших исследований.

Ключевые слова: *кишечник; ишемия; жизнеспособность; гиперспектральная камера; перфузия.*

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can develop in the patients with severe concomitant abnormal conditions, hypovolemia, as well as in the patients using vasoconstricting medicines [3, 4].

The surgical abdominal disorders causing intestinal ischemia also include such nosologies as incarcerated hernia, acute intestinal obstruction and mesenteric thrombosis.

According to clinical recommendations, the “Incarcerated hernia” [5] term is defined as the presence of an acute or gradual compression of one

or several abdominal cavity organs within the hernial orifice, which is accompanied by an impairment of the organ's blood supply and results in its necrosis. The hernial defects occur in 5% of population with a risk of incarceration being 1–3% of all the cases [6]. The prevalence of incarcerated hernia in the Russian Federation, according to data from A.Sh. Revishvili et al. [7], has been persisting for the last 3 years at a high level and equals to 36–37 cases per 100 000 of the adult population. In 2022, the number of patients hospitalized with incarcerated hernia was 19.3% higher comparing to the numbers reported during the last 20 years. V.I. Struchkov et al. [8] in their research work report that the hernial sac in 50% of the cases contains small intestine and in 21% — large intestine. Necrosis of the intestinal wall was observed in 9% of the cases [9].

By the degree of intestinal coverage, the incarceration can be complete and incomplete. The incomplete type of lumen coverage in the incarcerated organ includes the parietal Richter's hernia and the Littre's hernia [5]. The Richter's hernia is the incarceration of the antimesenteric part of the intestinal wall. As evaluated by the C.M. Regelsberger-Alvarez et al. [10], up to 10% of all the hernias are Richter's type ones. The frequency of developing necrosis with this hernia type reaches up to 69% at the moment of surgery. The Littre's hernia is a herniation of the Meckel's diverticulum and it is an extremely rare complication with a prevalence of up to 0.09% [11].

The main form of intestine incarceration within the hernial orifice, causing ischemia, is the antegrade one, which most frequently develops in case when a small opening exists in the muscle tissue along with a significant quantity of content within the hernia itself [6]. The retrograde form of incarceration, known as the Maydl's hernia, is represented by two intestinal loops in the hernial sac along with the third loop connecting them inside of the abdominal cavity [12]. Besides, another possible variant is the sudden incarceration at the hernial orifice in the absence of past medical history of hernia [5]. In case of the incarcerated hernia, the strangulation causes the venous stasis, which results in swelling of the intestinal wall, its impaired permeability and with blood/plasma elements entering the intestinal wall and the hernial sac. With this background, in the limited space of the hernial sac, the processes of intestinal content decomposition take place with the formation of toxins [13].

Acute intestinal obstruction is a syndrome integrating various non-oncological diseases, resulting in the impaired intestinal passage due to mechanical obstruction or insufficiency of the intestine's motor functions. By the mechanism of developing the acute intestinal obstruction, ischemia can be caused primarily by the strangulation form that includes the peritoneal adhesions of the abdominal cavity, the intestinal volvulus, the invagination and the closed-loop obstruction [14].

Adhesions of the abdominal cavity is a symptomless (developing without the impairment of the functions in the abdominal cavity organs) adhesion of the parietal and visceral peritoneum developing as a result of altered normal mesothelization stages [15]. The prevalence of peritoneal adhesions in the abdominal cavity reaches up to 93% in patients undergoing repeated abdominal cavity surgeries [16]. In the research work by R.P. Ten Broek [17], the rates of developing acute adhesive intestinal obstruction were reaching 2% of the total number of surgical patients admitted to the in-patient units. Adhesive obstruction of the small intestine represented 55–75% of the small intestine obstruction cases [18]. According to data from A.Sh. Revishvili et al. [7], the number of acute adhesive intestinal obstruction cases has increased by 8.6% comparing to 2021, while the hospital and postoperative mortality has decreased to the level of 2019 equaling 4.33% and 4.03%, respectively. There is no unambiguous opinion on the causes of developing adhesion process in the abdominal cavity [19], but most frequently it develops with a background of peritoneal impairment during surgical procedures [20]. The loss of tissue integrity during surgical intervention causes the activation of angiogenesis in the basal layer of the peritoneum, which causes the disruption of the fibrinolytic processes and initiates the formation of adhesions [21]. Upon damaging the peritoneum, the delaminated mesothelial cells express cellular adhesion molecules and various chemotaxis factors, which results in greater inflow of inflammatory cells, predominantly macrophages, producing inflammatory cytokines, such as interleukins 1 and 6 (interleukin, IL-1, IL-6) and the tumor necrosis factor (TNF). In the adhesion process, the main role belongs to IL-6, the potent inductors of which are IL-1 and TNF. These inflammatory reactions are directly proportional to the degree of peritoneal damage [22].

K.R. Pashkin et al. [23] report that the mesenteric volvulus represents 4–5% of all the types of intestinal obstruction. As for the location, the most common one is the sigmoid volvulus (60–75%), less frequent is the cecal one (20–35%), the jejunal (7–18%) and transverse colon volvulus (3–5%). Generally, the pathological process

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involves a large area of the intestine with significant necrobiotic changes and severe hemodynamical and systemic alteration of hemostasis [14]. According to the research by T.A. Nikanorova et al. [24], intestinal volvulus can be found in 5% of the whole cases in adults. In the pathogenesis of this type of intestinal obstruction, the main role is played by the strangulation and the obturation components. The obturation mechanism is caused by rigidity-related narrowing of the intestinal lumen resulted from the introduction of one part of intestine into the other part's lumen, while the strangulation mechanism is caused by the compression of mesenteric vessels of the intestine between the middle and internal segments of the invaginated part [25].

Among the severe forms of strangulation-related intestinal obstruction, 3–4% is represented by closed-loop obstruction, in which compression of the mesenteric vessels of both intestinal loops occurs, with one of which always being the jejunum [9].

In case of strangulation-related intestinal obstruction, the primary impaired component is the blood supply of the intestine involved into the process, which is caused by the compression of mesenteric vessels supplying the intestine and, as a result, it causes rapid necrosis of the intestinal wall. The second most often variant of developing intestinal obstruction is the obturation related intestinal obstruction. The main etiological factors of this type of intestinal obstruction include tumors of the large intestine, developing in 15–20% of the patients and occurring in all the age groups [26]. According to data for 2022 [7], the number of acute intestinal obstruction cases of tumor-related origin in the Russian Federation has decreased by 2.3% comparing to 2021, however, the hospital and postoperative mortality has increased, equaling 17.75% and 19.57% respectively. According to the materials from A.G. Khasanov et al. [27], the prevalence of gallstone-related obturation-type intestinal obstruction relative to the total number of observed intestinal obstruction ranges from 0.17% to 6.2%.

During the second phase of the acute intestinal obstruction (intoxication), an impairment of the intramural intestinal blood circulation takes place [28]. The blood supply of the area located above the obstacle is being impaired secondarily in connection with the over-extension with the intestinal contents due to massive fluid inflow into the intestinal wall and into the intestinal lumen, which results in systemic hypovolemia and hemoconcentration. The developing intestinal edema and decreased blood inflow/outflow lead to intestinal ischemia [29]. The ischemic impairment of the intestine is accompanied by a decrease in the adenosinetriphosphate production by cell mitochondria, by the activation of hydrolase, by the decreased selective permeability of cellular membranes and by the increase of calcium inflow into the ischemic cells. When the intestinal ischemia becomes critical, polyorgan insufficiency develops, being the main cause of mortality [30].

The traditional method for intraoperative determination of intestine viability is the Kerte's visual method [31] based on the color, the presence of peristaltic waves, pulsation, blood filling of vessels in the intestine, as well as the dynamic changes of these signs after injecting the local anesthetic agent into the mesenterium and after "warming" the intestine up using towels soaked in warm sodium chloride water solution (NaCl) with the weight percentage of NaCl being ~0.9% [14]. According to data from A. Karliczek et al. [32], the sensitivity of visual evaluation of the intestine viability is 61.3% with the specificity being 88.5%.

In 2020, a group of authors headed by A.A. Zakharenko [33] has published a review of such methods for objective intraoperative assessment of the intestinal viability as the ultrasonic Doppler sonography, the polarographic method, the laser Doppler flowmetry, the laser speckle-contrast visualization, the fluorescent angiography, the side-light dark-field microscopy, the optical coherent tomography and the micro-peritoneal dialysis. Laser fluorescent spectroscopy of oxidative metabolism co-enzymes was marked by this review as the potentially perspective intraoperative method for objective determination of the viability of the intestinal wall.

In 2022, a group of authors from Saint-Petersburg, headed by D.A. Vedyanskaya [34], has published a scientific review devoted to the modern methods of intraoperative evaluation of the perfusion of tissues, with the review focused on assessing the cutting edge methods for defining the microcirculation in the intestinal wall, in particular, the hyperspectral and ICG-visualization, as well as the photoplethysmography, taking into consideration the potential for its practical use and the necessity of large clinical trials.

In a literature review by A.A. Valiev et al. [35], devoted to the modern methods of assessing the viability of the intestine, it was reported that the most widespread method for intraoperative evaluation of the microcirculation in the intestinal wall is the visual one. In the opinion of the authors, fluorescent angiography, which is the widely used and most studied method,

along with the hyperspectral visualization and the multi-modal coherent tomography are the most promising methods of intraoperative assessment of the viability of the intestine.

In the research work from our group of authors, we have summarized the data from the current foreign and national literature on the methods of intraoperative objective assessment of the intestinal wall viability in case of acute surgical disorders associated with intestinal ischemia, on the types and the efficiency of the methods used, along with the demonstration of the results obtained when personally using the technologies of assessing the perfusion of the intestinal wall during an animal model experiment with using hyperspectral visualization.

METHODS OF INTRAOPERATIVE OBJECTIVE ASSESSMENT OF THE MICROCIRCULATION IN THE INTESTINAL WALL DURING THE COURSE OF SURGICAL PROCEDURES

Ultrasonic Doppler sonography

Ultrasonic Doppler sonography is a variation of ultrasound examination using the Doppler effect for the purpose of defining the level of circulation within blood vessels [36]. Intraoperative evaluation of the blood flow ultrasonography parameters in the mesenteric vessels is a credible criterion of intestinal viability [33]. In the research work by M. Cooperman et al. [37], involving more than 200 patients with colon resection, the usage of intraoperative ultrasonic Doppler sonography resulted in a decrease in the rates of anastomosis failure during the postoperative period down to 1%. However, the method, according to literature data, has a high number of false-positive and false-negative results [38], being practically comparable to visual evaluation [39]. The sensitivity of the method diminishes its contribution to the informative signal from the examined area due to the interference from the surrounding vascular structures [33].

Polarographic method

The polarographic method is based on registering the levels of interstitial fluid oxygen during the electrolysis process upon interacting with the charged electrode [40]. Based on the results of the research work by W.G. Sheridan et al. [41], direct intraoperative tissue oxymetry of the human gastrointestinal tract is applicable as the mean of evaluating the degree of oxygen saturation in the tissues. However, for the purpose of defining the viability of the intestinal wall, direct contact is required between the electrode and the serous layer of the intestine, while the precision of evaluating the perfusion of the intestinal wall does not exceed 57.7%.

Micro-peritoneal dialysis

Micro-peritoneal dialysis represents a method of obtaining biological fluids from the tissue during the metabolic process within the organism with its further compositional analysis [42–50]. The method is based on the diffusion of the analyte into the perfused fluid via the micro-peritoneal dialysis catheter, which is introduced into the tested tissue or near it [49, 50]. The differences in the perfusion of the intestinal wall are determined based on the levels of lactate, pyruvate, glucose and cytokines in the peritoneal dialyzate [44–46]. The invasiveness and the cost of the analyzers along with its expendables are the main downsides of this method [47].

Laser Doppler flowmetry

Laser Doppler flowmetry provides contactless optical measurements of blood perfusion in the microcirculation [48–51]. The method is based on the effect of Doppler shift used for the purpose of measuring the velocity of red blood cells by means of laser radiation [52]. This method is easily reproducible and it has sufficiently high sensitivity, also allowing for evaluating the perfusion degree and the microcirculation status in the examined tissue area. The specific feature of the method is the ability to assess the microcirculation in the examined area. This image is the result of overlaying the multidirectional movements of particles in great numbers of microvessels and the changes in the concentration of these particles in the given area [53]. A.I. Khripun et al. [54] have demonstrated the capabilities of intraoperative application of laser Doppler flowmetry as a fast, easily interpretable and effective method for assessing the perfusion of the intestine in cases of acute mesenteric arterial blood flow impairment, which was studied in a group of 109 patients. The method has shown high (91%) sensitivity when determining the viability margins for the small and large intestines. A significant decrease was demonstrated in the cases of intestinal necrosis in the early post-surgery period (from 48.6 to 9.1%) along with the decrease in the rates of postoperative complications (from 67.6 to 40.9%) [54]. The laser Doppler flowmetry method, being non-invasive and showing high measurement speed, does not reflect the whole variety of the capillary network of the

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intestinal wall, providing the possibility of registering the measured parameters in relative units only at a small examined area.

Laser speckle-contrast visualization

Laser speckle-contrast visualization is based on registering the accidental speckle-interference patterns, back-scattered from the surface of the tissue illuminated with the coherent laser with a wave length of λ=635 nm. The obtained image contains darker and lighter colored areas, based on the accidental speckle-interference figure, formed by changes in the back-scattered light. The shift of the intensity of particles moving inside the lighted area changes the fluctuation of the scattering radiation, registered by the detector, leading to changes in the patterns and in the spatial contrast of the speckles. The trial by S. Kojima et al. [55] has demonstrated the ability of laser speckle-contrasted visualization to adequately measure the changes in the perfusion of the intestine with outstanding reproducibility. Similar results were reported by R. Ambrus et al. [56], showing that the changes in the laser speckle-contrasted visualization show good correlation when assessing the microcirculation in the stomach, liver and small intestine (r2 0.857, 0.956 and 0.946; variation coefficients 6.0%, 3.2% and 6.4%). Laser speckle-contrast visualization, due to the absence of the probe contacting the tissue and due to the ability to investigate large impaired areas in the real-time mode, is a perspective method for intraoperative assessment of the intestinal viability. However, the authors report that respiratory movements strongly affect the data obtained [56]. The benefits of this method include the possibility of performing contactless wide-field measurements of microcirculatory abnormalities in real scale and real time modes [57–60]. The factors decreasing the informativeness of laser speckle-contrasted visualization, are the effects on the registered transmittable pulsation data inflicted by the cardiovascular system and by the mechanical movements of the internal organs [34], as well as the relativity of microcirculation parameters, which affects the objectiveness of the tests conducted.

Side-light dark-field visualization

The method of side-light dark-field visualization includes obtaining contrasted images of biological tissue perfusion due to selective absorption of stroboscopic light with a wave length of 530 nm by hemoglobin molecules in red blood cells [61]. F.J. de Bruin et al. [62] were using the side-light dark field to evaluate the intestinal viability in 17 patients using such microcirculation parameters as the microvascular circulation index, the percentage of perfused vessels, the density of perfused vessels and the total vessel density. The measurements were carried out in each patient using the sublingual area and the serous membrane of the intestine. The authors came to the conclusion that the technology is very promising in terms of visualizing and evaluating the microcirculation in the intestinal wall. C.M. Treu et al. [63] report that this visualization method is cost-effective, safe and very sensitive, which provides obtaining reliable diagnostic data. However, S.M. Jansen et al. [64] report in their research work that the method requires direct contact between the probe and the serous membrane of the intestine, which affects registration due to the effects of interfering factors from the operator's side (hand tremors, uneven probe application pressure) and from the examined object (respiratory movements, transmitted pulsation of the cardiovascular system).

Optical coherent tomography

Optical coherent tomography is a visualization method, which provides information on the cross-section of tissues with high resolution and does not require direct contact with the examined objects. The method is based on the analysis of backward reflected radiation with measuring the delay for the purpose of defining the depth, at which the reflection occurs. The optical coherent tomography uses the near infrared range light. The delay of backward-reflected waves cannot be measured directly, which is why reference measurement is used. When using the interferometer, the part of light is directed to the sample, while the other part — to the reference arm of known length [65]. Y. Tian et al. [66], when performing the experimental research using small laboratory animals, have measured the changes of density, the length and the mean diameter of vessels in various layers of the intestinal wall in the normal conditions and during the ischemia. As a result of the research, significant decrease was registered in the density of vessel perfusion in all the layers of the intestine when exposed to ischemia. The most significantly affected part is the mucosa [66]. The method of registering data using optical coherent tomography requires direct contact between the probe and the serous membrane of the intestine, with this, there are no standardized approaches to sterilizing the equipment of the optical coherent tomography, raising the necessity of using aseptic gaskets between the device and the zone of interest. Optical coherent

tomography, being an operator-dependent method due to the necessity of equipment sensor positioning at the zone of interest by the hand of an operator, is subject to the effect of such factors as the hand tremors, the transmissive pulsation from the major vessels and the respiratory movements of the patient. According to the opinion from S.M. Jansen et al. [67], optical coherent tomography can be implemented for the intraoperative evaluation of intestinal perfusion, but the existing devices require technical rework for enabling their use during surgeries.

Fluorescent spectroscopy

The basis of fluorescent spectroscopy is the assessment of the content of various fluorophores, reflecting the metabolic status of the biological tissues within the wavelength range of 340–370 nm and 450 nm [68–72]. A.A. Zakharenko [73] reports that measuring the fluorescence levels of the oxidative metabolism co-enzyme NADH is promising in the intraoperative evaluation of intestinal perfusion. The main downside of this technology is the required contact between the equipment's optical probe with the examined tissue [74]. However, the use of fluorescent visualization can solve this issue.

ICG-visualization (indocyanine green imaging)

ICG-visualization (indocyanine green imaging) is based on the ability of the staining agent (Indocyanine green) to emit fluorescent signal when being excitated by the light source with a specific wavelength (nearest infrared spectrum — 700–900 nm). The method has gained wide spreading during scheduled and urgent gastrointestinal tract surgeries [75]. K. Nohara et al. [76] in their research work have demonstrated the use of ICG in two patients with strangulation-type intestinal obstruction when evaluating the compromised area of the intestine. Both patients have resolved successfully and with no complications after surgery. The authors have found that fluorescent ICG visualization can be considered a method for making a decision on the intestinal resection-type intervention in patients with strangulation-related intestinal obstruction, however, with the warning that no quantitative evaluations of the fluorescence were carried out and the optimal ICG dosage for the evaluation of intestine is not currently well-defined. Certain difficulties were reported for the macroscopic identification of the fluorescence borders that allow for predicting the viability of the ischemic intestine. The authors note that ICG cannot be used in patients with allergy to iodine-containing medications [76]. Two meta-analyses have found a 70% decrease in the rates of anastomosis insufficiency when using the ICG [77]. The downside of the method is its invasiveness. The literature describes cases of allergic reactions developing when Indocyanine green was used [35]. The important aspect is the absence of quantitative evaluation of signal intensity, which depends on the distance between the intestine and the camera, along with the surgeon's subjective opinion [78].

Infrared thermography

Infrared thermography is based on detecting infrared radiation emitted by the surface of the object. This allows for registering the distribution of thermal fields in the biotissues, developing due to the microcirculatory, metabolic and vegetative activity [79]. Thermography cameras are capable of registering the radiation in the infrared range (0.9–14.0 μm) [80]. The benefits of the method may include its cost-effective implementation, low operating costs, significant comfort and operability. Besides, using the infrared thermography, single evaluations can be performed along with the repeated ones for the purpose of dynamic assessment [81]. Nevertheless, G.J. Tattersall et al. [82] report that this method does not allow for registering minimal thermal changes occurring in cases of inflamed tissues. Besides, a group of authors headed by A. Repež [83] reports that the temperature shift is not always correlating with the intestinal perfusion.

Photoplethysmography

Photoplethysmography is a non-invasive method for measuring the changes in the blood volume in the microcirculation, based on the optical properties, such as absorption, scattering and transmission of certain light wavelengths by the tissues [84]. The absorption and reflection of light by the intestinal wall are influenced by its hemoglobin content and by the total volume of circulating blood. Using the RGB-camera (red, green and blue ranges) allows for registering the shifts of the reflected light resulting due to changes in the blood volume. Among the benefits of this method, of note are the absence of the necessity of using exogenous contrasting reagent, the possibility of constant tracking the circulation in the intestinal wall, the accessibility of the equipment and simultaneous reading of several parameters (blood oxygen saturation, or saturation, SpO_2; heart rate; respiratory rate) [85, 86]. The downside of this method is the time delay required for obtaining the image of the intestinal wall perfusion. Besides,

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the fluctuations in the parameters of central blood circulation and the changes of blood pressure can also add interference to the measured parameters [34]. The use of RGB-camera together with the magnification system and with corresponding image processing algorithms allows for implementing the circulation rate measurements in the capillaries at any spontaneously selected area of the body [87]. Such an approach potentially allows for early detecting various diseases associated with microcirculation abnormalities. The disadvantage of this method also includes its sensitivity to respiration and body movements. Besides, uneven surface of the tissue can hamper the process of obtaining reliable data.

Hyperspectral visualization

Hyperspectral visualization is based on spatial spectrometry using the three-dimensional set of data (hypercube) and representing spatial coordinates in wide and continuous range of electromagnetic spectrum. Hyperspectral visualization allows for measuring the spectral characteristics of every pixel having a spectral curve [88–92]. During the last 5 years, more and more publications were found in the foreign literature, where the method used for assessing the viability of the intestine is the hyperspectral visualization. The method demonstrates high efficiency of analyzing intestinal ischemia with high sensitivity to changes in the microcirculation, especially in the near infrared range of the spectrum [93–95].

Within the premises of the Research and Development Center of Biomedical Photonics under the Federal State Budgetary Educational Institution of Higher Education "Orel State University (named after I.S. Turgenev)", experimental research was performed in rats with evaluating the capabilities provided by the hyperspectral visualization method for analyzing the intestinal ischemia [96]. The trial involved an original developed hyperspectral visualization system, consisting of a broad-band radiation source with the FRI61F50 fiber ring light source (Thorlabs, Inc.) and the Specim IQ hyperspectral camera with the range of 400–1000 nm (Specim, Spectral Imaging Ltd., Finland). The camera has the dimensions of 207×91×74 mm (objective — 125.5 mm), which is comparable to the size of Canon EOS 650D Kit EF-S photo-camera (133×100×79 mm) and which does not create any issues in terms of its mobile use when operating in the surgery room. The time required for evaluating the perfusion of the intestinal wall during the experiment, was not more than 5 minutes, which could not negatively affect the course of the surgical intervention. It was demonstrated that hyperspectral camera allows for obtaining information on the status of the microcirculation in the intestinal wall by examining the saturation of the tissues. Besides, this technology allows for evaluating the oxy-/deoxyhemoglobin and water indexes. Our research has shown that colored dimeric saturation maps compiled when modeling the intestinal ischemia, allow for specifying several SpO_2 intervals corresponding to the morphological changes in the intestinal wall, and thus allowing for judging on the reversibility of the intestinal damage.

CONCLUSION

Each method of assessing the microcirculation in the intestinal wall has its limitations. The intraoperative system intended for supporting the physician's decisions about the viability of the intestinal wall, based on quantitative parameters, is the indispensable element of surgical procedures in cases of intestinal ischemia. The methods of optical spectroscopy and visualization, in particular, hyperspectral visualization, represent the promising non-invasive equipments for assessing the ischemic damage in the intestinal wall, allowing for obtaining a complex information on the microcirculation status of the intestinal wall. However, it is important to define the indications and the place of each objective approach for evaluating the perfusion in the algorithm of intraoperative diagnostics of acute intestinal ischemia.

ADDITIONAL INFORMATION

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THE USE OF THE LONG PERONEAL MUSCLE TENDON AS AN AUTOGRAFT DURING THE PRIMARY PLASTICS OF THE ANTERIOR CRUCIATE LIGAMENT: A SYSTEMATIC REVIEW

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ABSTRACT

The anterior cruciate ligament injuries take the leading place among all the injuries of the knee joint. The rupture of the anterior cruciate ligament most frequently occurs during sports-related and high-energy traumas. The aim of the present systematic review is to compare the results obtained after the anterior cruciate ligament plastics with using the long peroneal muscle tendon and the autograft made from the common tendon of the semitendinous and gracilis muscles. The analysis includes the original articles from the PubMed, Google Scholar, eLibrary, Scopus and Web of Science search systems. The key words for the search included ("peroneus longus tendon" or "fibularis longus tendon") and ("anterior cruciate ligament reconstruction" or "ACL reconstruction"). In the Russian data bases, the same terms were used. From the articles found, the following parameters were extracted: the evaluation of the functional results using the Tegner–Lysholm scale and the questionnaire for subjective assessment of the status among the patients with various knee joint injuries — IKDC (International Knee Documentation Committee); the evaluation of the mean diameter of the autotransplant; the instability of the knee joint; as well as the possible complications; the evaluation of the functions in the ankle joint and the foot using the AOFAS (American Orthopaedic Foot and Ankle Society) and FADI (Foot and Ankle Disability Index) scales. These parameters were used for evaluating the clinical research works on using the autograft made from the long peroneal muscle tendon for the reconstruction of the anterior cruciate ligament. The authors have analyzed the treatment results in 2322 patients which underwent anterior cruciate ligament plastics using the long peroneal muscle tendon (n=1660) and the semitendinous muscle tendon (n=662) autotransplants. The parameters of the postoperative status according to the AOFAS and FADI scales for the long peroneal muscle tendon were 96.47±2.71 and 97.72±2.58, respectively, which does not differ from the uninjured side (p >0.05). The best IKDC scale scores were 94.13±4.66 for the long peroneal muscle tendon and 95.12±0.73 for the semitendinous muscle tendon, while the scores of the Tegner–Lysholm scale were 99.15±2.89 and 99.85±0.37, respectively. Thus, the autograft made using the long peroneal muscle tendon is a proper alternative for the reconstruction of the anterior cruciate ligament, for it is located outside the area of the knee joint.

Keywords: *arthroscopy; anterior cruciate ligament; long peroneal muscle tendon; semitendinous muscle tendon; gracilis muscle tendon.*

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INTRODUCTION

The injuries of the anterior cruciate ligament take the leading place among all the injuries of the knee joint [1]. The rupture of the anterior cruciate ligament is most frequently caused by sports-related and high-energy traumas, for example, motor-vehicle accidents or falling on the knee, in which the foot is positioned with plantar flexion [2]. The anatomic reconstruction of the anterior cruciate ligament is a modern gold standard for restoring the stability in the knee joint, for decreasing

ПРИМЕНЕНИЕ СУХОЖИЛИЯ ДЛИННОЙ МАЛОБЕРЦОВОЙ МЫШЦЫ В КАЧЕСТВЕ АУТОТРАНСПЛАНТАТА ПРИ ПЕРВИЧНОЙ ПЛАСТИКЕ ПЕРЕДНЕЙ КРЕСТООБРАЗНОЙ СВЯЗКИ: СИСТЕМАТИЧЕСКИЙ ОБЗОР

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АННОТАЦИЯ

Повреждения передней крестообразной связки занимают лидирующее место среди всех травм коленного сустава. К разрыву передней крестообразной связки чаще всего приводят спортивные и высокоэнергетические травмы. Цель настоящего систематического обзора — сравнить результаты пластики передней крестообразной связки при помощи сухожилия длинной малоберцовой мышцы и аутотрансплантата из сухожилия полусухожильной и нежной мышц. Проанализированы оригинальные статьи из поисковых систем PubMed, Google Scholar, eLibrary, Scopus и Web of Science. Ключевые слова для поиска включали «peroneus longus tendon» or «fibularis longus tendon» и «anterior cruciate ligament reconstruction» or «ACL reconstruction». В русскоязычных базах данных использовали аналогичные термины. Из статей извлечены следующие параметры: оценка функциональных результатов по шкале Тегнера–Лисхольма и опроснику для субъективной оценки состояния пациентов с различными повреждениями коленного сустава IKDC (International Knee Documentation Committee); оценка среднего диаметра аутотрансплантата; нестабильность коленного сустава; возможные осложнения; оценка функции голеностопного сустава и стопы по шкалам AOFAS (American Orthopaedic Foot and Ankle Society) и FADI (foot and ankle disability index). Эти параметры применялись для оценки клинических исследований использования аутотрансплантата из сухожилия длинной малоберцовой мышцы для реконструкции передней крестообразной связки. Авторами проанализированы результаты лечения 2322 пациентов, которым была выполнена пластика передней крестообразной связки с использованием аутотрансплантатов из сухожилия длинной малоберцовой мышцы (n=1660) и сухожилия полусухожильной мышцы (n=662). Показатели послеоперационного состояния по шкалам AOFAS и FADI для сухожилия длинной малоберцовой мышцы составили 96,47±2,71 и 97,72±2,58 соответственно, что не отличается от здоровой стороны (p >0,05). Лучшие баллы по шкале IKDC составили 94,13±4,66 для сухожилия длинной малоберцовой мышцы и 95,12±0,73 для полусухожильной мышцы, по шкале Тегнера–Лисхольма — 99,15±2,89 и 99,85±0,37 соответственно. Таким образом, аутотрансплантат из сухожилия длинной малоберцовой мышцы является подходящей альтернативой для реконструкции передней крестообразной связки, так как находится вне области коленного сустава.

Ключевые слова: *артроскопия; передняя крестообразная связка; сухожилие длинной малоберцовой мышцы; сухожилие полусухожильной мышцы; сухожилие нежной мышц.*

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the rates of secondary ruptures of the menisci and, as a result, for decreasing the rates of post-traumatic osteoarthritis [3, 4]. For performing the reconstruction of the anterior cruciate ligament, an autotransplant or an allotransplant or a synthetic prosthesis is required. The autograft made of the semitendinous and gracilis muscle tendons (SGMT (in Russian: СПНМ) is the most commonly used transplant for the reconstruction of the anterior cruciate ligament worldwide [5]. Along with the SGMT, other used autotransplants include the bone-patellar tendon-bone and the tendon of the quadriceps muscle, however, all of the abovementioned variants are associated with complications, in particular, the instability of the knee joint or the quadriceps/hamstring-imbalance, pain in the area of the patella and of the thigh, contractures of the knee joint and patellar fractures [6-8.]. In case of multiple injuries of the ligamentous apparatus of the knee joint, the SGMT autotransplant can be insufficient for the plastics of all the damaged structures. In a number of countries, the use of allotransplants and synthetic transplants is not possible [8]. Within this context, currently the surgeons more often use the alternative autografts for the anterior cruciate ligament plastics — the ones made from the long peroneal muscle tendon (LPMT) [9].

The use of the LPMT as an autograft for the reconstruction of the anterior cruciate ligament was first described by S. Kerimoğlu et al. in 2008 [10]. In 2012, J. Zhao et al. [11] have also demonstrated the efficiency of using LPMT as an autograft. In a research work performed in 2017 by R. Lukman et al. [12], the biomechanical properties of the SGMT and LPMT were studied *ex vivo*. Based on the research results, there was no significant difference in the tensile strength between the LPMT (446.1N±233.2N, where N is the force in newtons) and the quadruple SGMT transplant (405.8N±202.9N) with a similar cross-sectional area. In 2021, J. He et al. [12] have described the LPMT autograft as the comparable alternative option to the SGMT one from the point of view of the functional results, also, the authors have concluded that the use of the LPMT autograft provides better clinical results in the knee joint, expressed as the decrease in the knee joint pain syndrome and thigh muscle weakness, however, the assessment by the American Orthopaedic Foot & Ankle Society (AOFAS) was much lower comparing to the preoperational one [14].

The results of the abovementioned research works confirm that the LPMT autograft is a strong donor tissue for reconstructing the anterior cruciate ligament. Later on, a large cohort of clinical research works [15–21] have demonstrated good clinical results and minimal pain in the area of the autotransplant installation, by this proving the efficiency of using the LPMT as an autograft, nevertheless, the variability of the methods and parameters in various research works, as well as small number of cases in each research, add to the uncertainty, especially when comparing the results between various transplants [21].

This systematic review was carried out for the purpose of comparing and analyzing the results of anterior cruciate ligament plastics using the LPMT in terms of restoring the functions and the biomechanics of the knee joint and of the foot with restoring the knee joint stability, in the aspect of pain or paresthesia in the area of the transplant application, its survival rate, also included were the clinical research works, comparing the LPMT and SGMT autotransplants during the reconstruction of the anterior cruciate ligament [22].

METHODOLOGY OF SEARCHING THE SOURCES

The systematic review was compiled in accordance with recommendations of the PRISMA international protocol (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) issued on March 1, 2020 [23]. The research includes original articles, containing data with full text in English or Russian languages, accessible in the Internet (search systems: PubMed, Google Scholar, eLibrary, Scopus and Web of science) from 2018 until 2024. During the search, the following key words were used: (“peroneus longus tendon” or “fibularis longus tendon”) and (“anterior cruciate ligament reconstruction” or “ACL reconstruction”), while for the Russian data bases — “long peroneal muscle tendon”, “anterior cruciate ligament plastics” or “the use of long peroneal muscle tendon during the anterior cruciate ligament plastics”. The publications were informing about the clinical research works on the reconstruction of the anterior cruciate ligament (single-bundle or double-bundle) using the LPMT autotransplant (the anterior half or its whole thickness), the research works, in which direct comparison was made between the results of using the LPMT and the SGMT, as well as about the biomechanical research works. All the surgeries were initial, performed due to the onset of acute or chronic damage of the anterior cruciate ligament, with or without the meniscus damage.

The review did not include irrelevant articles or non-original research works, such as literature reviews, editorial opinions, corrections, meta-analyses, as well as publications, which contained the research

on allotransplants and research works analyzing the results after the reconstruction of other ligaments outside the knee joint using the LPMT autotransplant.

Quality assessment

For the evaluation of methodological quality of the research works included in the review, we have used the Methodological Index for Non-randomized Studies (MINORS), as well as a set of specialized instruments for quality evaluation developed in 2013 by the National Heart, Lung and Blood Institute (NHLBI).

Extraction and analysis of data

The parameters analyzed in this review were reflecting the functional results, including the mean points of the Lysholm scale, in which the percentage of points was more than 84 (excellent or good result); the mean subjective point of the International Knee Documentation Committee (IKDC) and the percentage of normal or almost normal subjective IKDC points; the mean diameter of the autotransplant; the instability of the knee joint, including the percentage of negative anterior drawer test cases; the possible complications, including paresthesia or pain syndrome in the area of the graft installation and the rates of unsuccessful transplantations; the results of treating the developing abnormalities of the foot and of the ankle joint after extracting the LPMT, including the mean parameters before and after surgery, assessed using the American Orthopaedic Foot and Ankle Society scale (AOFAS) and the Foot and Ankle Disability Index (FADI), as well as the evaluation of the biomechanical parameters of the foot and of the ankle joint.

All the data collected by us were presented in tables; a formal meta-analysis was carried out using the RevMan software (version 5.4, Cochrane Collaboration). Continuous variables were extracted and analyzed as the mean values with standard deviation (Standard Deviation, SD). The standard deviation was calculated using the available data in accordance with previously approved formula: [(the highest value of the range — the least value of the range)] or (interquartile range / 1.35). If the standard deviation was impossible to calculate using this approach, the highest standard deviation was used. For continuous variables, the mean difference (MD) was calculated along with the 95% confidence interval (95% CI).

We have also checked the sample heterogeneity using the χ^2 and Higgins I^2 tests. According to the Cochrane recommendations, the mean heterogeneity was calculated in case of I^2 >30% or p <0.5. We have used the conservative statistical approach, applying the Mantel–Haenszel random effects model in case of having the mean heterogeneity and the fixed effects model for cases when the p values were <30% and >0.5, respectively. The statistically significant p level was <0.5 for all the results.

LITERATURE SEARCH, SELECTION OF RESEARCH WORKS AND THEIR CHARACTERISTICS

Initially, as a result of literature search, a total of 927 articles were found (Fig. 1) [23]. After excluding the duplicate publications, 917 articles were remaining, while after screening the titles and abstracts — 26 articles were obtained, the full texts of which were verified for conformity to the inclusion criteria. All the selection criteria after the double-staged screening were met by 21 articles [24–43]: 16 articles, which were reporting about the results of reconstructing the anterior cruciate ligament using the LPMT autotransplant, and 5 articles, in which comparison was made for the results of using LPMT and SGMT autografts. All the articles (n=21) were compiled into a summary table (table 1). The total set of analyzed results included 2322 patients, of which 1660 had a reconstruction of the anterior cruciate ligament using the LPMT autotransplant, while the results for remaining 662 patients were extracted from the publications, in which comparison was made for the use of LPMT and SGMT autografts.

Assessment of the autotransplant diameter

Of the 21 research works included into the literature review, 16 have described using the whole thickness of the LPMT, while 5 have used the anterior LPTM part. In 8 publications, the mean transplant diameter was evaluated in 520 patients. In 5 research works, in which the LPMT and SGMT were compared [22, 40–43], the mean diameter of the LPMT autotransplant was significantly higher comparing to the SGMT transplant. The research by G. Wierer et al. [43] has also investigated the inter-relation of the body mass index and of the hip and shin circumference with the transplant diameter. Based on the research results, it was found that the body mass index and hip circumference parameters affected only the diameter of the SGMT transplant, while the shin circumference and body mass index had no significant effect on the LPTM transplant diameter. However, based on the results from the research work by D. Ertilav [31], a statistically significant correlation was found between the weight of the patient, the height, the body mass index, the length of the lower limb, the hip circumference, the shin circumference

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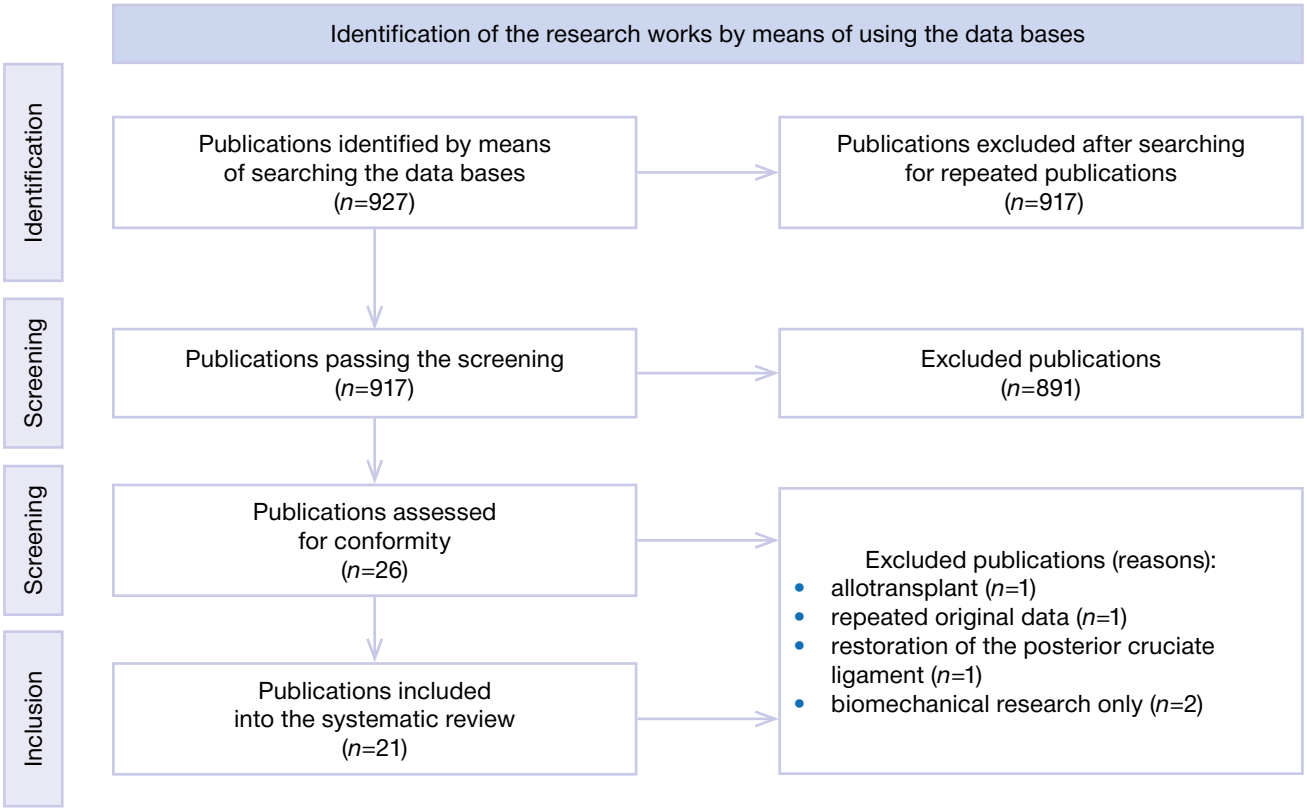

Fig. 1. Literature search diagram [23].

and the transplant diameter. In the research works evaluating the LPMT autotransplant diameter, the mean dimension was 7–9 mm.

Evaluation of the results using the American Orthopaedic Foot and Ankle Society (AOFAS) scale and the Foot and Ankle Disability Index (FADI)

Using the scale compiled by the American Orthopaedic Foot and Ankle Society (AOFAS) and using the Foot and Ankle Disability Index (FADI), a total of 1000 of patient data sets were analyzed with the patients operated using the LPMT (table 2). The post-operative mean AOFAS scores on the side of LPMT extraction were comparable to the mean values of the FADI index, with the difference from the uninjured side being statistically insignificant ($p > 0.05$). This have demonstrated good functional results and the possibilities of safely using the LPMT as an autograft without significantly affecting the functions of the foot and of the ankle joint.

Evaluation of the flexion and extension force in the ankle joint

In a series of clinical cases from S. Rhatomy et al. [33], a complex approach was used to evaluate the functions of the foot and of the ankle joint during the postoperative period. The results of muscle strength tests were collected in 31 patients in 6 months after surgery. For the purpose of measuring the isometric muscle strength, the patients were using the special hydraulic double-acting dynamometer. A research was conducted on the bilateral angled eversion and plantar flexion of the great toe. Each measurement of the muscle strength was carried out 3 times with registering the highest value. Foot eversion was measured in lying position. Based on the results of muscle strength testing, the mean foot eversion force was 65.87±7.63N in the area of the autotransplant installed and 66.96±8.38N on the unaffected side. The mean strength of plantar flexion was 150.64±11.67N on the side of the autograft installed and 152.10±12.16N on the unaffected side. As a result of this research work, no difference was observed in the strength of foot eversion and plantar flexion between the operated and the uninjured side.

Evaluation of the functions and stability of the knee joint

A total of 336 results of LPMT autotransplantations and 326 SGMT autotransplantations were analyzed.

Table 1

Publications selected for analysis

Author	Year	Country	Study design	Gender: males/ females	Age (min–max), years	Follow-up period, months (SD)	Tendon used
Research works with using only the long peroneal muscle tendon (LPMT) as an autograft							
[24]	2020	China	Retrospective	19/16	18–60	6.5±3.61	Layered
[25]	2023	China	Retrospective	55/32	20–45	24.5±14	Layered
[26]	2021	China	Case series	13/8	18–45	6.5±3.61	Anterior part
[27]	2023	Turkey	Retrospective	74/8	16–66	46.6±30.3	Layered
[28]	2019	Vietnam	Case series	19/11	18–51	14.5±8.22	Anterior part
[29]	2023	Bangladesh	Prospective	348/91	18–45	12.5±7.1	Layered
[30]	2020	Indonesia	Cohort, retrospective	59/16	18–45	5±2.74	Layered
[31]	2021	Turkey	Retrospective	38/14	17–51	12±6.8	Layered
[32]	2022	India	Prospective	78/35	17–39	11.5±6.5	Layered
[33]	2019	Indonesia	Case series	22/9	18–45	11.5±6.5	Layered
[34]	2022	India	Case report	1, male	25	12	Layered
[35]	2021	India	Prospective	36/12	18–36	17±9.67	Layered
[36]	2020	Russia	Prospective	407/171	35.29±12	24.5±14	Layered
[37]	2020	China	Prospective	20/12	16–45	6.5±3.61	Layered
[38]	2018	China	Prospective	11/5	35–65	27±15.44	Layered
[39]	2024	China	Prospective	6/14	18–44	4±2.16	Anterior part
Research works comparing the results of using the long peroneal muscle tendon (LPMT) and the semitendinous and gracilis muscles tendon (SGMT)							
[22]	2019	Indonesia	Prospective	Hamstring group: 24/4 Peroneus longus group: 20/4	16–45	12.5±7.1	Layered
[40]	2023	Pakistan	Prospective cohort	138/20 (158), of which peroneus longus: 85; hamstring: 73	18–51	36.5±20.92	Layered
[41]	2023	India	Prospective cohort	Hamstring group: 57/39 Peroneus longus group: 68/30	16–50	10±5.63	Layered
[42]	2022	Iran	Comparative cross-section	Hamstring group: 58/7 Peroneus longus group: 61/4	18–50	12.5±7.1	Layered
[43]	2023	Austria	Cross-section	Hamstring group: 64 Peroneus longus group: 64	18–45	6.5±3.61	Anterior part

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Table 2

Comparison of the results of the AOFAS and the FADI scales

Source	Number of patients	AOFAS scale	FADI scale
[25]	87, divided by body mass index: normal excessive obesity	In the first two groups, there were no significant differences in the AOFAS scores after surgery. In Group 1 — 94.61±3.48; in Group 2 — 94.00±3.82. In patients from Group 3, the values were lower — 89.47±3.37	-
[29]	439	Mean score — 97.63±3.20 (range 89.00–100.00)	Mean score — 98.46±2.31 (range 86.20–100)
[37]	32	Mean score — 94.7±6.8	-
[26]	21	Mean score — 96.8±3.01	Mean score — 97.6±2.66
		Post-operative results, assessed in 3 years, comparable with pre-operational data	
[27]	82	On the side of autotransplant extraction — 98.7±3.3 (range 87–100); on the contralateral side — 100	-
[33]	31	Mean score — 98.71±3.03 on the side of the autograft extraction and 99.03±3.00 on the contralateral uninjured side	Mean score 99.71±0.57 on the side of the autograft extraction and 99.71±0.61 on the contralateral uninjured side
		Based on the research results, no significant difference was shown for the AOFAS and FADI scores between the extraction side and the contralateral side	
[35]	48	Mean score — 98.4±1.23	-
[28]	30	Function of the ankle joint and foot before surgery — 97.3±1.67, after surgery — 97.3±1.54 (lesser score — 93, maximal — 100)	-
[30]	75	Mean score — 98.93±3.10	Mean score — 99.79±0.59
[42]	65	Mean score on the side of the transplant extraction — 93.42±1.7 (range 84–100; “excellent” — 90–100 points, “good” — 75–89 points, “satisfactory” — 60–74 points, “poor” — <60 points). Comparing to the uninjured side, no difference was observed	Mean score on the side of the transplant extraction — 92.78±0.57 (range 94–102) and 98.91±0.62 on the unaffected side. No significant difference comparing to the unaffected side
[41]	98	Mean score — 96.2±0.95, in 12 months — 99.05±3.56	-
[22]	24	Mean AOFAS score — 97.3±4.2	Mean FADI score — 98±3.4
[39]	20	Mean AOFAS score on the operated side — 98.05±1.73, on the unaffected side — 98.30±1.66	-

In the research work by A. Agarwal et al. [41], 98 patients were operated using the LPMT and 96 — using the SGMT. The results of the anterior drawer test in 187 patients in both groups in 12 months after surgery were negative. The “+” test result was reported for 6 patients. A single patient from the LPMT group had a (+++) positive anterior drawer test due to a repeated injury. According to the Lachman test data, 177 patients had a negative test result in 12 months; 16 patients had a positive test result. The functional results were evaluated using the IKDC and Lysholm scales (table 3).

In a research by S. Rhatomy et al. [22], an evaluation of the results registered before surgery and in 12 months after surgery using the Lysholm and IKDC scales was carried out in 28 patients, in which the SGMT autograft was used, as well as in 24 patients with the LPTM autograft used. Based on the research results,

no significant differences were observed between the Tegner–Lysholm and IKDC scores before surgery and after a 1 year of follow-up (p >0.05).

No significant differences were observed in the publications which have compared the LPMT and SGMT using the IKDC and Tegner–Lysholm scales. The Lachman test has shown satisfactory results in the majority of patients.

Thus, no statistically significant (p >0.05) differences were reported between two groups with the SGMT and LPMT autotransplants in terms of the functional parameters and stability parameters of the knee joint.

Complications

In the research work by U. Yadav et al. [34], a single clinical case was reported that was associated with iatrogenic neurological deficit in the foot after the extraction of the LPTM autotransplant. Surgical revision of the common peroneal nerve was performed for the purpose of ruling out the nerve damage when using the stripper. The revision surgery has revealed the presence of an intraneural hematoma. The nerve decompression was carried out by means of neurolysis. During further patient follow-up, the function of the anterior cruciate ligament was deemed satisfactory. The functioning of the patient's foot has completely restored in 3 months.

In a retrospective research by A. Cakar et al. [27], 15 patients had hypoesthesia along the dorsal-external surface of the foot and distally from the surgery scar in the area of the lateral malleolus, while 2 patients had hyperalgesia in the area of the distal part of the scar. Two cases of compartment syndrome were described, in both cases fasciotomy was carried out with complete regress of symptoms in 5 days. One patient had experienced a transient peroneal nerve injury and a neurological deficit in the foot: the functions have restored in 6 months.

CONCLUSION

Our research did not detect statistically significant differences (p >0.05) when using the Tegner–Lysholm and IKDC scales comparing to the SGMT autotransplant, also revealing a slight and statistically insignificant (p >0.05) decrease of AOFAS and FADI scores after extracting the LPTM autograft. Thus, it is deemed justified to make a conclusion that the LPMT autograft is a good alternative material for the reconstruction of the anterior cruciate ligament.

ADDITIONAL INFORMATION

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Authors' contribution. *A.P. Prizov* — conceptualisation, methodology, editing; *A.M. Vostrikov* — research, data processing and collection, writing the initial draft; *F.L. Lazko,*

Table 3

Comparative results on the IKDC and Tegner–Lysholm scales

Source	Number of patients	AOFAS scale	FADI scale
[40]	85 — LPMT 73 — SGMT	In the group using the LPMT autotransplant — 57.98±6.98, in the SGMT group — 58.34±5.57	In the group using the LPMT autotransplant — 61.78±4.41, of SGMT — 62.76±2.99
		In 6 months of follow-up in LPMT patients, the subjective function of the knee joint was significantly better than in a group of SGMT patients	
[41]	98 — LPMT 96 — SGMT	In the LPMT group: in 6 months — 83.28±3.71 in 12 months — 94.13±4.66 In the SGMT group: in 6 months — 79.73±6.83 in 12 months — 95.12±0.73	In the LPMT group: in 6 months — 97.00±0.00 in 12 months — 99.15±2.89 In the SGMT group: in 6 months — 96.35±1.60 in 12 months — 99.85±0.37
[42]	65 — LPMT 65 — SGMT	In the SGMT group: before surgery — 54.8±8.5 after surgery — 93.4±6.2 In a group of LPMT patients: before surgery — 55.2±2.4 after surgery — 92.5±9.8	-

Note. LPMT — long peroneal muscle tendon; SGMT — semitendinous and gracilis muscles tendon.

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"LUNG-ON-A-CHIP" AS AN INSTRUMENT FOR STUDYING THE PATHOPHYSIOLOGY OF HUMAN RESPIRATION

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ABSTRACT

"Lung-on-a-chip" (LoC) is a microfluidic device, imitating the gas-fluid interface of the pulmonary alveole in the human lung and intended for pathophysiological, pharmacological and molecular-biological studies of the air-blood barrier in vitro. The LoC device itself contains a system of fluid and gas microchannels, separated with a semipermeable elastic membrane, containing a polymer base and the alveolar cell elements. Depending on the type of LoC (single-, double- and three-channel), the membrane may contain only alveolocytes or alveolocytes combined with other cells — endotheliocytes, fibroblasts, alveolar macrophages or tumor cells. Some LoC models also include proteinic or hydrogel stroma, imitating the pulmonary interstitium. The first double-channel LoC variant, in which one side of the membrane contained an alveolocytic monolayer and the other side — a monolayer of endotheliocytes, was developed in 2010 by a group of scientists from the Harvard University for maximally precise in vitro reproduction of the micro-environment and biomechanics operations of the alveoli. Modern LoC modifications include the same elements and differ only by the construction of the microfluidic system, by the biomaterial of semipermeable membrane, by the composition of cellular and stromal elements and by specific tasks to be solved. Besides the LoC imitating the hematoalveolar barrier, there are modifications for studying the specific pathophysiological processes, for the screening of medicinal products, for modeling specific diseases, for example, lung cancer, chronic obstructive pulmonary disease or asthma. In the present review, we have analyzed the existing types of LoC, the biomaterials used, the methods of detecting molecular processes within the microfluidic devices and the main directions of research to be conducted using the "lung-on-a-chip".

Keywords: *lung-on-a-chip; blood-alveolar barrier; respiratory diseases; microfluidic devices.*

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INTRODUCTION

The diseases of respiratory organs take the leading positions within the structure of the total morbidity of the population in Russia. In the last decades, the prevalence of respiratory disease irreversibly grows world-wide. During the period from 2000 until 2022, the incidence rates in Russia have increased from 317.2 to 422 per 100 000 of the population [1]. The reasons of growing morbidity are caused by the fact, that humans constantly inhale toxic components of the modern urban environment, including various combustion products, micro- and nanoparticles, bacteria, viruses, fungal spores etc., which, in turn, result in chronic alteration of the terminal segments of the respiratory system with developing chronic obstructive diseases, asthma, pneumonia, interstitial and oncological diseases. The respiratory insufficiency that develops as a result of

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«ЛЁГКОЕ-НА-ЧИПЕ» КАК ИНСТРУМЕНТ ДЛЯ ИЗУЧЕНИЯ ПАТОФИЗИОЛОГИИ ДЫХАНИЯ ЧЕЛОВЕКА

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АННОТАЦИЯ

«Лёгкое-на-чипе» (от англ. Lung-on-a-Chip, LoC) — микрофлюидное устройство, имитирующее газожидкостный интерфейс лёгочной альвеолы человека и предназначенное для патофизиологических, фармакологических и молекулярно-биологических исследований гематоальвеолярного барьера in vitro. Устройство LoC включает систему жидкостных и газовых микроканалов, разделённых полупроницаемой эластичной мембраной, содержащей полимерную основу и клеточные элементы альвеолы. В зависимости от вида LoC (одно-, двух- и трёхканальное) на мембране могут находиться только альвеолоциты или альвеолоциты в сочетании с другими клетками — эндотелиоцитами, фибробластами, альвеолярными макрофагами, опухолевыми клетками. Некоторые модели LoC также включают белковую или гидрогелевую строму, имитирующую лёгочный интерстиций. Первый двухканальный вариант LoC, в котором с одной стороны мембраны находится монослой альвеолоцитов, а с другой — монослой эндотелиоцитов, был разработан в 2010 году группой учёных Гарвардского университета с целью максимально точного воспроизведения in vitro микроокружения и биомеханики работы альвеолы. Современные модификации LoC включают те же элементы и отличаются лишь конструкцией микрофлюидной системы, биоматериалом полупроницаемой мембраны, составом клеточных и стромальных элементов и решаемыми специальными задачами. Помимо LoC, воспроизводящих гематоальвеолярный барьер, существуют модификации для исследования определённых патофизиологических процессов, скрининга лекарственных препаратов, моделирования конкретных заболеваний, например рака лёгкого, хронической обструктивной болезни лёгких или астмы. В данном обзоре мы проанализировали существующие разновидности LoC, применяемые биоматериалы, методы детекции молекулярных процессов в микрофлюидных устройствах и основные направления исследований с помощью «лёгкого-на-чипе».

Ключевые слова: *«лёгкое-на-чипе»; гематоальвеолярный барьер; болезни органов дыхания; микрофлюидные устройства.*

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such abnormalities, takes the third place among the mortality causes world-wide [2].

An essential requirement for studying the respiration pathophysiology and for developing the methods of pathogenetic therapy is the presence of an adequate biological model. Most commonly, *in vivo* trials are being used for this purpose, involving the use of small rodents, which allow for investigating the pulmonary reactions in a real cellular environment with specific signals and with registering the functional changes.

Mice and rats are being used as an animal model and when testing the efficiency of medicinal products, including the screening of the functional activity. The animal experiments are complex, cost-intensive and long-term, besides, there is a number of important differences between the respiratory systems of rodents and humans, restricting the extrapolation of data obtained in mice to humans. For example, the epithelium of murine airways contains shorter columnar cells with large number of ciliated cells and lesser number of submucosal glands comparing to the similar epithelium of the human body [3]. These differences can result in obtaining artifacts when modeling the pathophysiological processes in the lungs, leading to the opposite-type reactions when testing the medicinal products on animals and in humans [4]. Despite the high percentage of successful pre-clinical tests, the probability of approving the drug candidates for clinical application by all the parameters is a little higher than 10%, which confirms the insufficient relevance of pre-clinical animal models [5].

Creating an alternative *in vitro* model, allowing for recreating the complex physiological reactions of the human lung in a medium that is convenient for further evaluation, is a promising direction of scientific research, which can both broaden our knowledge on the lung pathophysiology and act as a cost-effective and high-performance platform for screening the efficiency of therapeutic interventions.

Human lungs have a complex multi-level organization. The main structural and functional unit of the lungs is the acinus — the terminal bronchiole with an alveolar sac, consisting of alveoli (intensive vascularised bubble-like structures; Fig. 1, *a*; [6–8]). Upon deep inhaling, the functionally significant surface area of the alveoli, in which the gas exchange takes place, can expand up to 3.3-fold in the normal conditions. Thus, the high expansibility of the alveoli, which, in total, equals up to 0.2 l/gPa, is an essentially important morphological and functional parameter. The uniqueness of the alveolar system is that the alveoli represent the only gas-fluid exchange interface

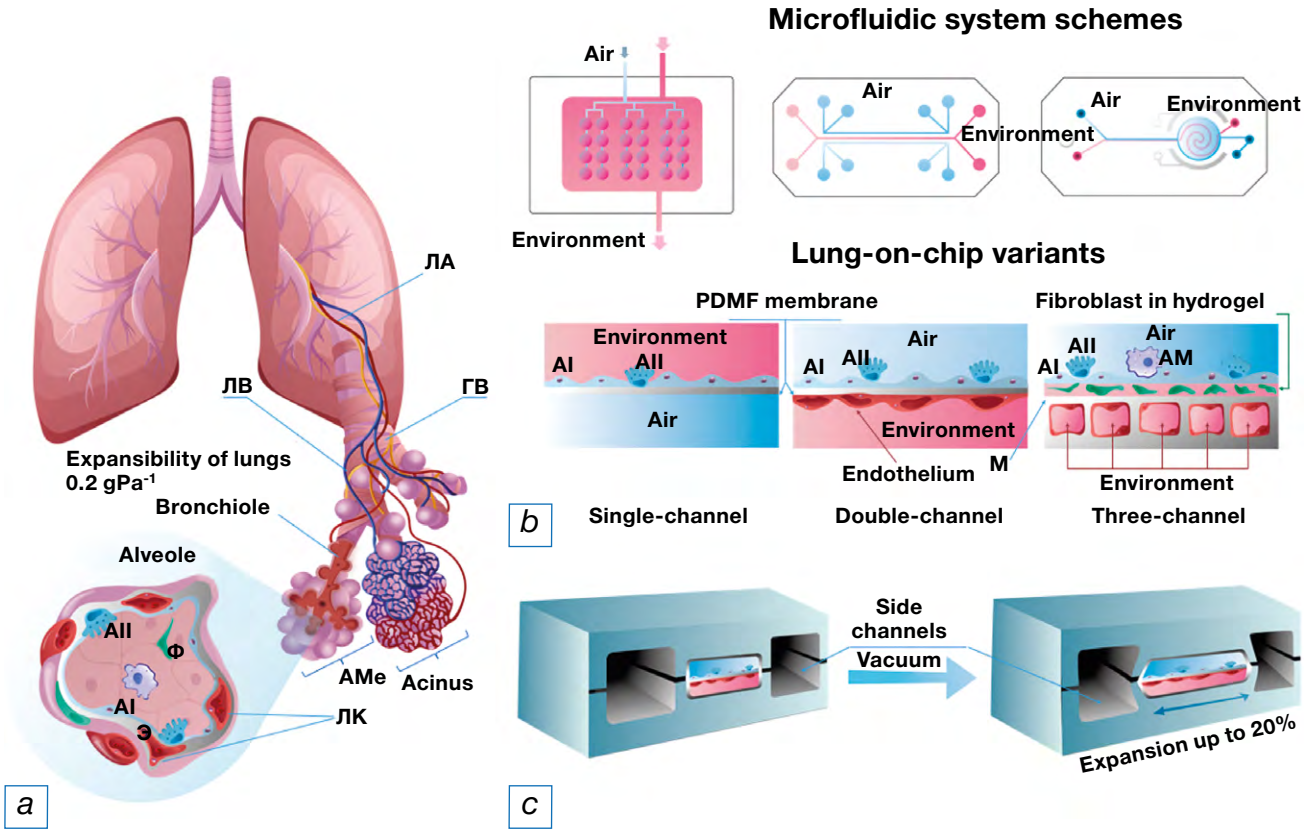

Fig. 1. The principal structure and the variants of the "lung-on-a-chip": *a* — human lung acinus structure; *b* — schemes, developed as of today for the microfluidic devices and LoC variants (from the left side to the right: single-channel — Y. Zhu et al., 2022 [6]; double-channel — D. Huh et al., 2010 [7], three-channel — A. Varone et al., 2021 [8]); *c* — imitation of respiratory movements using the negative pressure in the lateral LoC channels (courtesy of D. Huh et al., 2010 [7]). ЛА — pulmonary artery; ЛВ — pulmonary vein; ГВ — smooth-muscle fibers; AMe — alveolar sac; ЛК — pulmonary capillaries; AI — type I alveolocyte; AII — type II alveolocyte; AM — alveolar macrophage.

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present in mammals, with multiple biochemical and biophysical parameters. This is why the modeling of the alveole in the *in vitro* settings is considered a quite difficult task [9].

Usually, the screening *in vitro* research involve the dimeric (2D) cell cultures, which cannot imitate the microenvironment and by using which, it is not possible to assess the pathophysiological reaction of the tissue as a combination of various cells [10, 11]. In the last decades, the *in vitro* research began using the three-dimensional (3D) cellular spheroids of tissue-engineering constructions, which allow for imitating a more realistic biochemical and biomechanical microenvironment of the tissue or the organ, including the intercellular interactions, the space-time distribution of oxygen, of nutrients and of the final metabolites [12, 13]. However, for the purpose of modeling the functions of the pulmonary acinus, as we have mentioned before, one of the critically important pathophysiological factors is the expansibility of the alveolar structures.

"Lung-on-a-chip" (LoC) is a microfluidic device intended for cell cultivation, which imitates the 3D micro-architecture, the microenvironment and the main physiological functions of human alveoli [14, 15]. The microfluidic technologies allow for generating and precisely adjusting the dynamic flows of fluids with a microliter range, for creating the space-time pressure gradients and other parameters. The LoC technology has a number of significant advantages comparing to the 3D-cultures, in particular, the reproduction of respiratory movements, the possibility of monitoring the transepithelial resistance, the partial pressure of gases in the in-flow and out-flow microchannels, the biochemical composition of the environment and other physico-chemical parameters [16–18]. The LoC technology allows for modeling the specific functional elements of the human lung, such as the blood-air barrier or the mucociliary barrier of the airways. With this, one can recreate both the normal conditions and the specific abnormalities, for example, the condition of the alveoli in a patient with chronic obstructive pulmonary disease or with asthma [19]. The lively interest among the researchers with regard to this direction is confirmed by almost tenfold increase in the number of publications related to the "organ-on-chip" technology during the period from 2010 until 2020 [20].

This review has analyzed the existing varieties of LoC, the biomaterials used, the methods of detecting the molecular processes in the microfluidic devices, as well as the main directions of research involving the "lung-on-a-chip" technology.

THE CELL COMPOSITION OF THE ALVEOLE AND THE LIMITATIONS OF 3D-CULTURES

According to the data from transcriptome analysis of separate cells (single cell RNAseq), in the human lungs, a total of 58 various cellular populations were identified [21]. The alveolar barrier develops as a result of a complex interaction between the type I and II alveolocytes, macrophages, endothelial cells and the extracellular matrix, including the ultra-thin basal membrane. The total thickness of the alveolar-capillary barrier is appr. 1 μm, with the thickness of the basal membrane being less than 100 nm [22].

The basal membrane is porous and elastic (the linear deformation in the physiological settings reaches up to 10%) with the Young's module of 3–7 kPa [23]. Alveolocytes located at the border between the surrounding environment and the organism fulfill multiple important functions, including the barrier one, the maintaining of hydration balance, the elimination of solid particles, the initiation of immune reactions, the production of surfactant and glycocalyx, as well as the regeneration [24]. The unique feature of the pulmonary epithelial cells is the air-fluid interface required for the polarization of the epithelial cells along the apical-basal axis and the secretion of the protective surfactant nano-layer, which reduces the superficial tension and prevents the development of the atelectasis during the inhaling-exhaling [25].

When cultivated in the 3D settings, the alveolar cells form spheroids and organoids, partially imitating the lung acinus structure [26, 27]. Spheroids represent a relatively homogeneous spherical accumulation of cells. The spheroids show quite limited applicability for screening research, for they face problems both with the cultivation of spheroids of similar size and with the control of cell ratios in the co-cultures [28]. Unlike the spheroids, organoids can imitate several basic functions of the lungs in the *in vitro* settings, such as the functional signaling pathways and generating cells with functional cilia [27]. The benefit of the organoids is the relative simplicity of technology and much higher performance comparing to LoC. With this, the organoids practically do not contain the circulatory system and it is impossible to imitate the hematoalveolar barrier, as it is implemented in the LoC device. For solving some screening research tasks, besides organoids, acute slices of the lungs were used which remain viable for some time after its preparation [29]. Currently, the LoC technology in some areas of *in vitro* screening research has completely replaced spheroids, organoids and acute slices.

STAGES OF THE "LUNG-ON-A-CHIP" MICROFLUIDIC DEVICE DEVELOPMENT

Initially, the alveolar pulmonary chip was developed in 2010 by the American cell biologist and bio-engineering specialist Donald E. Ingber, which was describing it as a living three-dimensional cross-section of the functional unit of the lung [7]. The organ chip consists of a transparent elastic polymer, which contains hollow microfluidic canals colonized with living human alveolar cells, connected to the artificial vascular network layered with human endotheliocytes (see Fig. 1, *б*; [6–8]). For the reason the chip is manufactured using the transparent material, it is suitable for microscopy using the conventional biological microscope for the purpose of personal observing the processes that take place in it. The presence of two air chambers in the chip allows for creating the rarefication and by this imitating the respiratory movements, expanding the semipermeable membrane containing the cells (see Fig. 1, *в*; [7]) [30].

The technology was rapidly adapted for creating the microfluidic devices, imitating a number of other tissues or organs, including the liver [31], kidneys [32], intestines [33], bones [34], blood vessels [35], the cardiac muscle [36] etc. From the moment of developing the first lung chip, the technology has significantly progressed, becoming more and more complicated.

Single-channel "lung-on-a-chip"

The single-channel microfluidic devices contain only the alveolar epithelium cells [24]. Such a single-channel microfluidic model does not imitate the hematoalveolar barrier, but it can be useful for studying the functional changes in the alveolar epithelium during the respiratory movements, which are imitated by cyclic air injections. For the purpose of the microphysiological visualization of respiration cycles, the composition of the elastic membrane, onto which the alveolocytes were seeded, was augmented with silicon oxide nanoparticles with the size ranging from 225 to 300 nm. Upon expanding the membrane, a shift took place in the wavelength of the reflected light, thus, the respiration cycles could be visualized [6]. This model was used for investigating the dynamic interrelations between the deformations of cells and the phenotypes of the diseases, such as idiopathic pulmonary fibrosis.

More simple devices, containing only one type of cells cultivated in the hydrogel consisting of the extracellular matrix components, were used for studying the dynamic morphogenetic processes, such as the formation of blood vessels, the migration of immune and tumor cells through the epithelial layer into the interstitial space [24, 37]. A simplified single-channel microfluidic device consisting of proximal airways epithelium precursor cells, obtained from the induced pluripotent human stem cells, allowed for studying the development of ciliated cells and for modeling the primary ciliary dyskinesia [38].

Multichannel "lung-on-a-chip"

The first double-channel lung chip, constructed by D.E. Ingber et al., has imitated the structure and the functions of a human alveole by creating separate parenchymatous and vascular compartments (see Fig. 1, *б*; [6–8]). The channels in this case were defined as the microfluidic system with specific cell type. For the reason that, in this case, there are two types of cells — alveolocytes and endotheliocytes, the chip is considered double-channel. The microfluidic system has gas and fluid channels, separated by a flexible porous polydimethylsiloxane membrane. On the side of the gas channel, alveolocytes are cultivated on the membrane, forming an air-fluid interface in the manner similar to the one in the alveole. On the side of the fluid micro-channels, the membrane is seeded with endotheliocytes with the cultural fluid being perfused, imitating the microcirculatory network of capillaries, while the additional lateral vacuum channels imitate respiratory movements [7, 24, 37].

The three-channel LoC device includes an additional channel containing fibroblasts and the components of extracellular matrix, which, on the side of air channels, are layered in alveolocytes (see Fig. 1, *б*; [6–8]). The mechanical effects on the hydrogel during the respiratory movements, imitated by vacuum channels, promote to the production of extracellular matrix proteins. The presence of an additional stromal channel allows for modeling the interstitial diseases of the lungs.

The unique feature of the multichannel organ chips in general and of the LoC in particular is that, within the gas channel, just like in the alveolar cavity, co-cultivation can be performed for human alveolar cells with the viable symbiotic microbes within a long period of time (from days to weeks). Currently, it is the only method capable of letting us study how the complex microbiome of the human lungs affects the status of the human tissues over time [39, 40].

High-performance "lung-on-a-chip" systems

With the technologies being improved, chip models were developed for studying various pathological

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conditions of the respiratory organs [8, 26]. For example, during the COVID-19 pandemic, a group headed by C.R. Fisher [41] has developed a PREDICT96-ALI high-performance "organ-on-chip" microfluidic platform for the selective screening of pathogenetic medications intended to fight the SARS-CoV-2 virus in the settings of virus -infected alveolar epithelium. The platform consists of a plate with 96 individual devices and a perfusion system, activated by 192 microfluidic pumps, built into the plate cover.

Noteworthy is the AX12 Lung-on-Chip inhalational *in vitro* platform, developed by a Swiss company named "AlveoliX", which represents not just a chip, but a multiplex analyzer based on the microfluidic device allowing for seeding the cells directly along both sides of the ultra-thin membrane [42]. The company has created an immortalized cell line consisting of alveolar epithelial cells (AXiAECs), alveolar macrophages (THP-1) and endothelial cells (HLMVEC). The system is intended for toxicology studies of aerosols, for example, when screening the inhalational drugs being developed.

Using the examples of the projects listed above, it could be assumed that modern biomedical technologies will more and more integrate the microfluidic "organs-on-chip" into the analytical equipment, adding new technologies based on nano- and micro-electronics, acoustic electronics, optoacoustics for genetically coded biosensors, NGS-sequencing and other omics approaches.

Certain perspectives for creating the high-performance artificial lung platforms become available with the 3D-bioprinting [43]. This is a relatively novel technology, allowing for creating the organ-like structures by means of printing with living cells, mixed with hydrogel bioink. The carcass of the bioink usually consists of extracellular matrix protein or other natural biopolymer — collagen, gelatin, alginate, fibrin, chitosan or hyaluronic acid [44]. Recently, W. Kim et al. [45] have used the technology of piezoelectric 3D-bioprinting using the bioink to print the cellular components of the "lung-on-a-chip" on a polycarbonate membrane. The bioink (following the corresponding proportions) had admixtures of cells mimicking the alveolar epithelium of types I and II (the NCI-H1703 and NCI-H441 lines, respectively), of pulmonary fibroblasts (MRC-5) and of the endothelial cells found in human microvessels (HULEC-5a). As a result of bio-printing, a hematoalveolar interface was created, showing the acceptable parameters of transepithelial electric resistance.

THE MATERIALS OF MEMBRANES USED FOR BUILDING THE HEMATOALVEOLAR BARRIER IN THE LUNG CHIP

The basis of any LoC device is the porous and expansible membrane, which should have sufficient biocompatibility for cultivating the monolayer of epithelial or endothelial cells on its surface [40]. For recreating the structure of the hematoalveolar barrier, maximally similar to the physiological one, the choice of the membrane material with proper gas permeability, biocompatibility and expansibility is an actual problem [8, 23, 41]. In the text below, we shall discuss the materials most commonly used for manufacturing the lung chip membrane.

PDMS-membrane

In the last 15 years, the most commonly used membranes are the ones made of the linear polymer of dimethylsiloxane [46, 47]. Polydimethylsiloxane (PDMS) is biocompatible, elastic, permeable for gases, optically transparent and relatively simple in small-scale production, which, in total, makes it one of the most convenient polymers for creating the "organs-on-chip" [48]. Modern microfluidic devices based on PDMS, are most frequently created using the soft lithography method [7]. PDMS is the most commonly used polymer for manufacturing the carcasses of microfluidic devices due to the simplicity of its microprocessing and the adjustable underlayer mechanics [49, 50].

Due to the ubiquitous spreading of PDMS as the material for manufacturing the "organs-on-chip", we would like to examine in detail the downsides and limitations of this material (thickness limitations; poor cell adhesion; sorption of hydrophobic molecules; high rigidity; complexity of moulding automatization).

Thickness limitations. There are difficulties in the manufacturing of ultrathin porous PDMS slices [52]. The actual thickness of the hematoalveolar barrier is less than 1 μm [22], with the most commonly conducted research often requiring the thickness of the LoC barrier membrane being 10 μm [37]. For the comparison — in earlier publications, the membrane thickness was up to 40 μm. With this, the Swiss company AlveoliX has developed a LoC having a membrane thickness of 3.5 μm. Such a membrane thickness is the most similar to the very thin hematoalveolar barrier and, to the best of our knowledge, as of today, it is the thinnest porous PDMS membrane used in the "organ-on-chip" device.

Poor cell adhesion. Due to the fact the PDMS membranes do not show good cell adhesion properties, various coatings must be used — fibronectin, collagen

etc. [23, 26], with this, the additional coating increases the membrane thickness (~10 μm) and decreases its porosity, which should be kept in mind when modeling the hematoalveolar barrier. The improvement of adhesion characteristics of PDMS can be achieved by single application of polydophamine (PDA) onto the PDMS surface. In the samples where the PDMS wells were not preliminary coated with PDA, cell adhesion abnormalities took place within the first 4 days of cultivation, ultimately resulting in the complete delamination and spontaneous destruction of all the tissue constructions in 10 days [52].

Sorption of hydrophobic molecules. When modeling the functional processes, one should also keep in mind that the PDMS membrane can actively absorb hydrophobic biologically active compounds, as well as hydrophobic low molecular weight medicinal products [43, 53, 54], which decreases the available dosage of the drug, shifting the dose dependency curve and, thus, limiting the prognostic value of the research with testing a number of medicinal products [55].

In order to minimize the error caused by the PDMS absorption, strategies were described on the computational correction of the absorption effect by means of quantitative determination of the medicinal product content using mass-spectrometry [56]. M.W. Toepke et al. [53] have studied the absorption of hydrophobic small molecules in a qualitative manner using the fluorescent analysis, but this was not a quantitative method. J.D. Wang et al. [54] have conducted a quantitative evaluation of the final concentration of the compound over time and have determined the threshold value, which has distinguished the compounds with insignificant absorption and the ones with the significant one, based on the hydrophobicity parameter. Besides, for the purpose of decreasing the compound binding, methods are being tested that involve covering the PDMS with non-absorbing coatings [57], that involve alternative flexible elastomeric materials showing lesser absorbing capabilities (for example, some polyurethanes, styrole block copolymers, polycarbonate hybrids and the thermoplastic elastomer) [58, 59]. Tests are also being carried out for the coatings made of rigid thermoplastic materials (polystyrene or polycarbonate) [60], titanium dioxide [61], parylene [62] etc. The accessible literature has few research works on the direct comparison of absorbing various compounds by PDMS and other, more inert substrates, while the issue of cell cultures affecting the absorption was not studied at all. The use of lipophilic coatings may be useful for preventing the absorption of low molecular weight compounds by the PDMS.

High rigidity. The modulus of elasticity of the PDMS, depending on the thickness of the expanded membrane, can vary from 0.4 to 1.5 MPa, while in the alveolar tissues, according to various estimations, it varies from 1.4 to 7.2 kPa [63, 64]. Such a significant difference complicates the process of modeling the inhaling/exhaling processes on the membrane. Due to this cyclic expansion of the PDMS membrane, during the imitation of respiratory movements, deformations may develop in the porous membrane, which may corrupt the data on the integrity of the hematoalveolar barrier, affecting the adhesive properties of the cells and changing the permeability for various substances [65]. The deformation applied to the thin porous membrane, strongly depends on the viscoelastic properties of the expanded material and on the dimensions, in particular, on the PDMS wall thickness, which is why the most "physiologic" LoC can be considered the one with the thinnest PDMS membrane.

Complexity of moulding automatization. PDMS moulding still remains a complex process in terms of complete automatization and it significantly slows down the transition to serial research [66]. The need for materials to replace the PDMS is so important for this field, that The Small Business Innovation Research in the USA has recently funded the research on exploring the alternative materials different from the PDMS, but meeting the requirements of producibility, transparency, biocompatibility and minimal non-specific adsorption [67].

Due to all the limitation listed above, currently there is an urgent need for searching the alternative material, which could be optimal for modeling the hematoalveolar barrier.

PMMA, PET and PC membranes

Polymethylmethacrylate (PMMA), polycarbonate (PC), cyclic olefin polymers/copolymers (COP/COC) and polystyrene (PS) are some of the wide-spread materials which were used as a scalable alternative option during the earlier "organ-on-chip" models. Their main benefits include the commercial availability and the relative manufacturing simplicity for mass market. For example, a group of Chinese scientists, when researching the toxic effects of finely dispersed solid particles on the human respiratory system, have used the membrane made of microporous polycarbonate film with the pore size of 10 μm [68].

As an alternative option, the earlier LoC models were employing the membranes made of polyethyleneterephthalate (PET) and polycarbonate,

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showing the optical properties similar to the ones of the PDMS, however, the important modulus of elasticity values were within the range of 1–3 MPa. They are more convenient for integrating into the microfluidic device, they have pores with various sizes and they are commercially available.

The main downside of such membranes is their extremely high rigidity, which limits their use to only perfusion platforms (or flow cells) in the static cultivation settings (without imitating the respiratory movements) [69, 70].

PLA and PLG membranes

One of the most wide-spread new alternatives to PDMS is the polylactide (PLA) — the biodegradable, biocompatible and thermoplastic polymer, the monomer of which is the lactic acid. PLA is widely used in medicine and its biocompatibility is well established in a number of research works, which show absence of inflammatory processes after the implantation and compatibility with the surrounding tissues [71–72]. Besides, PLA can be easily processed, it can be moulded as sheets, it can be processed mechanically or using the laser, it can be integrated into other structures and assembled into complex microfluidic devices.

As for the manufacturing the LoC membranes, a group of Chinese scientists has used the modified version of this polymer — the PLG (a copolymer of lactic and glycolic acids) for testing the anti-tumor drugs. Its main distinguished benefits include small thickness (~3 μm), porosity, and permeability for molecules and good biocompatibility [74, 75].

OSTE membrane

OSTE (off-stoichiometry thiol-enes) is an non-stoichiometric mixture of thiols and allyls, developed as an alternative to PDMS in the field of "organ-on-chip" technologies for the purpose of overcoming the gap between the research prototyping and the commercial manufacturing of microfluidic devices. One of the main benefits of OSTE is that the mechanical properties can be precisely adapted to the requirements of the specific use by adjusting the non-stoichiometric ratio without changing the composition of the monomer [76].

A group of scientists from Latvia has tested the OSTE as the membrane material for the hematoalveolar barrier and compared its properties to the PDMS. As for the benefits of OSTE, they have reported much lower sorption of small hydrophobic molecules and simpler moulding process. The main disadvantage is low transparency, which significantly complicates monitoring the cells covering the membrane [77].

Gelatin-methacryloyl (GelMA) membrane

The materials in all the above mentioned "lung-on-chip" models, of which the membranes for the hematoalveolar barrier was made, have a very serious limitation — non-physiologically high rigidity, due to which the mechanical stimulation (modeling of inhaling/exhaling) is either very weak or completely absent. In one of the research works, for overcoming this disadvantage, a group of scientists has used the three-dimensional porous gelatin-methacryloyl hydrogel. The resulting structure has a close similarity to the natural human alveoli, in particular, in terms of their sac-like structure, their pores and rigidity. In order to create it, the authors have used the densely packed alginate microgranules (201±12 μm), the distance between which was filled with 7% GelMA solution. After this, the granules were dissolved in 0.01 M ethylenediaminetetraacetic acid (EDTA) solution. Due to the fact that the hydrogel cannot leak in the areas of contacting granules, the final structure not only forms the alveoli-like sacs, but also has pores connecting them [78]. The authors have followed the requirements on the mean size of the alveoli — ~200 μm [79], also, a very low rigidity was reported for gelatin-methacryloyl: the modulus of elasticity equals to 6.23±0.64 kPa, while in the alveolar tissues, according to various estimations, it varies from 1.4 to 7.2 kPa [63, 64].

Biological membrane

The material for the semipermeable biological membrane is the key factor for creating the "lung-on-a-chip". As we have discussed before, PDMS, being the most applicable material for manufacturing the membrane, has multiple disadvantages.

In one of the recent LoC research works, a carcass made of golden combs was used, onto which, a thin layer of collagen I and elastin mixture was applied. The thin golden mesh with the pore size of 260 μm was used as a carcass, supporting the structure of 40 alveoli. The resulting membrane is stable and it can be cultivated on both sides for several weeks [80]. This method was used to model the expansible alveolar sacs, in which the thickness and the rigidity of the membrane can be adjusted by the ratio of collagen and elastin in the gel mixture. The prepared membrane was integrated into the microfluidic chip, where it was compressed between the two microfluidic parts, the upper PDMS part with the apical reservoir and the lower polycarbonate part,

together forming the basolateral chamber. These membranes can be stored in the lyophilized state, retaining their properties for not less than 3 weeks at room temperature. The membranes shall be rehydrated by submerging it into the cultural medium 2 hours before the cell seeding [53]. Such a membrane is in many regards better than PDMS, it does not bind the hydrophobic medicinal products, being biogenic and biodegradable, with the capabilities of obtaining a very thin membrane (approximately 4 μm), but it was reported that the degree of its strength is insufficient.

The Canadian authors have made an "airway-on-a-chip" device which contained an ultra-thin membrane formed using the mixture of type I collagen and the Cultrex Basement Membrane Extract (BME) at a ratio of 1:2 (Cultrex is a soluble form of the basal membrane, made by the purification of the Engelbreth–Holm–Swarm tumor, which gelates at 37°C, forming a reconstituted basal membrane) [81]. The important feature was the device generating the bidirectional oscillating air flow, imitating the respiratory cycles. Such a combination of an ultra-thin biomimetic membrane and the oscillating air flow has resulted in the first ever demonstration of the glycocalyx layer formed on the airway epithelium in the "lung-on-a-chip" device and induced by air flow, with the glycocalyx layer being known for its important role in regulating the epithelial functions. The authors managed to demonstrate significant differences in the viability of airway epithelial cells and in the formation of dense connections, cilia or mucus depending on the speed of oscillating air flow. It was shown that the mechanic-biological effect of the shearing stress applied for a long period of time, has increased the formation of dense contacts among the epithelial cells and decreased the diffusion permeability.

Another team with a long and successful history of working in the field of replacing the PDMS with biomaterials having the properties and functions similar to the pulmonary tissue, has developed a biomimetic microfluidic platform, which reminds the multi-layer architecture of the alveolar-capillary barrier and the composition of the alveolar extracellular matrix, physiologically consisting of a thin basal membrane and dense fibrous interstitial spaces [82]. The "alveole-on-a-chip" included the membrane produced by electro-spinning of PCL-Gel (polycaprolactone-gelatin) between the two microstructurized PDMS layers, moulded using two master-models, obtained by means of poly-jet 3D-printing. Within this chip, three types of cells were cultivated simultaneously: on the surface of the membrane, there was a type I collagen hydrogel containing MRC-5 fibroblasts for reproducing the alveolar interstitial spaces; on the top of the hydrogel, the A549 epithelial cells were seeded for recreating the alveolar epithelium, while the basolateral chamber of the device was seeded with the HVEC endothelial cells. By means of the immunofluorescence assay, confirmation was obtained for the formation of the dense endothelial and epithelial barrier, while the high viability of cells remained for 10 days. The authors have demonstrated that exactly the presence of collagen hydrogel provided the optimal biomimetic environment for co-cultivating of fibroblasts and epithelial cells, while the presence of the interstitial layer significantly improving the bio-mimicry of the "alveoli-on-a-chip" model comparing to other systems, focused mainly on recreating the epithelial and endothelial barrier.

Though the hydrogel-based microfluidic technologies show the potential for *in vitro* — recreating the key properties of the tissues, they possess a wide number of disadvantages, mainly related to the low stability/reproducibility caused by swelling and limited rigidity range of the membrane and of the whole chip in general, which significantly restricts their applicability. Within this context, the interesting new methodological approach is the development of a soft microfluidic device with the cell filling based on hydrogels made of enzymatically cross-linked silk fibroin (eSF) and of the spider web silks (recombinant spidroins). The enzymatic processing of silk proteins with peroxidase induces the formation of intermolecular covalent bonds between the oxidized forms of tyrosine, which results in a sudden increase of strength and elasticity of the hydrogel. With this, the microfluidic platform with 14% eSF has demonstrated an outstanding structural stability, having the Young's module of 11.79 kPa, the elasticity (103%) and the capabilities of perfusing the fluid, while showing the biological reactions similar to the ones found *in vivo* [83]. Even though the research work has employed a combination of eSF and microfluidics for recreating the native dynamics of the three-dimensional microenvironment of the colorectal cancer and its reactions to chemotherapy, nevertheless, the demonstrated eSF properties (elasticity, strength, transparency, structural stability within not less than 7 days) give ground for expecting that these materials can be successfully used in designing the "lung-on-a-chip" platforms, especially keeping in mind that another research [84] has demonstrated that the tyrosine residues within the recombinant spidroins resulting in after processing with recombinant tyrosinase, migrate

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to dihydroxyphenylalanines (DOPA) and further into DOPA-quinones and other more oxidized forms that take part in the formation of the intermolecular covalent links in these proteins, which results in the formation of a hydrogel.

CELLULAR CULTURE SOURCES FOR CREATING THE LUNG CHIP

In the vast majority of the research works, all the sources of cellular cultures used for creating the "lung-on-a-chip", are allogenic cell lines originating from tumor or embryonic cells, for the primary cell cultures are not standardizable and operating with them requires special settings [81]. The primary cultures of alveolocytes upon passaging significantly change the phenotype. With this, it was reported that the differentiation of human bronchial epithelium into the ciliated and secretory cells has ceased after two passages [26]. As the analogues of the alveolar epithelium, the cell lines were used that originate from the biomaterial of resected pulmonary adenocarcinomas [81]: for example, the NCI-H1703 line, morphologically similar to type I alveolocytes and originating from the sample of the non-small-cell lung cancer, the NCI-H441 line — from the papillary adenocarcinoma of the lung, the SW-1573 line — from the alveolar carcinoma [85]. The cells of the NCI-H441 line, as well as the A549 line, originating from the lung adenocarcinoma, are morphologically similar to type II alveolocytes. Even more closer to the native primary alveolocytes are the immortalized lines of alveolar epithelial cells, originating from the primary cell cultures, as, for example, the AXiAECs line [42].

As for the pulmonary fibroblasts, the immortalized lines of embryonic lung fibroblasts are being used, originating from the abortive material, for example, the MRC-5, HFL1 or IMR-90 lines. For creating the microcapillary layer in two- or three-channel LoC, human endotheliocyte lines are used that originate from the endothelium of fetal lung capillaries, for example, the HLMVEC line, or from the lung endothelium of adult humans, for example, the HULEC-5a line [45]. The ones considered applicable are also the primary and immortalized HUVEC cells — the endotheliocytes of the fetal umbilical vein. There are also cell lines corresponding to the alveolar macrophages, for example, the monocyte line from the patient with acute monocytic leukemia (THP-1), as well as the cell lines corresponding to the upper airway epithelium, for example, the Calu3 tumor cell line. Practically all the cell types required for creating the LoC, can be obtained using the induced pluripotent human stem cells by targeted differentiation using the biologically active factors and small molecules [86].

The important requisite for the correct differentiation and polarization at the basolateral and apical poles of the alveolar epithelium cells is the cultivation at the air-fluid interface. Creating the gas-fluid interface and imitating the respiratory movements promotes to the formation of the polarized mucociliary epithelium, including the ciliary, the glomerulate, the goblet-like and the basal cells, with the formation of the surfactant and the glycocalyx, which in total maximally corresponds to the natural epithelium of the human alveole [87, 88].

RESEARCH METHODS IMPLEMENTED IN THE "LUNG -ON-CHIP"

The "lung-on-a-chip" system is compatible with a number of standard methods of laboratory and chemical analysis, including the electrochemical detection of various analytes, the registration of transepithelial electrical resistance (TEER), the permeability analysis of specific factors using the method of enzyme-linked immunoassay or the polymerase chain reaction, immunostaining, flow cytometry, confocal laser microscopy, multi-photon microscopy, FLIM-microscopy, optical coherent tomography, omics technologies etc. [89] (Fig. 2). The sensors and biosensors used during the "lung-on-a-chip" studies to detect oxygen, temperature and specific biomarkers, measure the additional biochemical and biophysical parameters [88]. The limiting factor for a number of methods is the relatively small number of cells in the micro-channels. For example, the recommended number of cells for the RNA-Seq single-cell assay is 1 000 000, while the number of cells contained within the microfluidic devices, can only reach thousands [51].

The LoC technology allows for analyzing the pathophysiological processes within the structures of the hematoalveolar barrier in the real time mode. For this purpose, the devices are made of transparent material and its walls are made being maximally thin and optimized for fluorescent microscopy; the microfluidic system is constructed in such a way that samples could be drawn from the incoming and out-coming micro-channels with reading the numbers from the sensors built into the chip [53]. For the intravitam fluorescent microscopy, the cells on the membrane have the genetically coded fluorescent proteins and biosensors included; the actine cytoskeleton of the cell can be labeled using phalloidin with the organellae being labeled using the selective tracer substances, etc. [90].

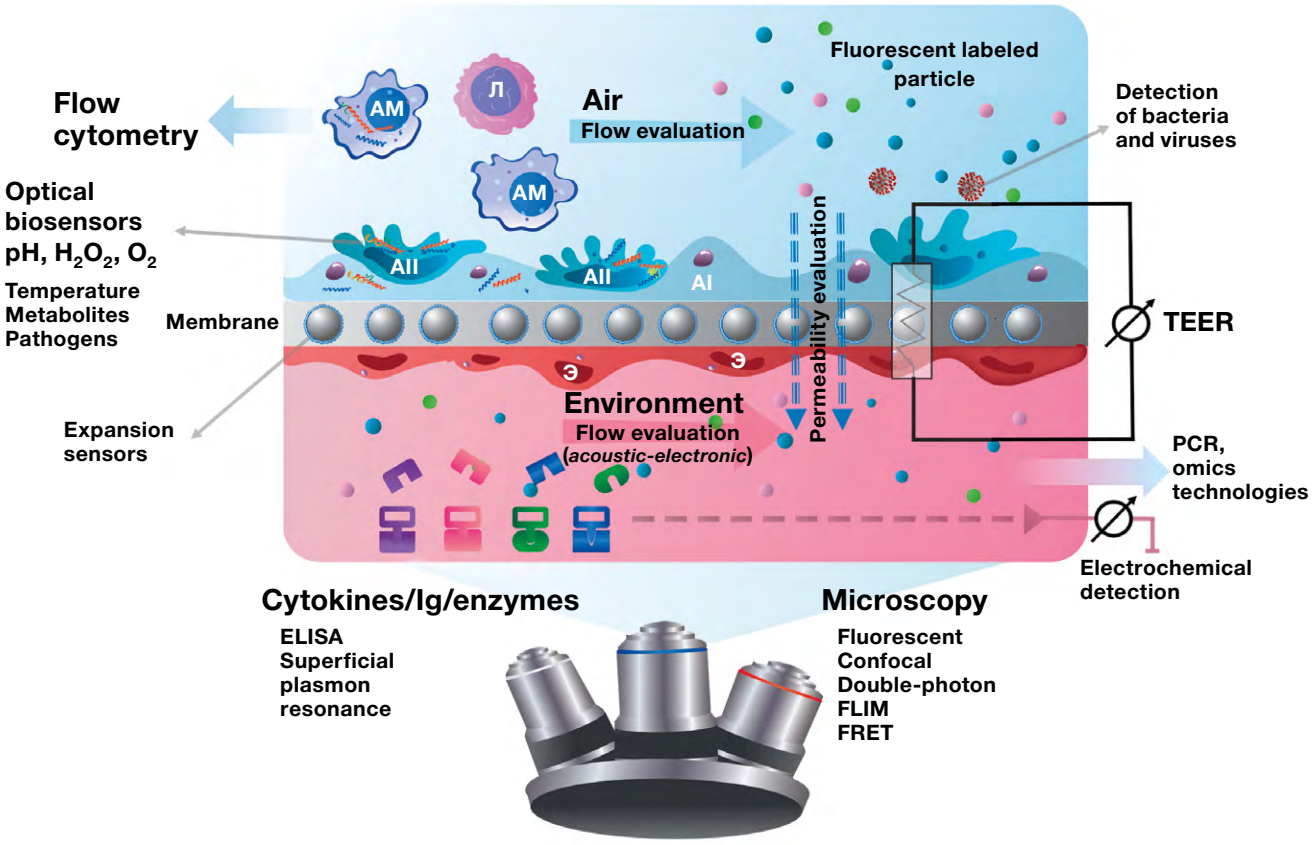

Fig. 2. Methods of "lung-on-a-chip"-associated research with an example of double-channel chip. ЛА — pulmonary artery; ЛВ — pulmonary vein; ГВ — smooth-muscle fibers; АМе — alveolar sac; ЛК — pulmonary capillaries; AI — type I alveolocyte; AII — type II alveolocyte; AM — alveolar macrophage; Э — endotheliocytes; FLIM — Fluorescent Lifetime Imaging Microscopy; FRET — Förster Resonance Energy Transfer.

TEER is considered the gold standard of cell barrier integrity monitoring. However, the integral registration of TEER in the microfluidic device has its limitations, for even a small area of impaired integrity of the cells significantly decreases the total TEER, despite the presence of a dense monolayer in all the other areas [91]. This problem can be solved using the microelectrode matrices, but this makes the device significantly more expensive [92]. The biophysical evaluation of the monolayer characteristics can be performed using the impedance analysis when cultivating on the golden microelectrodes, however, their presence reduces the transparent window for microscopy.

The important aspect of alveolar functioning are the mechanical-biological parameters of cells interacting with each other and of the cells interacting with the intercellular matrix. For the purpose of high-precision evaluation of the mechanical-biological properties in a cell, the traction force microscopy (TFM) and optical tweezers are being used, as well as the optical biosensor based on the Förster Resonance Energy Transfer (FRET) [93]. One of the sensors reacting to mechanical stimuli, to the rigidity and expansibility of the matrix, is the YAP/TAZ transcription factor [Yes-associated protein (YAZ) + WW domain-containing transcription regulator protein 1 (WWTR1, also known as the TAZ)]. This is the main effector of the Hippo pathway, activated during the mechanotransduction and in the settings of the mitochondrial stress [94].

Another method of gaining additional information on the processes taking place within the LoC is the use of acoustic-electronic technologies. In this case, the information-containing signal is the measured frequency or the attenuation of acoustic waves of various types in the piezoelectrical materials [95]. These wave parameters change as a result of changing the both the electrical and the mechanical parameters of the interacting biological objects. Acoustic waves are being actively used in the microfluidic devices for manipulating the biological objects, for changing the direction of movement, for detecting of viability etc. [96, 97]. Such an approach is quite promising in case of limitations applied to performing the direct optical measurements. The intravitam LoC tests using the methods mentioned

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above, allow for better understanding the molecular aspects of pathophysiology and mechanotransduction in human alveoli.

PRACTICAL APPLICATION OF THE "LUNG-ON-A-CHIP"

"Lung-on-a-chip" is a multi-purpose *in vitro* platform, which can be used for large numbers of research tasks. After the first publication of creating the model of alveolar lung chip, the team headed by E. Ingber has published several research works on modeling various respiratory diseases, including the models of pulmonary edema [98], pulmonary artery thrombosis [99] and lung cancer [100]. They have also developed LoC devices for modeling the chronic obstructive pulmonary disease and asthma [101], and just recently — the microfluidic system modeling the human airways for studying the diseases caused by the influenza virus and other viruses affecting the bronchoalveolar system (the "human-airway-on-a-chip" device) [102].

Models for asthma and chronic obstructive pulmonary disease

K.H. Benam et al. [101] have constructed a double-channel LoC with differentiated mucociliary bronchiolar epithelium and with the underlying lung vessel endothelium for studying the complex inflammatory changes in cases of asthma and chronic obstructive pulmonary disease. The chip was made of PDMS using soft lithography, with its upper channel having the height and the width of 1 mm (similar to the human bronchiole radius) and separated from the parallel lower microvascular channel [0.2 mm (height) × 1 mm (width)] with a thin (10 μm) porous (0.4 μm pores) polyester membrane, on both sides covered in type I collagen. The immune cells were circulating through the underlying liquid flow. Using this device, it was shown that the contact of small airways with the Interleukin 13 (interleukin, IL) increases the number of goblet-like cells, increasing the production of inflammatory cytokines and decreasing the rate of ciliary beats in the epithelium, which is comparable to the changes in the mucosa observed in asthma patients [103, 104].

The team headed by K. Benam et al. [101] has also arranged a series of experiments on using the lipopolyssacharide endotoxin and viral particles to stimulate the airways channel of the chip containing healthy epithelial cells and of the chip containing the epithelial cells taken from the patient with chronic obstructive pulmonary disease. It was shown that the chips with the cells from the patient with chronic obstructive pulmonary disease show increased secretion of the M-CSF and IL-8 cytokines comparing to the chips with normal epithelial cells. M-CSF promotes to the differentiation and survival of the macrophages, while the IL-8 is the attractant for neutrophils, both of which being the main types of immune cells observed in patients with chronic obstructive pulmonary disease [105]. Thus, using the LoC, it is possible to detect synergic effects of the pulmonary endothelium and epithelium in terms of cytokine secretion, to identify new biomarkers of disease exacerbation and to measure the anti-inflammatory reactions.

Modeling the thrombosis of pulmonary capillaries

The LoC platform can recreate complex reactions, including the dynamic interactions between the platelets and the endothelium, proposing a new approach to investigating the pathophysiology of the thrombosis of pulmonary microvessels in humans and promoting the development of medicinal products. A. Jain et al. [99] have modified the existing "lung-on-a-chip" model [98] and have covered the walls of the lower vascular channel with endothelial cells from the vessels, in order to create the lumen of the vessel followed by the vessel perfusion with whole human blood instead of the cultural medium. The inflammatory activation of the vascular endothelium with tumor necrosis factor alpha (TNF-α) has caused rapid recruiting of platelets and resulted in the formation of the thrombus, similarly to the manner in which it happens in the inflammatory-modified microvessels *in vivo* [106]. The dynamic changes of platelet binding have imitated the formation of thrombi in the *in vivo* murine model [107]. This model was also used to show that the lipopolyssacharide endotoxin indirectly stimulates the intravascular thrombosis, activating the alveolar epithelium, but not interacting directly with the endothelium. This model was also used to analyze the inhibition of the activation of the endothelium and of the thrombosis with protease-activated receptor-1 (PAR-1) [99].

Lung cancer model

B.A. Hassell et al. [100] have created a model of human non-small-cell lung cancer in chip for the purpose of investigating the behavior of cancer cells, the variations of growth and invasion in various

micro-environments, as well as for investigating the anti-tumor effects of tyrosine kinase inhibitors. The research has demonstrated that the presence of cyclic mechanical movements, imitating the respiration patterns, has significantly suppressed the growth of tumor cells. The tumor cells localized on a small area, were growing in the absence of movement, replacing the alveolar epithelium layer, migrating and invading the vascular layer. This discovery shows that the exponential proliferation of tumor cells in the alveolar space develops due to the loss of lung mobility.

As it was mentioned before, the model cells for LoC, fulfilling the functions of the alveolocytes, often include the tumor cell lines, which is why such devices can be easily adapted for investigating the anti-tumor medicines — in the setting of the "breathing" microenvironment. X. Yang et al. [76] have developed a "lung-on-a-chip" with PLG electro-spinning nanofiber membrane as a chip base and as a cells carcass. The PLG membrane with the controlled thickness of ~3 μm is porous and permeable for molecules, it shows high biocompatibility and suits well for imitating the alveolar respiratory membrane. On the chip, co-cultivated were the human non-small-cell lung cancer cells (line A549) and the human fetal lung fibroblasts cells (HFL1) with an evaluation of the effects of the Gefitinib antitumor medication targeting the epidermal growth factor receptors (EGFR).

The LoC devices are significantly inferior comparing to the 2D-cultures in terms of their throughput, which is why they cannot completely replace the initial cytotoxicity screening which is performed using cell cultures, however, the final selection of anti-tumor medicines can be implemented in such devices, taking into consideration the evaluation of the effects of the tumor microenvironment, the mechanic-biological factors and the hematoalveolar barrier parameters [15]. The chips contain tumor cells with specific mutations providing resistance to chemotherapy agents, also including the personified tumor lines [108].

Pulmonary edema model

The team headed by E. Ingber has studied the possibility of using the "lung-on-a-chip" device for the purpose of micro-engineered modeling of the pulmonary edema, characterized by the accumulation of intravascular fluid in the alveolar air spaces and in the interstitial tissues of the lung, caused by the impaired mechanisms of the homeostatic fluid balance [98, 109]. It was experimentally proven that the injection of IL-2 into the vascular channel of the LoC device resulted in an increase in the permeability of the cellular layer and the accumulation of fluid in the upper alveolar channel. With this, the increasing effect on the filling of air channel with the fluid, imitating the pulmonary edema, has resulted in the development of cyclic mechanical tension, imitating the respiratory movements. Further research has confirmed that mechanical respiratory movements play a significant role in the IL-2 -induced leakage from the vessels, leading to pulmonary edema [98]. A research from the E. Ingber team [98] has also revealed that the reaction to the leakage from the pulmonary vessels, induced by IL-2, does not require circulating immune cells, which differs from the previous *in vitro* and *in vivo* researches, showing that the blood-transported immune cells, such as lymphocytes and neutrophils, when activated by IL-2, play a central role in the induction of leakage from the pulmonary vessels [110]. This model has also recreated the sedimentation of fibrin clots in the alveolar areas due to enzymatic reactions between plasma proteins during the progression and exacerbation of pulmonary edema.

The obtained results show that the developed human pulmonary edema model with the aid of the "lung-on-a-chip" device can potentially replace the pre-clinical pulmonary edema animal models, currently used for developing the pharmacological products.

Toxicological research

Currently, more and more topicality is gained by the problem of air contamination with nanoplastics, which can easily reach the lungs and get accumulated there, leading to pathological processes [111]. The latest research works have demonstrated that microplastics are present in the lungs of birds [112], in the lower airways and in the lungs of humans, as well as in the sputum of the patients with chronic obstructive pulmonary disease [113]. Microfluidic lung chip was used by a group of Chinese investigators to estimate the relation of polystyrene nanoplastics and the pathogenesis of chronic obstructive pulmonary disease. It was shown that the viability of cells has significantly decreased along with the increase in the concentration of polystyrene nanoplastics, while the levels of transepithelial/transendothelial electric resistance were decreasing with an increase in the permeability of the alveolar-capillary barrier [114]. In general, the LoC combined with high-flow technologies, which we have mentioned previously, is a novel platform for investigating the pulmonary toxicity

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of nanoplastics and other inhalable substances, such as nanoparticles of titanium oxide (TiO_2) and zinc oxide (ZnO), silicon dioxide etc. [115]. When using the LoC, it was shown that the effects of silicon dioxide nanoparticles in the alveolar epithelium result in an activation of the underlying endothelium and an increase in the number of type 1 intercellular adhesion molecules (ICAM-1).

It is expected that, in the nearest future, the "organ-on-chip" models could be used when testing the toxicity, replacing or, at least, decreasing the need for animals testing.

The platform for personalized medicine

Theoretically, nothing except for high cost and methodological difficulties, is in the way of developing the personalized "lung-on-a-chip" devices, containing the cells obtained from separate patients or from the patient cohorts with a certain genetic profile, for the purpose of arranging the specific research and testing the individual reaction to drugs. Using such devices, personalized chemotherapy can be adjusted based on the individual drug resistance, along with the personified dosage adjustment, but it is worth noting that, for achieving these two tasks, more simple 2D or 3D personified cell cultures can be used. At the same time, personified LoC devices unveil the unique possibilities for creating individual or grouped *in vitro* platforms for investigating the chronic obstructive pulmonary disease, the idiopathic pulmonary fibrosis, the mucoviscidosis and other diseases, altering the alveole and the hematoalveolar barrier. The patient-specific cells or cells from a specific genetic group can be used for developing the patient-specific or cohort-specific "personalized lung-on-chip", reflecting the biometric parameters, the genetics and the physiology of a specific individual [116]. The authors understand that, currently such a concept sounds utopian, however, the development of biotechnologies can radically change everything. Just some 30 years ago, obtaining humanized antibodies to certain human cytokines also seemed utopian, while currently they are quite routinely used as the medications for clinical practice.

CONCLUSION

The "lung-on-a-chip" technology is an important achievement in a path of discovering the fragile pathogenetic mechanisms of pulmonary diseases and a promising *in vitro* platform for screening the medicinal products. The microfluidic technologies allow for recreating the respiratory movements and for real time monitoring the status of the elements in the epithelial and endothelial layers, for evaluating the transepithelial resistance, the partial gas pressures in the in-flowing and out-flowing microchannels, the biochemical composition of the environment, the concentration of cytokines and pathogens, the mechanotransduction, the acoustic-electronic phenomena and other physico-chemical parameters. We suppose that further improving the microfluidic lung chip is a perspective scientific field that shall allow for studying the pathophysiology of the hematoalveolar barrier, the molecular and cellular features of alveolar diseases, the cold and pressure injuries, the inhalable toxins, the bacterial and viral pathogens, as well as for arranging the efficient screening of pharmacological products, by this increasing the total efficiency, the validity and economical practicability of pre-clinical research.

ADDITIONAL INFORMATION

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Authors' contribution. *V.P. Baklaushev* — general concept of the paper; *Iu.V. Ozerskaya, O.A. Zhukova, D.V. Basmanov, V.Y. Stolyarov* — literature analysis and manuscript preparation; *V.V. Kolesov, K.A. Zykov, G.M. Yusubalieva* — manuscript editing. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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THE EFFECTS OF DENTAL IMPLANT MACRODESIGN ON THE SUCCES OF PROSTHETIC REPLACEMENT

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ABSTRACT

Currently dental implantation is widely used in the areas of denture defects during the orthopedic rehabilitation of the patients. The clinical success of the implantation-related prosthetic replacement depends on multiple factors, including the macrodesign of the implant (the specific features of its structure: the shape, the characteristics and the number of thread turns). However, there are not so many comparative clinical trials exploring the effects of the main characteristics of the implant on the success of prosthetic procedures. For the practical dentist, the problem of selecting the implant system remains topical, which is why the proposed review is focused on the effects of the dental implant macrodesign on the success of implantation. The search of publications was arranged in the PubMed and eLibrary search engines using the "dental implant", "dental implant macro-design", "number of dental implant turns" and "implant thread characteristics" search enquiries with focusing on the research works evaluating the effects of the main characteristics of the implant in terms of primary stability and osteointegration. Various geometric parameters of the implant were analyzed, such as the shape, the length, the diameter and the thread characteristics, with further evaluating their significance for optimal tension distribution, as well as the effects on bone remodeling during the process of osteointegration. The successful implantation is being achieved by synergetic combination of numerous factors. The majority of investigators adhere to the opinion that implants shall be selected individually for each specific case with taking into consideration the local and general factors. However, the characteristics of the implant thread and the number of its thread turns improve the primary stability and represent a prerequisite for successful osteointegration. The choice of implant thread construction plays an important role for a treatment result. It was shown that the macrodesign of the implant, specifically its shape (cone), its length and diameter, higher thread width and depth, lesser thread pitch and higher numbers of thread turns influence the primary stability. Specifically these characteristics, according to our opinion, assure the success of dental implantation.

Keywords: *dental implant; dental implant macro-design; number of dental implant turns; implant thread characteristics.*

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INTRODUCTION

Dental implantation is being successfully used in dentistry for orthopedic rehabilitation of the patients with dental arch defects. The topicality of using the implants is resulting from high occurrence rates of partial or complete absence of teeth along with the patients' need for effective restoration of the dental arch integrity [1, 2]. According to the World Health Organization data, complete absence of teeth can be found in 15% of adult patients, while the prevalence of patients with their partial absence is approximately 75% [3]. In cases of complete absence of teeth, the problem of rational prosthetic replacement is especially topical, for the majority of patients (up to 56%) do not wear the manufactured dental prostheses because of their unsatisfactory stabilization [4]. The benefits of dental implants in dentistry practice include high reliability, long service life, multi-functionality and, which is important, psychological comfort of the patient [5, 6].

Currently, reviewing and comparing the characteristics of dental implants, according to our opinion, is quite difficult for the reason of marketing and advertising campaigns from the manufacturers, for practically all the systems promise high-level

ВЛИЯНИЕ МАКРОДИЗАЙНА ДЕНТАЛЬНОГО ИМПЛАНТАТА НА УСПЕХ ПРОТЕЗИРОВАНИЯ

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АННОТАЦИЯ

В настоящее время дентальная имплантация широко применяется при дефектах зубных рядов с целью ортопедической реабилитации пациентов. Клинический успех имплантационного протезирования зависит от многих факторов, в том числе от макродизайна имплантата (особенностей его строения: формы, характеристики, количества витков резьбы). Однако не так много сравнительных клинических исследований, посвящённых влиянию основных характеристик имплантата на успех протезирования. Для практического врача-стоматолога проблема выбора системы имплантатов остаётся актуальной, поэтому в предлагаемом обзоре рассматривается влияние макродизайна дентального имплантата на успех имплантации. Поиск публикаций проводился в поисковых системах PubMed и eLibrary по поисковым запросам «дентальный имплантат», «макродизайн дентального имплантата», «количество витков имплантата», «характеристики резьбы имплантата» с фокусом на работы о влиянии основных характеристик имплантата на первичную стабильность и остеоинтеграцию. Проанализированы различные геометрические параметры имплантата, такие как форма, длина, диаметр, характеристики резьбы, с оценкой их значимости для оптимального распределения напряжения, а также реакций ремоделирования кости в процессе остеоинтеграции. Успех имплантации достигается за счёт синергичного сочетания многочисленных факторов. Большинство исследователей придерживаются мнения, что имплантаты следует подбирать индивидуально для каждого случая с учётом местных и общих факторов. Однако характеристика резьбы имплантата и количество его витков улучшают первичную стабильность и являются залогом успешной остеоинтеграции. Выбор конструкции резьбы имплантата играет важную роль в результате лечения. Показано, что макродизайн имплантата, а именно его форма в виде конуса, длина и диаметр, большая ширина и глубина резьбы, меньший шаг резьбы, большее количество витков, оказывает влияние на первичную стабильность. Именно эти характеристики, по нашему мнению, обеспечивают успех дентальной имплантации.

Ключевые слова: *дентальный имплантат; макродизайн дентального имплантата; количество витков имплантата; характеристики резьбы имплантата.*

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osteointegration outcomes [7, 8]. In the real-time practice of the dentist, the choice of the implant system depends on multiple factors, including the costs, the accessibility of training and the reputation of the brand. However, the issues of the best macrodesign parameters (number of thread turns and thread characteristics) taking into consideration the individual characteristics of the patients, as of today, remain topical in modern literature.

MACRODESIGN OF THE DENTAL IMPLANT: CLINICAL SUCCESS OF IMPLANTATION-RELATED PROSTHETIC REPLACEMENT

We have reviewed modern literature sources, which are focused on the dental implant macrodesign affecting the success of prosthetic replacement with further justification of the choice of implant.

Methodology of searching the sources

The literature review was carried out based on searching the scientific literature, related to the research topic, in the PubMed and eLibrary systems. The search of publications was performed using the following search queries: “dental implant”, “dental implant macro-design”, “number of dental implant turns” and “implant thread characteristics”.

After analyzing the obtained data, certain patterns and trends were found in the results, based on which, conclusions were made on the effects of dental implant macrodesign, including its shape, the number

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of thread turns and the thread characteristics, in terms of achieving the successful prosthetic replacement outcome.

Implant survival

Dental implants are the constructions that are installed into the bone tissue of the jaws for fixating the prostheses for the purpose of orthopedic rehabilitation of dentistry patients [9]. The macrodesign of the dental implant means the geometry of the implant (shape, length and diameter) and the thread geometry (pitch, shape and depth) [8, 10].

According to the opinion from many investigators, the most important criteria for the success of implant functioning is its survival [7–10]. Thus, during the research conducted by the American scientists headed by S. Jain [10] in the State of Indiana in 2021–2022, 91.4% of early survival was shown (in 128 patients undergoing a single implantation procedure, after the intervention, 117 implants have survived). The success of implantation was favored by the age of the patients — under 60 years old (odds ratio, OR, 2.54), immediate implantation (OR 3.74) and the implant length being less than 10 mm (OR 3.97). From 2006 until 2017, early survival of the implants was also studied by the Chinese researchers: the survival rate value was 96.15% (1078 cases were enlisted with a total of 2053 implants) [11]. The long-term survival of dental implants (for 20 years) was studied by J.R. Kupka et al. [12]: the authors have published five retrospective research works with a survival rate of 88% (95% CI 78–94) and with emphasizing the necessity of long-term follow-up after the implantation. In the Seoul National University, a research was carried out on evaluating the long-term implant survival during the period of 10 — 15 years [13]: the research included 86 patients and 247 implants, the total rate was 92.5%, 17 implants were extracted due to implant fracture (4.0%), peri-implantitis (2.4%) and screw fracture (0.4%).

B.R. Chrcanovic et al. [14] have structurized the main factors, which affect the implant survival:

- factors related to the selection of patients (nicotine dependence, bruxism, diabetes, alcoholism);
- factors related to the installation of the implant (primary stability, bone density, implant positioning at the alveolar process);
- factors related to the implant system (surface type, length, diameter, construction);
- factors related to the prosthetic replacement;
- biological factors (the assessment of periodontal tissues, the level of dental hygiene etc.).

OSTEOINTEGRATION AND PRIMARY STABILITY OF DENTAL IMPLANTS

One of the important criteria for implant survival is the osteointegration process. Osteointegration is the direct attachment of the bone tissue to the implant surface without introducing the connective tissue layer [15]. For successful attachment of blood components with forming the fibrin “bridges” for the purpose of osteogenic cell proliferation and developing the contact osteogenesis, the presence of well-developed topography of the intraosseous part of implant is necessary [16]. The long-term successful integration is affected by the primary stability of dental implants, which is determined by the size and the type of the direct first contact between the implant and the prepared bone tissue bed [17]. The measurements of the stability by means of the resonance frequency analysis (RFA) are being carried out using the measuring equipment (for example, Osstell), with the result provided, which lies within a range from 1 to 100 ISQ units (implant stability coefficient) [18].

The primary stability is mainly affected by such parameters as bone density, thickness of the cortical bone and the height of the alveolar process [19]. Within this context, various implant macrodesigns were developed. With this, according to the opinion by S. Kreve et al. [20], the dental implant thread directly affects the primary stability and the osteointegration, for which, it is necessary to evaluate the isolated characteristics, such as the design-related ones, including the shape, the length and the diameter of the implant, as well as the thread pitch, the thread width and the implant face angle. F. Javed et al. [21], upon evaluating the primary (mechanical) stability of the implant by analyzing the data base for the period of 1983–2013, have emphasized the importance of achieving primary stability for successful implant integration, pointing out that the primary stability of the implant is significantly affected by the quality and the quantity of the bone, by the implant geometry and by the surgical technique.

Implant body shape

The implant body shape (cylindrical, conical, mixed-type) also influences the primary stability and osteointegration (Fig. 1) [22, 23].

Currently, more and more popular are the conical implants, considering the simplicity of their clinical use, the shortened sequence of preparing the bone tissue and the lesser healing period. N. Lozano-Carrascal et al. [24], in particular, have defined that conical dental

Fig. 1. Design of dental implants. Property of Conexão Sistemas e Prótese Company, Brazil, distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike-3.0 license [23].

implants achieve higher primary stability (as measured using the ISQ) and higher torque values. The thing is that conical implants provide compressing lateral effects to the cortical bone, which can be the main reason for their increased primary stability. D. Heimes et al. [25] report that, among the hybrid forms, the increased primary stability is demonstrated by apical-conical implants.

Various forms of the integrated implant is also justified by the density of the bone tissue: for example, cylindric types are being installed into the dense bone (type D1–D2), the cone-shaped ones — into the D3–D4 type bone, while the root-shaped — into the D2–D4 type bone [26].

Implant length

The choice of such a parameter as the implant length is often defined by the extent of bone tissue loss and by the installation area (Fig. 2) [27]. For example, long dental implants are often used with high density and height of the bone tissue [28], the short ones are recommended for use in the areas, where its is necessary to decrease the probability of damaging the adjacent structures, for example, the maxillary sinuses.

Some research works describe that the primary stability significantly increases with the increase of the implant length [29], while the other state that various lengths do not define the difference in the primary stability parameters [25]. The conducted meta-analysis has demonstrated that short (≤6 mm) and longer (≥8.5 mm) implants do not show significant differences in terms of survival rates, which leaves the discussion open for further research [30]. D. Heimes et al. [25], on the contrary, report that higher implant length provides better primary stability, however, the linear dependence ends at 12 mm [25].

Implant diameter

The diameter of the implant also matters. There are implants of small and large diameter. The research works show that larger diameter implant provides better primary stability, which is why the diameter is considered the most important parameter for distributing the tension and the construction load [31]. With this, the survival rates of the implants with decreased diameter comparing to usual diameter (Straumann dental implants with a SLActive surface) during the comparative research by J. Herrmann et al. [32] were 97.4% and 98.5%, respectively. The RFA analysis has shown statistically significant lower values for implants with decreased diameter, while the satisfaction of the patients did not show significant difference. Thus, the Straumann dental implants with decreased diameter were demonstrating much lesser values than the ones in the usual diameter implants, also showing excellent values of survival rates and resonance frequency.

A research by G.E. Romanos et al. [33] has shown that narrow diameter implants (NDI; diameter ≤3.5 mm) can be installed even in the areas with limited space and bone volume. NDI represent an alternative option to standard diameter implants (SDI), which can be used to expand the range of indications for prosthetic replacement. The 5-year values of survival rate and successful implantation for NDI (97.3%) were slightly higher than the ones of the SDI (94.9%) [33]. A research conducted among 186 patients in Saudi Arabia [34], has provided other results: the implants with diameter

Fig. 2. Implant Length (l): *a* — standard (13 mm) and short (7 mm) cylindrical and conical implants (4 mm diameter); *b* — implants with abutments. The images are distributed under to the terms of the Creative Commons Attribution 4.0 license (CC-BY 4.0) [27].

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of 5 mm had the highest values of early survival rate (98.72%), while the implants with a diameter of 3.5 mm have shown the rates of 94.57%.

Implant thread

The construction of the implant thread is a significant decisive factor for initial primary and further secondary stability [35].

The following characteristics can be described in terms of the implant macro-construction: thread pitch; width and depth of thread; thread slope angle; apical surface angle (Fig. 3) [25].

The thread pitch of the implant is the parameter which is measured from the center of one thread to the next thread along the longitudinal axis of the implant [31]. A dental implant with lesser pitch is characterized by larger number of threads, which increases the surface of the implant and promotes to rational distribution of the load. However, this question is controversial, for the research work by L.C. Carmo Filho et al. [36] did not detect any statistically significant difference between the thread pitch of 0.6 mm, 1.0 mm and 1.5 mm in terms of implant stability. The ideal one, on the opinion of the authors, is the 0.8 mm pitch for V-shaped thread.

The width of the implant thread represents the distance between the most coronal and the most apical part of thread. The width largely determines the direction of the implant moving during its installation. According to the results of the research works, the optimal thread width in terms of its biomechanical characteristics can be considered the value of 0.19–0.23 mm [25].

The width of the thread is closely related to such a parameter as the thread depth, i.e. the distance between external contour of the thread and the implant base body. The thread depth is defined as the distance, by which the threads protrude from the implant base [37]. Larger thread depth is beneficial because of increasing the functional surface of the implant, which increases primary stability, however, it can decrease the precision of installation. Thus, implants with larger thread depth can increase primary stability without decreasing the mechanical strength [24]. According to the research by M. Menini et al. [38], the most optimal thread depth is 0.34–0.5 mm. However, despite the data provided, additional trials are necessary, both in vivo and clinical, to support these observations.

The thread slope angle defines the movement of the implant upon its installation: the bigger is the slope, the lesser number of turns is required for the implant to be installed at its whole length. However,

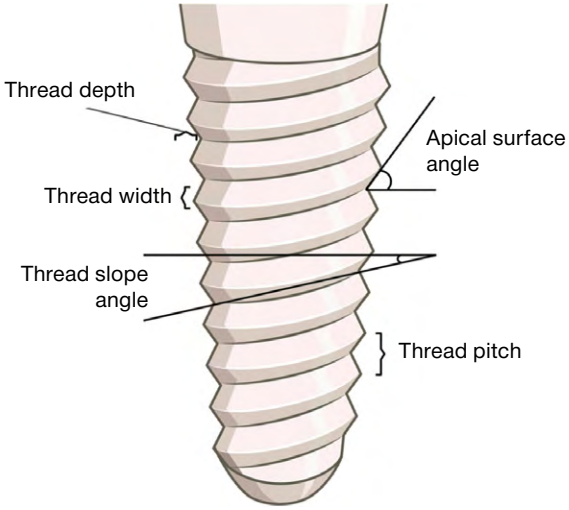

Fig. 3. Main characteristics of the implant thread (apical surface angle — the angle between the thread surface and the horizontal to the longitudinal axis of the implant; pitch — the distance from the thread center to the next thread turn along the longitudinal axis of the implant, or the length of the implant, divided by the number of thread turns; thread slope angle — the angle between the thread spiral and the horizontal to the longitudinal axis of the implant; thread width — the distance between the most coronal and the most apical part of the said thread; thread depth — the distance between the external contour of the thread and the implant base body) [25]. The images are distributed under the terms of the Creative Commons Attribution 4.0 International License.

larger slope angle of the thread helix can result in longitudinal rotation of the implant under axial load. The slope angle directly depends on the thread shape: thus, the V-shaped thread is characterized by an optimal frontal angle of 30°, while the reverse counter-force thread has an angle of 15°. K. Sadr et al. [39] have defined that the most favorable for successful osteointegration are the implants with a reverse thread with angles of 20° and 30°, as well as with the trapezoid thread with an angle of 35°.

However, the choice of thread characteristics is often defined by the individual characteristics of the patient, predominantly depending on the type of the bone tissue. For example, for the D1–D2 type bone tissue, the recommended implants are the ones with cylindrical thread profile, as well as the ones with V-shaped thread with small thread pitch and depth. For the bone tissue of D3–D4 type, the implants recommended for installation are the ones with V-shaped thread and with increased pitch and depth. This is why it is not possible to definitely state the benefits of one or another thread characteristic [40].

Besides the thread properties, the important, though insufficiently studied in modern literature, characteristic is the number of thread turns of the dental implant, for the small number of them cannot create the necessary surface area, which, upon loading, can negatively affect the functioning of the construction. In particular, during the research conducted by D. Kaplun et al. [41], it was found that 10 thread turns in a MegaGen Implant dental implant comparing to 5 thread turns of the Vitaplant VPKS device provides larger surface area, which increases the success rates regarding the primary stability and further osteointegration. In the research by A. Falco et al. [42], implants with larger and self-tapping threads have demonstrated significantly lower values of micro-mobility (p <0.05) comparing to the implants with small threads. The authors report that the implant geometry and the bone density are the main factors affecting the degree of primary stability of the prosthetic device, also reporting that the large thread constructions are preferable for low bone density.

In general, the implants shall be selected individually for each case with taking into consideration the local and general factors. It is important to evaluate the biological status of the patient and to examine various mechanical features in general for the specific clinical situation. The research works from many authors prove that the characteristics of the implant macro-construction improve primary stability and represent a pre-requisite for successful osteointegration. Upon analyzing the obtained data, a conclusion can be made that the parameters of the dental implant thread (thread pitch, width and depth, as well as the slope angle) along with the number of thread turns directly affect the surface of the implant contacting the bone tissue, hence, affecting the primary stability and further successful osteointegration of the implants, which defines the efficiency of orthopaedic therapy.

CONCLUSION

Based on the presented research data from the literature sources, a conclusion can be made that the macrodesign of the dental implant affects the success of prosthetic replacement. The correct choice of the implant is defined by the conical shape, by larger diameter and length (up to 12 mm), as well as by larger width and depth of the thread, by lesser thread pitch and by higher number of thread turns, which provides primary stability to the construction (resulting from larger area of contact between the dental implant and the surrounding bone). These specific characteristics, according to our opinion, assure the success of dental implantation.

In cases of low bone density, the implants with lesser thread pitch are useful due to enlarged area of the implant contacting the bone. The configuration of the micro-thread located at the neck of the implant can improve the formation of the bone and the distribution of tension for implants installed into the spongeous bone in cases of immediate loading.

Further trials are required for studying the interactions of the organism tissues with the dental implants, as well as for analyzing the effects of various parameters on the stimulation of bone tissue formation.

ADDITIONAL INFORMATION

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THE POSSIBILITY OF EFFECTIVE USING THE CONSERVATIVE AND THE MINIMALLY INVASIVE TREATMENT METHODS AT VARIOUS STAGES OF THE DUPUYTREN DISEASE

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ABSTRACT

A literature review is presented on the conservative and minimally invasive methods of treating the Dupuytren contracture. The investigators discuss both the methods implemented into clinical practice and those, which are currently at the stage of clinical and laboratory trials, including the minimally invasive methods, which can be used not only at the later stages, but also in cases of early manifestations of the disease. Among them there are the combined use of conservative methods, the radiation therapy, the injections of collagenase and steroids, the use of immunodepressive medicines and the needle aponeurotomy. These methods can be used at the earliest stages of the disease, however, the absence of proper evidence base often hinders their wide implementation. Up to the present moment, there is no commonly acknowledged approach to managing and treating the patients with early stage of the disease. The modern approach is focused on the invasive treatment of only later disease stages and of the severe contracture cases. This is why we would like to emphasize the potential of minimally invasive methods at the early stages of the Dupuytren disease, as well as the necessity of further research in this direction along with the importance of implementing such methods into everyday practice of the physicians.

Keywords: *Dupuytren contracture; palmar fibromatosis; needle aponeurotomy; percutaneous (needle) aponeurotomy.*

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INTRODUCTION

Dupuytren disease is a fibroproliferative disease, which affects the palmar fascia of the hand and results in the formation of the various degree fibrotic nodes and strands. Eventually, the disease may progress to developing a flexural contracture, which hampers and compromises the operation of the palm, decreasing the quality of life of the patients [1].

According to data from a comprehensive systematic review and meta-analysis with the total sample size of 6,628,506 individuals, conducted by a group of investigators from Iran, Great Britain and Malaysia, the occurrence rate of the Dupuytren disease worldwide is 8.2% (95% confidence level — 5.7–11.7), which confirms the worldwide topicality of the problem [2].

The most widespread methods currently used for the treatment of the Dupuytren disease include the needle aponeurotomy, the collagenase injections, the limited (segmental) fasciotomy (the gold standard) and the radiation therapy. The decision on using one of the methods should be based on the combination of factors, including the degree of contracture severity, the degree of joint involvement into the pathological process, the probability of recurrence and the complications, as well as the experience of the physician in performing the procedure [3]. The absence of pathogenetic therapy along with predominantly providing surgical aid to the patients that already have a disease degree of III–IV with the background of the currently available variety of treatment methods for this disease keeps the problem of recurrence very topical.

The provided review summarizes the updated data on the techniques of conservative and minimally invasive treatment of the Dupuytren disease at various stages of the disease, as well as on the options of the pathogenetic approach to solving this problem.

ВОЗМОЖНОСТЬ ЭФФЕКТИВНОГО ПРИМЕНЕНИЯ КОНСЕРВАТИВНЫХ И МАЛОИНВАЗИВНЫХ МЕТОДОВ ЛЕЧЕНИЯ НА РАЗЛИЧНЫХ СТАДИЯХ БОЛЕЗНИ ДЮПЮИТРЕНА

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АННОТАЦИЯ

Представлен обзор литературы по консервативным и малоинвазивным методам лечения контрактуры Дюпюитрена. Исследователи обсуждают как методы, внедрённые в клиническую практику, так и те, которые в настоящее время находятся на стадии клинических и лабораторных исследований, в том числе малоинвазивные методики, которые могут быть использованы не только на поздних стадиях, но и при ранних проявлениях патологии. Среди них комплексное применение консервативных методов, лучевая терапия, инъекции коллагеназы, стероидов, применение иммунодепрессивных препаратов, игольная апоневротомия. Эти методы могут применяться на самых ранних стадиях заболевания, однако отсутствие должной доказательной базы часто препятствует их широкому внедрению. До настоящего времени нет стандартов терапии пациентов с ранней стадией заболевания. Современный подход фокусируется на инвазивном лечении только поздних стадий заболевания с высокой степенью контрактуры. Поэтому мы хотим подчеркнуть потенциал минимально инвазивных методов на ранних стадиях болезни Дюпюитрена, а также необходимость дальнейших исследований в данном направлении и важность внедрения этих методов в повседневную практику врачей.

Ключевые слова: *контрактура Дюпюитрена; ладонный фиброматоз; игольчатая апоневротомия; чрескожная (игольная) апоневротомия.*

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CONSERVATIVE THERAPY OF THE DUPUYTREN DISEASE

Among the methods employed during the treatment of the early stages of the Dupuytren disease, there are manual methods, radiation therapy, injections of collagenase, steroids and immunodepressive medicines.

At the initial stages of the disease, many patients consider the primary conservative therapy as a treatment option. The latter includes using various types of ortheses, therapeutic exercises, laser and shock-wave therapy. According to the Dutch interdisciplinary guideline on Dupuytren disease, the primary conservative therapy can not be recommended as the primary treatment of the disease [4]. A systematic review of non-surgical treatment methods, conducted by our colleagues [5], shows that the combined use of conservative methods (ultrasound, nighttime splinting using wrist splints, stretching exercises and massage) at the early stage of the disease leads to the positive functional result (increased angle of active extension and the grip strength). Due to the qualitative and quantitative non-representativity of the sample in the provided trials, these methods cannot be considered evidence-based. The use of shock-wave therapy for decreasing the intensity of the disease symptoms was researched by the physicians of the Isfahan University and shows a tendency to decreasing the pain intensity within 14 weeks from the therapy date [6].

Radiation therapy

As of today, there are limited evidences of the efficiency of radiation therapy. The issue of the

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mechanism of action remains open for discussion, however, it is considered that the histological changes during the Dupuytren disease can be compared to the formation of keloid, while the mitotic cycle of the fibroblasts can be interrupted using radiotherapy, decreasing the development and the growth rate in the latter, as well as in the myofibroblasts [7]. A systematic review of the articles devoted to the use of this method [3] indicate that the most widespread daily radiation dosage was 30 Gr. According to data from J. Nanchahal et al. [5], doubtful results were obtained when using this method in more than 50% of the analyzed trials. The progression of the disease after radiation therapy is observed in 3–10% of the patients; also, the decrease of treatment efficiency was reported as the degree of the flexural contracture increases [8].

Among the main complications, skin dryness and redness were reported along with the erythema, edema and skin atrophy with telangiectasias. There were no reports on the radiation-induced malignant neoplasms, but the use of ionizing radiation does not rule out the probability of developing mutations. The risk calculations have demonstrated that, for medium age humans, radiation therapy increases the risk of deadly oncological process within the course of the statistical life expectancy by 0.02–0.05%. For younger individuals (aged up to 25 years), the risk percentage should be multiplied by 2, for elderly people (older than 60 years) — divided by 2.

Due to the low evidentiality, according to the Dutch interdisciplinary guideline, it is recommended to limit the application of radiation therapy to only clinical research.

MINIMALLY INVASIVE METHODS OF TREATING THE DUPUYTREN DISEASE

Collagenase injections

The *Clostridium histolyticum* collagenase is an injectable mixture of two purified collagenases (AUXI and AUXII), which predominantly cleaves type I and III collagen to form aminopeptide fragments, not interacting with the type IV collagen — the main component of the basal membranes of the blood vessels and of the epineurium.

The use of collagenase for the treatment of early stage diseases, due to its doubtful safety and efficiency, is not approved by the US Food and Drug Administration (FDA), just like in none of the European countries [9].

According to data from the double-blinded placebo-controlled trial [10], the registered findings included a decrease of the area and the density of the nodes. Two years of follow-up conducted by the American colleagues, demonstrate an improvement in the extension of the metacarpophalangeal joints by Δ=33.7°, of the proximal interphalangeal joints — by Δ=18° [11]. After three years of follow-up, the authors have reported the 16% rate of recurrences (defined as ≥20) for the metacarpophalangeal joints and 38% — for the proximal phalangeal joints, which has increased to 39% and 66%, respectively, to the end of 5 years.

The complications of using this method happen in approximately 80% of the patients. Among the most frequent ones are the swelling and the hematoma, the lymphadenopathy and the skin rupture. The rate of serious complications, such as tendon ruptures or neurovascular injuries, was reduced to the level of 1% [12]. When comparing to the open fasciotomy, lower complication rate was reported with the complications including neurovascular injuries and combined regional pain syndrome with the equal efficiency in terms of resolving the contracture and preventing recurrences [9]. The absence of certified collagenase medicines in some countries of Europe and Asia also acts as one of the main limitations for using this method.

Steroids

The justification of intranodular and intralesional injections of steroids was based on the early clinical and experimental research works exploring their inhibiting effects on the development of the connective tissue [13–15] and the degradation of mature collagen in the hypertrophic scars [16]. At the present moment, the largest trial is the retrospective review by L.D. Ketchum et al. [16], which included 63 patients (75 palms) with the early stage of Dupuytren disease. The patients were receiving injections at a dosage of 80–120 mg of Triamcinolon acetonide into each node with 6 weeks intervals. In 6 months, if necessary, the course could be repeated. The follow-up period lasted from 30 months to 27 years. The regression of the nodes by 60–80% was defined in 73 palms. In this group, there were no changes in the finger contractures. One patient with bilateral contracture (palms 74 and 75) has required surgical treatment. The repeated activation of the disease, leading to additional injections, has occurred in 50% of the patients in 1–3 years after the last injection. The adverse effects, including the transient depigmentation or subcutaneous atrophy in the injection area, which have resolved spontaneously

within 6 months after the last injection, were registered in 50% of the patients.

The use of hydrocortisone acetate in the treatment of the disease was studied by L. Zachariae et al. [14] within the research including 9 patients (9 palms) with the early stage of the disease, defined as palmar fibrosis without contractures or the contracture in all the joints of the finger by ≤30°. Six patients were receiving a total of 3 injections (25 mg), 1 patient — 2 injections of 50 mg, 1 patient — 2 injections of 10 mg, followed by 1 injection of 25 mg, and another patient had 2 injections of 25 mg. All the injections were given with an interval of 2–3 weeks within a period of 2–5 weeks. The follow-up period lasted from 2 to 24 months. The result was assessed clinically along with the subjective information on the decrease of pain with a background of decreasing dimensions of the nodes or their softening in all the cases. The recurrence was registered in 14 months in 1 patient who had two injections of 10 mg and a single 25 mg injections.

The research works evaluating the efficiency of intralesional injections of steroid medications are limited due to their insufficient number, due to the absence of blinded method or randomization, as well as due to using the subjective assessment of the results.

The research on the local application of steroids in cases of Dupuytren disease was described by the American colleagues in 1993 [17]. The research included 6 patients with the disease of interest and employed the local application of the Clobetasol cream twice daily and application of 0.1% Tretinoin before going to sleep. The average course duration and the details of the methods were not described by the authors. They have reported a positive treatment effect in all the patients expressed as the relief of pain and as the decrease of the contracture. No remote results of the research were provided.

The use of immunosuppressive medicines (Adalimumab, Pirfenidone)

The ideal therapy for Dupuytren disease should be aimed at the patients with the early stages of the diseases for preventing the progression and developing strands and further flexural contractures in the fingers. Currently, there is no approved therapy or the evidence-proven treatment in terms of the early stages of the disease.

Based on the results of examining the dissected fibrous tissue of the palmar aponeurosis from the patients, it was found that myofibroblasts in cases of Dupuytren disease get aggregated into nodules located near the affected joints, while the patients with later stages of the disease do not have such nodules [18]. The nodule contains the disseminated immune cells, including macrophages, T-cells and mast cells, with the nodular cells producing various cytokines — the interleukins (IL) 6 and 1β, the transforming growth factor beta (TGF-β) and the tumor necrosis factor (TNF). The comparison of the effects of each of these cytokines has shown that only TNF has turned the palmar fibroblasts of the Dupuytren disease patients into myofibroblasts with the observed low ex vivo concentrations, but not the non-palmar fibroblasts. On the contrary, TGF-β was unselectively turning all the fibroblasts into myofibroblasts. Unlike the TNF, other pro-inflammatory cytokines (IL-6 and IL-1β) did not affect the contractility of the cells. The Dupuytren myofibroblasts have demonstrated a dose-dependant decrease of their contractility during the treatment with anti-TNF with the concomitant decrease in the expression of the alpha-smooth muscle actin (α-SMA). All the approved anti-TNF agents that were clinically studied, were efficient in decreasing the contractility of the Dupuytren myofibroblasts *in vitro*, while the two completely human immunoglobulin G (IgG) molecules, the Adalimumab and the Golimumab, were shown as the most effective at the tested dosages [19].

The clinical and double-blind placebo-controlled research conducted by J. Nanchahal et al. [20], provides the evidence that the intranodular injections of 40 mg (0.4 ml) Adalimumab result in a significant decrease in the expression of α-SMA and I type procollagen, hence, the anti-TNF suppresses the phenotype of the myofibroblasts found in the Dupuytren nodules. Data from the next phase clinical research has allowed for supposing that the intranodular injections of Adalimumab can be efficient in delaying and preventing the progression of the early stage Dupuytren disease.

Due to the absence of the possibility to rule out the effects of the abovementioned TGF-β1 in the active recurrence of contractures in patients with Dupuytren disease, a group of American investigators [21] has studied the use of the TGF-β1 inhibitor (Pirfenidone) *in vitro*. It was found that Pirfenidone can inhibit the proliferation of cells and the contractions of the Dupuytren fibroblasts, also being able to suppress the expression of collagen and fibronectin — the two key components of the extracellular matrix in cases of the Dupuytren disease. The proven efficiency of Pirfenidone *in vitro* against the pathological fibroblasts

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in contracture patients can show similar *in vivo* efficiency, potentially softening the progression of the disease and its recurrence. The issue of the administration route for this medication for the purpose providing better effects in the target cells is still open for investigators.

Needle Aponeurotomy

Despite the short-term success of the open-access surgical methods, there are still cases of disease recurrences reported, as well as the presence of postoperative complications, such as delayed healing of the wounds and the vascular-neural damage. This has led to searching the minimally invasive treatment variants, including the transcutaneous needle aponeurotomy [22], which was done by means of mechanical disruption of the strands of cicatrically modified palmar aponeurosis at several levels using the percutaneous introduction of needles. The absence of radical excision of the palmar aponeurosis along with the absence of affecting the pathogenetical mechanisms of fibrosis results in high risk of recurrence (68%) [23].

With the development of plastic surgery in the treatment of Dupuytren contracture, the wide spreading was provided to the methods of combined surgical treatment with the transplantation of autologous adipose tissue — the lipofilling. The method includes the introduction (after previous needle aponeurotomy) of non-centrifugable sedimented lipo-aspirate at the volume of 8 to 10 ml to the supra-aponeurotic space [24]. The contents of the adipose tissue (which originates from the embryonic mesenchyma) in the adult human, besides fat cells, includes the so called stromal-vascular fraction cells: pre-adipocytes, endothelial and smooth muscle cells of the blood vessels, perivascular fibroblasts, the supporting fibrous collagen stroma and a number of immune cells, such as the adipose tissue macrophages. In the stromal-vascular fraction, a population of stem cells was found, showing the multi-linear differentiation potential, which are similar to the mesenchymal stem cells, originating from the bone marrow, which allows for using the stromal-vascular fraction of the adipose tissue for transplantation and tissue engineering. The easily available material (unlike the bone marrow) can be obtained in a sufficient quantity by means of lipo-aspiration of the subcutaneous fat under topical anesthesia [25]. The research conducted by A.A. Bogov et al. [26] on the application of the needle aponeurotomy combined with lipofilling, has demonstrated that, in patients with grade II–III contracture, the restoration of the palm functions in full range has occurred within the first 24 hours after surgery, and this was explained by the fact that the stromal cells of the adipose tissue (the adipose tissue-derived stromal cell, ADSC) inhibit the proliferation of contractible myofibroblasts, which are the key cells promoting the development of fibrosis. However, in patients with grade IV–V contracture, dermal ruptures were observed (due to the decreased elasticity of the skin), as well as the disease recurrences in 3 years after treatment (in 17% of the patients of the total number of examined individuals).

According to the Dutch interdisciplinary guideline on the Dupuytren disease, conducting the needle aponeurotomy is indicated to young patients willing to undergo minimally invasive interventions, as well as to elderly patients in case of the presence of the palpable strand with pointing out the high percentage of recurrences [4].

CONCLUSION

Currently, the surgical intervention for the treatment of the Dupuytren contracture is conducted only in case of later stages of the disease, in cases of significantly damaged functions of the palm. At early stages of the disease, taking into consideration the needs of patients for decreasing the post-operative pain, the faster restoration of the palm functions, and, respectively, its working capacity, as well as in cases of decreased quality of life after developing a severe contracture, there is a necessity of using the safe and effective treatment methods. Many of the described treatment methods show good results, helping in avoiding surgical interventions, simplifying the treatment and by this attracting the attention of the patients. For example, with the development of collagenase injections, the treatment of the Dupuytren disease has notably changed and started being more prone to the out-patient practice. Some patients in the hands of the experienced surgeons stay satisfied with the good result from the needle aponeurotomy, resulting in rapid recovery and helping with returning to everyday life. The detailed understanding of the molecular basis of the disease, the identification of TNF and TGF-β1 as a therapeutic target helps implementing a new pathogenetic approach with using the medicinal and cellular methods, capable of preventing both the progression and the recurrences of the disease.

Despite the presence of multiple publications describing the use of various minimally invasive methods, they often lack the clear pathogenetic and

biological justification, and the research works are starting to look empirical. The clinical results are reported without using the control groups, without blinding, bringing into question the benefits of the methods described. It is necessary to continue the conduct of more precise research works for better objectivization of the results from the conservative and minimally invasive approaches for the purpose of developing the standards of early treatment and prevention of contracture recurrences, as well as for preventing surgical interventions.

ADDITIONAL INFORMATION

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UNILATERAL REEXPANSION PULMONARY EDEMA (CLINICAL OBSERVATIONS)

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ABSTRACT

BACKGROUND: *In clinical practice, pulmonary edema still remains one of the threatening conditions with high mortality, despite the sufficiently large attention from the investigators. The classic pulmonary edema is well studied, having its specific x-ray signs, while the unilateral pulmonary edema occurs rarely and causes difficulties in the differential diagnostics performed by the radiologist.* ***CLINICAL CASE DESCRIPTION:*** *The presented material includes cases of ipsi- and contralateral unilateral reexpansion pulmonary edema. These complications have developed as a consequence of rapid evacuation of the pathological content from the pleural cavity.* ***CONCLUSION:*** *Reexpansion pulmonary edema is a rare, though potentially life-threatening condition, which usually occurs as a result of rapid expansion of long-term collapsed lung, for example, in cases of pneumothorax and pleural effusion. The edema may develop several hours after the expansion of the atelectasis.*

Keywords: *computed tomography; reexpansion pulmonary edema; contralateral edema; ipsilateral edema.*

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ОДНОСТОРОННИЙ РЕЭКСПАНСИВНЫЙ ОТЁК ЛЁГКОГО (КЛИНИЧЕСКИЕ НАБЛЮДЕНИЯ)

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АННОТАЦИЯ

Обоснование. *В клинической практике отёк лёгких продолжает оставаться одним из грозных состояний с высокой летальностью, несмотря на достаточно большое внимание со стороны исследователей. Классический отёк лёгких хорошо изучен, имеет определённые рентгенологические признаки, а односторонний отёк лёгкого встречается редко и вызывает затруднение в дифференциальной диагностике у врача-рентгенолога.* ***Описание клинического случая.*** *Представлены два случая ипси- и контралатерального одностороннего реэкспансивного отёка лёгких. Данные осложнения развились как следствие быстрой эвакуации патологического содержимого из плевральной полости.* ***Заключение.*** *Реэкспансивный отёк лёгкого — редкое, но потенциально опасное для жизни состояние, которое обычно возникает в результате быстрого расправления длительно спавшегося лёгкого, например, при пневмотораксе и плевральном выпоте. Отёк может состояться в течение нескольких часов после расправления ателектаза.*

Ключевые слова: *компьютерная томография; реэкспансивный отёк лёгкого; контралатеральный отёк; ипсилатеральный отёк.*

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BACKGROUND

In the normal conditions, the lungs have the part of blood plasma penetrating from the pulmonary circulation into the interalveolar space through the pulmonary capillaries and via the resorption of the interalveolar fluid into the venous part of pulmonary capillaries; the fluid is also being eliminated via the lymphatic vessels, by this maintaining the dynamic balance, the quantitative concept of which is the Starling equation [1, 2]. Pulmonary edema is a life-threatening pathological condition resulting due to the increased content of extravascular fluid in the interstitial and/or alveolar space of the lungs.

Pulmonary edema can be divided into four types: hydrostatic edema; edema with diffuse alveolar damage; edema that is not related to the diffuse alveolar damage and mixed-type pulmonary edema [2]. In an overwhelming number of cases, the edema develops in both lungs.

In everyday practice, the radiologist can face the unilateral form of pulmonary edema, which is a quite rare pathological condition, capable of presenting challenges upon the interpretation of the examination results and requiring thorough differential diagnostics between various pathological unilateral pulmonary lesions [1, 2]. During the last 15 years, in the accessible literature, we were able to find only the description of single cases of unilateral reexpansion pulmonary edema [3–5].

Here we provide our own clinical observations.

DESCRIPTION OF THE CASES

Clinical observation 1

Patient info. The female patient K., 38 years of age, was admitted to the hospital with a history of three days of progressing excruciating shortness of breath at rest, with pain in the chest area on the left side. Recently diagnosed with ovarian adenocarcinoma.

Laboratory and instrumental diagnostics. Upon performing the X-ray and computed tomography of the chest, pleural effusion was found, occupying the lower, the middle and partially upper segments of the left lung, along with the atelectasis of the lower lobe of the left lung (Fig. 1, 2, *a*).

Therapy. 12G draining tube was installed along the left anterior axillary line in the fourth intercostal space. One hour after the installation of the draining tube and after removing ~1.6l of serous-hemorrhagic fluid into the air-locked hermetically sealed draining container, the patient started experiencing coughing with developing an acute shortness of breath and tachypnea with desaturation (SpO_2) down to 83% (when inhaling oxygen, 5l/minute, via the simple breathing mask), accompanied by hypotension and tachycardia. Upon the computed tomography of the chest, the findings included a decreased transparency of the left lung (ground glass-type) with multiple intralobular foci of "consolidation" (see Fig. 2, *б*).

Diagnosis. Taking into consideration the anamnestic data and the clinical signs, the definitive diagnosis set was the following: "Reexpansion edema of the left lung, secondary in terms of hydrothorax of the left lung and in terms of the atelectasis in the lower lobe of the left lung".

Outcomes and prognosis. The draining tank was lifted up and up to 400 ml of pleural fluid were returned into the pleural cavity. Then followed the controlled periodical draining of pleural fluid at a rate of not more than 500 ml/h until achieving the "dry" condition. Each

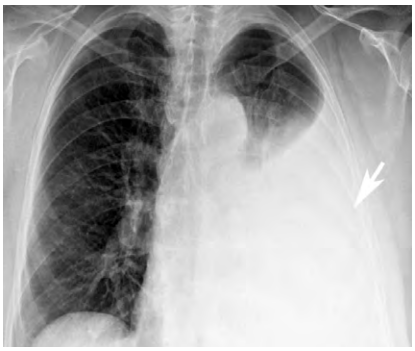

Fig. 1. Female patient K., 38 years of age. Radiology image of the thoracic cavity: subtotal shadowing of left half of the chest cavity to the level of the anterior segment of the 2nd rib on the left side, resulting due to pleural effusion (arrow).

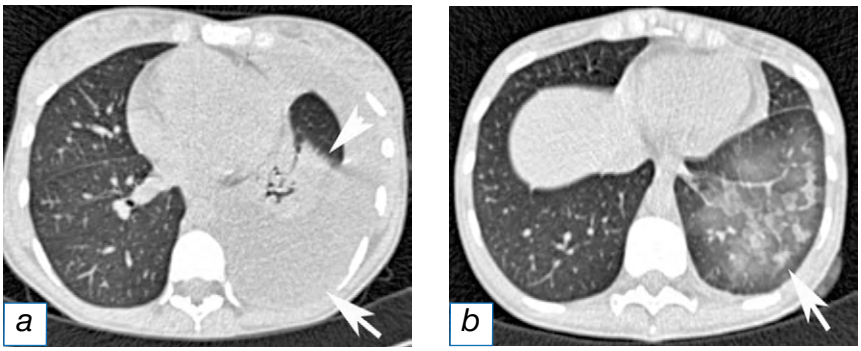

Fig. 2. Female patient K., 38 years of age. Computed tomography image of the thoracic cavity: *a* — effusion in the pleural cavity (arrow), collapsed lower lobe of the left lung (point of arrow); *b* — one hour after draining the pleural cavity: decrease transparence of the pulmonary tissue (ground glass-type), foci of consolidation within the basal segments left lung, caused by the reexpansion edema (arrow).

time the patient was assessed for presence of cough symptoms and shortness of breath.

The complete radiological resolving of pulmonary edema occurred in 2 days. The female patient was discharged with no complications for further follow-up by the district Oncologist.

As it can be suggested from the observations provided, the reexpansion pulmonary edema has developed as a result of rapid removal of large quantities of fluid from the pleural cavity.

Clinical observation 2

Patient info. The female patient A., aged 53, with chronic obstructive pulmonary disease of emphysematous type, has visited the hospital due to having pain in her chest and due to developing progressive shortness of breath.

Laboratory and instrumental diagnostics. The initial assessment has revealed tachypnea (respiratory rate — 39 per minute), tachycardia (heart rate 115 per minute) with the blood pressure levels of 110/70 mm Hg along with the blood oxygen saturation (SpO_2) levels being 93%. The parameters of the clinical hematology and biochemistry panels were within the reference ranges. Upon the radiography of the chest cavity organs: status post resection of segments I–II of the left lung, signs of massive spontaneous pneumothorax on the right side (Fig. 3).

Therapy. Thoracostomy was performed with further draining of 1500 cm^3 of air. Upon the control computed tomography, the findings included an incomplete expansion of the right lung and emphysema in the soft tissues of the chest cavity (Fig. 4, *a*). The female patient has tolerated the procedure well and the symptoms of her pathological condition have decreased. The next morning, the patient had increased shortness of breath and her oxygen saturation (SpO_2) has dropped to 86%. Upon the repeated computed tomography, multiple intralobular foci of decreased transparency were found in the left lung (ground glass-type) with gravity-related density gradients (see Fig. 4, *б*). Combined with the anamnestic data, this symptom has provided the possibility to come to the conclusion on the development of reexpansion edema, for the patient had no fever or leukocytosis, characteristic for pneumonia; there were no signs of aspiration or fluid overload, as well as signs of renal or cardiac failure.

Diagnosis. The definitive diagnosis was stated as the following: “Reexpansion contralateral edema of the left lung, secondary in terms of pneumothorax in the right lung”.

Outcomes and prognosis. After proper oxygen therapy along with the administration of corticosteroid medications and draining of the pleural cavity (using the Bulau’s method), within 5 days the right lung has completely expanded without the development of ipsilateral reexpansion edema, while the reexpansion edema of the left lung has completely resolved.

As it can be suggested from the observations provided, reexpansion pulmonary edema also can develop in the contralateral lung.

DISCUSSION

Unilateral pulmonary edemas can be divided into two large groups — the ipsilateral and the contralateral ones [6]. Ipsilateral pulmonary edemas develop on the side of the pathological process. Such a type of pulmonary edema includes the aspirating form [7], the edemas with a background of pulmonary vein thrombosis [8], the cases of cardiac defects with severe

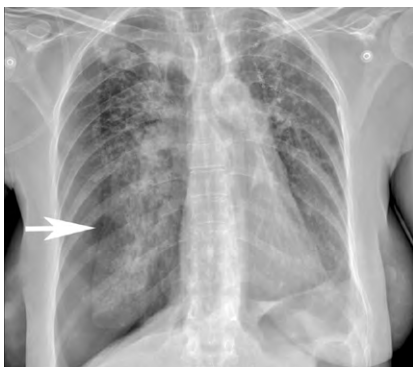

Fig. 3. Female patient A., aged 53. Radiology image of the thoracic cavity: spontaneous pneumothorax on the right side, the collapsed right lung (arrow).

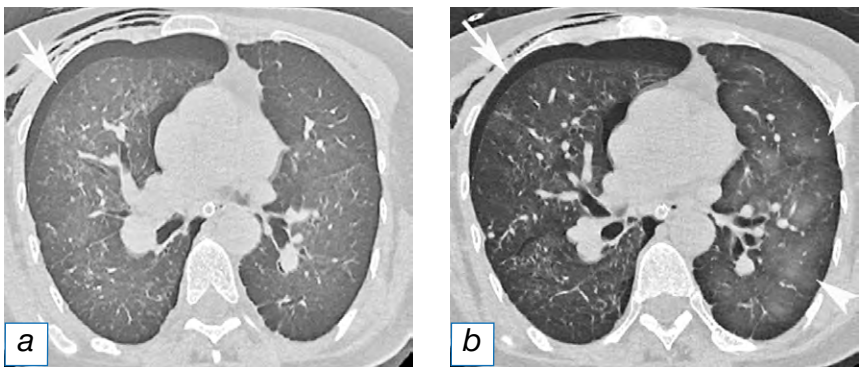

Fig. 4. Female patient A., 53 years of age. Computed tomography image the thoracic cavity: a — air accumulation in the right pleural cavity (arrow), emphysema in the soft tissues in the anterior wall of the chest; *b* — air accumulation in the right pleural cavity (arrow), emphysema in the soft tissues in the anterior wall of the chest; decreased airness in the parenchyma of the left lung (ground glass-type), resulting due to reexpansion edema (point of arrow).

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mitral regurgitation [9] and the edemas developing after pulmonary thrombendarterectomy [10]. The left ventricular insufficiency can also be the reason of unilateral pulmonary edema upon the forced attitude of the patient being positioned on one side [5, 11].

The contralateral edemas are characterized by swelling of the unaffected lung and they occur due to an increase of hydrostatic pressure in the normal lung. The unilateral pathological conditions include asymmetrical emphysema, the Swyer–James–MacLeod syndrome and the status post lobectomy [12, 13].

A remarkable example of unilateral conditions is the reexpansion pulmonary edema. Most frequently, it an ipsilateral edema, developing with 24 hours after rapid fluid or gas evacuation from the pleural cavity. The clinical manifestations of reexpansion pulmonary edema may vary from the changes in the radiography images without any clinical symptoms to hypoxia or even haemodynamic instability of the patient. The computed tomography images in cases of reexpansion pulmonary edema contain peripheral focal areas of decreased transparency (ground glass-type) with perivascular distribution, which is usually associated with interstitial indurations and, probably, with consolidation.

The pathogenesis of reexpansion pulmonary edema is not yet clearly studied. The main reasons of developing this pathological condition should be considered the changes in the permeability of capillaries, playing the most important role in this process, as well as the increase of hydrostatic pressure. The possible predisposing factors to the development of this type of edema include the hypoxic and mechanical damage of the pulmonary capillaries and of the alveolar membrane, along with the decrease in surfactant production. Oxidative stress that develops during long-term collapsing of the lung, results in an increase of the superficial tension in the alveolar membrane, preventing the resorption of fluid. Due to rapid evacuation of the pleural cavity content, there occurs a rapid decrease in the pleural cavity content pressure, which results in rapid restoration of the circulation in the damaged capillaries. Re-perfusion induces the release of cytokines and free radicals, damaging the alveolar-capillary membrane, which results in fluid transudation into the interstitial and alveolar space [2, 14].

Very occasionally, but still possible, reexpansion edema can develop in a contralateral non-collapsed lung. The hypotheses of developing the contralateral reexpansion pulmonary edema include the subconscious aspiration; the compressing forces caused by significant dislocation of the mediastinum; the systemic inflammatory reaction that follows the reexpansion in patients with lung diseases; the significant increase of cardiac output after rapid lung expanding [15]. In case of the presence of radiology findings, corresponding to the reexpansion edema, this type of lung disease can be diagnosed by means of exclusion method in the absence of signs of aspiration, fluid overload, renal or cardiac failure or infection, as well as based on the good response to steroid therapy.

The challenges in the differential diagnostics of unilateral pulmonary edemas may occur in cases of carcinomatous lymphangitis, radiation-induces damage and pneumonias. In the differential diagnostics, the main role is played by the anamnestic data, for the presence of radiation therapy for malignant neoplasms in the affected hemithorax can aid in setting the correct diagnosis, while the presence of such significant clinical signs as fever, coughing, leukocytosis and unilateral shadowed area shall lead the physician to stating the diagnosis of pneumonia [12].

The risk factors of developing the reexpansion edema shall include the time of existing pleural effusion (more than 72 hours) and the proposed volume of fluid/air evacuated (more than 1500 ml). It is also necessary to keep in mind the presence of pulmonary hypertension, hypoxemia and cardio-vascular diseases. In case of the presence of various levels of deficit in the contractility of myocardium, the haemodynamic consequences, which may occur after emptying the pleural cavity, have a tendency of deteriorating. The diseases of lungs or other organs contribute to the increased general risk by altering the pulmonary or cardio-vascular compensation capabilities [16]. In the majority of the research works, the rate of developing the reexpansion edema after relieving the pneumothorax or draining the pleural cavity ranges from 0 to 1%.

The recommendations issued by the British Thoracic Society (BTS) suppose that, during a single procedure, not more than 1.5l of pleural fluid should be drained. In the absence of respiratory symptoms, it is practicable to drain larger volumes “until dry”, but caution should be exercised to avoid creating high negative intrapleural pressure. The gradual evacuation of the pleural cavity content may be required in patients with high risk of developing the reexpansion edema, namely — in case of extended pneumothorax, in patients of young age, in cases of pneumonia with a duration of more than 7 days and, probably, in patients having more than 3l of pleural fluid [17].

CONCLUSION

Thus, unilateral pulmonary edemas may have both the cardiogenic and the non-cardiogenic origin; there can be both ipsilateral and contralateral locations. It is important to know about the probability of developing the reexpansion pulmonary edema, for this condition is a rare iatrogenic complication of draining the pleural cavity. The complexity of pathogenesis and the low knowledge among the radiologists about this disease can result in incorrect interpretation of the examination results and, hence, the loss of time required for adequate treatment of the patient.

ADDITIONAL INFORMATION

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Consent for publication. A written voluntary informed consent was obtained from the patients to publish a description of the clinical case in the journal "Journal of Clinical Practice", including the use medical data (results of examination, treatment and observation) for scientific purposes (date of signing 21.06.2019, 07.11.2023).

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PRIMARY PULMONARY MENINGIOMA — A RARE LUNG TUMOR

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ABSTRACT

BACKGROUND: *Primary pulmonary meningioma is a rare and clinically non-diagnosable tumor. Foreign literature describes not more than 70 cases of this disease. The tumor represents a single solid node, not having any specific features, which does not allow for setting the clinical diagnosis before the pathologic examination. The disease has various occurrence rates both among women and men. The diagnosis is to be set based on the morphological examination of the surgical material with small dimensions of the tumor (or biopsy samples for cases of large tumor).* ***CLINICAL CASE DESCRIPTION:*** *The patient A. (54 years of age) with a history of combined treatment 9 years ago due to being diagnosed with pT2aN1M0, stage IIIB cervical cancer. According to the results from the computed tomography of the chest cavity organs, in segments S8/9 of the lower lobe of the right lung, the findings included a subpleural solid mass lesion with the size of 14×11 mm. According to data from further examinations (computed tomography of the chest cavity organs, of the abdominal cavity and of the minor pelvis; magnetic resonance tomography of the brain; esophagogastroduodenoscopy; colonoscopy), no other abnormalities were detected. Surgical treatment was arranged at the extent of thoracoscopic atypical resection of the lower lobe of the right lung. Anatomic pathology examination report on the resected tumor indicates the presence of "Pulmonary meningioma".* ***CONCLUSION:*** *This clinical case represents the first documented experience of surgical resection of primary pulmonary meningioma in Russia.*

Keywords: *primary pulmonary meningioma; rare tumor of the lung; surgical treatment; thoracoscopic resection of the lung.*

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BACKGROUND

The first case of pulmonary meningioma was described by P. Kemnitz et al. in 1982 [1]. Meningiomas are the most commonly occurring primary tumors of the central nervous system (more than 1/3) [2]. In extremely rare cases (not more than 2%), primary meningioma can be found in the extracranial and extraspinal organs [3]. Malignant forms of primary pulmonary meningioma can also develop, with the exception of pulmonary metastases in cases of atypical meningiomas of the brain [4]. The numbers of primary malignant pulmonary cases do not exceed 10% of all the pulmonary locations for this tumor [5].

The English-speaking literature sources reviewed for the period of the last forty years reveal 70 cases of primary pulmonary meningioma [6], while the Russian literature sources do not contain a single clinical case of this rare tumor until the present moment [7]. Our article reflects the first experience of surgical treatment of primary pulmonary meningioma in Russia.

The majority of primary pulmonary meningioma cases show an asymptomatical course, being detected accidentally during radiology examination as an isolated solid node with relatively small dimensions (the mean diameter is 2 cm). Very rare are the cases when the tumor dimensions exceed 5 cm [8]. The largest ever described primary pulmonary meningioma was measuring 9.5×8.4×5.3 cm — presented in the research work by Chinese surgeons [9].

CLINICAL CASE DESCRIPTION

Patient's info

Patient A., (F) aged 54 years. Past medical history (9 years ago) of combined treatment of cervical cancer (pT2aN1M0, stage IIIB). During the process of dynamic follow-up (during scheduled examination), according to data from computed tomography of the chest cavity organs, a solid mass lesion was found in the lower lobe of the right lung. On admission to the in-patient department, the patient had no complaints.

Physical, laboratory and instrumental diagnosis

Upon scheduled out-patient radiology examination, in the lower lobe of the right lung, the findings included

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ПЕРВИЧНАЯ ЛЁГОЧНАЯ МЕНИНГИОМА — РЕДКАЯ ОПУХОЛЬ ЛЁГКОГО

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АННОТАЦИЯ

Обоснование. *Первичная менингиома лёгкого является редкой и клинически не диагностируемой опухолью. В зарубежной литературе описано не более 70 случаев этого заболевания. Образование представляет собой единичный солидный узел, не имеющий никаких отличительных черт, что не позволяет поставить клинический диагноз до патологоанатомического исследования. Заболевание с различной частотой встречается как у женщин, так и у мужчин. Диагноз устанавливается на основании морфологического исследования операционного материала при малых размерах опухоли или биоптата — при больших.* ***Описание клинического случая.*** *Больная А. (54 года) перенесла 9 лет назад комплексное лечение по поводу рака шейки матки pT2aN1M0, стадия IIIB. Согласно результатам компьютерной томографии органов грудной клетки, в S8/9 нижней доли правого лёгкого имеется субплевральное солидное образование размером 14×11 мм. По данным обследований (компьютерная томография органов грудной клетки, брюшной полости и малого таза; магнитно-резонансная томография головного мозга; эзофагогастродуоденоскопия; колоноскопия) иной патологии не выявлено. Выполнено хирургическое лечение в объёме торакоскопической атипичной резекции нижней доли правого лёгкого. Патологоанатомическое заключение удалённой опухоли: «Менингиома лёгкого».* ***Заключение.*** *Данный клинический случай представляет собой первый задокументированный опыт хирургического удаления первичной менингиомы лёгкого в России.*

Ключевые слова: *первичная менингиома лёгкого; редкая опухоль лёгкого; хирургическое лечение; торакоскопическая резекция лёгкого.*

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a single hyperdense focal mass, due to which, the patient was referred to the in-patient department for comprehensive examination and further surgical treatment.

Computed tomography of the chest cavity organs with contrasting (Fig. 1): in segments S8/9 of lower lobe of the right lung, there is a subpleural solid mass (in the lower lobe of the right lung) with the dimensions of 14×11 mm.

According to data from pre-operational examinations (computed tomography of the abdominal cavity and of the minor pelvis with intravenous contrasting; magnetic resonance tomography of the brain; esophagogastroscopy; colonoscopy; consultation by an oncologist-gynecologist), no other abnormalities were detected.

Diagnosis

Based on the findings from the pre-operational examination and on the data from computed tomography of the chest cavity organs, the diagnosis set was the following: “Peripheral mass of unknown etiology in the lower lobe of the right lung”.

Treatment

Taking into consideration the solitary type of tumor, as well as the absence of other tumor-related diseases, including the absence of data confirming the progression of cervical cancer, a thoracoscopic atypical resection of the lower lobe of the right lung was carried out.

Pathohistological examination of the surgical material: a fragment of the lung (Fig. 2): subpleurally,

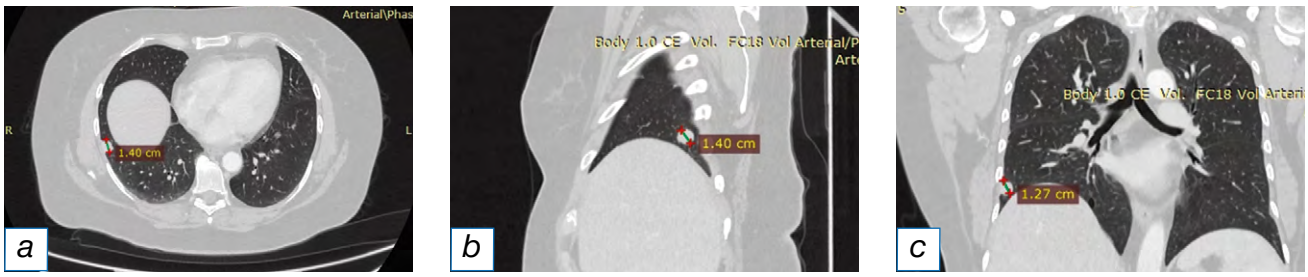

Fig. 1. Computed tomography of the chest cavity organs: solid solitary focus in the lower lobe of the right lung for axial (*a*), sagittal (*b*) and frontal (*c*) projections.

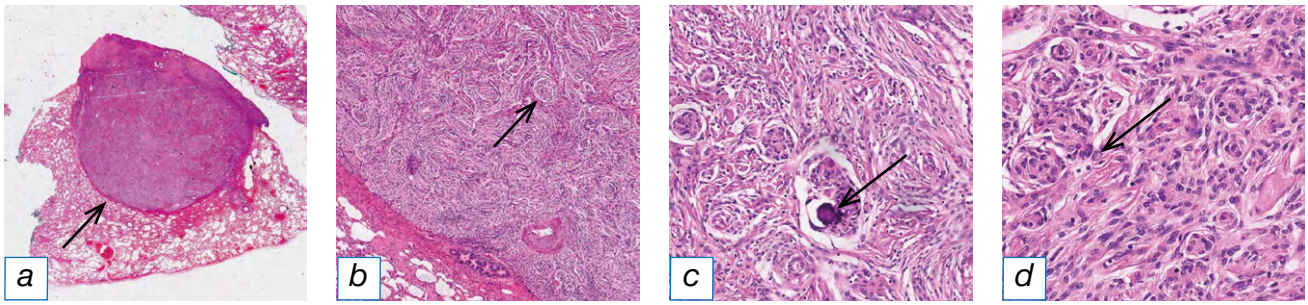

Fig. 2. Pathohistological examination of the lung fragment, staining with hematoxylin-eosin: *a* (×40) — subpleural clearly contoured node (arrow); *b* (×100) — circular growth pattern and concentric structures (arrow); *c* (×400) — psammoma bodies (arrow); *d* (×400) — characteristic nuclear inclusions (arrow).

but with the involvement of the visceral pleura, there are signs of growth of unclearly contoured tumor with lobular locular and concentric structures, with circular growth patterns, containing cells of polygonal shape, weakly eosinophilic dust-like cytoplasm and oval moderately polymorphous nuclei with lumpy chromatin and small nucleoli, with nuclear inclusions and with no visible mitotic activity. Other findings include calcification foci and psammoma bodies (see Fig. 2, *в*). The tumor structures contain trackable intact (flattened) small bronchioles. No perineural or lymphovascular invasion was detected. The visceral resection margin is intact. Maximal tumor size — 1.3 cm.

Differential diagnosis

For the purpose of differential diagnosis with squamous cell cancer and solitary fibrous tumor of the pleura, further immunohistochemical examination was performed (Fig. 3): the tumor cells express the following markers: focal significant nuclear expression of progesterone receptors (PR), focal membranous expression of epithelial membrane antigen (EMA), significant expression of vimentin with complete absence of keratin expression (data not provided). No expression was detected for p63 and STAT6 (data not provided).

Thus, the morphological pattern and the immunophenotype confirm the diagnosis of primary

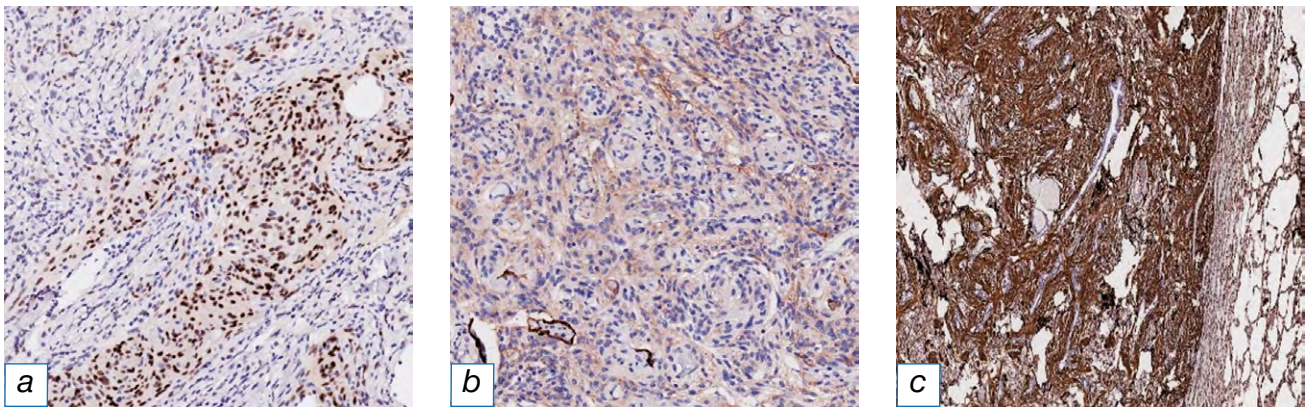

Fig. 3. Immunohistochemical examination using the antibodies: *a* (×200) — to progesterone (PR), nuclear expression; *b* (×200) — to epithelial membrane antigen (EMA), membrane expression; *c* (×200) — to vimentin.

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pulmonary meningioma (WHO Grade 1, similar to meningotheliomatious meningioma).

Outcome and prognosis

The postoperative period was smooth. The female patient was discharged on day 4 after surgery. The control examinations after 3 months did not reveal any abnormalities. The prognosis is favorable.

DISCUSSION

From the moment of the first publication in 1982, only 70 cases of primary pulmonary meningioma were described. All the articles on this rare tumor were published by foreign authors in the international journals. The article brought to your attention and describing the clinical case of operated primary pulmonary meningioma in a female patient aged 54, is the 71st documented clinical example in the world practice and the first ever described in the Russian scientific medical literature.

The extremely low occurrence rate of primary pulmonary meningioma, the relatively small dimensions of the disease focus in the lung, as well as the absence of any specific features allowing for differentiating this neoplasm from other pulmonary neoplasms — all of these preclude the possibility of precise diagnosing this disease (in case the biopsy was not performed). In all the clinical cases, the tumor itself is occasionally identified upon the anatomic pathology examination of the surgical or biopsy material.

CONCLUSION

The presented clinical case is the first ever documented experience of surgical resection of rare and clinically non-diagnosable tumor (primary pulmonary meningioma) in Russia. The differential diagnosis of primary pulmonary meningioma shall include with a number of other solid lesions located in the pulmonary tissues, including both the malignant (initial lung cancer or secondary foci) tumors and the foci of benign origin.

ADDITIONAL INFORMATION

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Competing interests. The authors declare that they have no competing interests.

Authors' contribution. *G.A. Baksiyan* — patient treatment, manuscript writing; *A.A. Zavialov* — patient treatment, approval of the concept and design of the study, editing; *S.V. Lishchuk* — performing morphological and immunohistochemical studies with preparation of relevant photographic material. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

Consent for publication. Voluntary written informed consent was obtained from the patient for publication of his images for scientific purpose in the medical journal "Journal of Clinical Practice", including its electronic version (date of signing 10.04.2024).

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SPINAL ISCHEMIA: THE REHABILITATION POTENTIAL. A CLINICAL CASE

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ABSTRACT

BACKGROUND: *Spinal myeloischemia is a rare but severe neurological disease, associated with high incapacitation level and high social-economical costs due to complications developing during the acute phase. The reasons for its development can include vascular malfomations, spinal stroke, extra- and intramedullary tumors, compression of the spinal cord in cases of vertebral fractures, intervertebral disc herniations, stenosis of the spinal canal at the cervical segment, medical manipulations and impaired segmental circulation during the anesthesia, lumbar puncture and surgical interventions.* ***CLINICAL CASE DESCRIPTION:*** *The presented clinical observation provides a description of the iatrogenic complication that has developed in a patient aged 52 years after discectomy and installation of the disc prosthesis due to the development of disco-radicular and spinal conflict, resulting due to the C5/C6 dorsomedial intervertebral hernia, the clinical manifestations of which, besides pain, included weakness in the left upper limb, causally related to the focus of intramedullary ischemia at the unilateral side. At the early post-surgery period, asymmetrical tetraparesis was revealed with the predominance in the distal segments of the left upper limb and with impaired functions of the pelvic organs, caused by the expansion of the ischemia zone in the gray and white matters in the anterior areas of the lower cervical segments of the spinal cord.* ***CONCLUSION:*** *The timely initiation of combined medication therapy and the staged rehabilitation, conducted by the multi-disciplinary team, have provided the restoration of the impaired functions and the quality of life for the patient. The proposed methods can be useful in the treatment of patients with compression-related and non-compression-related vascular myelopathies.*

Keywords: *discectomy; spinal stroke; myeloishemia; rehabilitation.*

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BACKGROUND

Spinal stroke, spinal ischemia and vascular myelopathy are the forms of acute or subacute impairment of circulation in the spinal cord, caused by the thrombosis of spinal arteries or veins, by their compression during the vertebral column injury, during the stenosis of the spinal canal, after surgical interventions in the vertebral column, aorta, brachiocephalic arteries and after their concomitant hemodynamic complications with further segmental focal softening in the ischemia zone, with developing neurological syndromes characteristic for each level of decreased perfusion [1].

The diagnosis of spinal stroke is more often set clinically, while the visualization methods are employed for the purpose of ruling out the presence of myelopathies of other etiology [2, 3]. The outcomes of impaired spinal circulation represent a medical-social economical problem. Though their occurrence is not high (from 1% to 2% [4]), the reasons and forms may vary [2, 5]. The difficulties occurring during setting the diagnosis include the defects of collecting the anamnestic data, the assessment of neurological symptoms, as well as low confidence levels of the results obtained during the electrophysiological tests and neurovisualization.

With all the variety of methods and means of rehabilitation therapy, there is no consensus on managing such patients and no widely acknowledged criteria for the clinical evidences of their use both during the post-surgery period and at the later stages of rehabilitation.

СПИНАЛЬНАЯ ИШЕМИЯ : РЕАБИЛИТАЦИОННЫЙ ПОТЕНЦИАЛ. КЛИНИЧЕСКИЙ СЛУЧАЙ

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АННОТАЦИЯ

Обоснование. *Спинальная миелоишемия — редкое тяжёлое неврологическое заболевание, сопровождающееся высоким уровнем инвалидизации и большими социально-экономическими издержками из-за возникших в остром периоде осложнений. Причиной её развития могут быть сосудистые мальформации, спинальный инсульт, экстра- и интрамедуллярные опухоли, компрессия спинного мозга при переломе позвонка, межпозвонковой грыже, стенозе позвоночного канала в шейном отделе, врачебных манипуляциях, нарушении сегментарного кровообращения при анестезии, люмбальной пункции, оперативных вмешательствах.* ***Описание клинического случая.*** *В представленном клиническом наблюдении даётся описание ятрогенного осложнения, случившегося у пациента в возрасте 52 лет после дискэктомии и установки протеза диска в связи с развитием у него диск-радикулярного и спинального конфликта, обусловленного дорсомедиальной межпозвонковой грыжей C5/C6, клиническими проявлениями которого, помимо боли, была возникшая слабость в левой руке, причинно связанная с очагом интрамедуллярной ишемии на одноименной стороне. В раннем постоперационном периоде выявлен асимметричный тетрапарез с преобладанием в дистальных отделах левой руки и нарушением функции тазовых органов, возникший из-за расширения зоны ишемии серого и белого вещества в передних отделах нижних шейных сегментов спинного мозга.* ***Заключение.*** *Своевременно начатая комплексная лекарственная терапия и этапная реабилитация, проводимая мультидисциплинарной командой, обеспечили восстановление нарушенных функций и качества жизни пациента. Предложенные методики могут быть полезными при лечении больных с компрессионными и некомпрессионными сосудистыми миелопатиями.*

Ключевые слова: *дискэктомия; спинальный инсульт; миелоишемия; реабилитация.*

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CLINICAL CASE

Patient info

Male patient aged 52, hospitalized to the Neurosurgery Department in Astrakhan city with the complaints of moderate pain in the cervical segment of the vertebral column (5 points of the visual analogue scale), weakness in the left upper limb, numbness in the shoulder, forearm and fingers I–II.

Case history. The anamnestic data show that the patient has been suffering from the neck pain for 5–6 years, repeatedly receiving courses of conservative therapy prescribed by the neurologist with temporary positive effect. A year before admission, based on the results of magnetic resonance imaging (MRI) of the lower area of the cervical spine, degenerative-dystrophic changes and the dorsal-medial subligamentous left-sided hernia was found in the C5/C6 intervertebral disc, measuring 0.7 cm and showing signs of caudal migration at an area with a length of up to 0.5 cm, spreading into the intervertebral foramen, with signs of discal-radicular conflict. The spinal cord and the radices show no signs of any changes. There were no clinical manifestations of compression. The dimensions of the spinal canal corresponded to the age-corrected reference ranges (1.4 cm).

laboratory and instrumental diagnosis

Paresis, hypotension in the muscles of the left upper limb (2 points), anisoreflexia D>S, radicular-type hypesthesia in segments C5 and C6. No pathological

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reflexes or symptoms of longitudinal-transverse damage of the spinal cord were found. The tests of scalenus syndrome or Adson syndrome on the left side were positive.

Due to the presence of distal paresthesia, ultrasound examination of the radices and nerves of the upper limbs was carried out: no solid evidence of their local compression were obtained.

MRI findings obtained using the modes T2-WI, T2-STIR (1.5 Tesla, slices thickness — 3 mm): disco-radicular conflict at the level of C5/C6; in the lower cervical segments of the spinal cord, the findings included a local intramedullary "pin" type focus — the marker of vascular myelopathy.

Taking into consideration the obtained data, surgery was performed at the extent of discectomy of C5/C6, resection of the disc hernia and prosthetic replacement (M6 disc prosthesis).

On the next day after surgical intervention, the aggravation of already existing neurological symptoms was noted: decreased muscle strength in the limbs (tetraparesis), more in the left (palm and foot); impaired functions of the pelvic organs expressed as insufficient control of urination. Upon the examination, the following was noted: the tendon reflexes are intensified, more on the right side; impaired superficial sensitivity matching the segmental radicular type on the left side (C5/C6); decreased muscle tone and strength S>D (down to 2 points). The proprioceptive sensitivity was intact. After assessing the data from the MRI scans of the cervical spine at the sagittal and axial planes, MRI-signs of postoperative changes were revealed along the surgical access area. Comparing to previous images, negative changes were reported — enlarged area of the myelopathy focus at the level of the lower segments with damaging the gray and white matters, predominantly in the left half of the spinal cord, which indicates that the patient is developing an iatrogenic complication — focal spinal ischemia (the anterior cord syndrome, the impairment of the afferent branches of the left lower cervical radiculomedullary artery), manifesting with asymmetrical tetraparesis and with the dysfunction of pelvic organs. No local hyperintensity was found in the slices obtained using the diffusion weighted images (DWI), but additional data obtained at the ventral-lateral area of the C5 vertebral body, showing the presence of a hyperintensive ovoid shape focus of bone tissue remodeling for modes T1, T2-WI, T2-STIR with unclear and uneven contours — the extramedullary sign of local ischemia, which was not found in the previous images.

Treatment

The physician has prescribed analgesics (Ketoprofen — 100 mg twice daily), hormonal medications (Dexamethasone — 8 mg, intravenous); the gastroprotective drug Omeprazol (40 mg); Pentoxifylline (100 mg + 200 ml 0.9% NaCl solution, intravenous); antioxidants, neurometabolic drugs (Cytoflavin — 10 ml intravenous, thioctic acid — 600 mg, intravenous); for the prevention of thromboembolic and infectious complications — Fraxiparine at a dosage of 0.4 ml subcutaneously and Ceftriaxon (1.0 g, intramuscular), respectively. Insignificant positive changes were noted in terms of the neurological status (level D of the ASIA scale).

The patient had received the recommendations to continue medication treatment at the 2nd stage, with further courses of individual differentiated medical rehabilitation taking into consideration the potential present, the parameters of the functional independence status and the clinical recommendations [6, 7].

Diagnosis

On admission to the Medical Rehabilitation Unit, the patient was examined by the physicians of the multidisciplinary rehabilitation team, consisting of the neurologist, the Head of Medical Rehabilitation Unit, the rehabilitation therapist, the medical psychologist, the physical therapist and the nurse. According to the examination results, the patient had his rehabilitation diagnosis set according to the categories of the International functional classification (table 1) and underwent an assessment of the motor and psychosomatic status in accordance with the scales (table 2).

Medical rehabilitation

The short-term objective of the second stage medical rehabilitation was restoring the ability of self-care (dressing/undressing, personal care) and the ability to walk with additional support to Day 21. The objective of the motor and household rehabilitation were the following: to restore the motor function of the left limbs, to have the capability of fully move in the bed, to be able to sit down without assistance, to sit and to use the technical means of rehabilitation (walking aid, walking cane), to stand up, to go to bathroom and to dress/undress.

Taking into consideration the age of the patient, the severity degree of the neurological deficit, his rehabilitation potential was assessed as medium, with the thing to be taken into account being the

Table 1

Rehabilitation diagnosis in the categories of the International functional classification

Diagnosis[1]	Key words[2]	Specialist[3]	Intervention[4]	Qualifier[5]
b28010.1 Pain in the head and neck	Pain with a background of degenerative changes in the vertebral column	Neurologist	Medication therapy, physiotherapy	b28010.0
b620.2 The urination functions	Control of urination	Neurologist	Medication therapy, physiotherapy	b620.2
b7603.3 Supporting functions of the hand or the leg	Leaning on the damaged leg	Physical therapist	Training of leaning on the leg	b7603.2
b7352.2 Muscle tone on one side	Hypotension on the left side	Physical therapist, neurologist	Active and passive gymnastics, robot-assisted mechanotherapy	b7352.1
b 7302.3 Muscle strength on one side of the body	Hemiparesis 3 points	Physical therapist, neurologist	Active and passive gymnastics, robot-assisted mechanotherapy	b 7302.2
S120.2 The spinal cord and related structures	Focus at the level of the lower segments of the spinal cord C5/C6 with damaging the substance of the spinal cord, according to data from MRI	Neurologist	-	S120.2
d4500.44 Walking short distances	Getting up, going to the toilet and to the wash basin with support	Physical therapist	Learning the correct algorithm of supported walking	d4500.23
d465.44 Moving using technical aids	Walking with the walking aids	Physical therapist	Training on the correct walking with the walking aids to a distance of not less than 50 m	d465.02
d4153.23 Staying at the sitting position	Sitting down and holding the sitting positions	Physical therapist	Training of long-term staying at the sitting position	d4153.00
d445.34 Using the palm and hand	Using the palm and hand in the household situations	Physical therapist	Training of leaning on the hand, of using the hands in everyday situations, such as taking meals, washing, dressing, other hygienic activities, the use of walking aids	d445.12
d540.03 Dressing	Dressing and undressing the upper and lower half of the body, putting on the shoes	Nurse	Training the patient on the methods of dressing and putting on the shoes	d540.01
d550.02 Taking meals	Eating and drinking	Nurse	Training on eating and drinking	d550.00
e1101.0 Medicinal substances	Symptomatic, pathogenetic therapy	neurologist	Symptomatic, pathogenetic therapy	e1101.+4
e310.0 Family and near relatives	Discussions with the relatives and the patient	Nurse, psychologist	Discussions with the relatives and the patient	e 310.+4
e340.0 Personnel, providing care and aid	Assisting with the care for the patient	Nurse	Assisting with the care for the patient	e340.+4

Note. [1] The rehabilitation diagnosis according to the categories of the International functional classification; [2] Key words for understanding what exactly the multidisciplinary rehabilitation team is discussing; [3] Specialist of the multidisciplinary rehabilitation team, responsible for the issue; [4] Rehabilitation intervention, allowing for solving the problem in the patient; [5] Repeated assessment.

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Table 2

Assessment using the scales

Scale	Assessment	
	On admission	On discharge
Rehabilitation routing scale (RRS)	5	4
Modified Rankin Scale (mRS)	5	4
Hauser Ambulation Index (HAI)	8	5
Rivermead Mobility Index (RMI)	3	7
Visual Analogue Scale (VAS) for pain in the cervical segment of the vertebral column	3	1
Functional Independence Measure (FIM)	63	88
American Spinal Injury Association (Asia)	D	D
Hospital Anxiety and Depression Scale (HADS): anxiety	5	4
Hospital Anxiety and Depression Scale (HADS): depression	7	6

high motivation of the patient in terms of undergoing rehabilitation and achieving the positive treatment result. Taking this into consideration, an individual rehabilitation program of activities was compiled:

- individual sessions of physiotherapy exercises with the physical therapist at the initial lying position with further verticalization of the patient (twice daily);
- verticalization using the "Imitron" active-passive mechanotherapy device;
- mechanotherapy (Thera-vital active-passive rehabilitation device, treadmill with the Rea-terra suspension system);
- physiotherapy (laser therapy — cervical spine, electrostimulation of the urinary bladder muscles);
- manual massage of limbs, electrostatic massage of the left limbs using the на "Hivamat" apparatus;
- medical psychologist sessions;
- medication treatment: neuroprotection (Cerebrolysin at a dosage of 10 ml, intravenous; Neuromidin, 15 mg/1.0 ml, intravenous); hormonal therapy (Dexamethasone at a dosage of 8 mg, intravenous), vascular medicines (2.4% Euphylline + 200 ml 0.9% NaCl, intravenous) and metabolic drugs (Thioctic acid — 600 mg, intravenous); multivitamin therapy.

Follow-up and outcomes

After the conducted treatment course, positive dynamic changes were noted — the gradual increase of the strength in the left upper limb up to 3 points, in the left lower limb — up to 4.0 points. The patient was verticalized using the walking aids, besides, he started moving with support within the hospital ward.

The everyday activities of the patient were restored to the level of self-care with minimal assistance (Fig. 1):

Fig. 1. The degree of compensation of the impaired functions before (*a*) and after (*b*) the first stage of the rehabilitation therapy.

the patient is capable of using the toilet by himself, to perform the daily hygiene and to walk not less than 100 m using the walking aids, also having full control of his urination.

Thus, the intermediate objectives of rehabilitation were achieved, a good level was reported for restoring the motor and pelvic functions.

Prognosis

The prognosis for life and functioning in this patient with a background of conducted therapy is favorable.

DISCUSSION

The surgical treatment of vertebral column diseases is always associated with a risk of developing iatrogenic (early and delayed) intra- and postoperative complications, such as spinal ischemia, vascular myelopathies, spinal ischemic or hemorrhagic stroke and venous congestive (hypertensive) myelopathies [8–13]. The local anterior and posterior compression of arteries and veins by the intervertebral disc herniations; the damage or compression of the vessels in the spinal cord during injuries; the congenital and acquired deformations of the vertebral column; the stenosis of the spinal canal; the presence of vascular malformations, tumors, episodes of arterial hypotension, blood loss, thrombosis, fibrotic-cartilage embolism during surgery and after it — all of these are significant causes of impaired spinal circulation [14–17]. The clinical manifestations and the mechanisms of developing the hypo-perfusion, the vasogenic myelopathy and the spinal stroke cord, to a significant extent, depend on the anatomic features of spinal circulation supply — the level of vessel origination, the diameter, the number of anterior and posterior afferent arteries [1, 18, 19]. The main ones, located along the spinal cord, are the azygos anterior cerebral artery, formed as a result of the confluence between the ascending and the descending branches of the radiculomedullary arteries and supplying the anterior 2/3 of the spinal cord, and the paired posterior spinal artery, supplying its posterior third. The level and the type of blood supply, the individual variants of origination and dimensions of the vessels lumen, the involvement of borderline zones (watershed/border zone infarct), the duration of occlusion, the dimensions of the infarction focus, the length of the transverse-longitudinal injury of the structures, the absence of anastomoses, the venous stasis and the variations of blood pressure are the factors defining the degree of severity, the duration, the reversibility of neurological deficit and the restoration of impaired functions [20–22]. Spontaneous and iatrogenic damage of spinal circulation most frequently develops during the aortic stenosis, coarctation, aneurism, arteriitis, parietal thrombosis, dissection of aorta, embolism in the bifurcation area, massive blood loss, clamping of aorta, as well as upon reconstructive or emergency surgical interventions related to it [23–27], much less frequently — during the dissection, stenosis and thrombosis of the vertebral artery, in cases of discal-osteo-arterial conflict or scheduled surgeries in the cervical and thoracic segment of the vertebral column [28–31].

The diagnosis of the forms of spinal arterial or venous ischemia is usually set clinically, but the neurovisualization of the spinal cord structure for its verification is the obligatory option. The magnetic resonance imaging (MRI) using T1- and T2-weighted images (T1-WI, T2-WI) with using the fat suppression program (Short Tau Inversion Recovery, STIR), with the administration of the paramagnetic contrasting agent and with the evaluation of the DWI signal is also, besides CT and MRI-angiography, the gold standard of examining the patients at the acute phase of developing complication. Additional information, allowing to define the cause and the rehabilitation potential of the segmental injury, can be obtained upon digital subtraction angiography and functional MRI [1, 32–36].

The acute focus of ischemia, the spinal stroke in the sagittal T2-WI and T2-STIR is most commonly represented by the rod-shaped (looking like a “pencil”, “white cord”, or the “pin”) hyperintensive signal within several damaged spinal segments (white cord syndrome) [37–39]. Due to the high susceptibility of the gray matter to ischemia, using the T2-WI at the axial plane, during the first 24 hours, one can also detect the other characteristic pattern — the bilateral hyperintensive signal in the area of the anterior horns (snake-eye appearance or owl’s eyes), in case of venous congestive myeloischemia (venous hypertensive myelopathy, Foix-Alajouanine syndrome) — hyperintensive signal along the posterior surface of the brain, the “flow voids sign” in the sagittal slice, the axial one is showing the “black round dots” (perimedullary dilated veins) [12, 13, 40–45]. The assessment of these markers at all stages of treatment and rehabilitation is important, for it additionally characterizes the local sanogenesis and the reparation mechanisms in the damaged zones. The ischemia focus not related to the injury is rarely visualized within the first hours after developing the neurological symptoms [1, 45].

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The analysis of clinical manifestations and of the obtained images allows for detecting not only the type, but also the circulation segment involved in the development of ischemia. The reasons for circulation "switch-off" in the blood supply zones of the anterior and posterior spinal artery along with its branches and anastomoses (hypo-perfusion) include the significant decrease of blood pressure, the local stenosis, the occlusion of the lumen by the thrombus, the embolism, the vasogenic swelling of the spinal cord, the impaired collateral circulation, the venous outflow during the mass effect, the narrowness of the spinal canal, the prolapse of the intervertebral disc, as well as the compression by hematoma, by bone tissue (during the fracture), by hypertrophic/ossified posterior longitudinal ligament (in case of type I and II ischemia), developing after the restoration of the lumens of the magistral arteries and after the surgical decompression; re-perfusion of ischemic zones [46–49]. The clinical manifestations, the dimensions and the degree of transverse-longitudinal injury for all the types are defined by the anatomical features of the blood supply at this level. The blood supply of the lower-cervical segments of the spinal cord is provided by the azygos anterior cerebral artery, by the paired radiculomedullary and sulcal arteries, as well as by the spinal vasocorona [50, 51].

Depending on the reason, the ischemia zone can be limited to the anterior horns of the spinal cord (the poliomyeloischemia syndrome), to the half of the cross-section (incomplete ischemic Brown-Séquard syndrome); it may involve the anterior segments (ischemia syndrome of the ventral and central zones), the lateral or the posterior funiculi ("lateral" or "posterior" damage syndromes, Posterior Funiculus syndrome (Williamson's)), the whole cross-section (the syndrome of complete transverse damage in cases of totally impaired circulation) [1, 35, 45, 52–56]. Besides, there are also descriptions of other verified phenotypes, reflecting the damage of the spinal structures in the cross-section involving the same segments: isolated post-surgical upper monoparesis, paraparesis [57–60]; the man-in-the-barrel syndrome [61, 62]; the sulcal artery syndrome [63–65]; the symmetrical lower paraparesis [66]; the ipsilateral hemiparesis [67, 68]; the symmetrical and asymmetrical tetraparesis [69, 70], as well as the extremely rare combined variants, and, like in our case, with the ischemia/infarction of the vertebral body [45, 71, 72].

Currently, there are no commonly acknowledged recommendations on the treatment of vascular myeloischemia. The absence of clear recommendations on managing the patients at the acute and subacute periods of the arterial infarction or venous thrombosis significantly complicates and oftentimes negatively affects the process of treatment and restoring the impaired functions in cases of iatrogenic complications. The rehabilitation potential in cases of spinal stroke depends on the correct assessment of the initial neurological deficit: more significant neurological deficit determines the less favorable outcome [6, 25, 26]. Using the individual approach when prescribing the medicinal products, when selecting the methods and the means of medical-social rehabilitation, allows for sufficiently restoring the damage of the spinal cord within a short period of time and adapting the patient to various aspects of life-sustaining activity [73–80].

CONCLUSION

Spinal ischemia, myelopathy and spinal stroke are serious complications, caused by vascular, compression-related or other reasons, less frequently — by surgical interventions. The damage pattern depends not only on the hemodynamical characteristics and the capabilities of the collateral circulation in the spinal cord, but also on the location, on the extent and the length of the ischemic focus. The commonly used protocols and clear recommendations on the treatment of vascular myelopathies are lacking; the degree of evidence of the applied programs of rehabilitation therapy corresponds to classes II–IV. The important direction in the rehabilitation of patients with acutely developing neurological deficit is the obligatory participation of the dedicated specialists within the cross-disciplinary teams at all the stages of rehabilitation.

ADDITIONAL INFORMATION

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Consent for publication. A written voluntary informed consent was obtained from the patient to publish

a description of the clinical case in the journal "Journal of Clinical Practice", including the use of his medical data (results of examination, treatment and observation) for scientific purposes (date of signing 11.03.2022).

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