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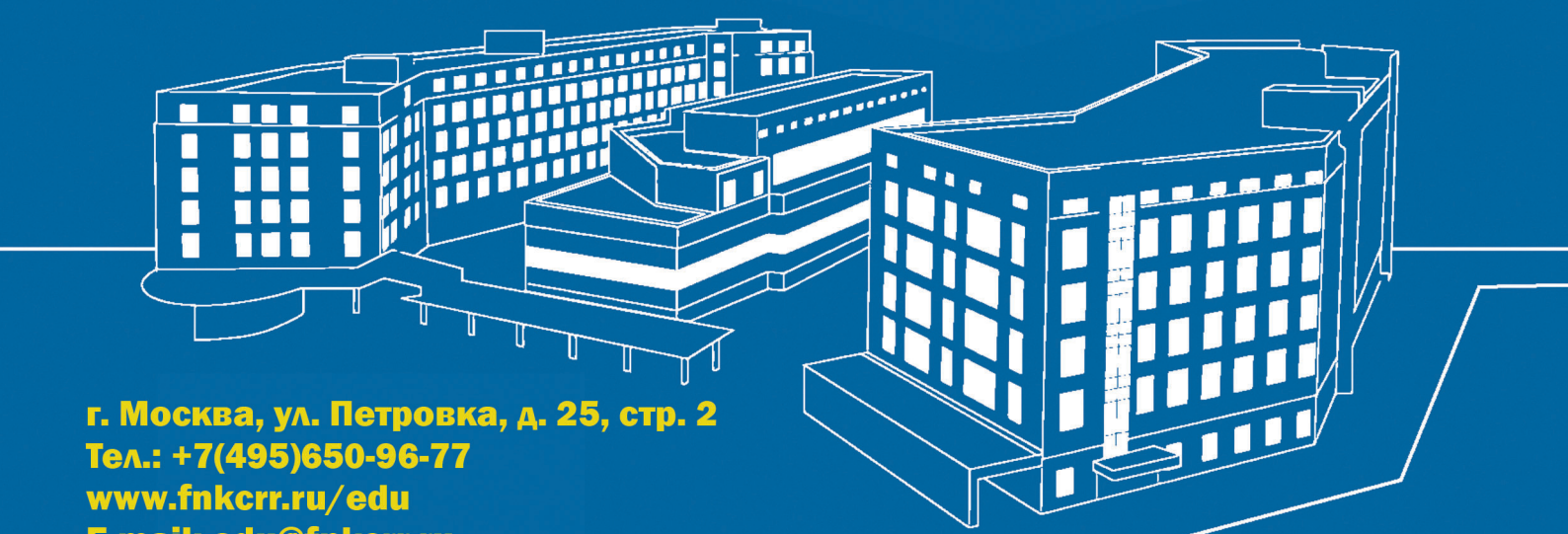

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Choice of Respiratory Support During Cardiac Bypass in Cardiac Surgical Patients (Pilot Study)

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Выбор тактики респираторной поддержки в период искусственного кровообращения у кардиохирургических пациентов (пилотное исследование)

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Summary

Currently, there is no uniform respiratory support strategy during cardiopulmonary bypass (CPB) in cardiac anesthesiology.

The aim of the study was to examine possible variants of respiratory support during CPB and determine the most effective technique capable to reduce the incidence of postoperative pulmonary complications.

Material and methods. Ninety cardiac surgery patients were enrolled in the pilot study and divided into groups (CPAP, VC, and apnea). In the CPAP group, positive airway pressure of + 5 cm H_2O was maintained during CPB. The VC group patients underwent mechanical ventilation during CPB with a reduced tidal volume of 3 mL/kg, respiratory rate of 6/min, and REER of + 5 cm H_2O. In the apnea group, patients received no respiratory support (non-rebreathing system).

Results. In both the apnea and CPAP (constant positive airway pressure) group, there was a decrease in oxygenation index (OI) at the end of the CPB compared with baseline values. In the apnea group, the OI dropped from 316.31±81.76 to 230.10±102.48, while in the CPAP group it decreased from 319.37±80.01 to 223.17±152.36 (P<0.001). No significant changes in this parameter were observed in the VC group. The frequency of recruitment maneuvers after CPB to correct the impaired respiratory oxygenation was maximal in patients from apnea group (22 cases (73%) versus 13 cases (43%) in the CPAP group and 5 cases (16%) in the VC group) (P<0.001). Frequency of pulmonary atelectasis on chest radiology in postoperative period was 47, 37, 10% in apnea, CPAP, and VC groups, respectively, and the difference was also significant (P=0.006).

Conclusion. Low-volume ventilation is the preferable method of respiratory support in cardiac surgery patients during CPB.

Keywords: respiratory support; cardiopulmonary bypass; mechanical lung ventilation; pulmonary complications; cardiac surgery; prevention of complications

Conflict of interest. The authors declare no conflict of interest.

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Introduction

According to clinical research results, the search for an optimal respiratory strategy is currently relevant when developing organ protective techniques in cardiac anesthesiology, particularly those aimed at protecting the lung during cardiopulmonary bypass (CPB).

However, a unified concept of respiratory support has not yet been developed. This is corroborated by surveys of anesthesiologists world-wide showing that in most centers (75%) ventilation during CPB is discontinued [1, 2], while in the remaining centers the main types of respiratory support during CPB include CPAP with various pressure levels (from 5 to 15 cm H_2O) and low-frequency low-volume ventilation [1–4].

Previously, we reported the results of two strategies of respiratory management of patients during CPB [5]. Here, based on previous and novel data, we present and compare the results of three possible strategies.

The aim of this pilot study was to examine possible strategies of respiratory support during CPB for identifying the most effective technique capable of reducing the incidence of postoperative pulmonary complications.

Material and Methods

Study design.

It was a prospective pilot study with parallel groups approved by the Local Ethical Committee of Sechenov University.

Inclusion/exclusion criteria.

Patients who met the following criteria were included in the study:

- 18 years of age or older;
- signed informed consent;
- elective primary cardiac surgery with cardioplegia and CPB.

Patients were excluded from the study if they refused to participate for any reason at any stage of the study.

The non-inclusion criteria were:

- elective thoracotomy with single-lung ventilation
- mechanical ventilation prior to surgery
- history of lung resection or pneumonectomy
- pregnancy.

The study endpoints.

The primary endpoint of respiratory support efficacy during CPB was the oxygenation index (OI, calculated as PaO_2/FiO_2) at different stages of surgery:

T1 — after tracheal intubation and the start of ventilation

T2 — before the start of CPB

T3 — after the CPB completion

T4 — the end of surgery

T5 — immediately after the admission to ICU

T6 — 6 hours after the admission to ICU

T7 — 12 hours after the admission to ICU.

Secondary endpoints included frequency of postoperative respiratory complications (atelectasis, pneumonia, etc.), the need and number of recruiting lung maneuvers during surgery and in ICU, duration of postoperative ventilation, frequency of noninvasive ventilation after tracheal extubation, cases of tracheal reintubation, length of stay in ICU, length of stay in the hospital, and mortality.

In addition, the volume of pulmonary extravascular fluid (PEVF) was assessed in selected patients of each group using the transpulmonary thermodilution technique. For this purpose, the right internal jugular vein was catheterized, a catheter with a PICCO 5F 20 cm thermistor was inserted into the femoral artery, and then during T2 and T3 stages of surgery the PEVF was measured using PICCOplus (PULSION Medical Systems, Germany) device.

Study groups and methods.

All patients recruited for the study were assigned to one of the three study groups using the envelope method. The patients, their attending physicians (in case they were not members of the surgical team), and intensive care unit physicians were «blinded» in this study.

In group 1 the constant positive airway pressure (CPAP, *n*=30) of +5 cm H_2O was maintained during CPB using the GE Avance CS2 anesthesia machine (USA).

In group 2 (volume control [VC], *n*=30), the patients received low-volume lung ventilation (up to 3 ml/kg of ideal body weight) during CPB, with RR of 6/min, PEEP + 5 cm H_2O using the GE Avance CS2 (USA) anesthesia machine.

In group 3 (apnea, *n*=30), the patients did not receive respiratory support.

In the respiratory support groups, oxygen-air mixture with FiO_2 21% was used during CPB.

During the surgery (except for CPB), all patients underwent protective ventilation with volume control using the GE Avance CS2 (USA) anesthesia machine. The target parameters were Vt = 6–8 ml/kg of ideal body weight, I/E = 1:2, RR = 12–16/min, PEEP = 4–8 cm H_2O, FiO_2 of breathing mixture = 50%, $EtCO_2$ = 34–36 mmHg. Peak airway pressure did not exceed 30 cm H_2O.

Protective ventilation was performed in ICU using Puritan Bennett 840 (Medtronic, USA), Dräger Savina 300 (Dräger, Germany) machines with Vt = 6–8 ml/kg of ideal body weight, I:E = 1:2, RR (respiratory rate) and MV (minute ventilation) were chosen depending on the results of arterial blood gases on admission, PEEP was 6–8 cm H_2O, FiO_2 of

breathing mixture was 50%. Peak airway pressure did not exceed 30 cm H_2O.

Cardiopulmonary bypass was performed with S-3 machine with integrated CDI500 real-time gas analyzer and Dideco 703 oxygenator. Blood cardioplegia according to Calafiore was used to protect myocardium during aortic clamping. Volumetric perfusion rate was chosen depending on patient's body surface area and its values ranged from 4.3 to 5.3 L/min. Perfusion was performed in normothermia mode (body temperature at least 35.3°C). When performing surgery on the aortic arch, hypothermia was applied; when the temperature reached 25°C, circulatory arrest was initiated and antegrade cerebral perfusion of 10 ml/kg/min was performed under the control of cerebral oximetry.

Statistical analysis.

The statistical analysis of the data was done using the Statistica 10 and jamovi 2.2.5 software. Data distribution was tested using the Shapiro–Wilk criterion. The results were presented using median and interquartile range or mean and standard deviation, where appropriate. When testing statistical hypotheses, the critical level of significance was set at P=0.05. For comparison of the obtained results, we used analysis of variance (Student test with Bonferroni correction), Kruskal–Wallis test, Friedman test with Durbin–Conover paired comparison test, depending on the type of data distribution and the type of analysis. Pearson correlation test or Spearman rank correlation coefficient were used to evaluate linear relationship between the variables. Fisher exact test was used to compare the frequency of complications between the groups.

Results

The characteristics of the three study groups are summarized in Table 1.

Data from the Table 1 shows that the groups do not differ in the specified parameters.

The changes in oxygenation index (OI) in groups according to the stage of the surgery are shown in Table 2.

The intragroup analysis of each group, has demonstrated no significant decrease of the OI compared with the VC group (331.43±55.07 at T1) at all study stages.

On the contrary, decrease in OI values was found in the CPAP group compared with the outcome at stages T3 and T4 (P<0.001) (Table 2).

The largest negative changes in OI was recorded in the apnea group where it dropped significantly vs the baseline values at all stages after the end of CPB (T3) (P<0.001), except for T7 (P=0.21) (Table 2).

On intergroup analysis of OI values, no significant differences were noted until the T3 stage. In turn, at the T3 stage (after CPB), we found a significant difference (P=0.02), with the maximum OI values found in the VC group (289.60±100.32), while in the CPAP and apnea group they were significantly (223.17±152.36 and 230.10±102.48, respectively). Similar differences persisted at all further stages of the study (T4–T7), see Table 2.

The mean values of dynamic compliance in the patients of the study groups are presented in Table 3.

A decrease in compliance was observed in the apnea group (P<0.001), and a significant difference was also found between all three studied groups at the end of surgery (P=0.005 as per univariate analysis of variance for independent groups).

Regardless of the study group, all patients in the postoperative period were found to have fluid in the pleural cavity according to chest radiography or ultrasound. However, the necessity of pleural puncture was not always obvious and depended on the volume of the fluid. Thus, pleural puncture was necessary in 13 patients (43%) in the apnea group, 12 (40%) in the CPAP group, and 8 (26%) in the VC group (P=0.37 according to χ^2-test for three groups. The Fischer exact pair test was used to check the significance of differences between the studied groups and yielded the following results: for apnea-VC comparison P=0.27, for CPAP-VC comparison P=0.41, and for apnea-CPAP comparison P=1.

According to chest radiography, the proportion of patients with postoperative atelectasis in the apnea, CPAP, and VC groups was 47%, 36.6%, and 10%, respectively (P=0.006 according to χ^2-test for three groups), while the Fisher exact test yielded P=0.003 for apnea-VC, P=0.03 for CPAP-VC, and P=0.6 for apnea-CPAP comparisons.

The recruitment maneuvers after CPB completion (T3) for correction of impaired oxygenation function were most frequently used in patients of apnea group (n=22, 73%), CPR group (n=13, 43%), and VC group (n=5, 16%) (P<0.001 according to χ^2-test for three groups), while Fisher's exact test yielded P<0.001 for apnea-VC, P=0.47 for CPAP-VC, and P=0.03 for apnea-CPAP paired comparisons.

Similar results were obtained in the postoperative period: the frequency of the «lung opening» technique in the apnea group was 66%, in the CPAP group, 26%, and in the VC group, 7% (P<0.001 according to the χ^2-test for three groups). The Fisher exact test results were as following: P<0.001 for apnea-VC, P=0.07 for CPAP-VC, and P=0.004 for apnea-CPAP paired comparison.

Noninvasive lung ventilation (NILV) sessions after the cessation of mechanical ventilation were required in two patients in the CPAP group, whereas there were no such patients in the VC group and 9

Table 1. Demographic and clinical characteristics of the studied patients (*M*±σ).

Characteristic	Values in groups			*P*
	CPAP (*n*=30)	VC (*n*=30)	Apnea (*n*=30)	
Sex	70% male (*n*=21), 30% female (*n*=9)	60% male (*n*=18), 40% female (*n*=12)	63% male (*n*=19), 37% female (*n*=11)	0.71
Mean age (years)	53.33±13.59	55.77±16.90	55.20±14.67	0.57
Obstructive lung function impairment, *n* (%)	12 (40%)	11 (36%)	13 (43%)	0.25
History of diabetes mellitus, *n* (%)	3 (10%)	3 (10%)	4 (13%)	0.89
Duration of CPB, min	141.83±56.18	157.10±49.17	144.26±46.30	0.25
History of hypertension	12 (40%)	15 (50%)	14 (47%)	0.87
History of coronary heart disease, *n* (%)	12 (40%)	15 (50%)	13 (43%)	0.73
History of COPD, *n* (%)	3 (10%)	3 (10%)	2 (7%)	0.87
History of MI, *n* (%)	6 (20%)	5 (17%)	5 (17%)	0.92
Surgery, *n* (%):				
• AVR	12 (40%)	15 (50%)	11 (37%)	
• MVR	6 (20%)	3 (10%)	4 (13%)	
• CABG	3 (10%)	9 (30%)	8 (27%)	
• ITAG	9 (30%)	3 (10%)	5 (17%)	
• Bentall-De Bono procedure	7 (23%)	5 (16%)	5 (16%)	
• Aortic arch replacement	2 (6%)	2 (6%)	1 (3%)	
• David procedure	1 (3%)	2 (6%)	1 (3%)	

Table 2. Changes in the oxygenation index at different stages of surgery in the studied groups (*M*±σ).

Group	Stage of surgery						
	T1	T2	T3	T4	T5	T6	T7
CPAP	319.37±80.01	319.43±56.48	223.17±152.36	275.27±90.03	324.03±115.81	319.67±61.18	326.77±60.44
VC	331.43±55.07	333.13±64.93	289.60±100.32	318.70±73.81	321.90±68.91	330.47±62.12	337.77±70.13
Apnea	316.31±81.76	338.53±71.55	230.10±102.48	199.20±73.22	242.70±59.82	237.03±24.88	283.04±40.26
P-value	0.98	0.32	0.02	<0.001	<0.001	<0.001	<0.001

Table 3. Dynamic compliance at various stages of surgery in patients of the study groups (*M*±σ).

Group	Compliance		*P*-value
	At the beginning of the surgery	At the end of the surgery	
CPAP	42.8±9.37 ml/mm H_2O	41.3±12.5 ml/mm H_2O	0.26
VC	40.1±9.1 ml/mm H_2O	39.7±8.07 ml/mm H_2O	0.35
Apnea	40.9±7.2 ml/mm H_2O	32.6±11.3 ml/mm H_2O	<0.001
P-value	0.66	0.005	

Table 4. Changes in pulmonary extravascular fluid (PEVF) volume (*M*±σ).

Group	PEVF volume	
	before CPB	after CPB
CPAP	3.07±0.29 ml/kg	5.60±0.94 ml/kg
VC	2.32±0.30 ml/kg	4.27±0.70 ml/kg
Apnea	2.58±0.49 ml/kg	6.25±0.86 ml/kg

(30%) of them in the apnea group. Tracheal reintubation and reinitiation of mechanical ventilation due to respiratory failure were required only in one patient in the CPAP group and two patients in the apnea group.

There were no differences in the duration of postoperative ventilation between the study groups.

Total pulmonary extravascular fluid was measured in 7 patients per each study group (Table 4).

According to the data obtained, during CPB, the PEVF volume increased compared to the baseline values in all study groups. The largest increase of PEVF volume (by 152%) was recorded in the apnea group, with the mean value of 6.25±0.86 ml/kg after CPB. In the VC and CPAP group, the increase in PEVF volume was much less dramatic (by 86.6% and 85.6%, respectively). The mean values of this parameter were 4.27±0.70 ml/kg and 5.6±0.94 ml/kg, respectively, at the T3 stage.

The length of stay in the ICU for all groups was almost the same (31.76±12.68 h in the apnea group, 31.93±14.25 h in the CPAP group, and 30.70±11.59 h in the VC group).

The mean length of hospitalization after surgery was 15.86±5.12 days in the apnea group, 16.53±6.48 days in the CPAP group, and 13.57±5.38 days in the VC group and did not differ between the groups.

Discussion

Lung atelectasis is known to be one of the factors affecting pulmonary oxygenation function in the postoperative period in cardiac surgery patients who have undergone cardiac bypass. Accumulation of extravascular lung fluid during CPB is another factor influencing venous blood oxygenation [6–10].

Obviously, there are also other causes of postoperative atelectasis such as inadequate ventilation parameters, severe pain syndrome due to sternum retraction, mediastinal and pleural drains [11, 12]. Immobilization, pain increase on deep inspiration and cough also negatively affects the breathing act [13] by making it superficial thus reducing the alveolar ventilation and the number of non-ventilated lung segments and further increasing the high risk of postoperative pulmonary complications [12]. The type of surgical access can also influence the incidence of postoperative respiratory complications. Thus, according to the study of V. Shmyrev et al., respiratory failure during mitral valve correction using minimally invasive access was found in 7.4% of patients, whereas respiratory failure did not develop when sternotomy access was chosen. According to the authors, atelectasis (even total) of the right lung was one of the most frequent causes of this complication in minimally invasive access group [14].

In this study such factors were minimized, as all patients in the ICU received protective ventilation until tracheal extubation, and, if necessary, non-invasive assisted ventilation after extubation. In addition, postoperative pain was continuously controlled in the ICU and multimodal analgesia was modified depending on its severity (target values < 4 points according to the visual analogue scale or < 2 points according to visual scale). Multimodal analgesia allowed achieving necessary level of analgesia with minimal side effects [15]. For postoperative analgesia, intravenous ketorolac 30 mg 2–3 times daily and paracetamol 1 g continuously for 15 min up to 4 times daily were used in combination with the opioid analgesics such as intravenous promedol 20 mg or tramadol 100 mg depending on severity.

According to some researchers, the frequency of pulmonary atelectasis development after surgery with CPB can reach 54–92% [4], which agrees with our results. We found postoperative atelectasis in 47% of patients in patients without respiratory support during CPB, which is significantly more frequent than in those who underwent CPAP or low-volume ventilation (36.6% in CPAP and 10% in VC groups). Different severity of atelectasis in the studied groups is an important factor affecting various parameters characterizing the pulmonary system function. Thus, oxygenation index after CPB and surgery was significantly higher in patients who were on continuous low-volume ventilation (VC group) than in CPAP and apnea group. Similar results were reported by J. Gagnon et al. who compared 2 groups of patients, one of them ventilated with Vt = 3 ml/kg and PEEP = 0 cmH_2O during CPB, and the other group was not on ventilator during the CPB. In the group with low-volume ventilation higher OI values and lower length of stay with no difference in the frequency of postoperative complications were found [16]. L. S. Nguyen et al. performed a study with a very similar design which compared groups of patients identical to those participating in the previous one, but aimed at evaluating the rate of atelectasis development. According to the results, the incidence of postoperative pulmonary complications (atelectasis) in these groups did not differ [3]. On the contrary, we revealed differences in the incidence of atelectasis development which was 47% in apnea group, 36.6% in the CPAP group, and 10% in the VC group (P=0.006).

In patients of apnea group compared with the other groups much more corrective measures to achieve normal oxygenation function were taken. They included higher oxygen fraction used immediately after CPB and more frequent recruiting maneuvers. Moreover, decreased oxygenating function of lung in patients of apnea group could not always be corrected in the operating room and later in ICU. In these patients, higher frequency of recruiting maneuvers and assisted ventilation after tracheal extubation was observed.

Another factor impairing the pulmonary oxygenation function, as mentioned above, can be the accumulation of PEVF which depends both on the preoperative infusion therapy and on hemodilution during CPB. The patients of the studied groups did not differ in water balance and hematocrit value during CPB. The only difference was in the respiratory strategy used during CPB.

One more aspect merits mentioning. The use of apnea and CPAP during the CPB led to a greater accumulation of PEVF compared with low-volume ventilation. This, in turn, led to a significant decrease of compliance parameters, and in the apnea group this reduction was significant (P<0.001). In other words, under equal conditions (equal water balance and degree of hemodilution), respiratory strategy during CPB affects the accumulation of pulmonary extravascular fluid. This is supported by the results of correlation analysis between the obtained values of OI and volume of PEVF at the stage after CPB in the studied groups. The analysis showed an intermediate strength negative correlation (R=–0.6512, P<0.05), which proves the importance of PEVF accumulation in decreasing the oxygenation index.

Our data correspond to the results obtained in the study of K.Iha et al. who demonstrated extravascular fluid accumulation in the lungs at different time stages (2, 4, 8, 24 and 48 hours) after CPB surgery [17]. J.Boldt et al. measured the volume of PEVF 15 and 45 min after the end of CPB. According to their report, PEVF values increased after CPB, and PaO_2 values decreased [18].

Unfortunately, accumulation of pulmonary extravascular fluid is inevitable due to CPB, prolonged pulmonary ischemia with underlying limited collateral blood flow, mechanical impact on lung tissue in the operating field, massive transfusions. In this regard, it is crucial to use methods that reduce PEVF. According to our results, this can be improved by low-volume lung ventilation.

Another relevant issue when providing respiratory support during CPB could be uncomfortable conditions for the surgeon's work because lung motions can interfere with the stability of the surgical field. There is a report [3] that in 21.4% of cases, the surgical team requested to stop ventilatory support during the main stage of surgery. In our study, the surgeons reported some discomfort while performing surgery only in 10% when low-volume ventilation was used for respiratory support. Notably, there were no cases of switching from low-volume ventilation to CPAP or apnea during CPB at the surgeons' request.

Conclusion

Low-volume ventilation is the first-choice technique for respiratory support during CPB in cardiac surgery patients. This is demonstrated by:

— lack of significant decrease of oxygenation index in patients from low-volume ventilation group, in contrast to apnea and CPAP groups, at all study stages;

— less frequent development of atelectasis in the VC group (10% vs 36.6% in the CPAP group, and 47% in the apnea group);

— lower frequency of recruiting maneuvers for correction of oxygenation during surgery in the VC group (16% vs 43% in the CPAP group and vs 73% in the apnea group);

— reduced use of recruitment maneuvers for correction of oxygenation function after surgery in the VC group (7% vs 26% in the CPAP group and vs 66% in the apnea group).

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Prognostic Tests of Intolerance to Postpyloric Feeding in Early Acute Pancreatitis

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Прогностические тесты непереносимости постпилорического энтерального питания в раннюю фазу острого панкреатита

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Summary

Aim. To evaluate the effectiveness of postpyloric feeding in early predicted severe acute pancreatitis using acetaminophen absorption test and gastric emptying rate.

Material and methods. An open observational prospective cohort study in the intensive care unit of OAO «Neftyanik» hospital in the city of Tyumen, Russia, from November 2012 to October 2018 was performed. All included patients were diagnosed with predicted severe acute pancreatitis (inclusion criterion). The rate of gastric emptying was assessed using an original ultrasound technique which involved measuring the fluid volume 30 min and 60 min after administering of 200 mL aliquote of water into the stomach. Acetaminophen absorption test was performed according to the following procedure: 0.5 g of acetaminophen was administered through the nasojunal tube placed 30–40 cm distal to the Treitz ligament using endoscope, the blood level of the drug was measured 5–20 min later.

Results. Gastric fluid volume at 60 min (OR=1.049, 95% CI: 1.028–1.07, P<0.001 with AUC=0.921, 95% CI: 0.808–0.944 and cutoff value of 73.5) was a significant predictor of residual gastric volume ⩾500 mL/d and intolerance to enteral feeding through the nasojejunal tube (OR=1.023, 95% CI: 1.009–1.036, P=0.001 with AUC 0.752, 95% CI: 0.629–0.875, with cutoff value of 79.5). The acetaminophen small intestine absorption test was reliable in predicting the residual gastric volume ⩾500 mL/d for the early period of disease. The acetaminophen absorption test was a significant predictor of intolerance to enteral feeding through the nasojejunal tube only in patients with severe acute pancreatitis (OR=0.834, 95% CI: 0.733–0.949, P<0.001 with AUC=0.894, 95% CI: 0.770–0.1 with cutoff value of 14.6).

Conclusion. Throughout the early period of acute pancreatitis, gastric fluid volume measured 60 min after the administration of 200 mL of water, accurately predicts the residual gastric volume ⩾500 mL/day. Acetaminophen absorption test in the small intestine can reliably predict intolerance to postpyloric feeding only for patients with severe acute pancreatitis.

Keywords: pancreatitis; enteral feeding; feeding intolerance; gastric ultrasound; acetaminophen

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Early phase of acute pancreatitis (AP) is always associated with acute injury to the gastrointestinal tract, which can result in feeding intolerance (FI) syndrome, where adequate enteral feeding is impossible due to a clinical reason (vomiting, high residual gastric volume (RGV), diarrhea, meteorism, gastrointestinal bleeding, intestinal fistula, etc.) [1]. There are no clearly defined constellation of signs and symptoms or quantitative characteristics to support and classify the FI. Enteral delivery of nutrients can be carried out through nasogastric (NG) or nasojejunal (NJ) tube. Most studies on early enteral nutrition (EN) in AP were performed before a new form of AP, moderately severe (MSAP), was identified in 2012 [2]. The form of disease is known to significantly affect the tolerance of early EP in the early AP [3], and existing predictors of severe disease are not always capable of correct prediction of the form of disease [4], which complicates the choice of nutrient delivery way. The FI is considered to be present if the EP is less than 20 kcal/kg body weight per day for the first 72 h or it has to be discontinued due to some reason [1]. At present there are enough methods capable to estimate the gastric emptying in seriously ill patients [5]. However, only one of them, paracetamol absorption test, allows to assess not only the gastric emptying, but also the intestinal absorption of nutrients [6, 7], which is important because even with minimal functional changes of the intestine its ability to absorb nutrients, drugs (in particular, acetaminophen) is reduced [8]. If the necessary equipment is available, it is not difficult to place a nasojejunal tube 30–50 cm distal to the Treitz ligament and deliver the nutrients into the small intestine, but no method can determine the extent of absorption. Finding a simple and reproducible routine test capable of determining the tolerability of post-pyloric feeding in the early phase of predicted severe acute pancreatitis would help to improve the outcome in these patients.

The aim of the study was to evaluate the tolerability of post-pyloric feeding in the early phase of predicted severe acute pancreatitis using acetaminophen absorption test and gastric emptying rate assessment.

Material and Methods

An open observational prospective cohort study was conducted in the intensive care unit of OAO «Neftyanik» hospital in Tyumen from November 2012 to October 2018.

Inclusion criteria were diagnosed AP and at least one predictor of severe disease. Exclusion criteria were age over 80 years, terminal chronic diseases, pancreatogenic shock, lactate > 4 mmol/L, need for adrenomimetics to maintain mean arterial pressure > 70 mm Hg, hepatic failure, acetaminophen (paracetamol) intolerance. The diagnosis of AP was made based on typical clinical presentation, laboratory and instrumental findings [2]. Predictors associated with severe AP included C-reactive protein (CRP) level > 150 mg/L, APACHE (Acute Physiology and Chronic Health Evaluation) II score >8 points and SOFA (Sequential Organ Failure Assessment) score >2 points [9]. The rate of gastric emptying was assessed using an original ultrasound technique from 08:00 to 12:00 a.m. by two intensive care physicians, who had completed a 6-hour gastrointestinal ultrasound training course. Nasogastric tube was inserted while the patient was in the supine position with the head elevated at 30°, the stomach was emptied and then 200 ml of water was introduced. Immediately after introduction and 30 and 60 minutes later, a Mindray M7 portable ultrasound scanner (Shenzhen Mindray Bio-Medical Electronics Co., Ltd., China), with the C5-2s convex transducer performed ultrasound scan of stomach in B-mode in two mutually perpendicular planes, transverse and longitudinal, with subsequent calculation of volume (ml) using the formula A×B×C×0.523. After the last volume determination, gastric contents were evacuated through the NG tube and an acetaminophen absorption test (AAT) was performed. Through a 7 CH nasojejunal tube installed using a gastroscope, acetaminophen 0.5 g («Perfalgan», Bristol-Myers Squibb, France) was introduced 30–50 cm distal to the Treitz ligament, then 5 ml of venous blood was drawn within 5 to 20 minutes after the drug administration [10]. Acetaminophen concentration in blood serum was determined using an AxSYM (Abbott Laboratories, USA) immunoassay analyzer, using the fluorescent polarization immunoassay. Subsequently, the daily balance of administered (water + food) and excreted through the NG tube volume was recorded. Standard isocaloric enteric nutrition formula enriched with dietary fiber (Nutricom Standard Fiber, Bbraun, Germany) was administered into the tube. Additionally, the patient was able to drink water if necessary. The following criteria for feeding intolerance were used: loss of ⩾500 ml through NG tube either momentarily or during a day, increased pain, abdominal bloating, diarrhea (loose stool more than 3 times per day), nausea, and vomiting. If intolerance occurred, the rate of infusion of the formula was reduced by 50% or the infusion was discontinued. Later, after the symptoms of intolerance had subsided, the rate was gradually increased to the proper level. All operated patients underwent abdominal drainage through a laparoscopic access, under total intravenous anesthesia with muscular relaxation and lung ventilation. The study was performed if >6 hours elapsed after surgery. We included 39 patients, some of whom had undergone one to three exami-

Table 1. Clinical and laboratory data in the studied groups.

Parameter	Values in the groups							
	1 (*n*=62)	2 (*n*=17)	3 (*n*=23)	4 (*n*=22)	*P* (for groups 2–4)	5 (*n*=34)	6 (*n*=28)	*P* (for groups 5, 6)
Sex. m/f	43/19	11/6	16/7	16/6		20/14	23/5	
Age, years	50 [37; 58]	46.4±12.4	52 [37; 58]	52 [37; 58]	0.919[e]	56 [44; 58]	44.4±13.5	0.103[g]
P value (Shapiro–Wilk test)	<0.001	0.351	0.043	0.041		<0.001	0.103	
BMI[a], kg/m^2	29.3 [24.1; 31.1]	27.6±4.8	28.3±4.4	28.1±4.6	0.954[f]	29.6 [26.1; 30.9]	29.0 [24.1; 32.8]	0.635[g]
P value (Shapiro–Wilk test)	0.003	0.6	0.236	0.131		0.001	0.01	
APACHE-II[b], points	10 [7; 13]	8.9±4.3	11.1±4.8	9 [6; 13]	0.447[e]	12[10;15]	7.3±3.3	<0.001[g]
P value (Shapiro–Wilk test)	<0.001	0.716	0.159	<0.001		0.001	0.091	
SOFA[c], points	2 [1; 3]	2 [1; 2]	2.5 [2; 4]	2 [0; 4]	0.142[e]	3 [2; 4]	1 [0; 2]	<0.001[g]
P value (Shapiro–Wilk test)	<0.001	0.001	<0.001	<0.001		<0.001	<0.001	
CRP[d], mg/l	154.3±58.8	94.7±52.0	179±40.3	175.5±46.9	0.001[f]	168.3±57.1	137.9±57.5	0.038[h]
P value (Shapiro–Wilk test)	0.175	0.626	0.116	0.31		0.404	0.441	
Lung ventilation, *n* (%)	8/(12.9)	1(5.9)	3(13)	4(18.2)	0.324[j]	9 (26.5)	0 (0)	0.003[i]
Moderate severe disease, *n* (%)	34/28 (54/46)	9/8 (53/47)	13/10 (56/44)	12/10 (55/45)	0.974[j]	34/0 (100/0)	0/28 (0/100)	—
Surgery 6–12 h prior to the examination	27 (43.5)	7 (41.2)	9 (39.1)	2 (9.1)	0.037[j]	9 (26.5)	9 (32.1)	0.78[i]

Note. [a] — body mass index; [b] — Acute Physiology And Chronic Health Evaluation II; [c] — Sequential Organ Failure Assessment; [d] — C-reactive protein; [e] — Kruskal–Wallis test; [f] — ANOVA; [g] — Mann–Whitney U-test; [h] — Student's test; [i] — Fisher's exact test; [j] – Pearson's χ^2 test.

Table 2. Frequency of etiological factors and comorbidities in the studied groups.

Parameter	Values in the groups							
	1 (*n*=62)	2 (*n*=17)	3 (*n*=23)	4 (*n*=22)	*P* (for groups 2–4)	5 (*n*=34)	6 (*n*=28)	*P* (for groups 5, 6)
Cholelithiasis, *n* (%)	5 (8.1)	1 (5.9)	2 (8.7)	2 (9.1)	0.926[b]	5 (14.7)	0 (0)	0.058[a]
Alimentary etiology, *n* (%)	19 (30.6)	9 (52.9)	13 (56.5)	13 (59.1)	0.929[b]	19 (55.8)	16 (57.1)	1.0[b]
Alcohol, *n* (%)	35 (56.5)	6 (35.3)	7 (30.4)	6 (27.3)	0.865[b]	10 (29.4)	9 (32.1)	1.0[a]
Other, *n* (%)	3 (4.8)	1 (5.9)	1 (4.3)	1 (4.5)	0.972[b]	0	3 (10.7)	0.87[a]
Hypertension, *n* (%)	29 (46.8)	7 (41.1)	11 (47.8)	11 (50.0)	0.854[b]	20 (58.8)	9 (32.1)	0.044[a]
Coronary heart disease, *n* (%)	13 (20.9)	3 (17.6)	5 (21.7)	5 (22.7)	0.922[b]	10 (29.4)	3 (10.7)	0.116[a]
Chronic heart failure, *n* (%)	11 (17.7)	3 (17.6)	3 (13.0)	3 (13.6)	0.91[b]	6 (17.6)	3 (10.7)	0.317[a]
Type 2 diabetes mellitus, *n* (%)	3 (4.8)	1 (5.9)	2 (8.7)	2 (9.1)	0.924[b]	5 (14.7)	0 (0)	0.243[a]
Other, *n* (%)	3 (4.8)	1 (5.9)	1 (4.3)	1 (4.5)	0.972[b]	0	3 (10.7)	0.087[a]

Note. [a] — Fisher's exact test; [b] — Pearson's χ^2 test.

nations. Six groups of parameters were identified. Group 1 included parameters for all days of the study (*n*=62), group 2 included investigations done during day 1 of ICU stay (*n*=17), group 3 comprised tests performed on days 2 and 3 (*n*=23), group 4 included tests carried out on days 4 and 5 (*n*=22), group 5 included patients who later progressed into severe AP (*n*=34), and group 6 included patients with moderate AP (*n*=28). The time after the last paracetamol administration was more than 24 h.

Statistical analysis was done using the SPSS 26.0 software package. The data distribution was assessed using the Shapiro–Wilk criterion, the data were presented as mean (*M*) with mean square deviation $M\pm\sigma$ or median (*Me*) with quartiles [Q25; Q75]. Parametric and nonparametric criteria were used for intergroup comparison. We used logistic regression to identify variables with prognostic significance. Total explained variance was assessed using the Nagelkerke R^2 method, and the constant of the regression equation was indicated. The discriminant ability of parameters was determined by ROC-analysis based on maximum combined sensitivity and specificity of the model. Model quality was assessed using an expert scale of Area Under Curve (AUC) values: 0.9–1.0 was considered excellent; 0.8–0.9, very good; 0.7–0.8, good; 0.6–0.7, average, and 0.5–0.6, poor. The null hypothesis was rejected at $P<0.05$.

Results

As shown in Table 1, male patients outnumbered female ones; lung ventilation was used only in 8 patients, and the number of patients who progressed into severe disease later did not differ from the patients with moderate severe acute pancreatitis. The groups were comparable by age, sex, and body mass index. Groups 2, 3 and 4 were comparable in severity scores (APACHE II, SOFA). Patients in the group with subsequent severe disease were more

Table 3. Symptoms, signs and test of enteral feeding tolerance and balance.

Parameter	Values in the groups							
	1 (*n*=62)	2 (*n*=17)	3 (*n*=23)	4 (*n*=22)	*P* (for groups 2–4)	5 (*n*=34)	6 (*n*=28)	*P* (for groups 5, 6)
Pain, *n* (%)	20 (32.3)	9 (47.1)	2 (8.7)	2 (9.1)	0.003[f]	8 (23.5)	4 (14.3)	0.521[e]
Nausea/vomiting, *n* (%)	39 (62.9)	11 (64.7)	6 (26.1)	6 (27.3)	0.022[f]	16 (47.1)	7 (25)	0.113[e]
Abdominal bloating, *n* (%)	37 (59.7)	3 (17.6)	8 (34.8)	8 (36.4)	0.392[f]	18 (52.9)	1 (3.6)	<0.001[e]
Diarrhea, *n* (%)	1 (1.61)	1 (5.9)	0	0	0.26[f]	0 (0)	1 (3.6)	0.456[e]
Loss >500 ml/day, *n* (%)	25 (40.3)	9 (52.9)	9 (39.1)	7 (31.8)	0.224[f]	20 (58.8)	6 (21.4)	0.004[e]
At least 1 clinical sign of feeding intolerance, *n* (%)	36 (58)	16 (94.1)	11 (47.8)	9 (40.9)	0.002[f]	25 (73.5)	11 (39.3)	0.007[e]
Gastric fluid volume after administration of 200 ml of water	196 [186; 210]	194 [186; 219]	198 [194; 205]	192 [184; 210]	0.466[a]	197 [189; 210]	198.1±16.8	0.432[c]
P value (Shapiro–Wilk test)	0.003	0.031	0.31	0.039	—	0.014	0.056	—
V30, ml	119. 8±26.8	124.5±30.8	123.7±24.3	112±25.5	0.262[b]	130.2±24.2	107.5±24.8	0.001[d]
P value (Shapiro–Wilk test)	0.708	0.928	0.694	0.802	—	0.592	0.781	—
V60, ml	25 [0; 101]	84 [0; 104]	25 [0; 101]	0 [0; 84]	0.256[a]	84 [0; 104]	0 [0; 12]	0.001[c]
P value (Shapiro–Wilk test)	<0.001	0.006	<0.001	<0.001	—	0.001	<0.001	—
AAT, μg/ml	17.2±9.1	18.8±9.9	16.7±7.1	16.6±10.4	0.734[b]	10.4 [7.1; 18.3]	22.2±6.7	<0.001[c]
P value (Shapiro–Wilk test)	0.211	0.694	0.474	0.389	—	0.02	0.108	—
Fluid ingested, ml/day	300 [250; 500]	250 [250; 500]	300 [250; 350]	325 [250; 500]	0.717[a]	450 [250; 500]	275 [250; 300]	0.007[c]
P value (Shapiro–Wilk test)	<0.001	<0.001	0.002	0.003	—	<0.001	<0.001	—
Administered through the NJ tube, ml/day	500 [500; 700]	500 [350; 500]	500 [500; 500]	750 [700; 750]	<0.001[a]	500 [500; 700]	500 [500; 750]	0.282[c]
P value (Shapiro–Wilk test)	0.001	0.015	<0.001	<0.001	—	0.008	0.043	—
Loss through the NG tubey, ml/day	350 [150; 1000]	650 [50; 1000]	300 [75; 950]	275 [180; 1100]	0.73[a]	722±482	175 [50; 400]	0.001[c]
P value (Shapiro–Wilk test)	<0.001	0.02	0.005	0.001	—	0.092	<0.001	—
Balance between the enterally administered and lost through the NG tube, ml/day	500 [–50; 800]	173.5±469	525 [–50; 800]	750 [–50; 950]	0.065[a]	0 [–100; 500]	800 [575; 837]	0.014[c]
P value (Shapiro–Wilk test)	0.001	0.063	0.031	0.038	—	0.012	<0.001	—

Note. [a] — Kruskal–Wallis test; [b] — ANOVA; [c] — Mann–Whitney *U*-test; [d] — Student's *t*-test; [e] — Fisher's exact test; [f] — Pearson's χ^2 test; V30 — gastric fluid volume after 30 min; V60 — gastric fluid volume after 1 h; AAT — acetaminophen absorption test.

severely ill than those with moderate severe disease. The proportion of patients who were examined within 6 and 12 h after surgery was 43.5%.

The most frequent etiology of AP was alimentary cause (30.6%). Hypertension was the most common comorbidity (46.8%) (Table 2).

The volume of nutrition administered through the NJ tube in group 4 was significantly greater than in groups 2 and 3, but there were no significant intergroup differences in the volume of orally ingested fluid, the daily loss through the NG tube, and the daily balance of enterally administered and excreted through NG tube (Table 3). Gastric fluid volume during gastric evacuation test at 30 and 60 minutes, as well as AAT results did not differ significantly between groups 2,3, and 4. Significant differences were found in APACHE II, SOFA scale scores, CRP level, proportion of patients with hypertension, frequency of lung ventilation, abdominal bloating, NG tube loss >500 ml/day, volume administered into the stomach, NG tube balance per day, residual gastric volume during the gastric evacuation test at 30 and 60 minutes, and AAT results between the group 5 (severe AP only) patients and those with MSAP (Tables 1–3).

Based on the obtained results, a binary model was formulated where the loss through the NG tube >500 ml/day was selected as the dependent variable.

In all groups except group 4, the percentage of exact responses was higher in the models where V30 and V60 min were the independent variables. The model with AAT as the independent variable was significant only in group 1 (Table 4). ROC analysis was performed to assess the quality of the models and determine the discriminatory values, the results are presented in Table 5.

ROC analysis corroborated the results obtained by logistic regression. The small intestinal AAT failed to predict nasogastric tube loss ⩾500 ml/day. We created another model where «at least one clinical sign of feeding intolerance» (nausea and vomiting, abdominal bloating, diarrhea, pain) was selected as the dependent binary variable (Table 6).

In almost all groups, the percentage of exact responses was higher with AAT. The second group's model for AAT was not significant because the pain

Table 4. Prognostic significance of acetaminophen absorption test and gastric evacuation capacity for the loss through nasogastric tube ⩾500 ml/day in the early phase of acute pancreatitis.

Independent variables	*P* value	Constant	B	Nagelkerke R^2	OR	95% confidence interval for the OR		Se	Sp	% exact responses
						Lower limit	Upper limit			
Group 1 (all days)										
AAT, μg/ml	0.01	6.63	–0.087	16.0	0.917	0.858	0.979	0.5	0.8	67.2
V30, мл	<0.001	–8.299	0.066	42.5	1.068	1.03	1.107	0.654	0.861	77.4
V60, мл	<0.001	–2.658	0.048	69.6	1.049	1.028	1.07	0.808	0.917	87.1
Group 2 (day 1)										
AAT, μg/ml	0.373	1.279	–0.48	6.5	0.953	0.857	1.06	0.8	0.286	58.8
V30, ml	0.071	–7.74	0.67	45.0	1.069	0.994	1.15	0.8	0.714	76.5
V60, ml	0.013	–2.27	0.045	67.0	1.046	1.01	1.084	85.7	0.9	88.2
Group 3 (days 2–3)										
AAT, μg/ml	0.264	0.889	–0.77	8.1	0.926	0.89	1.06	0.444	0.769	63.6
V30, ml	0.037	–14.679	0.114	56.0	1.12	1.077	1.246	0.556	0.929	78.3
V60, ml	0.008	–3.053	0.057	72.7	1.059	1.015	1.104	0.889	0.929	91.3
Group 4 (days 4–5)										
AAT, μg/ml	0.05	4.139	–0.428	75.5	0.652	0.425	1.0	1.0	0.867	90.9
V30, ml	0.052	–6.313	0.048	28.9	1.049	1.0	1.1	0.571	0.93	81.8
V60, ml	0.006	–2.637	0.041	64.0	1.042	1.012	1.73	0.857	0.933	90.9
Group 5 (severe AP)										
AAT, μg/ml	0.23	1.11	–0.051	6.0	0.951	0.875	1.033	0.8	0.154	54.5
V30, ml	0.043	–4.669	0.039	19.4	1.04	1.001	1.081	0.8	0.571	70.6
V60, ml	0.001	–2.036	0.039	56.5	1.04	1.016	1.064	0.9	0.786	85.3
Group 6 (MSAP)										
AAT, μg/ml	0.161	1.438	–0.132	13.4	0.876	0.728	1.054	0	0.955	75.0
V30, ml	0.031	–16.756	0.131	62.3	1.14	1.012	1.283	0.5	0.955	85.7
V60, ml	0.01	–3.356	0.064	75.3	1.067	1.016	1.12	0.833	1.0	96.4

Note. AAT — acetaminophen absorption test; V30 — gastric fluid volume after 30 min; V60 — gastric fluid volume after 1 h; B — regression equation coefficients; OR — odds ratio; Se — sensitivity; Sp — specificity.

Table 5. ROC analysis of acetaminophen absorption test and gastric evacuation capacity as a predictor of nasogastric tube loss ⩾500 mL/day.

Parameter	*P*-value	AUC	95% confidence interval for AUC		Cutoff value		
			Lower limit	Upper limit	Value	Se[a]	Sp[b]
Group 1 (all days)							
AAT, μg/ml	0.004	0.715	0.582	0.848	14.6	0.8	0.538
V30, ml	<0.001	0.830	0.723	0.936	111.5	0.885	0.611
V60, ml	<0.001	0.921	0.843	0.999	73.5	0.808	0.944
Group 2 (day 1)							
AAT, μg/ml	0.145	0.6	0.316	0.884	8.3	1.0	0.3
V30, ml	0.019	0.843	0.613	1.0	111.0	0.9	0.714
V60, ml	0.003	0.936	0.83	1.0	78.0	0.9	1.0
Group 3 (days 2–3)							
AAT, μg/ml	0.483	0.59	0.334	0.846	15.25	0.769	0.556
V30, ml	0.006	0.849	0.688	1.0	120.5	0.889	0.643
V60, ml	<0.001	0.948	0.852	1.0	52.5	0.889	0.929
Group 4 (days 4–5)							
AAT, μg/ml	0.113	0.665	0.477	0.854	8.0	0.923	0.5
V30, ml	0.062	0.752	0.489	1.0	126.5	0.714	0.933
V60, ml	0.005	0.881	0.7	1.0	54.5	0.857	0.933
Group 5 (severe AP)							
AAT, μg/ml	0.113	0.665	0.477	0.854	11.7	0.615	0.700
V30, ml	0.026	0.727	0.553	0.9	118.5	0.8	0.571
V60, ml	0.001	0.875	0.747	1.0	52.5	0.9	0.786
Group 6 (MSAP)							
AAT, μg/ml	0.263	0.652	0.454	0.849	15.8	0.909	1.0
V30, ml	0.001	0.936	0.846	1.0	112	1.0	0.818
V60, ml	0.002	0.99	0.722	1.0	62.5	0.833	1.0

Note. AAT — acetaminophen absorption test; V30 — gastric fluid volume after 30 min; V60 — gastric fluid volume after 1 h; Se — sensitivity; Sp — specificity; AUC — area under the curve.

Table 6. Prognostic significance of acetaminophen absorption test and gastric evacuation capacity for feeding intolerance in the early phase of acute pancreatitis.

Independent variables	*P* value	Constant	B	Nagelkerke R^2	OR	95% confidence interval for the OR		Se	Sp	% exact responses
						Lower limit	Upper limit			
Group 1 (all days)										
AAT, μg/ml	<0.001	3.367	–0.171	40.7	0.843	0.77	0.923	0.8	0.577	70.5
V30, ml	0.021	–2.842	0.027	13.0	1.027	1.004	1.051	0.833	0.423	66.1
V60, ml	0.001	–0.554	0.022	28.4	1.023	1.009	1.036	0.694	0.769	72.6
Group 2 (day 1)										
AAT, μg/ml	0.445	15.36	–0.433	50.2	0.649	0.214	1.971	1.0	0	94.1
V30, ml	0.463	–0.326	0.027	9.1	1.027	0.956	1.105	1.0	0	94.1
V60, ml	0.998	1.609	0.323	33.6	1.385	0	2.431	1.0	0	94.1
Group 3 (days 2–3)										
AAT, μg/ml	0.011	6.4	–0.296	71.5	0.744	0.592	0.936	0.889	1.0	95.5
V30, ml	0.22	–3.123	0.025	9.4	1.025	0.985	1.066	0.455	0.833	65.2
V60, ml	0.176	–0.612	0.013	10.9	1.013	0.994	1.032	0.636	0.667	65.2
Group 4 (days 4–5)										
AAT, μg/ml	0.006	7.589	–0.181	43.6	0.834	0.733	0.949	87.5	44.4	75.8
V30, ml	0.081	–1.677	0.38	21.4	1.039	0.995	1.084	0.556	0.846	72.7
V60, ml	0.014	–1.511	0.032	47.2	1.032	1.006	1.059	0.667	0.923	81.8
Group 5 (severe AP)										
AAT, μg/ml	0.006	3.722	–0.181	43.6	0.834	0.733	0.949	0.875	0.444	75.8
V30, ml	0.337	–1.176	0.017	4.2	1.017	0.982	1.054	1.0	0	73.5
V60, ml	0.04	–0.004	0.018	19.2	1.019	1.001	1.037	0.84	0.667	79.4
Group 6 (MSAP)										
AAT, μg/ml	0.083	2.355	–0.13	17.0	0.878	0.758	1.017	0.455	0.706	60.7
V30, ml	0.253	–2.544	0.019	6.6	1.02	0.986	1.054	0.273	0.941	67.9
V60, ml	0.073	–0.871	0.02	18.5	1.02	0.998	1.043	0.364	0.882	67.9

Note. AAT — acetaminophen absorption test; V30 — gastric fluid volume after 30 min; V60 — gastric fluid volume after 1 h; Se — sensitivity; Sp — specificity; B — regression equation coefficients; OR — odds ratio.

Table 7. ROC analysis of the prognostic significance of the acetaminophen absorption test and gastric evacuation capacity for feeding intolerance in the early phase of acute pancreatitis.

Parameter	*P*-value	AUC	95% confidence interval for AUC		Cutoff value		
			Lower limit	Upper limit	Value	Se[a]	Sp[b]
Group 1 (all days)							
AAT, μg/ml	<0.001	0.83	0.726	0.934	14.6	1.0	0.629
V30, ml	0.009	0.696	0.564	0.827	103.5	0.861	0.423
V60, ml	0.001	0.752	0.629	0.875	79.5	0.528	0.885
Group 2 (day 1)							
AAT, μg/ml	0.221	0.875	0.713	1.0	30.5	1.0	0.875
V30, ml	0.221	0.875	0.713	1.0	95.0	0.875	1.0
V60, ml	0.262	0.844	0.597	1.0	25	0.688	1.0
Group 3 (days 2–3)							
AAT, μg/ml	0.001	0.942	0.838	1.0	15.2	1.0	0.8
V30, ml	0.196	0.659	0.43	0.888	111.5	0.909	0.417
V60, ml	0.176	0.667	0.440	0.893	52.5	0.545	0.650
Group 4 (days 4–5)							
AAT, μg/ml	<0.001	0.983	0.941	1.0	12.25	1.0	0.9
V30, ml	0.077	0.726	0.501	0.952	100.0	0.889	0.385
V60, ml	0.01	0.829	0.636	1.0	12.5	0.778	0.846
Group 5 (severe AP)							
AAT, μg/ml	0.001	0.894	0.777	1.0	14.6	1.0	0.875
V30, ml	0.226	0.638	0.418	0.858	118.5	0.720	0.556
V60, ml	0.114	0.704	0.481	0.928	12.5	0.84	0.667
Group 6 (MSAP)							
AAT, μg/ml	0.095	0.69	0.484	0.896	17.6	0.706	0.364
V30, ml	0.279	0.623	0.399	0.847	105.0	0.727	0.529
V60, ml	0.269	0.626	0.398	0.853	81.5	0.364	1.0

Note. AAT — acetaminophen absorption test; V30 — gastric fluid volume after 30 min; V60 — gastric fluid volume after 1 h; Se — sensitivity; Sp — specificity; AUC — area under the curve.

syndrome in this group was most likely not related to food intake but was a clinical manifestation of the underlying disease and/or recent surgery (Table 1). To assess the quality of the models, ROC analysis was performed, which is shown in Table 7.

From the day 2 onward, the prognostic significance of the AAT increased in comparison with the residual gastric volume test. In patients with MSAP, the AAT test was not informative.

Discussion

Acute pancreatitis and its progression are associated with GI injury. As a result, serious systemic complications are triggered, since the impairment of intestinal barrier is associated with translocation of bacteria and inflammatory and toxic products produced in the intestinal wall, which can result in infection of necrotic pancreatic tissues, systemic inflammatory response, and sepsis [11, 12].

Non-inflammatory apoptosis of intestinal epithelial cells is known to occur every 4–5 days [13]. R. Tian et al. suggested that inflammatory factors such as tumor necrosis factor-α (TNF-α) and ischemia-reperfusion of the intestinal mucosa in AP caused severe oxidative stress accompanied by a significant increase in the apoptosis of intestinal mucosal cells [14].

Impairment of intestinal chemical barrier, which consists of mucins, antimicrobial peptides and other digestive enzymes, occurs. Mucins are the main component of the intestinal chemical barrier, covering enterocytes and forming the intestinal mucus layer. This is the first line of the intestinal mucosal barrier [15]. The intestine contains inner and outer mucosal layers, which accelerate nutrient absorption, provide adhesion sites for symbiotic bacteria, and limit pathogen binding to enterocytes [16]. Fishman et al. have shown that the loss of the mucosal layer, followed by disruption of the intestinal barrier, is an indirect effect of AP [17].

The biological intestinal barrier formed by the close adhesion of symbiotic bacteria (such as Bifidobacterium and Lactobacillus) to the mucosal surface of the intestinal epithelium, which counteracts pathogenic bacteria, is also compromised [18]. Symbiotic bacteria play a crucial role in regulating the function of the intestinal barrier and host health. Their functions include formation of the intestinal mucous layer and secretion of immunoglobulin A, building bacterial membrane barrier against foreign pathogens [19], regulation of intestinal paracellular permeability by enhancing intercellular connections with occlusion of intercellular spaces [20], expression of anti-inflammatory genes accompanied by a decrease in inflammation of the intestinal epithelium [20]. Kelly et al. found that bacteria-derived butyric acid can stabilize the expression of a hypoxia-inducible factor and its target genes, strengthening the intestinal barrier [21]. Multiple studies have shown that the gut microbiota is significantly altered in AP. A retrospective clinical study of 108 patients with AP showed a correlation between an increase in Enterococcus and a decrease in Bifidobacterium with the severity of inflammation, multiple organ failure, and the frequency of infectious complications [22]. Zhu et al. found that the number of beneficial bacteria, such as Blautia, decreases with increasing severity of AP and the degree of gut microflora impairment correlates with the severity of AP [23]. The impact of bacterial translocation on severe AP is very strong, because upon entering the bloodstream, bacteria and endotoxins can trigger a series of reactions, stimulating the production of various cytokines, such as TNF-α, IL-6 and IL-12, which promotes systemic inflammatory response and multiple organ failure [24]. Many studies have shown that bacteremia in severe AP is associated with an increased risk of infected pancreatic necrosis, multiple organ failure, and mortality [25–27].

The immune intestinal barrier, which consists of lymphoid tissue associated with the intestine and scattered immune cells, is also compromised. The intestinal lymph vessels link the gut and lungs, bypassing the portal circulation and directly transporting toxic components such as toxins, trypsin, activated cytokines and immune cells directly from the gut to the pulmonary circulation [28]. This connection is sometimes referred to as the «gut-mesentery-lung axis» and plays a key role in the development of acute lung injury in AP. Aydin et al. demonstrated 100% bacterial translocation to the mesenteric lymph node in AP [29]. Most infections in AP occur within the first week after the onset, which was an independent predictor of death [25]. Fritz et al. [30] in an experimental murine model after ileostomy and selective digestive system (either small or large intestines) decontamination with gentamicin and polymyxin B solution, induced experimental AP and showed that bacterial translocation occurred much more frequently from the small than from the large intestine. These findings highlight the importance of EF in the early stages of AP for maintaining the integrity of the small intestinal barrier. This is supported by reduced mortality, frequency of sepsis, number of surgical procedures and length of hospital stay in patients with AP and EF compared with complete parenteral nutrition [31–33]. Thus, EF is a key element of AP therapy [34] which supports normal activity of physiological intestinal barriers [35]. Enteral feeding reduces overall disease severity as measured by CRP level, severity of hyperglycemia, and promotes faster improvement (judged by the duration of systemic inflammatory response and length of hospital stay) [36]. Additional advantages of EF include decreased intra-abdominal pressure

and improved postoperative closure of pancreatic fistula [37]. The diagnosis of EF intolerance is controversial, as its development is impacted by the rate of formula administration, mode of administration (continuous or bolus), access (gastric or post-pyloric), ingredients, individual patient characteristics, intestinal motility, intra-abdominal pressure, and the skills of medical staff [38]. Several prospective randomized small-sample studies have shown that NG feeding is not inferior to the NJ one by assessing the incidence of infectious complications and analgesic use, as well as the changes in the levels of inflammatory markers [39, 40]. To date, there is no convincing evidence of superiority of any of these methods [41], so both are acceptable. Transition to post-pyloric feeding is recommended only in gastric feeding intolerance despite prokinetic drug administration or in patients with a high risk of aspiration. Routine use of feeding through the NJ tube is not supported [43, 44], as in rare cases it can cause severe dilatation of the small intestine and its perforation [1]. The survival of a critically ill patient is known to be related to the dietary energy content. This relationship can be represented as a U-shaped curve. Post-pyloric feeding improves survival in patients with high nutritional risk and gastric feeding intolerance [45]. Thus, objective assessment of feeding adequacy is a crucial aspect of initiating the NJ tube feeding. The identified patterns can be used as a guidance in daily practice of intensive care unit physicians to determine feeding tolerance through the NJ tube, helping verify patients with small intestinal feeding intolerance and timely introduce the parenteral feeding to maintain optimal energy and protein intake.

Conclusion

In the early phase of acute pancreatitis, plasma acetaminophen level, measured between minutes 5 and 20 after the administration of the drug into the small intestine at a dose of 0.5 g, and residual gastric volume values as measured 30 and 60 minutes after gastric administration of 200 ml of water, independently predict the feasibility of a complete post-pyloric feeding. In patients with severe acute pancreatitis, the acetaminophen absorption test is the best predictor of post-pyloric feeding intolerance diagnosed based on clinical signs and symptoms (nausea, vomiting, pain, abdominal bloating, diarrhea). Moreover, regardless of the disease form, on days 4-5 of the patient's stay in the intensive care unit this test helps effectively predict high daily residual gastric volumes (⩾500 ml/day). The gastric fluid volume determined 60 min after the administration of 200 ml of water posseses very good to excellent prognostic value for residual gastric volume ⩾500 ml/day during the entire early period of the disease, regardless of its future progression.

Authors' contribution to the work

Oleg G. Sivkov was responsible for developing the concept and design of the study, collecting data, analyzing and interpreting the data, as well as completing the manuscript and verification of essential intellectual content.

Ilya N. Leiderman was responsible for concept and design development, data interpretation, and verification of essential intellectual content.

Alexey O. Sivkov performed collection of material, statistical analysis of the data and participated in writing the draft version of the manuscript.

Anatoly A. Kolchanov collected material and performed statistical analysis of raw data.

Georgy D. Bashlykov was responsible for collection of material and statistical analysis of raw data.

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The Efficacy and Safety of Automatic Modes During Respiratory Support After Cardiac Surgery

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Респираторная поддержка после кардиохирургических операций: преимущества и безопасность автоматизированного управления

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Summary

Aims. To compare the efficacy and safety of semiautonomous Adaptive Support Ventilation (ASV) and fully automated (closed-loop, Intellivent-ASV) mechanical ventilation and oxygenation versus conventional mechanical ventilation mode during respiratory support in cardiac surgery patients.

Material and methods. In this study, 40 adult patients were ventilated by conventional mechanical ventilation managed by 8 physicians (control group), whereas other two groups patients were ventilated by Intellivent-ASV (n=40) or in a semiautomatic ASV mode (n=40). The groups received standard care, except for the modes of ventilation.

Results. In the Intellivent-ASV group, the number of manual changes in ventilator settings was significantly lower: 0 (0–0) versus 2 (2–3) (ASV) and 4 (3–5) in the control group (P<0.0001). There were significant differences in the duration of respiratory support in ICU which was 226±31 min (Intellivent group) vs 259±66 (ASV) and 271±78 min (control) (P=0.0042; P_{1-2}=0.0167; P_{1-3}=0.009). The Intellivent-ASV group patients received more protective ventilation than patients in the semiautomated and physician-controlled groups (lower values of driving pressure (6 (6–7) cm H_2O vs. 6 (6–7) and 7 (7–9) cm H_2O (P<0.0001)), tidal volume (6 (6–7) vs. 7 (7–7.7) and 7 (7–8) ml/kg/PBW (P<0.0001)), FiO_2 (26 (24–30)% vs. 34 (30–35)% and 34 (30–38)%) with no differences between the groups in paO_2/FiO_2. There were no significant differences between the groups in frequency of undesirable events and duration of ICU stay.

Conclusion. The use of intelligent technologies makes it possible to interactively individualize respiratory support, significantly reducing clinician's involvement in this process without compromising patient safety and the quality of ventilation.

Keywords: automatic weaning, Intellivent-ASV; intellectual modes of ventilation; ASV; cardiac surgery; intensive care

Conflict of interest. The authors declare no conflict of interest.

The full text version of the paper is available at www.reanimatology.com.

Introduction

Mechanical ventilation (MV) is an important and integral step in the rehabilitation of patients after open-heart surgery.

Current protocols and guidelines for rapid recovery after surgical interventions recommend striving to minimize the time of postoperative respiratory support. [1] It is becoming a worldwide trend to transfer the patient to spontaneous breathing after cardiac surgery after warming the patient up, achieving sufficient arterial gas exchange, hemodynamic stability and adequate hemostasis [2]. However, even during short-term ventilation support, it is important to follow basic principles of MV: safety, comfort, fast transition to assisted modes [3]. Clinicians pay great attention to safety of respiratory support, taking into consideration the possibility of ventilator-associated damage in

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initially intact lungs when setting damaging ventilatory support parameters such as respiratory volume more than 6 ml/kg of ideal (predicted) body weight or low PEEP [4].

Thus, present-time intensive care unit (ICU) physicians are under a heavy burden of compliance with all standards of protective mechanical ventilation for each patient. As the number of patients per physician is always more than one, keeping track of the ever-changing respiratory needs of a patient becomes very challenging. Contrary to popular belief, there is currently no convincing evidence in favor of using any particular ventilatory mode in clinical practice [2].

Improvements in ventilators and feedback (control systems) have made it possible to use «intelligent respiratory support technology», where devices continuously adapt to the patient's breathing patterns and respiratory needs. They provide patient-ventilator-patient feedback (working in a closed loop control), not only reducing the load on the medical staff, but often selecting the optimal parameters of ventilation with greater speed and accuracy [5]. In fact, the device can replace some functions of a physician in selecting the optimal ventilation mode.

Published studies have shown the effectiveness and safety of these regimens in patients with various respiratory conditions (ARDS, bronchoobstructive syndrome, chronic obstructive pulmonary disease), brain lesions, and for postoperative respiratory support [8–20]. However, almost all studies compared intelligent technologies with traditional modes, while comparisons of ASV and Intellivent-ASV modes are lacking.

The aim of the study was to compare the efficacy and safety of intelligent modes with partial and fully autonomous control of ventilation (ASV and Intellivent-ASV) and traditional protocol with control of ventilation parameters by ICU physician in the early postoperative period of cardiac surgery patients.

Material and Methods

This single-center prospective randomized observational comparative study was approved by the local ethical committee of B. V. Petrovsky Russian Research Center of Surgery and was carried out at the department of cardiac intensive care of the Center. The envelope method was used for randomization.

The study included 120 patients, 40 patients per each group, who underwent heart or major vessel surgery from January 2016 to December 2019. The envelope method was used for randomization. Patient characteristics are shown in Table 1. The number of patients in the groups was calculated using G*Power 3.1 software. Based on the previous pilot study, which included 3 groups of 15 patients, we determined the mean value of the «need to manually change ventilator settings», which was 1, 2, and 4, respectively, and the standard deviation was 2.

We also estimated the effect size, which was 0.62. With a significance level of 0.05, the power of the study was 95%, the minimum required total number of subjects was 45 in total or 15 in each group.

The secondary endpoint «tidal volume in ml/kg PBW» was also calculated.

The mean value in the groups was 6, 7, and 7, respectively, and the standard deviation was 1. The estimated effect size was 0.47. With a significance level of 0.05, the power of the study was 95%, the required total number of subjects was 75 in total or 25 per group.

To get some reserve in case of unforeseen circumstances, we selected 40 people in each group, or 120 in total, which exceeded the minimum required number.

Inclusion criteria were admission to the intensive care unit after cardiac and ascending aorta surgery; age over 18 years; body mass index from 18 to 35 kg/m^2.

Preoperative exclusion criteria were severe renal (GFR < 30 ml/min), hepatic (aspartate and alanine aminotransferases [AST and ALT] > 80 IU/L) or cardiac failure (left ventricular ejection fraction less than 30%). Postoperative exclusion criteria were bleeding, perioperative myocardial infarction, hemodynamic instability, need for high doses of vasopressors drugs (vaso-inotropic score >12) or need for intra-aortic balloon pump counterpulsation, resistant hypoxemia with PaO_2/FiO_2 less than 150 mmHg, allergic reactions in perioperative period, seizures, delirium, and cerebrovascular accident.

The primary endpoint of the study was a comparative assessment of the burden on the ICU medical staff based on the number of approaches to the machine, manipulations with ventilator parameters, and time spent on changing manual ventilator settings. The secondary endpoint of the study was the duration of postoperative ventilatory support in the ICU, the incidence of adverse events during patient weaning, and the safety of the ventilation performed.

The anesthesiological specifics of patient management, doses of analgesics, hypnotics, and muscle relaxants were taken into account. There were no significant differences between the groups in the intraoperative oxygenation, respiratory volumes, and PEEP values used in the operating room (Table 1).

In the conventional approach group, ventilation was performed using Hamilton G-5 or C-2 ventilators by Hamilton, Switzerland, and Servo-I ventilators by Maquet. Intellivent-ASV and ASV modes were used on Hamilton G-5 and C-2 (ASV) machines.

Table 1. Baseline characteristics of patients, types of surgery, and perioperative data.

Parameter	Values in groups			*P*
	Intellivent-ASV (*n*=40)	ASV (*n*=40)	Conventional mode (*n*=40)	
Age, years	59±8	59 (55–66)	59±11	0.9185
Sex (male/female)	27/13	24/16	30/10	0.1701
Height, cm	171±9	170±9	174 (167–177)	0.8706
Weight, kg	84 (71–95)	84±14	82±12	0.3755
PBW, kg	68 (52–75)	65±10	67±8	0.1529
BMI, kg/m^2	27.9±4	28.6±4	27.2±3.6	0.9185
Preoperative SpO_2 on ambient air	96 (95–97)	96 (95–96)	96 (95–97)	0.6971
PaO_2/FiO_2 before transfer to ICU, mmHg	310 (290–345)	319±88	336±90	0.4534
Vt, ml/kg PBW	8 (7–9)	9 (8–10)	9 (8–9)	0.0757
PEEP; cmH_2O	7 (6–8)	7 (5–8)	6 (5–8)	0.2159
CABG	18	20	16	
CABG + valve surgery	2	5	2	
Valve surgery (replacement or repair)	12	9	12	
Aortic root replacement (David/Bentall procedure)	8	4	10	
Extended septal myectomy	0	2	0	

Note. Data are given as median (interquartile range) or mean (±SD) SD — standard deviation. Vt — tidal volume; BMI — body mass index; PBW — predicted body weight; PEEP — positive end expiratory pressure; CABG — coronary artery bypass graft.

The choice of ventilation mode was made upon admission to ICU using the envelope method.

The adaptive support ventilation (ASV) is a partially automatic mode that continuously adjusts respiratory support to the patient's condition and clinical needs based on respiratory biomechanics. In fact, it is designed to interactively maintain the «respiratory comfort» state and focused on «weaning» the patient from the ventilator as soon as possible. In this mode, the ventilator's microprocessor adjusts the inspiratory pressure to achieve the target tidal volume and respiratory rate, minimizing respiratory work, based on OTIS [6] and Mead [7] equations. In addition, the number of mandatory and spontaneous breaths is automatically adjusted depending on the patient's respiratory drive.

The Intellivent-ASV mode provides fully automatic control of patient ventilation parameters to achieve adequate gas exchange by adjusting Vt (tidal volume), MV (respiratory minute volume), PEEP (positive end expiratory pressure) and FiO_2 (inspiratory fraction of oxygen). This algorithm is implemented through continuous monitoring of respiratory biomechanics parameters and information from pulse oximetry and capnography sensors integrated into the device. Inspiratory pressure and optimal respiratory rate to minimize respiratory work are calculated, as in the basic mode, based on the OTIS and Mead equations. Also in this mode, there is an option for early activation of automated patient weaning.

After surgical intervention, the patients were admitted to the intensive care unit under continuous drug sedation with propofol (1–2 mg/kg/h) being on the Oxylog transport ventilator. Medication-assisted sedation was continued until the patient was warmed up and the oxygenation and hemodynamic parameters were stabilized (60–90 minutes after admission to the ICU) (no significant differences in the duration of sedation between the groups were recorded).

The patients were treated according to standard protocols for cardiac surgery postoperative patients [2]. Analgesia was performed according to a multimodal protocol with a combination of nonsteroidal anti-inflammatory drugs and paracetamol with central analgesics (nefopam, tramadol).

Respiratory support in the study groups.

In the Intellivent-ASV group, during initial setting of the ventilator, the physician adusted height and sex of the patient (for the microprocessor to calculate the ideal body weight), permission to automatically control the minute ventilation, FiO_2 and PEEP level, if necessary, to alter the $EtCO_2$ and SpO_2 target values, as well as the permission to automatically perform spontaneous breathing test. Further respiratory support was carried out in automatic mode, minute ventilation was changed continuously if necessary, according to $EtCO_2$ values. Optimal respiratory rate ratio, supportive pressure level, tidal volume were calculated by the microprocessor of the machine to reduce respiratory work based on individual pulmonary biomechanics, while PEEP and FiO_2 were also controlled automatically according to pulse oximetry data. When respiratory drive was restored and the patient's own respiratory activity increased, the sequence of mandatory and spontaneous breaths gradually changed. After a complete restoration of spontaneous breathing and a short observation period (10–60 minutes' duration preset by a physician when setting the mode), the machine conducted the spontaneous breathing test. If the test was successful, the machine alerted the medical staff prompting the physician to decide whether the tracheal extubation was possible.

In the ASV group, when setting up the device, the physician adjusted the height and weight of the patient, the target «minute ventilation replacement percentage» (with the «physiological» minute ventilation calculated as 100 ml/kg ideal body weight/min considered as 100%). Intensivists also set the FiO_2 and PEEP levels, the limit of maximum airway pressure, ETS (expiratory trigger sensitivity, the threshold flow value as a percentage of maximum which prompts expiration-inspiration switch), as well as the inspiratory trigger sensitivity. Noteworthy, when performing respiratory support, most doctors leave the initial settings of inspiratory trigger sensitivity and ETS unchanged and only adjust FiO_2, PEEP and percentage of minute ventilation replacement (increasing or decreasing its value depending on capnography or $PaCO_2$ results [20]).

In the physician-guided group, the initial mode of ventilation was Synchronized Intermittent Mandatory Ventilation (SIMV) with breaths controlled by volume (Volume Control, VC) or pressure (Pressure Control, PC). The doctor manually set FiO_2, PEEP, tidal volume or inspiratory pressure, respiratory rate, and inspiration-expiration ratio. After the patient awakened and muscle tone was restored, the physician reduced the number of mandatory breaths and, if necessary, adjusted the tidal volume and support pressure of spontaneous breaths. After the patient's respiratory drive was restored, respiratory support until spontaneous breathing initiation was continued in Pressure Support (PS) Ventilation mode.

The parameters of respiratory support and the decision to extubate the trachea in all three groups were decided by the intensivist treating the patient. The study involved 8 doctors, each of whom participated in respiratory support in four to five patients per each group. The researcher recorded and documented all the physicians' actions and measured the time spent.

The researcher recorded the following parameters:

1) Directly related to the setting of respiratory support such as changes in mechanical and assisted ventilation modes (changes in the frequency of mandatory and spontaneous breaths), the frequency of parameter correction; the values of Vt, PS, PEEP, driving pressure, and FiO_2.

2) Physician-related such as number of approaches and adjustments made to settings, total time spent at the ventilator, and the need for adjustment if apnea or bradypnea develops.

3) Related to the duration of respiratory support such as total time of respiratory support in ICU, the time of mechanical and assisted (without mandatory breathing) ventilation, time from awakening to restoration of spontaneous breathing, and the time from restoration of spontaneous breathing to the start of assisted ventilation.

Arterial gas exchange and acid-base status were analyzed during ventilation, 30 minutes after the start of assisted ventilation, and 15 minutes before tracheal extubation using blood gas and electrolyte analyzer (Gem Premier 4000, Instrumentation Laboratory, USA).

In all three groups, readiness for extubation was assessed according to local criteria based on the international «Evidence-based guidelines for weaning and discontinuation of ventilatory support» which included full awakening, following commands, absence of agitation, with FiO_2 less than 0.4, PaO_2/FiO_2 more than 200 mmHg, positive end-expiratory pressure <7 cm H_2O, stable hemodynamics, arterial blood pH>7.3, $PaCO_2$ between 35 and 45 mmHg, body temperature above 36°C.

To assess the safety of respiratory support, the Vt (tidal volume), driving pressure ($\triangle$P, which can be calculated as expiratory plateau pressure minus applied PEEP), FiO_2, and PEEP were recorded, and mechanical power (an aggregate measure of ventilation aggressiveness based on respiratory rate, PEEP, $\triangle$P, and Vt) was calculated [22] using simplified equations [23].

The data were processed using parametric and nonparametric statistical methods. The raw data were collected, adjusted, organized and visualized using Microsoft Office Excel 2016 software. Statistical analysis was performed using STATISTICA 10.0 (StatSoft.Inc.) software. Normality of quantitative variable distribution was assessed using the Shapiro–Wilk test. Normally distributed quantitative variables were pooled into variational series, where the arithmetic mean (*M*) and standard deviations (*SD*) were calculated. Quantitative variables with non-normal distribution were characterized using median (*Me*) and interquartile range (25^{th} and 75^{th} percentiles) values. Nominal data were described using absolute values and percentiles. The significance of intergroup differences in quantitative variables with normal distribution was assessed using the single-factor analysis of variance by performing the Bonferroni multiple comparison test or *F*-test. When comparing several samples of quantitative data with non-normal distribution, the Kruskal–Wallis test was used. Nominal data were compared using Pearson's χ^2 test and Fisher's exact test. Differences were considered significant if *P*-value was < 0.05.

Results and Discussion

According to the obtained data, the more the machine was involved in the ventilator control (transition from physician control to ASV and Intellivent-ASV modes), the less the physician participated in the respiratory support. The time spent on ventilation control in the Intellivent-ASV group was almost three times less than in the ASV group and four times less than in the physician-guided group (Table 2). In the Intellivent-ASV mode, there

Table 2. Respiratory support in the study groups.

Parameter	Values in groups			*P*
	Intellivent-ASV (*n*=40)	ASV (*n*=40)	Conventional mode (*n*=40)	
Duration of respiratory support in ICU (time to tracheal extubation), min	226±31	259±66	271±78	0.0042 p_{1-2}=0.0167 p_{1-3}=0.009
Number of physician's approaches to the ventilator per patient	2(1–2)	3 (2–4)	4 (3–5)	<0.0001 p_{1-2}=0.0001 p_{1-3}<0.0001 p_{2-3}=0.0112
Numbers of manual ventilator setting changes per patient	0 (0-0)	2 (2–3)	4 (3–5)	<0.0001 p_{1-2}<0.0001 p_{1-3}<0.0001 p_{2-3}=0.0003
Physician's time spent at ventilator per patient, sec	35 (27–45)	99±35	164±69	<0.0001 p_{1-2}<0.0001 p_{1-3}<0.0001 p_{2-3}=0.0045
During mechanical ventilation (with mandatory breaths)				
PaO_2/FiO_2, mmHg	358 (330–380)	373±64	372±50	0.3038
SpO_2, %	98 (97–99)	100 (99–100)	99 (99–100)	<0.0001 p_{1-2}<0.0001 p_{1-3}=0.0001
FiO_2, %	26 (24–30)	34 (30–35)	34 (30–38)	<0.0001 p_{1-2}<0.0001 p_{1-3}<0.0001
PaO_2, mmHg	95 (85–104)	123 (109–133)	125 (107–140)	<0.0001 p_{1-2}<0.0001 p_{1-3}<0.0001
$PaCO_2$, mmHg	42 (40–44)	39(37–42)	38 (37–41)	0.0002 p_{1-2}=0.005 p_{1-3}=0.0003
pH	7.39±0.04	7.4±0.04	7.41±0.04	0.0469
Tidal Volume (Vt), ml/kg PBW	6 (6–7)	7 (6–7.7)	7 (7–8)	<0.0001 p_{1-2}=0.0016 p_{1-3}=0.0001
△P (driving pressure), cmH_2O	6 (6–7)	6 (6–7)	7.3 (7–9)	<0.0001 p_{1-3}=0.0001 p_{2-3}=0.0005
PEEP, cmH_2O	5 (5–7)	8 (7–10)	7 (6–9)	<0.0001 p_{1-2}=0.0001 p_{1-3}=0.0004
Mechanical power, J/min	8 (6–9)	8 (6–9)	9 (7–11)	0.0797
Duration of mechanical ventilation, min	132±36	169±68	189±71	0.0002 p_{1-2}=0.0012 p_{1-3}=0.0002
During the period without mandatory breaths in Intellivent-ASV and ASV groups and in PSV mode in control group				
PaO_2/FiO_2 mmHg	371±45	364±62	385±49	0.19
Increase in PaO_2/FiO_2 ratio from the admission to ICU, *n*	34 (85%)	29 (72.5%)	27 (67.5%)	0.147
SpO_2, %	98 (97–98)	99 (99–100)	99 (98–100)	<0.0001 p_{1-2}<0.0001 p_{1-3}=0.0001
FiO_2, %	26±4	31 (30–35)	30 (30–36)	<0.0001 p_{1-2}<0.0001 p_{1-3}<0.0001
PaO_2, mmHg	91 (84–104)	115 (105–130)	120 (109–137)	<0.0001 p_{1-2}=0.0001 p_{1-3}<0.0001
$PaCO_2$, mmHg	40±2	38 (37–41)	38 (36–40)	0.0553
pH	7.39±0.03	7.4±0.04	7.4±0.03	0.406
Tidal Volume (Vt), ml/kg PBW	8 (7–8)	7.5 (7–8)	8 (7–9)	0.0573
PS, cmH_2O	5 (5–5)	5 (5–7)	8 (7–9)	<0.0001 p_{1-3}<0.0001 p_{2-3}<0.0001
PEEP, cmH_2O	5 (5–5)	7 (5–8)	7 (5–8)	<0.0001 p_{1-2}<0.0001 p_{1-3}<0.0001
Duration of spontaneous ventilation*, min	90 (75–103)	80 (60– 110)	60 (60–105)	0.0462 p_{1-3}=0.0162

Table 2.

Parameter	Values in groups			*P*
	Intellivent-ASV (*n*=40)	ASV (*n*=40)	Conventional mode (*n*=40)	
Time from awakening to spontaneous ventilation, min	0 (0–0)	0 (0–12)	30 (0–60)	<0.0001 p_{1-3}<0.0001 p_{2-3}=0.0087
Time from the restoration of spontaneous breathing to the change of mandatory breathing mode, min	0	0	39 (25–46)	<0.0001 p_{1-3}<0.0001 p_{2-3}<0.0001
Follow-up after tracheal extubation				
Tracheal reintubation	0	0	0	
NIV during first 12 hours after tracheal extubation	2	1	1	
Length of stay in ICU, days	1 (1–1)	1 (1–1)	1 (1–1)	—
Postoperative length of stay in hospital, days	7 (7–8)	8 (7–10)	8 (8–10)	0.0411
Hospital mortality, *n*	0	0	0	

Note. Data are given as median (interquartile range) or mean (±SD). SD — standard deviation. NIV — noninvasive ventilation. * — here, «duration of spontaneous ventilation» means time spent without any mandatory breaths in the Intellivent-ASV and ASV groups and time spent in Pressure Support Ventilation in the control group.

was practically no need for parameter adjustments, while in the ASV group such correction was necessary twice less frequently compared to the physician-controlled group.

The compared groups also had significant differences in the time from the patient's admission to the ICU to tracheal extubation. In the fully automatic parameter control group, the duration of respiratory support was, on average, 15% shorter than in the semiautomatic group and in the physician-guided group (Table 2).

In groups using intelligent modes, the number of mandatory breaths was automatically reduced upon restoration of the patient's respiratory drive and actually assisted ventilation was initiated with full restoration of spontaneous breathing by awakening. This is in line with the current guidelines recommending assisted MLV without physician-guided mandatory breaths for most patients needing respiratory support, since it enables better inflation of lung bases, prevents atrophy of respiratory muscles, promotes more equal gas distribution, shortens respiratory support duration and reduces the frequency of ventilator-associated pneumonia [24]. Besides, the level of pressure support during assisted MLV is significantly lower when using intelligent technologies.

In the physician-controlled group, the time from the restoration of spontaneous breathing to the physician-guided decrease of ventilator-delivered breaths or switching to PSV mode was on average 39 minutes, and the patient's awakening and recovery of spontaneous breathing did not always coincide with the switching to less aggressive modes, and this period averaged 30 minutes. Perhaps, this could be the cause of more common incidence of such adverse events as anxiety, associated with tachycardia, tapping on the bed, tachypnea episodes and interfering with the machine work in the physician-controlled group. In the Intellivent-ASV group such episodes were observed in five patients out of 40 (12.5%), in the ASV group in 4 out of 40 (10%), while in the control group in 9 out of 40 (22.5%), but the differences were not significant.

During the transition to spontaneous breathing, a proportion of patients developed bradypnoea (20(50%) in the Intellivent-ASV group, 12 (30%) in ASV group and 15 (37.5%) in conventional mode group. However, in the Intellivent-ASV group mandatory breaths were activated automatically, and mechanical respiratory support continued until the possibility to minimize the ventilator-delivered breathing appeared again, while in the physician-controlled group, backup ventilation was activated with mandatory breaths in the pressure mode (full mechanical ventilation), which entailed the need to correct the ventilation mode by the physician and in some cases led to asynchrony. No significant differences were found between the groups for such episodes. Importantly, in the automated groups, mandatory breaths after resuming spontaneous breathing were reduced automatically, while in the physician-controlled group, this required physician's intervention.

The data obtained in the study suggest that the use of intelligent modes can significantly reduce the workload on the staff, increasing the safety of postoperative ventilation. With limited resources available, the use of these techniques can be an important factor in improving patient outcomes.

The results of our study are largely comparable with those of studies conducted in cardiac surgical patients: in the Intellivent-ASV group, staff participation in controlling the machine and changing ventilation parameters was required less frequently [13–15]. In ASV group, staff participation was required more often than in fully automatic group, but both time spent at the ventilator and frequency of settings adjustments were still significantly lower than in fully physician-controlled group.

Table 3. Main parameters of respiratory monitoring after tracheal extubation.

Time	Parameter	Values in groups			*P*
		Intellivent-ASV (*n*=40)	ASV (*n*=40)	Conventional mode (*n*=40)	
30 minutes after tracheal extubation on air	SpO_2	94 (93–95)	94±2	94±2	0.1614
	PaO_2/FiO_2	335 (321–345)	317 (300–352)	337 (302–365)	0.3071
	$PaCO_2$	39 (38–41)	39 (36–41)	38 (37–41)	0.3400
12 hours after tracheal extubation on air	SpO_2	95 (94–96)	95 (93–95)	94.5 (93–96)	0.0489
	PaO_2/FiO_2	347 (335–361)	338 (302–397)	332 (300–369)	0.2725
	$PaCO_2$	39±2	39 (38–41)	39 (38–41)	0.7742

Note. Data are given as median (interquartile range) or mean (±SD) SD — standard deviation.

In contrast to our results, A. J. Beijers and E. Fot [13, 15] have demonstrated that the duration of machine support in the studied groups did not differ, which can be explained by the difference in local protocols of ventilation. Meanwhile, when the semi-automatic technique was used, the respiratory support time in ASV group was almost the same as the data obtained by the researchers, while the duration of ventilation in the group of conventional modes in their study was longer, which again can be explained by the difference in local protocols [16–20].

Significant differences between the groups were observed for almost all parameters used to assess the safety of respiratory support (tidal volume, driving pressure (△P), FiO_2, PEEP level) (Table 2). Tidal volume was lower during mandatory ventilation in the Intellivent-ASV mode, while during assisted ventilation the tidal volume values were equal in all three study groups with lower PS value in «intelligent» groups. Very importantly, in these groups lower driving pressure during the ventilation with forced inspiration was found.

The level of FiO_2 and PEEP in all phases of respiratory support was lower in the Intellivent-ASV group. We consider it an important achievement to be able to work at lower values of FiO_2, because prevention of hyperoxia is one of the aims of protective ventilation, while the disadvantages of hyperoxia (increased frequency of absorptive atelectasis and lung injury) were well demonstrated by S. R. Pannu and R. Panvar [25, 26].

No significant differences in the values of mechanical power were obtained.

During respiratory support we noted that PaO_2 and SpO_2 values were significantly lower in the Intellivent-ASV group, while they were absolutely physiological and no significant differences in PaO_2/FiO_2 ratio was observed in all groups neither during ventilation (Table 2), nor after transition to spontaneous breathing, nor 12 hours after tracheal extubation (Table 3). Despite the obtained differences in $PaCO_2$ values, the parameters remained within the physiological ranges in all groups (Tables 2 and 3).

Intelligent modes belong to autonomous robotic and semi-robotic technologies operating in a fully closed circuit, when based on pulse oximetry, capnography and breathing mechanics data, the ventilator automatically selects the optimal ventilation parameters to achieve the target gas exchange rates and, as the patient stabilizes, switches from full mechanical ventilation through assisted modes to spontaneous breathing, without the participation of medical staff performing the supervising and controlling functions. In semi-robotic technology, the ventilator selects the most appropriate and safe respiratory support pattern for a specific patient, making it much easier to personalize the respiratory support provided without the relentless supervision of the physician.

Better understanding of modern principles of protective ventilation and subsequent implementation of the acquired skills in practice is a positive aspect of intelligent modes. We noted that after starting to use intelligent technologies our colleagues significantly more often in routine practice set lower values of inspiratory/expiratory pressure, lower values of Vt and FiO_2 and more actively and earlier switched the patients on «conventional» ventilation modes to spontaneous breathing.

Among the study limitations one can consider the «human factor»: as mentioned earlier, the study involved 8 doctors, each of whom has his own experience and long-held algorithms when performing lung ventilation. In addition, the number of physician approaches to the machine and the time spent on changing ventilation modes may have depended on personal characteristics and basic training in ventilation.

Conclusion

Compared with the conventional protocols of mechanical ventilation in the early postoperative period of cardiac surgery patients, the use of intelligent technologies of respiratory support was characterized by interactive personalization and adjustment of respiratory support, significantly reducing physician involvement in this process and providing the safest ventilation parameters.

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The Effect of Erythrocyte-Containing Donor Blood Components in the Priming of the Cardiopulmonary Bypass Circuit on the Development of Systemic Inflammation During Correction of Congenital Heart Defects in Children

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Значение эритроцитсодержащих компонентов донорской крови в объеме первичного заполнения контура искусственного кровообращения в развитии системного воспаления при коррекции врожденных пороков сердца у детей

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Summary

Various pathological factors accompanying any cardiac surgery can cause intraoperative systemic inflammatory responses (SIR). As the number of cardiac surgical interventions grows worldwide, the issue of SIR prevention appears highly relevant.

Aim of the study. To determine the effect of not using donor blood components in the priming of the cardiopulmonary bypass circuit in children with septal congenital heart defects, operated under cardiopulmonary bypass, on the severity of SIR.

Material and methods. A prospective, randomized study included 40 children with a median age of 14 [12–22.5] months and weight of 8.8 [7.25–11] kg. All patients underwent radical correction of septal defect under cardiopulmonary bypass. The patients were divided into two groups depending on the use of donor blood components for priming the CPB. The severity of SIR was assessed using four specific serum biomarkers such as interleukin 1b (IL-1b), interleukin 6 (IL-6), interleukin 10 (IL-10), and tumor necrosis factor alpha (TNF-α), measured before the operation, after the CPB and 16 hours after the surgery. In addition, the intra- and postoperative periods were evaluated.

Results. The safety of the proposed strategy of skipping the donor blood was confirmed by lack of any organ dysfunction in all patients, as well as a significant difference in the balance of oxygen delivery and consumption. In addition, the levels of systemic inflammation markers after CPB were significantly higher in patients who had transfusion: IL-1b was 3.3 [3.2–3.48] pg/mL vs 2.86 [2.7–3.11] pg/mL (P=0.003) and TNF-α reached 1.81 [1.37–3.3] pg/mL vs 1.33 [1.26–1.76] pg/mL (P=0.034). Meanwhile, 16 hours post surgery, IL-6 and IL-10 levels were significantly higher in the group using donor blood components with IL-6 being 48.91 [33.89–57.6] pg/mL vs 31.56 [26.83–48.89] pg/mL (P=0.087) and IL-10 reaching 0.8 [0.76–1.43] pg/mL vs 0.69 [0.6–0.83] pg/mL (P=0.005).

Conclusion. The study demonstrates and confirms the safety and efficacy of cardiopulmonary bypass without using donor blood components to reduce the severity of the systemic inflammatory response in children undergoing correction of septal congenital heart defects.

Keywords: children; cardiac surgery; cardiopulmonary bypass; systemic inflammatory responses

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Any surgery is associated with factors such as anesthetics, changes in blood gas and acid-base balance, hemodynamic instability and many others, which can initiate systemic inflammatory responses (SIR) [1]. All these factors can be seen in pediatric congenital heart defects surgery characterized by large volume, invasiveness, and tissue damage as well as the use of cardiopulmonary bypass (CPB). The latter is associated with such abnormal factors as blood contact with the surface of the CPB circuit and the ambient air in the cardiotomy reservoir, hemodilution, exposure of blood cells to roller pumps, and non-pulsatile blood flow [2–4]. All these and other factors can trigger the first phase of SIR that initiates both humoral (complement system, coagulation system, cytokine release) and cellular (activation of white blood cells and platelets) reactions. Then the second phase ensues due to ischemia-reperfusion caused by aortic constriction and non-physiological nature of blood flow during CPB [2]. Besides, children, especially in their first year of life and weighing less than 10 kg, are highly susceptible to SIR development due to physiological characteristics [5, 6]. Multiple underlying mechanisms and causes of SIR warrant employment of various approaches to SIR control including intraoperative administration of steroids [7]. However, several studies demonstrated lack of effect of steroids on the risk of SIR even at high doses as pulse therapy [8, 9]. Increased hopes were pinned on hypothermia, but even its deep level, up to 24°C, during CPB in children also failed to reduce the risk of CHD [10]. Several interesting studies have shown a decrease in the level of inflammatory mediators during CPB in hypothermia group, however, no difference was found between the groups immediately after the main stage of surgery, indicating a delay release, rather than reduction in the total level of mediators [11]. In pediatric cardiac surgery, both standard and modified ultrafiltrations have proven to be effective in significant reducing the SIR intensity [12]. The similar effect was observed when using the WBC filters during CPB [13].

Another way of controlling CPB during cardiac surgery could be restricting transfusion of donor blood components. A mismatch between extracorporeal circuit volume and circulating blood volume of the child, especially in the first year of life, which can lead to critical hemodilution, is characteristic of surgeries using CPB. To prevent this complication, donor blood components (most commonly, red blood cell mass) are used for priming the CPB. However, several studies have demonstrated that transfusion itself can trigger SIR [14]. Currently, there is no common strategy on the use or avoidance of transfusion in children, especially those weighing 7 to 10 kg. Therefore, the issue of so-called «bloodless perfusion» in children is relevant both in terms of safety and effectiveness for the reduction of intraoperative SIR.

Material and Methods

The study was performed at the Department of Anesthesiology and Critical Care of the Research Institute for Complex Issues of Cardiovascular Diseases (RICID), Kemerovo, Russia. Forty children aged 6 to 36 months, mean age 14 [12–22.5] months, weight 8.8 [7.5–11] kg, who underwent planned radical correction of interventricular or interatrial septal defect under CPB, were examined. Power analysis was performed according to the formula $\mathbf{n=(t2*P*Q)/\triangle 2}$, where t is the critical value of Student test at the appropriate significance level (0.05); $\triangle$ is the marginal error (%); p is the proportion of cases in which the studied parameter was found (%); Q is the proportion of cases where the studied parameter was not found (100-P). According to this calculation, 196 patients were to be included in the study. However, since the effect of limiting red blood cell transfusion in reducing the severity of SIR was significant, a smaller sample of patients participating in the study was sufficient to prove that this effect was not random. This study was a pilot and at least 200 patients will be included in the future ones to be published. This was a prospective, randomized study approved by the local ethical committee of the RICID.

Using the envelope method, the patients were randomized into one of two following groups:

- Main group (CPB priming solution based on colloid/crystalloid solutions without red blood cell mass, 20 patients);
- Control group (CPB priming solution based on colloid/crystalloid solutions with red blood cell mass, 20 patients)

The patient characteristics are shown in Table 1.

All patients received anesthesiological support according to the same local regimen. After the patient was moved to the operating room, peripheral vein catheterization was performed under local anesthesia. Anesthesia was induced by administering propofol 2–3 mg/kg and fentanyl 5 mcg/kg. Pipecuronium bromide 0.1 mg/kg was used for muscle relaxation. Then tracheal intubation, central vein, radial artery and bladder catheterization were performed. At the beginning of the surgery, bolus injection of fentanyl 5 μg/kg was done. Maintenance anesthesia included continuous infusion of propofol 2–4 mg/kg/hr and fentanyl 5 μg/kg/hr using infusomate, and sevoflurane inhalation at 1.0–1.5 MAC.

Mechanical ventilation was performed using Datex-Ohmeda Avans (General Electric) semi-closed circuit (SIMV mode) under standard parameters in-

Table 1. Patient characteristics.

Characteristic	Values in groups		*P*
	Main	Control	
Number of patients	20 (50%)	20 (50%)	1
Male	7 (35%)	9 (45%)	0.52
Female	13 (65%)	11 (55%)	0.52
Age (months)	15 [12–23.3]	13 [11–21.3]	0.27
Height (cm)	81 [76–86]	75 [71.3–84.3]	0.14
Body weight (kg)	10.5 [9.2–11.3]	9.2 [8.7–11.8]	0.15
Laboratory blood parameters before surgery			
WBC count, $\times 10^9$/l)	7.4 [6.6–7.9]	7.5 [7–9]	0.17
RBC count, $\times 1^{012}$/l)	4.6 [4.5–4.75]	4.6 [3.9–5]	0.7
Hemoglobin, g/L	118.5 [115–121.3]	117 [112.8–119]	0.29
Hematocrit, %	36 [34–38]	35 [33–37]	0.34
Direct bilirubin, μmol/l	2.4 [2.1–3.3]	2.9 [2.1–3.7]	0.54
Indirect bilirubin, μmol/l	4.3 [2.5–5.5]	4.5 [2.4–6.7]	0.68
Creatinine, μmol/l	38.5 [30.5–44.3]	31 [24.3–43.3]	0.23
Urea, mmol/l	3.8 [3.4–4.3]	4 [3–5]	0.98
Preoperative NGAL, ng/ml	49.19 [24.3–100.1]	45.98 [34.58–98.98]	0.3
Surgery			
Diagnosis			
ASD	15 (75%)	15 (75%)	1
VSD	5 (25%)	5 (25%)	1
Surgical approach			
Median sternotomy	14 (70%)	15 (75%)	0.85
Lateral sternotomy	6 (30%)	5 (25%)	0.85
Duration of surgery	196 [188–203]	189 [181–200]	0.3
CPB duration (min.)	40.5 [33–47]	45 [35–49.5]	0.5
Duration of aortic clamping (min.)	27.5 [20.3–33]	29 [22.3 –36.3]	0.59

Note. Differences were considered significant at $P<0.05$. ASD — atrial septal defect; VSD — ventricular septal defect; CPB — cardiopulmonary bypass; WBC — white blood cells; RBC — red blood cells; NGAL — neutrophil gelatinase-associated lipocalin

cluding FiO_2 = 0.25–0.3, Vt = 6–8 ml/kg; Pi = 10–15 cm H_2O; PEER = 5–8 cm H_2O; Ti:Te = 1:2. CO_2 in exhaled air was monitored.

The CPB was performed according to the standard local procedure. The Maquet HL 20 device was used. The Terumo Baby Fx-05 and Sorin Dideco D101 membrane oxygenators werre used. Priming volume was 300 ml for both types of oxygenators. The choice of oxygenator depended on the estimated perfusion volume rate on CPB machine. All patients received 15% mannitol 500 mg/kg, 5% sodium bicarbonate 1.5 ml/kg, and heparin 6 units for each ml of the priming solution. The colloid fluid was 10% albumin 1 g/kg body weight (added only to the CPD machine). The crystalloid fluid was sterofundin, which volume was calculated as the difference between the total volume of priming solution and the rest of the components. Erythrocyte suspension 10 ml/kg with the removed WBC and platelets layer and storage time not exceeding 5 days was added. All patients received heparin 300 IU/kg with mandatory follow-up AST measurement prior to CPB. The composition of the priming volume in the groups is shown in Table 2.

The CPB was performed with perfusion index of 3.0 L/min/m2 in normothermic mode (nasopharyngeal probe temperature 37°C, without using pulsatile mode). Gas mixture flow into oxygenator was approximately 2 times less than the perfusion volume rate. Oxygen fraction in the gas mixture was regulated according to acid base balance data and ranged between 40 and 60%. Blood CO_2 tension was monitored using arterial blood analysis and controlled using the tidal volume of the gas mixture.

For cardioplegia, the cold Custodiol solution 50 ml/kg was used with exposure of at least 8 minutes. Cardioplegic solution was delivered in the antegrade direction into the aortic root. Special kits with Medtronic heat exchanger were used to deliver the solution. The waste cardioplegic solution was aspirated into the cardiotomy tank of oxygenator. Excessive hemodilution during cardioplegia and after it was avoided since during the whole CPB ultrafiltration aimed at elimination of excessive fluid perfusate was being performed. The Maquet BC 20 plus ultrafiltration column was used. Blood sampling for the column was performed from the arterial line, after its exit from the oxygenator for Terumo Baby Fx-05 and after the arterial filter for Sorin Dideco D101. Blood from the column was returned to the venous line at the connection point with the cardiotomy reservoir. Necessary rarefaction for ultrafiltration was created by vacuum pump connected to the column.

After completion of CPB, all patients underwent modified ultrafiltration with the same connection scheme for blood collection as in conventional ultrafiltration described above, but with return of concentrated blood into the cannula of inferior vena cava.

Table 2. The priming composition of CPB circuit in the groups.

Priming component, ml	Mean volume in groups, ml		*P*
	Main	Control	
Sterofundin	199.1 [192.2–212.8]	166,8 [154.2–174.9]	0.08
Mannitol, 15%	34.,0 [29.4–36.3]	29,7 [27.9–32.5]	0.05
Sodium bicarbonate, 5%	15.5 [13.7–16.5]	13,5 [13.0–14.8]	0.06
Albumin, 10%	51.5 [44.5–55.0]	—	—
RBC suspension	—	90 [84.5 – 98.5]	—

After completion of modified ultrafiltration, the vacuum ultrafiltration of perfusate remaining in cardiotome according to our original novel medical technique was done. After that, concentrated blood from ultrafiltration column was reinfused. This technique is necessary for maximum preservation of the patient's blood and allowed to maintain hemoglobin and hematocrit without transfusion.

The study used several specific markers such as interleukin 1 (IL-1), interleukin 6 (IL-6), interleukin 10 (IL-10) and tumor necrosis factor alpha (TNF-α), whose concentration in blood serum, according to literature data, can objectively assess the intensity of SIR [1, 15].

Blood test for measurement of the above-mentioned markers was performed at three time points points. FThe first, when the patient was admitted to the operating room, after the main vein catheterization, before the surgery. The second, immediately after CPB. The third, 16–18 hours after the surgery. Blood sampling was performed from the central venous catheter in the internal jugular vein.

In the perioperative period several laboratory and instrumental parameters were monitored during surgery and 16–18 hours after it. The results obtained at three time points are presented in the tables. The «before surgery» values were recorded after the central venous catheter placement, the «during CPB» values were registered 15 minutes after CPB initiation, and the «end of surgery» values were observed after the skin suturing.

Compliance between tissue oxygen delivery and consumption was assessed using venous blood saturation, blood lactate measurement and cerebral oximetry (rSO_2), the pulse oximetry (SpO_2) data were also evaluated. Renal function was monitored using urea and creatinine levels on day 1 post surgery and the neutrophil gelatinase-associated lipocalin (NGAL) level (marker of renal damage) [16]. Liver function was monitored using the direct and indirect bilirubin levels. The early postoperative period was evaluated, in addition to all of the above, by measurement of drainage losses, duration of ventilation and ICU stay, frequency of use and dosage of inotropic drugs. Epinephrine 0.05 μg/kg/min was used as the inotropic agent. The groups did not differ significantly in the duration of hemodynamic support. Polyionic solution (Sterofundin) and 5% glucose (1:1) were used for intravenous fluid therapy. The volume of intravenous fluid and urine output were assessed during 16 hours after the surgery.

Statistical analysis was done using the BioStat Pro 5.9.8 software. The nonparametric statistics was mostly employed due to non-normal distribution of variables as determined by Shapiro–Wilk criterion at $P<0.05$. Data were presented as median (*Me*), upper (*Q1*), and lower quartiles (*Q3*). Comparative analysis of quantitative variables was performed using Mann–Whitney test [17]; Wilcoxon criterion was used for paired variables. Comparative analysis of qualitative variables was performed using a 2×2 contingency table and Chi-square test for absolute values. Differences were considered significant at $P<0.05$.

Results and Discussion

The intraoperative values in both groups are compared in Table 3. Hemoglobin and hematocrit values were significantly higher during and after CPB in the control group patients received the RBC mass. However, despite the risk of hemic hypoxia in the main group, oxygen delivery and consumption values were within the reference range. Venous blood saturation did not differ between the groups during the CPB, but was different at the end of surgery (71% [69.8–73] vs 73% [71.8–77], $P=0.01$), with higher values in the control group. Meanwhile, the blood lactate level did not differ between the groups at both time points. Monitoring of oxygen status showed that values of pulse oximetry at all time points also did not significantly differ. When assessing the risk of cerebral perfusion disorders, we found that the intergroup difference according to NIRS monitoring results was seen only at the end of the surgery. Current research in this area emphasizes the importance of the change in the NIRS monitoring parameters versus baseline rather than their absolute values. Thus, a decrease by 20% [18], and according to some data, even by 10% [19] of NIRS values vs the baseline appears to be dangerous, which was not observed among the studied patients.

The postoperative parameters are characterized in Table 4. Hemoglobin and hematocrit levels did not change compared with the intraoperative period, being significantly higher in the transfusion group, as well as the red blood cell count. Similarly, venous blood saturation was higher in the controls than in the main group: 76.5% [73 to 80] vs 70% [68.8 to 73.3], respectively ($P=0.001$), with no difference in blood lactate level. In addition, the groups differed in blood leukocyte counts, $8.5*10^9$ [7.9–11.1] and

Table 3. Intraoperative parameters in the studied groups.

Parameter	Values in groups		*P*
	Main	Control	
Laboratory			
Hemoglobin during CPB, g/l	87 [81.0–91.3]	92 [87.3–97.3]	0.008
Hematocrit during CPB, %	25,5 [24.0–27.0]	29 [27.8–31.0]	<0.001
Hemoglobin at the end of surgery, g/l	106.0 [101.8–110.3]	130.5 [104.0–125.5]	<0.001
Hematocrit at the end of surgery, %	31.5 [30–33.3]	40.0 [38.8–41.5]	<0.001
Venous blood oxygen saturation during CPB, %	85.0 [83.8–89.0]	88.5 [86,0–90.0]	0.26
Venous blood oxygen saturation at the end of surgery, %	71.0 [69.8–73.0]	73.0 [71.8–77.0]	0.01
Blood lactate during CPB, mmol/l	1.5 [1.3–1.8]	1.5 [1.2–1.9]	0.87
Blood lactate at the end of surgery, mmol/l	1.5 [1.3–1.7]	1.5 [1.2–1.7]	0.46
Preoperative NGAL, ng/ml	49.2 [24.3–100.1]	46.0 [34.6–99.0]	0.3
Monitoring			
Preoperative SpO_2, %	97.0 [90.5–98.0]	98.0 [95.5–98.5]	0.33
SpO_2 at the end of surgery, %	99.0 [98.0–99.0]	99.0 [99.0–100.0]	0.03
Preoperative rSO_2, %	65.0 [61.5–73.5]	67.0 [61.5–70.5]	0.77
rSO_2 during CPB, %	83.0 [80.5–86.5]	85.0 [81.5–87.0]	0.40
rSO_2 at the end of surgery, %	70.5 [69.8–75.0]	77.0 [74.5–78.0]	0.008
Inotropic drug use			
Number of patients on inotropic drugs	4 (20%)	5 (25%)	0.7
Water balance			
Intravenous infusion volume, ml/kg	15.6 [13.5–16.4]	15.7 [12.8–17.4]	0.31
Urine output, ml/kg	11.0 [9.0–12.4]	10.5 [9.3–12.3]	0.43
Ultrafiltration volume during CPB, ml/kg	11.0 [10.1–13.3]	11.7 [10.2–13.5]	0.37

Note. The volume of intravenous fluid and urine output were monitored during the intraoperative period. For intravenous infusion, a polyionic solution (Sterofundin) was used. SpO_2 — blood oxygen saturation; rSO_2 – regional tissue oxygen saturation. Differences were considered significant at $P<0.05$.

Table 4. Postoperative parameters in the studied groups.

Parameter	Values in groups		*P*
	Main	Control	
Laboratory parameters			
Hemoglobin, g/l	101.0 [98.8–107.0]	124.0 [113.0–127.0]	<0.001
Hematocrit, %	30.0 [29.0–32.0]	34.0 [33.0–36.0]	<0.001
Oxygen saturation in venous blood, %	70.0 [68.8–73.3]	76.5 [73.0–80.0]	<0.001
Blood lactate, mmol/l	1.2 [1.1–1.35]	1.2 [1.08–1.3]	0.67
RBC count, $\times 10^{12}$/l	3.8 [3.6–4.1]	4.8 [4.5–5.0]	<0.001
WBC count, $\times 10^{9}$/l	8.5 [7.9–11.1]	10.8 [9.3–12.8]	0.013
Direct bilirubin, μmol/l	2.9 [2.2–3.2]	3.3 [2.3–4.4]	0.29
Indirect bilirubin, μmol/l	3.8 [2.7–4.9]	9.5 [4.9–13.0]	<0.001
Creatinine, μmol/l	26.5 [19.8–31.0]	32.5 [26.0–40.0]	0.015
Urea, mmol/l	3.7 [3.1–4.9]	4.5 [4.0–5.5]	0.032
Postoperative NGAL, ng/ml	87.3 [41.3–159.1]	74.5 [49.5–136.2]	0.46
Monitored parameters			
Drainage loss on Day 1 after surgery, ml/kg	54.6 [46.4–84.0]	68.0 [53.3–82.4]	0.3
Duration of stay in the ICU, hours	23.5 [21.0–29.0]	23.0 [21.8–41.5]	0.97
Duration of mechanical ventilation, hours	7.0 [6.0–8.0]	8.0 [6.8–9.0]	0.34
Inotropic drugs			
Number of patients on inotropic drugs	4 (20 %)	5 (25 %)	0.7
Water balance			
The volume of fluid infusions during ICU stay, ml	64.0 [6270–69.2]	61.0 [59.4–64.9]	0.1
Urine output during ICU stay, ml	24.0 [22.0–26.5]	28.0 [22.5–30.0]	0.08

Note. The table shows parameters recorded on the day following the surgery. The duration of mechanical ventilation was defined as the time from the moment of intubation to the moment of extubation and initiation of spontaneous breathing. The volume of fluid infusions included intravenous + enteral fluid intake. Differences were considered significant at $P<0.05$.

$10.8*10^9$ [9.3–12.8] (P=0.013), with higher values among patients who received red blood cell mass intraoperatively. Direct bilirubin concentrations did not differ between the groups, and indirect bilirubin levels were higher in the controls being 9.5 μmol/L [4.9–13] vs 3.8 μmol/L [2.7–4.9] (P=0.013). Although bilirubin level was within the reference range in both groups, significant increase of indirect bilirubin the control group was probably due to hemolysis of donor erythrocytes [20], rather than any liver damage. Postoperative blood creatinine levels were 26.5 μmol/L [19.8–31] in the main group and 32.5 μmol/L [26–40] in the control group (P=0.015). Blood urea level was 3.7 mmol/L [3.1–4.9] in the main group vs 4.5 mmol/L [4– 5.5] in the controls (P=0.032). The NGAL concentration did not differ

Table 5. Changes in SIR markers.

Parameter	Values in groups		*P*
	Main	Control	
IL-1b BS, pg/ml	2.6 [2.2–2.8]	2.6 [2.5–3.0]	0.16
IL-1b ES, pg/ml	2.9 [2.7–3.1]	3.3 [3.2–3.5]	0.003
IL-1b 16 hours after surgery, pg/ml	2.7 [2.6–3.1]	2.8 [2.7–3.1]	0.46
IL-6 BS, pg/ml	2.5 [2.4–2.7]	2.6 [2.4–5.9]	0.21
IL-6 ES, pg/ml	29.1 [15.5–40.6]	27.6 [16.9–48.5]	0.18
IL-6 16 hours after surgery, pg/ml	31.6 [26.8–48.9]	48.9 [33.9–57.6]	0.087
IL-10 BS, pg/ml	0.6 [0.6–0.7]	0.6 [0.6–0.9]	0.39
IL-10 ES, pg/ml	7.9 [4.5–12.1]	8.8 [5.6–38.5]	0.07
IL-10 16 hours after surgery, pg/ml	0.7 [0.6–0.8]	0.8 [0.8–1.4]	0.005
TNF-α BS, pg/ml	1.3 [1.1–1.5]	1.2 [1.2–1.3]	0.19
TNF-α ES, pg/ml	1.3 [1.3–1.8]	1.81 [1.4–3.3]	0.034
TNF-α 16 hours after surgery, pg/ml	1.2 [1.1–1.6]	1.3 [1.2–1.9]	0.1

Note. BS — before surgery; ES — end of surgery. Differences were considered significant at $P<0.05$.

between the groups before surgery (49.19 ng/mL [24.3–100.1] vs 45.98 ng/mL [34.58–98.98] for the main and control groups, respectively) and 16 hours after surgery (87.3 ng/mL [41.3–159.02] vs 74.5 ng/mL [49.46–136.15], respectively). The increase in NGAL level on the next day after surgery was significant for both main (P=0.036) and control (p=0.039) groups. There were no differences between the groups in the volume of drainage loss, duration of mechanical ventilation and ICU stay, as well as the frequency of inotropic drugs administration.

The IL-1 level peaked at the 2nd time point (after completion of CPB) (2.86 ng/mL in the main group and 3.3 ng/mL in the control group) for both groups, and was significantly higher ($P<0.001$) than the baseline values (2.57 ng/mL in the main group and 2.58 ng/mL in the control group). Sixteen hours after surgery, the concentration of this marker decreased while remaining significantly higher than the baseline values (2.72 ng/mL in the main group and 2.82 ng/mL in the control group) ($P<0.001$). Intergroup comparison revealed a significant difference only at 2nd time point (P=0.003) with a higher IL-1 concentration in the group which underwent transfusion.

The peak IL-6 concentration, unlike the previous marker, was found at the 3rd time point for both groups. Blood levels of IL-6 were significantly higher in the main and control groups compared with baseline values (2.47 ng/mL and 2.64 ng/mL, respectively), both after completion of CPB (29.1 ng/mL in the main group and 27.58 ng/mL in the controls) and the morning after surgery (31.56 ng/mL in the main group and 48.91 ng/mL in the controls) ($P<0.001$). There was a trend towards differences in this parameter between the groups at 3rd time point (P=0.087).

The level of IL-10 significantly increased vs baseline values (0.62 ng/mL in both main and control groups) after completion of CPB (7.92 ng/mL in the main group and 8.78 ng/mL in the control group, $P<0.001$). However, on the following day in the main group no significant difference from the baseline value was observed (0.69 ng/ml, P=0.49), unlike the control group, where the value was significantly higher (0.8 ng/ml, P=0.006). An intergroup difference was revealed 16 hours post surgery: IL-10 level was significantly higher in the control group (P=0.005). After CPB completion, only a trend to an increase in this parameter was found (P=0.07).

The levels of TNF-α did not differ between patient groups at the first measurement (1.29 ng/mL in the main group and 1.21 ng/mL in the controls, P=0.19). Maximum concentration of the cytokine was recorded at the second timepoint in both groups (1.33 ng/ml in the main group and 1.81 ng/ml in the control group). Main group values, however, did not differ significantly versus baseline (P=0.21), unlike the control values (P=0.006). At timepoint 3, TNF-α values in the main group did not differ from baseline. TNF-α concentration after CPB completion was significantly higher in the group using red blood cell mass than in the main group (P=0.034).

From the perspective of SIR development, it is important that the WBC count (an indicator of inflammation) was significantly higher in the transfusion group during early postoperative days (Table 5). When analyzing the changes in specific SIR markers, such a difference becomes evident: 3 of the 4 markers studied (IL-1, IL-10 and TNF-α) had higher levels in the group receiving red blood cell mass immediately after the completion of CPB. This relationship with transfusion has its own explanation: any component of donor blood is a foreign agent for the patient's immune system and the activation of the inflammatory response is quite natural, as shown in many recent studies [21–23].

The study did not find any other negative sequelae of transfusion, except for higher SIR. Other publications, however, discuss the risk factors of transfusions that include increased mortality due to infections, lung damage [24, 25] and even postoperative delirium [26, 27]. Our study posits that the development of techniques to reduce the perioperative use of donor blood components is prom-

ising that corraborates current trends in cardiac anesthesiology [28].

Conclusion

There is strong evidence of safety and effectiveness of cardiopulmonary bypass without the use of donor blood components to reduce the severity of the systemic inflammatory response in children during correction of septal congenital heart disease.

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Parameters of the Blood Oxidant/Antioxidant System in Elderly Patients with Acute Poisoning

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Оценка оксидантно-антиоксидантной системы крови у гериатрических пациентов с острыми отравлениями

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Summary

The aim of the study was to assess the oxidant/antioxidant status in elderly patients in the early period of acute poisoning by psychotropic drugs or corrosive substances.

Material and methods. An open prospective observational study with retrospective control was conducted in 80 patients (age ⩾60 years) with acute poisoning, of which 49 patients aged 72.1±9.55 years had psychotropic drug poisoning (PDP) and 31 subjects aged 73.0±10.3 years had corrosive substance poisoning (CSP). Patients with mild poisoning were excluded from the study. The control group consisted of 39 volunteers aged 68.3±6.3 years. Total antioxidant status (TAS), blood levels of malondialdehyde (MDA), stable nitric oxide metabolites (nitrite/nitrate, NOx), and oxidative stress index (MDA/TAS) were measured on days 1, 3 and 5 after hospital admission.

Results. When analyzing the changes in the parameters of the oxidant/antioxidant system, we observed lower values of the studied parameters in patients with both PDP and CSP compared to the control group. In patients with PDP, several parameters were reduced: MDA by 1.2 times on days 1 and 3 (P=0.002; P=0.008, respectively), NOx by 1.7 times (P<0.001) at all stages of the study, MDA/TAS by 2.4–2.9 times (P<0.001). In patients with CSP, MDA level decreased by 1.1–1.2 times at all study timepoints (P=0.003; P=0.010; P=0.046, respectively), NOx dropped 1.4–1.6-fold (P=0.012; P=0.004; P=0.023, respectively), and MDA/TAS decreased by 2.3–2.4 times (P<0.001). While comparing patients with favorable and fatal outcome, we found that in survived patients an increase of MDA/TAS along with growing NOx level was seen by day 5 with no significant changes of MDA and TAS, while in non-survivors MDA/TAS dropped continuously due to progressive fall of NOx level, reaching values 2.8–2.9 times (P<0.001) lower than those of the controls.

Conclusion. In elderly patients with acute poisonings due to psychotropic drugs or corrosive substances, an inadequate response of the oxidant/antioxidant system occurs manifesting as a reduced blood level of peroxidation products with simultaneous normal or slightly decreased concentration of antioxidant protection system components. Thus, the oxidative stress develops, which contributes to the death of the patients.

Keywords: acute poisoning; oxidative stress; elderly patients; lipid peroxidation; antioxidant activity

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Acute chemical poisonings are among current medical challenges impacting the demographic situation in Russia, as they are associated with considerable medical and socio-economic costs [1, 2]. The pathogenesis of acute chemical poisonings involves disorders of various body functions and systems, including peroxide homeostasis [3, 4].

Currently, researchers focus their attention on the concept of «oxidative stress» as a key pathogenetic factor in the development of various chronic and acute diseases [5–8]. It leads to disruption of cellular structures, their functional activity change and ultimately to their death [3, 7, 8].

Peroxidation processes were shown to play a critical role in the pathogenesis of acute chemical injury [3, 4, 9]. The trigger mechanism is the entry of a toxicant into the body with subsequent oxidative stress maintained by endotoxemia [10]. Currently, there are sufficient data on the role of peroxide homeostasis disorders in middle-aged patients with acute toxicosis.

Only a few studies (especially comparative ones with different age groups) on acute chemical poisoning in geriatric patients have been available. The elderly and senile patients, in contrast to the middle-aged ones, are characterized by higher levels of malondialdehyde (4.2 (3.74–4.59) vs. 2.27 (2.11–2.47) μmol/l) and lower values of total antioxidant status (1.5 (1.28–1.59) vs. 1.61 (1.56–1.68) μmol/l) [9]. In poisoning with corrosive substances, the lack of adequate response to acute chemical injury in elderly and senile patients was also shown, which manifested by primary activation of venous blood lymphocyte apoptosis, and only then by peroxidation processes [9]. The structure and functional capabilities of the body organs and systems decrease with age [11].

The aim of this study was to examine the oxidant/antioxidant status in geriatric patients in the early phase of acute poisoning by psychopharmacological drugs and corrosive substances.

Material and Methods

An open prospective observational study with retrospective control was conducted in the department of acute intoxications and somatopsychiatric disorders of the N.V. Sklifosovsky Research Institute of Emergency Medicine during 2015–2020 after obtaining approval of the biomedical ethics committee. The inclusion criteria were moderate to severe psychopharmacological drug poisoning (PDP) according to the classification of E. Luzhnikov widely accepted in Russia [1], moderate to severe corrosive substance poisoning (CSP) according to the classification of S. Volkov et al. modified by Pinchuk [12, 13], and age 60 years and older. All patients with CSP underwent esophagogastroduodenoscopy to determine the severity and extent of chemical burns of upper gastrointestinal tract (GIT). Patients with mild PDP and CSP were not included in the study.

Eighty patients with acute poisoning were enrolled and divided into 2 groups including 49 patients aged 72.1±9.55 years with PDP and 31 patients aged 73.0±10.3 years with CSP. Each of these groups was divided into subgroups with favorable and lethal outcomes. The parameters of oxidant/antioxidant system were also studied in 39 volunteers aged 60 to 85 years (mean age 68.3±6.3 years) (control group). Of the 119 patients included in the study, 82 (68.9%) were women and 37 (31.1%) were men. Women (86%) were predominant among patients with PDP, and men (71%) were predominant among patients with CSP. This was probably due to the fact that men more commonly experience accidental poisonings with corrosive substances when intoxicated with alcohol.

Patients with PDP received forced diuresis, intestinal lavage, fluid and symptomatic therapy. Patients with CSP were treated with fluid, analgesic, antispasmodic, hormonal and local therapy.

The primary study endpoints were level of malondialdehyde (MDA) as a product of lipid peroxidation (LPO), total blood antioxidant status (TAS) to assess the antioxidant protection status, the blood levels of stable nitric oxide metabolites (NOx), and oxidative stress index (MDA/TAS ratio). The secondary endpoint was mortality. The serum MDA level was measured according to method by Gavrilov [14], TAS was determined using spectrophotometry on Olympus AU2700 biochemical analyzer (Beckman Coulter, USA) with the TAS kit (Randox, UK). Blood NOx was measured according to P. Golikov and N. Nikolayeva method [15]. MDA/TAS for each patient was calculated as the ratio of serum MDA to the serum TAS. The studied parameters were recorded at an early phase of acute poisoning, on days 1, 3, and 5 after hospital admission.

Statistical analysis was performed using the IBM SPSS Statistics 27.0 software. The data distribution was assessed using the Shapiro–Wilk test (for $n \leqslant 50$). In normal distribution, the arithmetic mean (M) and standard deviation (*SD*) were calculated. For nonparametric data, median (*Me*) and 25th and 75th percentiles were reported (as *Me* (*Q25–Q75*)). Intergroup comparisons of quantitative data were performed using Student's *t*-test (at normal distribution of variables) or Mann–Whitney test and Wilcoxon test with Bonferroni correction (related groups) (if distribution of variables was not normal). Relative variables were compared using Fisher's exact test. Spearman's correlation coefficient (rho) was calculated to assess the strength of relation between various parameters. Differences were considered significant at $P<0.05$.

Table 1. Changes in oxidant/antioxidant markers in geriatric patients with acute poisoning with psychotropic drugs.

Parameter	Values at study stages			
	Control	Day 1	Day 3	Day 5
MDA, μmol/l	4.2 (3.74–4.59)	3.5 (2.9–4.22) [1]*p*=0.002*	3.52 (3.0–4.3) [1]*p*=0.008* [2]*p*=0.584	4.0 (3.12–4.8) [1]*p*=0.356 [2]*p*=0.007* [3]*p*=0.169
TAS, mmol/l	1.5 (1.28–1.59)	1.47 (1.27–1.91) [1]*p*=0.347	1.46 (1.24–1.7) [1]*p*=0.256 [2]*p*=0.437	1.57 (1.29–1.83) [1]*p*=0.237 [2]*p*=0.167 [3]p=0.182
MDA/TAS, c.u.	2.26 (1.86–2.76)	0.78 (0.67–1.02) [1]*p*<0.001*	0.86 (0.73–1.06) [1]*p*<0.001* [2]*p*=0.004*	0.93 (0.71–1.33) [1]*p*<0.001* [2]*p*=0.118 [3]*p*=0.520
NOx, μmol/l	27.2 (18.9–31.4)	15.8 (12.4–21.9) [1]*p*<0.001*	15.6 (8.12–23.5) [1]*p*<0.001* [2]*p*=0.846	15.4 (10.5–26.5) [1]*p*<0.001* [2]*p*=0.745 [3]*p*=0.634

Note. C.u. — conditional unit. [1] — differences between variables vs the control values (*P*<0.05) (Mann–Whitney test); [2] — versus Day 1 (*P*<0.017) (Wilcoxon test with Bonferroni correction); [3] — versus Day 3 (*P*<0,017) (Wilcoxon test with Bonferroni correction). * — significant differences. The data are given as *Me* (*Q25–Q75*).

Table 2. Changes in the oxidant-antioxidant markers in geriatric patients with acute poisoning with corrosive substances.

Parameter	Values at study stages			
	Control	Day 1	Day 3	Day 5
MDA, μmol/l	4.2 (3.74–4.59)	3.48 (3.34–4.05) [1]*p*=0.003*	3.81 (3.34–4.07) [1]*p*=0.010* [2]*p*=0.312	3.92 (3.16–4.28) [1]*p*=0.046* [2]*p*=0.431 [3]*p*=0.644
TAS, mmol/l	1.5 (1.28–1.59)	1.35 (1.19–1.65) [1]*p*=0.103	1.38 (1.2–1.57) [1]*p*=0.132 [2]*p*=0.312	1.19 (1.01–1.33) [1]*p*<0.001* [2]*p*<0.001* [3]*p*=0.018
MDA/TAS, c.u.	2.26 (1.86–2.76)	0.92 (0.78–1.18) [1]*p*<0.001*	0.99 (0.76–1.2) [1]*p*<0.001* [2]*p*=0.645	1.19 (0.94–1.4) [1]*p*<0.001* [2]*p*<0.001* [3]*p*=0.265
NOx, μmol/l	27.2 (18.9–31.4)	18.0 (11.2–23.4) [1]*p*=0.012*	16.7 (13.8–26.6) [1]*p*=0.004* [2]*p*=0.925	19.8 (13.3–24.1) [1]*p*=0.023* [2]*p*=0.728 [3]*p*=0.225

Note. C.u. — conditional unit. [1] — differences between variables vs the control values (*P*<0.05) (Mann–Whitney test); [2] — versus Day 1 (*P*<0.017) (Wilcoxon test with Bonferroni correction); [3] — versus Day 3 (*P*<0,017) (Wilcoxon test with Bonferroni correction). * — significant differences. The data are given as *Me* (*Q25–Q75*).

Results

Serum MDA concentrations in patients with PDP on both days 1 and 3 of hospital stay were significantly lower than the control values (by 16%). On day 5, they were close to the control values (Table 1).

No significant differences in TAS level versus the control group were found at all stages of the study. However, MDA/TAS ratio in this category of patients was 2.4–2.9 times (*P*<0.001) lower than the age-specific reference values at all stages of the study. Blood NOx level during the whole period of observation was 1.7 times lower than in the control group (*P*<0.001).

Table 2 presents similar changes of lipid peroxidation and antioxidant protection parameters in geriatric patients with CSP.

A significant decrease of MDA/TAS ratio during the whole study was observed. In the first two stages, the ratios were 2.4 and 2.3 times lower, respectively, versus the control group (*P*<0.001); on day 5, it increased up to 1.19 (0.19–1.4) c.u., which was 1.9 times below the reference value (*P*<0.001). The indicated changes in the oxidative stress coefficient by day 5 were due to a slight increase in lipid peroxidation and a significant decrease in the antioxidant plasma activity. There was a significant difference in the serum level of nitric oxide metabolites compared to the controls throughout the study (1.5, 1.6 and 1.4 times higher).

The data presented in Table 3 show that with a favorable outcome of the disease, there were no differences vs the baseline values in the blood levels

Table 3. The oxidant/antioxidant system parameters in favorable and lethal outcomes of acute poisonings with psychopharmacological drugs in geriatric patients.

Parameter	Control values (*n*=39)	Outcome					
		Favorable (*n*=33)			Lethal (*n*=16)		
		Day 1	Day 3	Day 5	Day 1	Day 3	Day 5
MDA, μmol/l	4.2 (3.74–4.59)	3.73 (2.95– 4.42) [1]*p*=0.028*	3.61 (2.92–4.31) [1]*p*=0.015* [3]*p*=0.276	3.69 (3.27–4.93) [1]*p*=0.026* [3]*p*=0.435 [4]*p*=0.835	3.47 (3.18–4.05) [1]*p*=0.002* [2]*p*=0.198	3.85 (3.33–4.24) [1]*p*=0.165 [2]*p*=0.276 [3]*p*=0.287	4.3 (3.7–4.43) [1]*p*=0.527 [2]*p*=0.165 [3]*p*=0.126 [4]*p*=0.476
TAS, mmol/l	1.5 (1.28–1.59)	1.6 (1.33–1.92) [1]*p*=0.645	1.6 (1.29–1.77) [1]*p*=0.745 [2]*p*=0.894	1.5 (1.26–1.78) [1]*p*=0.832 [3]*p*=0.745 [4]*p*=0.834	1.4 (1.27–1.88) [1]*p*=0.672 [2]*p*=0.378	1.46 (1.29–1.77) [1]*p*=0.728 [2]*p*=0.498 [3]*p*=0.827	1.67 (1.47–2.0) [1]*p*=0.698 [2]*p*=0.892 [3]*p*=0.038 [4]*p*=0.049
MDA/TAS, c.u.	2.26 (1.86–2.76)	0.77 (0.64–1.05) [1]*p*<0.001*	0.81 (0.71–0.98) [1]*p*<0.001* [3]*p*=0.598	0.93 (0.71–1.66) [1]*p*<0.001* [3]*p*=0.049 [4]*p*=0.167	0.79 (0.68–2.76) [1]*p*<0.001* [2]*p*=0.823	0.89 (0.76–1.03) [1]*p*<0.001* [2]*p*=0.623 [3]*p*=0.276	0.79 (0.65–0.96) [1]*p*<0.001* [2]*p*=0.287 [3]*p*=0.923 [4]*p*=0.027
NOx, μmol/l	27.2 (18.9–31.4)	15.7 (12.3–23.1) [1]*p*<0.001*	18.8 (11.8–24.4) [1]*p*<0.001* [3]*p*=0.267	20.2 (13.1–28.3) [1]*p*=0.004* [3]*p*=0.105 [4]*p*=0.328	15.8 (12.8–19.3) [1]*p*<0.001* [2]*p*=0.834	11.7 (4.62–20.6) [1]*p*<0.001* [2]*p*=0.046* [3]*p*=0.083	11.0 (8.02–23.0) [1]*p*<0.001* [2]*p*=0.034* [3]*p*=0.113 [4]*p*=0.623

Note. [1] - differences in parameters compared with the control values ($P<0.05$) (Mann–Whitney test); [2] — differences between groups (favorable and lethal outcome) ($P<0.05$) (Mann–Whitney test); [3] — versus Day 1 ($P<0.017$) (Wilcoxon test with Bonferroni correction); [4] — versus Day 3 ($P<0.017$) (Wilcoxon test with Bonferroni correction); * — differences are significant. The data are presented as *Me* (*Q25–Q75*).

of MDA and TAS on days 3 and 5. Meanwhile, a 1.3-fold increase in NOx level vs the initial value was seen by day 5.

The oxidative stress coefficient increased 1.2-fold from the baseline values by day 5 ($P=0.049$). In patients who died later, there was a trend toward increasing the MDA and TAS by day 5, whereas NOx level dropped 2.5 times lower than the control values ($P<0.001$). Meanwhile, the oxidative stress coefficient at all stages of the study was 2.9, 2.5 and 2.9 times lower versus control values ($P<0.001$).

In subjects with CSP and a favorable outcome, an increase in the initially low blood level of MDA and NOx and the corresponding «consumption» of TAS were observed by day 5 (Table 4).

A trend was detected toward an increase in the oxidative stress index: on Day 5 it was 1.12 times higher than the baseline values. In non-survivors we observed a decrease of oxidative stress index: by Day 5 it was 65% below the reference value ($P<0.001$) and 1.54 times lower than the baseline value ($P=0.063$). This was accompanied by a simultaneous decrease in blood MDA, NOx, and TAS levels at this stage of study.

In patients with PDP, a strong correlation between MDA and NOx was revealed at all stages of the study (on Day 1, $r=0.75$, $P<0.001$; on Day 3, $r=0.78$, $P<0.001$; on Day 5, $r=0.84$, $P<0.001$) and inverse intermediate and strong correlation between TAN and NOx (on Day 1, $r=-0.67$, $P<0.001$; on Day 3, $r=-0.74$, $P<0.001$; on Day 5, $r=-0.78$, $P<0.001$).

In patients with CSP, on Day 1 there was an intermediate strength correlation between NOx and TAN ($r=0.63$, $P<0.001$). At the second stage of the study, the correlation between these parameters was not significant ($r=0.23$, $P=0.025$). On Day 5, a significant intermediate strength correlation was found ($r=0.51$, $P=0.018$).

Discussion

Currently, lipid peroxidation and disorders of antioxidant protection are considered essential in the progression and outcome of various diseases, including acute poisoning [3, 4, 9]. The reactive oxygen species and free radical reactions under stress are known to perform a regulatory function and, with their adequate production, increase the body's resistance. However, excessive accumulation of peroxide products causes imbalance in the lipid peroxidation and antioxidant protection system, which contributes to the disruption of cellular structures and changes in their functional activity [7–9, 16–23].

The production of NO is an important link in the pathophysiology of oxidative stress. This active form of oxygen, which rapidly interacts with superoxide anion radical, forms the strongest oxidizing agent, peroxynitrite, which is involved in the initiation of oxidative stress. NO is also a powerful endogenous

Table 4. Comparative assessment of the oxidant/antioxidant system parameters in geriatric patients with acute poisoning with corrosive substances depending on the outcome.

Parameter	Control values (*n*=39)	Outcome					
		Favorable (*n*=22)			Lethal (*n*=9)		
		Day 1	Day 3	Day 5	Day 1	Day 3	Day 5
MDA, μmol/l	4.2 (3.74–4.59)	3.61 (3.39– 4.26) [1]*p*=0.019*	3.84 (3.3–4.18) [1]*p*=0.218 [3]*p*=0.187	4.0 (3.43–4.31) [1]*p*=0.329 [3]*p*=0.176 [4]*p*=0.285	3.35 (3.23–3.57) [1]*p*=0.006* [2]*p*=0.327	3.56 (3.35–3.78) [1]*p*=0.009* [2]*p*=0.219 [3]*p*=0.295	3.16 (3.1–4.28) [1]*p*=0.003* [2]*p*=0.094 [3]*p*=0.385 [4]*p*=0.178
TAS, mmol/l	1.5 (1.28–1.59)	1.36 (1.19–1.65) [1]*p*=0.179	1.37 (1.24–1.42) [1]*p*=0.139 [3]*p*=0.829	1.23 (0.99–1.4) [1]*p*=0.003* [3]*p*=0.003* [4]*p*=0.041	1.45 (1.29–2.43) [1]*p*=0.692 [2]*p*=0.132	1.38 (1.21–1.61) [1]*p*=0.193 [2]*p*=0.729 [3]*p*=0.149	1.13 (1.09–1.19) [1]*p*=0.004* [2]*p*=0.259 [3]*p*=0.167 [4]*p*=0.394
MDA/TAS, c.u.	2.26 (1.86–2.76)	0.96 (0.78–1.33) [1]*p*<0.001*	1.07 (0.85–1.33) [1]*p*<0.001* [3]*p*=0.828	1.08 (0.71–1.66) [1]*p*<0.001* [3]*p*=0.729 [4]*p*=0.839	1.22 (1.02–1.48) [1]*p*<0.001* [2]*p*=0.328	0.89 (0.76–1.03) [1]*p*<0.001* [2]*p*=0.428 [3]*p*=0.332	0.79 (0.65–0.96) [1]*p*<0.001* [2]*p*=0.182 [3]*p*=0.063 [4]*p*=0.628
NOx, μmol/l	27.2 (18.9–31.4)	17.5 (11.8–31.7) [1]*p*=0.008*	16.7 (13.9–26.1) [1]*p*=0.004* [3]*p*=0.628	20.4 (15.7–26.0) [1]*p*=0.078* [3]*p*=0.259 [4]*p*=0.217	22.2 (18.2–23.2) [1]*p*=0.176* [2]*p*=0.329	19.6 (14.2–26.6) [1]*p*=0.093* [2]*p*=0.294 [3]*p*=0.318	17.1 (13.3–19.5) [1]*p*=0.021* [2]*p*=0.145 [3]*p*=0.192 [4]*p*=0.584

Note. [1] - differences in parameters compared with the control values ($P<0.05$) (Mann–Whitney test); [2] — differences between groups (favorable and lethal outcome) ($P<0.05$) (Mann–Whitney test); [3] — versus Day 1 ($P<0.017$) (Wilcoxon test with Bonferroni correction); [4] — versus Day 3 ($P<0.017$) (Wilcoxon test with Bonferroni correction); * — differences are significant. The data are presented as *Me* (*Q25–Q75*).

vasodilator which alters tissue perfusion, decreases adhesion of leukocytes and platelets to the vascular endothelium, platelet aggregation, thus preventing the critical progression of the inflammatory response [10, 24–27].

The level of stable NO metabolites (NOx) has been found to increase due to elevated inducible NO-synthase (NOS) activity in systemic inflammatory response, sepsis, thoracic and abdominal trauma, as well as in rheumatoid arthritis, systemic lupus erythematous, etc.

In contrast, several studies have reported a decrease in blood NOx levels. Thus, in patients with preeclampsia, the blood NOx concentration is significantly lower than in women with normotensive pregnancy. The authors attributed this to the inhibition of endothelial constitutive NO synthase (NOS) [26, 28, 29]. In patients with myocardial infarction, a low blood level of NOx on day 1 was considered as a marker of severe disease and unfavorable outcome [24]. Thus, the contradictory data on NOx levels cannot be always definitively explained.

A decreased blood level of NOx compared with the control values was found in the patients with PDP and CSP at all stages of the study. However, a strong correlation between MDA and NOx was detected at all stages only in those with PDP. Thus, NO deficiency could be associated with inhibition of NOS activity. Previously, a significant increase in NO generation due to NOS activation was found in working-age patients with clozapine poisoning. In contrast, methanol poisoning was associated with a decrease in NO production by leukocytes (by 2 times) and platelets (by 6.4 times) compared to controls, as well as with a 16.5-fold decrease in blood nitrite level [24]. Currently there is no consensus on the interaction of the above-mentioned markers in various conditions and their role in the disease development.

In this study, abnormal parameters were assessed in relation to the control values. In elderly and senile patients with PDP and CSP, there was an inadequate response from the lipid peroxidation and antioxidant system manifested as a low peroxide potential due to a reduced level of NO and MDA at all stages of the study with low or normal values of TAS. The oxidative stress index during the study period was low. In our opinion, this indicates the development of oxidative stress, which contributes to a more severe disease in this age group compared with younger adults. Also, this could be due to the general low adaptive body potential, which we have previously found in geriatric patients with PDP [30].

A comparative assessment of peroxide homeostasis parameters in patients with various outcomes of PDP showed that in the survivors the level of

MDA and TAS during the study period did not differ from the initial values. At the same time, an increase in NOx level was detected by day 5. This situation resulted in an increase in the oxidative stress index, whose baseline value was 2.9 times lower than normal by day 5. In non-survivors, an increase in MDA and TAS by this stage of the study with low NOx values were found, which probably could not provide an increase in the initially low MDA/TAS ratio. This could suggest impaired self-regulation of the peroxide homeostasis system and worsened oxidative stress.

In patients who survived in CSP, an increase in the oxidative potential and MDA/TAS ratio was observed indicating physiological functioning of the lipid peroxidation and antioxidant system. In those who did not survive oxidative stress was obvious, as in patients with PDP. This was evidenced by a decrease in blood MDA, TAS, and NOx by day 5 associated with a drastic reduction of oxidative stress index.

Thus, in geriatric patients with acute poisoning by psychopharmacological drugs and corrosive substances, an inadequate response of the oxidant-antioxidant system is observed, which is manifested by reduced blood level of peroxidation products with normal or slightly reduced level of antioxidant protection components. Oxidative stress develops, and its progression results in death.

The limitation of this study consists in a small size of patient sample. Further research with a larger number of patients is required.

Conclusion

In elderly patients with acute poisoning by psychopharmacological drugs and corrosive substances, lipid peroxydation and antioxidant system occur manifesting as reduced blood levels of MDA and NOx with reduced or subnormal antioxidant protection parameters.

Reduction of oxidative stress index values in poisoning with psychopharmacological drugs and corrosive substances by 2.4–2.9 times and 1.9–2.4 times, respectively, at all stages of the study demonstrates the development of strong poison-induced oxidative stress.

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Choice of Anesthesia for Orthopedic Surgery in Elderly and Senile Patients (Review)

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Выбор метода анестезиологического обеспечения у пациентов пожилого и старческого возраста при ортопедических вмешательствах (обзор)

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Summary

Management of elderly and senile patients is a major challenge due to significant comorbidity, especially in surgery under general anesthesia.

The aim of the review was to identify the optimal method of anesthesia for knee arthroplasty in elderly patients based on the available clinical and experimental studies.

We searched PubMed, Medline, and Elibrary.ru databases for relevant sources. Out of more than 300 publications initially analyzed, 113 literature sources (dating from 1951 to 2021) were included in the review, of which 80 were published within the last five years (2016–2021). The inclusion criteria were high informative value and relevance, except for sources cited as historical references. Both randomized multicenter studies and individual case reports were included in the review. Exclusion criteria were low informative value, outdated and repetitive data.

We reviewed the physiology of elderly and senile patients, various variants of anesthesia, the use of neuroaxial anesthesia and peripheral regional blocks, xenon-based general anesthesia, assessed the advantages and drawbacks of each method, and discussed the monitoring of the depth of anesthesia and the issues of intraoperative awareness during knee arthroplasty in elderly and senile patients.

Conclusion. The choice of anesthesia for knee arthroplasty in elderly and senile patients should be based on the risks of decompensation of cardiovascular comorbidities and cognitive impairment. No known anesthetic method is ideal in terms of safety. The use of xenon as the main anesthetic seems promising due to its cardio- and neuroprotective properties. However, its use is limited due to relatively high cost. Therefore, the search for optimal (lower than recommended) inhalation concentrations may lead to expanding use of xenon in elderly and senile patients. At the same time, the use of lower concentrations of the drug is associated with the intraoperative awakening and the need for its combination with narcotic analgesics or amnestic agents, which may not be optimal. In addition, the protective effect of xenon retrograde amnesia against the stress of unintended intraoperative awakening has not been studied, and routine methods of monitoring the depth of hypnosis when using xenon often yield skewed measurement results inconsistent with the clinical manifestations of anesthesia.

Therefore, there is a need for further studies concerning the retrograde amnesic effect of xenon and search for optimal methods of assessing the depth of hypnosis when using this gas to safely reduce its inhalation concentration.

Keywords: xenon; EEG; monitoring the depth of hypnosis; intraoperative awakening; knee arthroplasty; anesthesia safety

Conflict of interest. The authors declare no conflict of interest.

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Introduction

The aging of the world's population is steadily increasing. According to the United Nations (UN), by 2050 there will be more than 1 billion people over the age of 60 [1]. In Russia, the average life expectancy in 2019 was 67.8 years for men and 72.9 years for women [2]. Another trend is an increase in the number of patients with degenerative and destructive diseases of large joints of the lower extremities, including osteoarthritis of the knee joints being a leading codition associated with activity limitation and disability [3–5]. According to current estimates, 18% of women and about 10% of men in the older age group have knee osteoarthritis, including severe one. Surgical intervention remains the most effective treatment option. Knee arthroplasty is a highly traumatic procedure which is often associated with severe pain in the postoperative period [6]. Medical management of such patients can be challenging due to multiple comorbidities, which is particularly true for surgical interventions under general anesthesia [7,8]. Therefore, the choice of anesthesia method is a major task helping select the safest possible technique with minimal risk of decompensation of comorbidities. The search for optimal anesthesia support for knee arthroplasty in elderly patients is still under way, and the problem has not yet been fully solved [6, 9, 10].

The aim of the review was to identify the optimal method of anesthesia in knee arthroplasty in elderly patients based on the available clinical and experimental studies.

We searched for sources in PubMed, Medline, and Elibrary.ru databases. From over 300 publications, 113 literature sources (dating from 1951 to 2021) were included in the review, of which 80 papers were published in 2016-2021. The inclusion criteria were high informative value and relevance, except for the sources cited as historical references. Both randomized multicenter studies and individual case reports were included in the review. Exclusion criteria were low informative value, outdated and repetitive data.

Physiological Characteristics of Elderly and Senile Patients

When planning anesthesia in elderly and senile patients, the physiology of the elderly organism should be considered together with the specific pharmacokinetics and pharmacodynamics of drugs used in the perioperative period.

More than 30% of patients in the older age group have three to five comorbidities. Age-related decline in body functions is inherent to aging and occurs at a rate of approximately 1% per year after the age of 40. There is a gradual decrease in the body reactivity, which in turn limits the adequate physiological response to stress factors, including surgical intervention, anesthesia, as well as preoperative preparation [11]. Age-related cardiac changes include impaired diastolic function and left ventricular hypertrophy, reduced number of cardiomyocytes, focal dystrophy of muscle fibers, increased connective tissue, reduced activity of sinus node, slower impulse conduction through interatrial septum, which can lead to reduced ejection fraction and arrhythmias. Sensitivity to catecholamines and acetylcholine increases, which can also provoke arrhythmias. In the elderly, reduced baroreceptor sensitivity and altered sensitivity to angiotensin II can result in a failure to adequately respond to intraoperative changes in blood pressure and hypovolemia. Increased arterial stiffness increases is associated with age-related destruction of collagen and elastin. Low exercise tolerance is essential when the ejection fraction can still be preserved, but drops on physical load due tio inability of the myocardium to fully respond by increasing the rate and contractility in accordance to the end-diastolic volume (volemia). Thus, the risk of ischemic organ and tissue damage increases [8, 11]. Decline of pulmonary function occurs mainly due to the reduction of pulmonary compliance and the number of elastic elements in lungs, resulting in increased risk of expiratory collapse of small bronchioles which causes an increase of dead space, reduction of diffusion capacity, and impaired gas exchange [8, 11]. Changes in the kidneys of older patients include their weight reduction up to 35%, loss of urine concentration and dilution capacity, caused by atrophy, mainly of cortical layer, and reduction of the number of active glomeruli. The ability to regulate sodium metabolism decreases, which leads to increased sodium retention and accumulation of fluid in the intercellular space. Renal dysfunction can also be associated with the nephrotoxic effect of long-term medications (nonsteroidal anti-inflammatory drugs, ACE inhibitors) [12]. There is a slowdown of drug biotransformation due to age-related atrophy of the liver parenchyma and reduction in the number of active hepatocytes, decreased enzyme activity and slowed metabolism with the hepatic blood flow reducing by 10% every 10 years after the age of 50. Activity of cytochrome P-450 enzymes, phase I and phase II nonmycrosomal oxidation enzymes of hepatic metabolism is impaired, resulting in a hepatic extraction clearance decrease of up to 40% [12].

Impaired cerebral vascular function, reduced concentration of such neurotransmitters as dopamine, acetylcholine, norepinephrine and serotonin contribute significantly to the development of delirium and cognitive impairment in the postoperative period. In the elderly, there is a decrease in the epidural space and cerebrospinal fluid volume.

In peripheral nerves, the distance between schwann cells decreases which increases sensitivity of the elderly to neuroaxial techniques and blockades. Decreased parasympathetic and increased sympathetic tone leads to a limited compensatory increase in heart rate and blood pressure when preload rises.

Frequent anemia in the elderly is probably associated with resistance to erythropoietin and «aging» of stem cells. Decreased immunity leads to ineffective infection resistance and prevents rapid healing of wounds [12]. In older patients, the proportion of adipose tissue increases up to 40% and that of water up to 15% of the total body weight, while the muscular mass decreases, even if a constant weight is maintained. Decreased muscle mass and function and reduced mobility increase the rate of thromboembolic complications [11].

The changes in pharmacokinetics and pharmacodynamics in elderly and senile patients are also remarkable. Aging is accompanied by a decrease in plasma albumin by an average of 10–25% due to reduced protein intake and hepatic protein synthesis. Hypoalbuminemia leads to a decrease in the protein-bound fraction of medications and an increase in the concentration of the free fraction, which alters the drug distribution and increases their pharmacological activity with increased risk of overdose and toxic reactions [13]. Minimum alveolar concentration (MAC) of inhaled anesthetics decreases approximately by 6% every decade after 40 years. For intravenous hypnotics (propofol) a 20% reduction in induction dose is required. Respiratory arrest due to low clearance of drugs in chronic renal failure is the major complication due to opioids in the elderly. Sensitivity to fentanyl increases and its activity doubles with age presumably because of sensitization of brain receptors. Pharmacodynamics of muscle relaxants does not change significantly with age. Pharmacokinetics may change toward an increase in duration of drug action due to reduced hepatic metabolism and renal function. The use of local anesthetics in elderly patients is not associated with an increased risk of adverse events, but systemic toxicity should be considered when choosing these drugs [8].

Types and Methods of Anesthesia Support for Total Knee Arthroplasty

Both general anesthesia and regional methods are used for anesthesia during total knee arthroplasty (TKA). The regional anaesthesia is considered the method of choice [14, 15] associated with less intra- and postoperative stress and more reliable block of nociceptive afferent signaling. «Standard» general anesthesia often does not provide adequate protection of the central nervous system from perioperative stress due to the complexity of selecting a timely adequate dose of intraoperative opioid analgesics [15]. Therefore, anesthesiologists can use combined anesthesia, which is especially relevant in elderly patients, adding various components of regional methods to ensure sufficient anesthesia and minimize the risk of complications.

General Anesthesia

Currently, second- and third-generation halogenated anesthetics (isoflurane, sevoflurane, desflurane) are most commonly used for anesthetic support of surgical interventions. They all have an identical mechanism of action, which consists in enhancing the inhibitory effect of GABA by interaction with GABA receptors of the central nervous system [16, 17].

The advantages of general anesthesia based on halogenated anesthetics include their availability, low cost and compatibility with a wide range of anesthesia machines. Moreover, additional training of physicians switching to these anesthetics is not required. The distinct bronchodilator effect, sufficient myorelaxant properties, the effect of anesthetic preconditioning of the myocardium typical of this group of anesthetics can also be emphasized [18–20].

At the same time, these anesthetics may cause side effects and complications in older patients. Thus, isoflurane, a second-generation inhalation anesthetic, may irritate bronchial mucosa, increase bronchial gland secretion and mucus accumulation in the airways, which subsequently may lead to bronchial obturation and lung atelectasis [16]. Halogenated anesthetics in high concentration (more than 1 MAC) reduce peripheral vascular resistance, left and right ventricular contractility, left ventricular diastolic function, and baroreceptor-mediated reflex control of blood pressure [21], which may affect patients with limited cardiovascular functional capacities. Halogenated anesthetics can also act as triggers of malignant hyperthermia [22–24].

The perioperative use of narcotic analgesics as a component of general anesthesia in elderly patients increases the risk of cognitive impairment with possible delirium [25, 26]. This requires additional sedation, hampers early activation, and can certainly lead to an increased risk of failure of cardiovascular compensatory capacity, decompensation of comorbidities, and various complications, including infectious ones, and can result in a prolonged hospital stay.

Currently, tracheal intubation is by far the most common, efficient and reliable technique for airway maintenance. However, this method has several limitations including invasive character and

possible traumatic effect (direct laryngoscopy, tracheal intubation, cuff overblowing with the risk of tracheal wall damage, injury to esophagus and bronchi), hyperdynamic response of blood circulation, laryngeal mucosal edema, laryngospasm, and requirements for muscle relaxants and narcotic analgesics [27].

In recent decades, the use of laryngeal masks (supraglottic airway devices) as an alternative to tracheal intubation has become widespread worldwide. First described by British anesthesiologist Archibald Brain in 1983, the laryngeal mask quickly gained popularity worldwide [28]. And already in 1992, 59% of all general anesthesias in Great Britain were performed using this supraglottic airway [29]. It is placed non invasively and lacks negative aspects associated with tracheal intubation [30, 31].

The use of laryngeal mask has practically no adverse effect on pharyngeal and laryngeal structures thereby reducing the risk of their injury. Mask placement in laryngeopharynx causes minimal reflexogenic and hemodynamic changes and is better tolerated by patients after surgical intervention [32]. This technique also has its limitations. In particular, the laryngeal mask should not stay in oropharynx more than 4 hours, it is relatively contraindicated in patients weighing over 100 kg and fully contraindicated in those in prone position. Complications include oral mucosal injury, hematoma, rarely arytenoid cartilage dislocation or laryngeal and recurrent laryngeal nerve paralysis. A laryngeal mask is also not recommended if the patient is not deeply sedated [28].

Neuraxial Blocks

Spinal anesthesia is one of the modern methods widely used in knee arthroplasty surgeries. The main risks of spinal anesthesia are severe hypotension, bradycardia due to severe sympathetic block [33, 34] and, as a consequence, possible cardiovascular deterioration. Usually, the period of anesthesia when using this method lasts no more than 11–13 hours, and is realized by using adjuvants (clonidine, morphine), among others. The use of adjuvant drugs can lead to such side effects as respiratory depression, nausea, vomiting, profound sedation, urinary retention, skin itching, and hypotension [35]. Despite all the positive effects and cost-effectiveness, the role of this method for postoperative pain management is questionable due to the possible negative effects of adjuvants [15].

Epidural analgesia could be considered rather effective method of anesthesia during knee arthroplasty surgery. This method, as well as the perioperative use of opioid analgesics, provides sufficient analgesia and its efficiency is not inferior to that of peripheral nerve blocks [35]. Some evidence suggests that the use of regional anesthesia techniques in older patients reduces the risk of delirium [36]. The most serious disadvantages of neuraxial blocks include infectious complications at the injection site and post-dural puncture headache [37]. In modern anesthesiology, epidural analgesia should be used on strict indications with the mandatory assessment of risk/benefit ratio [38].

Peripheral Nerve Block

Peripheral nerve block is an effective method with a high safety profile. It effectively relieves acute postoperative pain, according to several studies, prevents its persistence [39], as well as reduces the use of opioid analgesics, and, as a result, increases patient satisfaction with the quality of treatment [40]. There is an opinion that peripheral nerve blocks of the lower extremities can promote motor neuropathy of the quadriceps femoris muscle [41], which can slow down motor function recovery and thus increase the risk of patient falls [42]. L.Turbitt et al. list the factors increasing the risk of inpatient falls which include male sex, water and electrolyte disorders, obesity, delirium, old age and anemia. The researchers found no significant relationship between the incidence of falls and the method of analgesia: with general anesthesia, the risk of falls was 1.6%, while with peripheral nerve blocks, it was 1.3% [43].

Systemic toxicity of local anesthetics in various regional blocks was also reported [35]. All currently used local anesthetics are effectively employed for infiltration anesthesia, but the anesthetics with the longest duration of action and the least toxicity are still preferred. Levobupivacaine and ropivacaine have a clinical profile similar to bupivacaine, however, these three drugs have different strength of analgesic effect: bupivacaine > levobupivacaine > ropivacaine [14]. Lower toxicity suggests the use of levobuvicaine and ropivacaine in sutuations where the risk associated with unintentional intravascular injection or overdose is high, e.g., in peripheral nerve blocks. With its low toxicity, ropivacaine can be considered the anesthetic of choice for regional blocks of the lower extremities, given its adequate analgesic effect and duration of action.

Despite uncommon side effects, regional blocks have a high safety profile and minimally affect hemodynamic parameters in elderly and senile patients, which is critical for patients with low functional capacities.

Ultrasound Navigation in Peripheral Nerve Blocks

The long-term experience of performing peripheral nerve blocks under ultrasound (US) control has conclusively demonstrated their usefulness.

According to experts, there is no significant advantage of ultrasound navigation over neurostimulation [38] when performing peripheral blocks. Important advantages of ultrasound navigation include visualization of the needle tip and surrounding tissues, as well as the visual assessment of anesthetic distribution, which ultimately results in shorter procedure time [44], lower volume of injected anesthetic, and, consequently, lower risk of systemic toxicity. The risk of postoperative neuropathy is believed to decrease when using ultrasound control due to the possibility of nerve visualization and prevention perineural injection of anesthetic, which cannot be completely avoided when using neurostimulation due to the specific character of the nerve motor response [45]. The main limitations of ultrasound navigation are the cost of ultrasound devices and the need for additional training of physicians.

Thus, there is no ideal anesthesia techniques with all of them having obvious pros and cons. The choice of anesthesia technique is particularly difficult in elderly patients with comorbidities. In knee arthroplasty in this group of patients, anesthesia should meet such requirements as sufficient analgesic effect with minimal use of opioid analgesics, cardio- and neuroprotective properties with no significant effect on hemodynamics. These beneficial effects allow to avoid postoperative decompensation of vital organs.

A combination of peripheral nerve conduction block of the lower extremity and xenon-based general anesthesia with a laryngeal mask can satisfy these requirements. Moreover, the use of xenon alone anesthesia has certain limitations reported in the literature.

Xenon

Xenon (Xe) is called a «noble» gas because it is present in the atmosphere in very small concentration of as low as 0.0000087%. Xenon was first discovered by the English scientists W. Ramsay and M. Travers in 1898. They performed slow evaporation of liquid air and spectroscopic examination of its most volatile fractions. This gas is used in the manufacturing of lasers, filling the incandescent light bulbs, passivation of metals, X-ray tubes, in the space industry, as well as in medicine for sedation and anesthesia [46, 47]. For about 70 years xenon has been used in anesthesiology [48]. During this time, a large body of clinical data has been accumulated demonstrating its safety and efficacy [49], absence of teratogenic and toxic properties [50]. Various studies have shown numerous benefits of xenon when compared with inhaled anesthetics of other classes. Xenon has the lowest blood/gas solubility ratio (0.14) which is responsible for a faster onset and termination of action [51]. The gas does not depress cardiovascular psrsmeters maintaining hemodynamic stability [52] and possesses neuro- and organoprotective properties which is very important in elderly patients with comorbidities [53, 54]. It has adequate analgesic properties [55].

Moreover, xenon is characterized by high-level environmental safety and lacks ozone-depleting properties. Wide use of xenon anesthesia in clinical practice is impeded by its high cost and the need for a special closed circuit of anesthesiological and ventilatory equipment, as well as additional staff training for working with xenon. Recycling techniques, improved technology of xenon production and use, avoidance of open circuit inhalation could reduce the cost of anesthesia and provide a rationale for its broader administration [56].

Mechanisms of Anesthetic Action of Xenon

Mechanisms of action and «targets» of xenon remain unclear. Some researchers believe that xenon acts through inhibition of N-methyl-D-aspartate (NMDA) receptors). N.Franks et al. demonstrated 60% inhibition of NMDA-receptor activity on exposure to xenon at concentration of up to 80% [57]. Xenon differs from other drugs blocking NMDA receptors in inhibiting 5NT3-receptors responsible for postoperative nausea and vomiting, as well as central and peripheral nociception [58].

Anesthesiological Aspects of Xenon Use

The minimum alveolar concentration of xenon ranges from 63 to 71% [59]. For this reason, its use for monoanesthesia is hazardous due to the dangerous reduction of inhaled oxygen fraction below 30% for reaching the 1 MAC level, which can be especially harmful in patients with limited functional capacities. The awakening MAC of xenon is 33% (0.46 of 1 MAC), which is less than that of nitrous oxide (0.61 MAC) but greater than that of the second- and third-generation halogenated anesthetics sevoflurane and isoflurane (0.35 MAC). Prolonged inhalation of xenon mixture had no effect on the ultimate prolongation of awakening time [60]. Faster recovery of consciousness in patients receiving xenon versus propofol anesthesia was clearly demonstrated (3 min 11 sec vs. 25 min 23 sec), as well as faster awakening and recovery period in patients older than 60 years (260 sec vs. 590 sec) [61]. In elderly and senile patients, awakening after anesthesia with xenon, compared with desflurane, was also faster, with complete cognitive restoration within half an hour after the end of anesthesia [62].

V. Likhvantsev describes xenon performance as follows: «In some cases, for example, for gastric resection, its use as a single agent is enough, while

in other cases it is not sufficient for a routine hernioplasty» [63]. In the clinical setting, an increased frequency of postoperative nausea and vomiting (PONV) in patients after anesthesia with xenon mixture vs propofol anesthesia has been reported [58]. Frequency of postoperative nausea and vomiting was 66.2% in xenon anesthesia group and 26.8% in propofol group, according to M. Coburn et al. data [64]. Pharmacoeconomic burden of xenon anesthesia varies from about $60 per 1 liter of xenon in USA to 30$ and higher in European countries [65]. Possible prospects of cost reduction are still remote. According to our own data, the average consumption of xenon gas in cost-effective automatic mode of Taem (France) apparatus is about 20 liters during a 3-hour long anesthesia. Moreover, not all current anesthesia machines are able to operate on a closed circuit, as required for economic consumption of xenon and its further recycling.

Effect of Xenon Znesthesia on the Cardiovascular System

According to literature and clinical data, xenon inhalation anesthesia is characterized by stablility of hemodynamic parameters and lack of cardiovascular adverse effects in the perioperative period [66-70]. The repeatedly recorded and clinically observed decrease in heart rate during xenon anesthesia can be explained by its impact on the sympathetic/vagal balance [71]. A 2018 meta-analysis, which included 13 studies, compared xenon anesthesia with propofol-based total intravenous anesthesia. Xenon anesthesia was shown to provide higher mean arterial pressure (MAP) values in the intraoperative period (87.5±14.06 mmHg with xenon vs 80.3±14.53 mmHg propofol; $P<0.01$), lower heart rate (56.75±10.78 beats per minute with xenon, 65.87±12.37 beats per minute with propofol; $P<0.01$) [59]. More severe decrease of heart rate in xenon anesthesia in comparison with propofol has been described by J. Höcker et al, the frequency of vasopressor drugs did not differ between the groups [72]. The authors, who based their studies on stability of epinephrine and cortisol levels in plasma, believe that hemodynamic stability during xenon anesthesia is due to sympathetic activation in response to surgical stress [73]. A. Belov et al. have shown that hemodynamic parameters were more stable throughout the surgery in xenon group compared with nitrous oxide group during endoscopic operations in gynecology [74]. Animal studies have demonstrated cardioprotective properties of preconditioning with xenon during a 60-minute occlusion of anterior interventricular artery in pigs [75]. In other experiments, no significant differences were observed between patients who had inhalation anaesthesia with 50% xenon mixture, those who had 50% nitrous oxide and 95% oxygen anesthesia. The coronary perfusion pressure was 44±1 mmHg in the 95% O_2 group, 40±1 mmHg in the 50% Xe group, and 38±2 mmHg in the 50% N_2O group, left ventricular perfusion pressure was 102±3 mmHg in the 95% O_2 group, 66±3 mmHg in the 50% Xe group, and 73±4 mmHg in the 50% N_2O group. The decrease in these parameters when using anesthetics was mainly due to overall reduction of oxygen delivery (DO_2) associated with the reduction of its fraction in the breathing mixture (it was 130±4 ml/min with 95% O_2 and 66±2 ml/min with 45% O_2) [76]. In an experiment of 60 male rats subjected to 60-minute coronary artery occlusion and then 120-minute reperfusion, the xenon group showed a smaller reduction in cardiac output (62±9%) than the isoflurane group (49±7%) after 4 weeks [77]. Experiments with pigs administered with 70% xenon have demonstrated cardiac output reduction by 30% on average and increase in pulmonary artery compliance by 60%, which resulted in right ventricular ejection fraction reduction by 25% [78]. Another study has revealed that 20% xenon in combination with hypothermia down to 34°C, reduced infarct size in rats who underwent 25-min coronary artery occlusion followed by 120-min reperfusion [79]. In an experiment performed on rabbits with left ventricular dysfunction (after coronary artery ligation), inhalation of 50% xenon neither reduced myocardial function nor caused significant ECG changes [80].

Neuroprotective Effects of Xenon

The neuroprotective effects of xenon have been clearly demonstrated [81].

The damaging effects on the brain in hemorrhagic or ischemic stroke, traumatic brain injury, and cardiac arrest have a similar pathogenesis, realized through the mechanism of excitotoxicity directly involving the NMDA. The mechanisms determining neuronal damage are multifactorial, but excitotoxicity is the major one. NMDA-receptor activity is important for many neurological functions, which require synaptic compliance, mood control, memory formation, motivation, progression of brain activity and neuronal survival [82–85]. At the same time, excessive activation of NMDA receptors under stress conditions can lead to neuronal death, a process described as excitotoxicity [83, 86]. It occurs when neurons are exposed to high doses of glutamate, which leads to increased calcium influx through calcium channels and activates an excessively high inflow of extracellular calcium [87, 88]. Excitotoxicity is the underlying mechanism of many neurodegenerative disorders, both acute (brain injury, stroke) and chronic (Parkinson's disease, Alzheimer's disease). After obtaining data on the

mechanism of action of xenon (NMDA-receptor inhibition), several papers have been published on the protective effects of xenon on experimental neuronal cell cultures exposed to glutamate or oxygen-glucose deprivation [89, 90].

Xenon can realize neuroprotection by acting on bipolar potassium channels (TREK-1) which provide an ionic current reducing neuronal excitability and protecting neurons from damaging effects (a similar mechanism has been reported for the preconditioning effect of sevoflurane [58]).

Currently, there is an ongoing discussion about the importance of adenosine triphosphate (ATP)-sensitive potassium channels of the cell membrane in the mechanism of neuroprotective effects of xenon. In vitro studies have shown that in neuronal culture xenon exhibited protective effects due to activation of ATP-sensitive potassium channels in the outer cell membrane [91].

In traumatic brain injury, according to experimental data, prolonged inhalation of xenon (at least for 3 hours) improved vestibulomotor function and memory in the late period of injury. The neuroprotective effects of xenon were shown to be associated with a decrease in neuroinflammation in the brain areas that play a role in the implementation of associative memory. Xenon showed its neuroprotective properties up to 20 months after the injury episode [92].

A review paper reported that inhalation of xenon after a transient ischemic attack in rats resulted in reduction of the infarct volume and neurological deficit within 7 days after the ischemic episode [53].

R. Laitio et al. have shown that inhalation of 40% xenon combined with hypothermia during 24 hours after an out-of-hospital cardiac arrest leads to less brain damage in comparison with hypothermia alone. This was further confirmed by magnetic resonance imaging. Half-year mortality was 27% in the xenon group with hypothermia and 35% in the hypothermia alone group. The difference between the groups, though, was not significant (p=0.053) due to insufficient sample size (110 patients). Similar results were obtained in other experiments [93, 94].

The Problem of Intraoperative Awareness and Assessment of the Depth of Hypnosis with Xenon

Despite the above-mentioned advantages of xenon for anesthesia in high-risk patients, there are also several challenges in its use in anesthesiology. In particular, this refers to objective instrumental assessment of the depth of hypnosis, which is directly related to the issue of intraoperative awareness.

The American Society of Anesthesiologists (ASA) has recognized the importance of studying intraoperative awareness episodes and in March 2007 opened a registry to collect detailed and current information to increase knowledge about intraoperative awareness and its risk factors. Unintended awareness during operation can occur in patients for a variety of reasons. After such episodes, patients may develop postoperative psychological disorders of varying severity [95]. Sleep disturbances are observed in 19% of patients, nightmares in 21%, fear of anesthesia in 20% of patients, and persistent anxiety in 17%. Delayed psychological signs that can lead to posttraumatic stress disorder were first described by Meyer and Blacher in 1961. According to Samuelsson et al, these symptoms develop in 33% of patients who have had an episode of intraoperative awareness [96]. However, the rate of intraoperative awareness episodes has decreased from 1.2% and 0.8% in the 1960s and 1970s to the current rate of 0.1–0.2% as anesthesia techniques have improved [97, 98].

To prevent intraoperative awareness, including in operations with inhalation anesthetic concentration below 0.7 MAC, preoperative low-dose midazolam, subanesthetic doses of ketamine, or preventive myorelaxant antidotes on hypnotic discontinuation at the end of surgery or a combination of general inhaled anesthesia with regional anesthesia should be considered [99].

The use of hypnotic depth monitoring is intended to reduce the frequency of intraoperative awareness episodes and can also be useful for preventing excessive sedation, which may lead to increased risk of cognitive decompensation, especially in elderly and senile patients [100, 101]. Researchers are still seeking ways to effectively assess the depth of xenon hypnosis, but the issue remains poorly understood.

The most common and generally accepted method for objective instrumental assessment of hypnotic depth is bispectral index (BIS) monitoring. Several studies report relatively low informative value of BIS during xenon anesthesia [102]. The BIS algorithm is based on the electroencephalogram (EEG) database validated on the drugs interacting with GABA receptors (propofol), and this method is completely inappropriate for anesthetics with NMDA-blocking properties (ketamine, xenon) [103, 59]. The literature data on relationship between BIS values and clinical presentation are inconsistent [104]. J. Höcker et al. made conclusions about the possible comparability of BIS monitoring parameters during anesthesia with xenon mixture and propofol anesthesia in elderly patients, but at the same time the authors were not entirely confident in their findings [105].

In the early 2000s, a digital method of spectral assessment of EEG based on entropy was introduced [106]. In their studies evaluating BIS values and entropy changes during propofol and xenon anesthesia, Höcker J. et al. showed that entropy level was significantly lower than the similar BIS index level in xenon anesthesia group, while in propofol group the data were comparable [72]. Laitio R. et al. in their study reported that BIS and entropy monitoring data correlated with the clinical presentation in the main phase of surgery during deep anesthesias but were not consistent with the clinical picture during the induction phase and at the end of anesthesia, during awakening, when xenon was used. Thus, the use of BIS and entropy monitoring techniques during xenon anesthesia appears to be only an adjunctive method and should not downplay the clinical presentation assessment [107].

The method based on the measurement of auditory evoked potentials (AEPs) can be used in assessing the depth of hypnosis and during the awakening phase [108]. This monitoring technique uses the mechanism of measuring the attenuation of evoked auditory potentials during surgical treatment under the impact of drugs used during anesthesia. An increase in latency and a decrease in AEP peaks corresponds to an increase in anesthetic concentration and directly correlates with the level of sedation of the patient. In a randomized study including 60 patients anesthetized with xenon, sevoflurane, and isoflurane in combination with epidural anesthesia, Goto T. et al. demonstrated that AEPs significantly correlated with clinical picture of awakening and recovery after anesthesia [109]. The technique of AEP is not commonly used in clinical practice, and no data on inconsistency of its results with the clinical presentation when xenon is used have been found.

EEG monitoring provides more complete and objective information about the depth of hypnosis compared with processed EEG parameters (BIS, EAP, entropy) even after the use of muscle relaxants, hypnotics or narcotic analgesics [110]. When the patient is awake, the raw EEG usually has predominant beta activity (20 to 30 Hz), the awake patient with eyes closed has sequential alpha rhythm waves (8–14 Hz) with an increase in slow-wave Theta (4–8 Hz) and Delta rhythms (0.5–3 Hz) noted during the transition from the initial to deep sleep stage [111]. The raw EEG waveform during general anesthesia varies depending on the classes and combinations of anesthetics administered and appears to be more valuable when specially trained specialists are available in the operating room. There is convincing evidence showing the feasibility of assessing the depth of hypnosis based on EEG changes during anesthesia using the validated Kugler scale, in which the stages of sedation depth are divided into 16 levels depending on the predominance of EEG rhythm type at the time of signal recording [112]. In clinical practice, this is difficult to implement due to the need to decode the EEG signals obtained during surgery in the operating room.

The character of EEG changes during xenon anesthesia was discussed in selected papers, which can be used to assess the depth of hypnosis. The electroencephalogram changes are identical during anesthesia with xenon mixture and nitrous oxide. A decrease in the activity of alpha rhythm and increase in theta and delta waves are observed as the concentration of gas in the mixture increases [107]. V. Potievskaya et al. evaluated EEG changes during inhalation of xenon-oxygen mixture and pointed out that with increasing concentration of xenon-oxygen mixture on inhalation, a clinically evident increase in the depth of sedation (up to –2 points on the RASS scale) is seen, along with the replacement of the fast-wave alpha rhythm by slow-wave theta and delta waves and subsequent gradual recovery to their original ratios with decreasing xenon concentration in the inhaled mixture [113].

The literature data on EEG changes corresponding to xenon anesthesia stages, comparable with the validated Kugler scale, cases of intraoperative awakening associated with xenon anesthesia, as well as retrograde amnesia effect when using xenon were not found. This issue requires an additional research.

Conclusion

The choice of anesthetic method for knee arthroplasty in elderly and senile patients requires assessment of the risks of decompensation of cardiovascular and cognitive disorders. None of the known methods of anesthesia is ideal in terms of safety. The use of xenon as the main anesthetic seems promising with regard to its cardioprotective and neuroprotective properties. However, its use is limited by relatively high cost, and therefore, the search for optimal (reduced compared with the recommended) concentration on inhalation may expand its administration in elderly and senile patients. However, lower xenon concentrations are associated with intraoperative awareness and the need for its combination with narcotic analgesics or amnestic drugs. In addition, the effect of retrograde amnesia of xenon to protect the patient from intraoperative stress of unintended intraoperative awareness has not been studied, and routine methods of hypnotic depth monitoring when using xenon often produce results that do not correlate with the clinical presentation. Therefore, further research is needed to examine the effects of xenon on retrograde amnesia and to find optimal methods for assessing the depth of hypnosis on xenon to safely reduce its concentration on inhalation.

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Current View on the Use of Extracorporeal Detoxification Methods for the Treatment of Rhabdomyolysis (Review)

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Современный взгляд на применение методов экстракорпоральной детоксикации при рабдомиолизе (обзор)

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Summary

Rhabdomyolysis is a syndrome caused by destruction and necrosis of muscle tissue, which is accompanied by the release of intracellular contents into the systemic circulation. The etiology of rhabdomyolysis is multifaceted, however, regardless of the etiological factor, the central element of its pathophysiology is systemic endotoxemia with multiple organ failure syndrome. Acute renal failure is one of the most common manifestations of organ dysfunction. Considering the pathogenetic model of the development of systemic endotoxemia, the timely use of extracorporeal therapy, which reduces mortality in organ failure, seems promising. All the current types of extracorporeal therapy can be divided into convection (hemofiltration), diffusion (hemodialysis), convection/diffusion (hemodiafiltration), sorption (hemoperfusion) and plasma exchange (plasmapheresis, plasma exchange, plasma sorption, etc.) methods based on physical principle.

The aim of the review was to summarize the available clinical data on extracorporeal treatments for rhabdomyolysis and to assess the feasibility and best indications for these methods based on the current pathogenetic model of rhabdomyolysis.

Material and methods. The search for information was carried out in the Web of Science, Scopus, Medline, PubMed, RSCI, E-library and other databases. Eighty-one sources were identified containing current therapeutic approaches and relevant data of clinical and scientific research on the subject of this review.

Results. In this review, the main etiological, epidemiological and pathogenetic models of acute renal injury in rhabdomyolysis have been discussed. The main methods of extracorporeal therapy have been reviewed and evaluated based on current understanding, and latest clinical data on their effectiveness have been summarized.

Conclusion. The choice of the optimal extracorporeal treatment method, the time of initiation and duration of the procedure still remain controversial. The solution to this issue can potentially help to better correct the electrolyte disturbances and could protect against organ dysfunction, which would improve the outcome in patients with rhabdomyolysis.

Keywords: rhabdomyolysis; acute kidney injury; renal replacement therapy; plasma exchange; selective hemoperfusion; review

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Introduction

The incidence of acute kidney injury (AKI) in rhabdomyolysis ranges from 10 to 55% [1–5]. Moreover, rhabdomyolysis accounts for 5–25% of all causes of AKI, and mortality among patients with rhabdomyolysis complicated by AKI is over 10% [6-9]. Myoglobin plays a specific and significant role in the pathogenesis of AKI in rhabdomyolysis, causing endogenous intoxication. For eliminating myoglobin from the bloodstream, various methods of extracorporeal detoxification (ECD) are included in the management of rhabdomyolysis [11–13]. The effectiveness of various ECD techniques at different stages of this condition remains controversial. According to current literature, the most effective methods include hemodiafiltration and hemofiltration, or hemodialysis using ultrahigh-flow membrane [11, 14–16]. Many studies report the use of ECD in rhabdomyolysis associated with plasma separation, as well as non-selective methods apheresis, such as plasmapheresis and plasma exchange. The use of these methods, however, is limited by their insufficient safety and efficiency [17–19]. Currently, selective hemoadsorption appears to be the most promising and safe among them. However, this method is most widely used in the treatment of patients with sepsis and septic shock [20].

The choice of optimal and safe method of extracorporeal treatment is an important challenge of current medicine, and the data on the effectiveness of various machines in patients with rhabdomyolysis complicated by AKI are lacking in the available literature.

Definition and Epidemiology

Rhabdomyolysis is a clinical and laboratory syndrome that develops as a result of damage and destruction of myocytes of skeletal striated muscle tissue, accompanied by the release of myolysis products into the bloodstream and toxemia of varying severity [21, 22]. The incidence of rhabdomyolysis remains unknown, but risk groups have been identified (patients with elevated body mass index of 40 kg/m^2 or more, those taking long-term hypolipidemic therapy or patients after surgery) [23].

The most life-threatening and common complication of rhabdomyolysis is acute pigmented nephropathy, often referred to as «myoglobinuric acute kidney injury».

The incidence of acute kidney injury (AKI) in rhabdomyolysis ranges from 10 to 55% [24, 25]. Moreover, rhabdomyolysis underlies 5–25% among all causes of AKI [26, 27], and mortality among patients with rhabdomyolysis complicated by AKI reaches 10% [28, 29].

According to literature data, rhabdomyolysis is caused by various exogenous intoxications (alcohol and drugs) in 60% [30, 31]. Long-term compression syndrome (crush syndrome) is also one of the frequent causes of this syndrome [32, 33]. Excessive physical activity often leads to exertional rhabdomyolysis [34–36]. Rhabdomyolysis occurring with the malignant hyperthermia during general anesthesia also was reported [37]. In general, the etiological factors of rhabdomyolysis include physical (trauma, electrical injuries, hyperthermia, burns) and non-physical (toxic substances, drugs, metabolic myopathies, electrolyte disorders, infectious diseases, endocrinological disorders) ones.

Pathogenesis of Acute Kidney Injury in Rhabdomyolysis

The most frequent and life-threatening complication of rhabdomyolysis is AKI, which largely determines the outcome of the disease [38]. In the pathogenesis of rhabdomyolysis-associated AKI three main mechanisms were identified, including renal vascular constriction, formation of renal tubular casts, and direct cytotoxic effect of heme [39, 40].

Myoglobin plays a specific and significant role in the pathogenesis of AKI in rhabdomyolysis. During filtration, myoglobin freely passes through the basal glomerular membrane and accumulates in the renal tubules. In the tubules, due to water reabsorption, myoglobin concentration increases, which leads to its precipitation and formation of casts which obstruct the tubular lumen [41, 42]. In addition, myoglobin potentiates smooth muscle spasm, leading to renal vasoconstriction, which along with dehydration increases water reabsorption and reduces fluid flow in the renal tubules [43–45].

Massive damage of muscle tissue results in a significant increase in urinary production and excretion of uric acid with the formation of crystals, which further obstruct the tubular lumen. Myoglobin and uric acid precipitation is also promoted by intravesical acidosis [46].

Free iron released as a result of myoglobin breakdown has a damaging effect on the kidneys. Free iron can activate lipid peroxidation with the production of free radicals that have a cytotoxic effect on the renal tubules [47, 48].

Moreover, dehydration underlying early rhabdomyolysis can lead to systemic hypoperfusion with associated organ ischemia, including intestines. Intestinal ischemia leads to translocation of microflora into the bloodstream with the development of endotoxinemia, cytokinemia and, later, sepsis and septic shock. These conditions worsen renal hypoperfusion and promote progression of AKI [49, 50].

The Use of Extracorporeal Detoxification Methods in the Treatment of Rhabdomyolysis

After skeletal muscle injury, various substances enter the systemic circulation, causing endogenous intoxication. Given the developing failure of detoxification systems, the use of methods eliminating these substances from the bloodstream is considered a necessary component of pathogenetic therapy. To achieve this goal in the management of rhabdomyolysis, various methods of extracorporeal detoxification (ECD) are used. In the current literature, the effectiveness of ECD at different stages of rhabdomyolysis remains controversial.

Various modifications of renal replacement therapy (RRT) are most commonly used in the treatment of rhabdomyolysis [51, 52]. As a rule, they are employed when AKI has already occurred in order to replace the lost renal function and prevent further kidney damage by circulating endogenous toxins. The concept of proactive use of RRT recommending its initiation before the development of clinically significant AKI in rhabdomyolysis, has not been recognized to date due to the lack of evidence of effectiveness. Recent publications report the results of treatment of patients with rhabdomyolysis complicated by AKI receiving ECT based on diffusion or convection mass transfer and techniques combining both types of mass transfer. Myoglobin has been considered the major pathogenetic factor of kidney damage in rhabdomyolysis, thus the prevention of further progression of AKI lies in the use of RRT techniques capable of myoglobin elimination. With myoglobin molecular weight being 17.8 kDa, the use of RRT in hemodialysis mode with standard dialyzers removing low molecular weight substances is ineffective [53, 54].

Given the pathogenesis of rhabdomyolysis and mechanisms of kidney damage, the so-called cut-off point of the hemofilter membrane and its pore diameter is the crucial factor of choosing the technique of RRT. According to current opinion, the preferred techniques to correct the water, electrolyte and acid-base disorders and azotemia, as well as to effectively eliminate myoglobin in patients with rhabdomyolysis complicated by AKI, are hemofiltration with dialysis or hemodialysis using ultrahigh-flow membrane [55]. The use of continuous hemofiltration using ultrahigh permeability membrane (cut-off point 100 kDa) is characterized by higher values of sieving ratio, clearance and degree of reduction of serum myoglobin compared with the continuous hemofiltration using standard polysulfone hemofilter with cut-off point of 20 kDa [56] in the treatment of AKI-associated rhabdomyolysis.

High efficacy of myoglobin elimination during RRT in hemofiltration mode during treatment of rhabdomyolysis with AKI has been shown [57]. According to the results of this study, myoglobin clearance after 2, 6, 12, and 24 hours after starting the prolonged hemofiltration was 14.3±3.1, 11.5±3.2, 7.5±0.9, 5.6±1.0 ml/min, respectively.

Also, according to many authors, the most effective in terms of myoglobin elimination from the systemic blood flow is the hemodiafiltration technique, which combines diffusion and convection mechanisms of mass transfer. The use of hemodiafiltration is associated with better clearance of myoglobin and larger reduction of its blood level compared with hemofiltration using similar hemofilters. The obtained result is attributed to the implementation of double type mass transfer during hemodiafiltration [58].

A case observation comparing the efficacy of hemodiafiltration and hemofiltration in pre- and post-dilution modes in treating a patient with exertional rhabdomyolysis complicated by AKI has been published. Efficacy of different modes of RRT was assessed by myoglobin clearance and elimination (relative clearance). Clearance and elimination of myoglobin during hemodiafiltration in pre- and post-dilution modes was 10.8 ml/min and 4.3%, 69 ml/min and 23.1%, while during hemofiltration in pre- and post-dilution modes it was 13.3 ml/min and 5.3%, 17.5 ml/min and 5.8%, respectively. The findings indicate greater efficacy of hemodiafiltration in post-dilution mode compared with other studied modes of RRT [59].

A prospective clinical trial also showed the efficacy of hemodiafiltration to reduce blood myoglobin levels. Eighteen patients with severe AKI-associated rhabdomyolysis underwent RRT using ultrahigh-flow hemofilters (cut-off point 45 kDa). Myoglobin clearance during one session was between 90 and 94 ml/min, while its blood level dropped by 80%. Half of myoglobin was eliminated during the first 3–5 hours after the beginning of RRT, and 7% more of total myoglobin level were removed during the next hour of the session [60].

Some researchers believe that RRT based on the diffusion mechanism of mass transfer, also is highly effective in rhabdomyolysis complicated by AKI if a mass exchange device with a high cut-off point is used. Thus, the results of a study comparing the effectiveness of hemodialysis with dialyzers of various permeability in AKI-associated rhabdomyolysis showed that the use of a dialysis machines with 60 kDa cut-off point leads to a 50% reduction in myoglobin over 4 hours of RRT. In contrast, after hemodialysis using a standard machine with 15 kDa cut-off point, there was no decrease in blood myoglobin level [61]. A more recent study confirmed the effectiveness of prolonged hemodialysis using ultra high-permeability membranes for

AKI-associated rhabdomyolysis [62]. Moreover, there are reports of effective use of intermittent hemodialysis using ultra-high permeability machines [63].

Thus, the results of studies reported in the current literature indicate a sufficient efficacy of RRT based both on diffusion and convection mass transfer, using high and ultra-high permeability dialysis machines in the treatment of rhabdomyolysis, complicated by AKI, not only to replace the lost renal function, but also to remove factors of endogenous intoxication from the systemic circulation, primarily myoglobin, thereby preventing the progression and helping eliminate

AKI. Summarizing the research results, we can conclude that the preferred technique of RRT in rhabdomyolysis complicated by AKI is hemodiafiltration, which allows to remove myoglobin and endogenous toxins from the systemic circulation with greater efficiency due to implementation of diffusion and convectional mass transfer. For increasing the efficiency of RRT, dialysis machines with a higher cut-off point and longer duration of the RRT sessions can be used.

The Use of Plasma Separation Methods

To date, there are many studies devoted to the use of apheresis-based ECD methods. The most widely used is plasmapheresis, which consists in non-selective removal of plasma with all its substances, including myoglobin and molecules responsible for the development and maintenance of endogenous intoxication. The main advantages of plasmapheresis include technical simplicity, accessibility and relative low cost. All this makes it possible to perform plasmapheresis sessions in almost any hospital. In addition, the use of plasmapheresis in the treatment of patients with traumatic rhabdomyolysis at the pre-hospital stage in the field has been described. During plasmapheresis, plasma separation can be performed using special devices with plasma filters, gravitational method on a centrifuge or machine-free method [39].

There are few clinical observations of the use of plasmapheresis reported in literature. The application of this technique in a patient with exertional rhabdomyolysis, who underwent three sessions of plasmapheresis with the plasma replacement volumes of 1300-1500 ml was reported. This therapeutic approach was associated with a significant reduction in myoglobin in the blood and urine, the recovery of renal function was also noted [64]. Similar positive results were obtained when using plasmapheresis with a replacement volume of 29.3% (1000 ml) in a patient with long-term compression syndrome due to acute heroin poisoning [65]. Successful use of plasmapheresis in a patient on simvastatin and gemfibrozil with toxic rhabdomyolysis has also been reported [66]. The effectiveness of plasmapheresis in the management of rhabdomyolysis was explained by the removal of medium weight molecular factors of endogenous intoxication, including myoglobin, from systemic circulation. Elimination of these molecules can in some cases prevent damage of the target organs, including kidneys, and, as a consequence, improve the patient's condition and increase the likelihood of a favorable outcome [67]. Entire volume of myoglobin and other toxic substances is distributed throughout the fluid sectors of the body, hence a single plasmapheresis session with replacement of up to 50% of the circulating plasma volume would not lead to a steady decrease in the blood levels of these substances. This disadvantage limits the effective use of plasmapheresis in patients with rhabdomyolysis, complicated by AKI, for detoxification. Several sessions could partially mitigate this disadvantage due to an increase in detoxification efficacy by preventing the release of continuously produced endogenous toxins into the circulation. However, in most cases, even a series of sessions cannot provide the required detoxification [68].

In order to increase the detoxification efficiency, some researchers have proposed to modify the plasmapheresis technique. The main idea of this modification was an increased volume of plasma replacement (more than 50% of the circulating plasma volume). Meanwhile, a direct correlation between the volume of replacement and the efficacy of removal of toxic substances from the blood has been revealed. Thus, the successful use of plasmapheresis in the treatment of rhabdomyolysis caused by fibrates in a patient with terminal chronic kidney disease was reported [69]. The number of publications on successful use of non-selective plasmapheresis in the management of rhabdomyolysis is limited.

The authors of current publications mainly focus on the disadvantages of non-selective plasmapheresis. This method of ECD has restrictions on the plasma replacement volume, which should not exceed 1.5–2.0 times circulating plasma volume, corresponding to 4–6 liters of plasma. Such volume of replacement of the total volume of body fluid, where endogenous toxins are distributed, is not enough to achieve a significant and sustained reduction of toxic substances.

The use of non-selective plasma exchange is inevitably accompanied by a decrease in the blood levels of albumin, immunoglobulins and clotting factors, which can cause serious complications.

Thus, presently, most researchers do not recommend wide and routine use of non-selective methods of apheresis, such as plasmapheresis and plasma exchange, in rhabdomyolysis, due to insufficient safety and limited effectiveness [51, 68, 70].

Selective plasma exchange can potentially have wider application. This option of plasma exchange is safer and more effective compared with the non-selective plasma exchange. Selective plasma exchange consists in filtration of water and some substances dissolved in blood plasma through a microporous membrane. The range of substances eliminated from the blood depends on the pore size of the membrane and, accordingly, the molecular weight of the substances in the blood plasma. The maximum molecular weight of the eliminated substances is comparable to that of albumin (about 66 kDa) or less. This specific feature of the method makes it possible to remove toxic substances with an average molecular weight from the bloodstream and retain important large molecular weight substances, including immunoglobulins and coagulation factors [71].

There exist a variety of plasma separators which differ in the membrane pore size, determining the cut-off point and sieving ratio and, accordingly, the spectrum of substances removed from the plasma. The amount of albumin removed from the plasma directly depends on the pore size of the membrane. Depending on the goals and blood albumin level, the most appropriate plasma separator for clinical use can be selected [71, 72]. The use of plasma separator with smaller pore size leads to less albumin loss and allows elimination of a narrower range of endogenous toxins compared to the plasma separators with larger pore size [71]. If we compare non-selective plasma exchange with selective one, the latter has a greater detoxification effect due to a larger volume of plasma replacement with the same volume of transfusion media (fresh frozen plasma and/or albumin solutions) [73]. Based on a review of the literature on the subject, selective plasma exchange is used mainly in the treatment of hepatic failure [74]. The data of its use in rhabdomyolysis, though, are lacking.

Although there is some evidence of the successful use of plasmapheresis and non-selective plasma exchange in the treatment of patients with rhabdomyolysis for prevention of AKI or its progression, most authors believe that the existing data cannot conclusively demonstrate the positive impact of these methods on the outcome. In addition, some researchers point out that the use of apheresis methods in early rhabdomyolysis can delay intensive therapy or hamper its delivery.

Sorption Methods of Extracorporeal Detoxification

Creation of new selective adsorptive devices capable of removing a certain range of endogenous toxins from the bloodstream has prompted the study of the effectiveness of sorption ECD techniques in rhabdomyolysis. The interest in this subject grew when the CytoSorb adsorption device (Cytosorbents Corp., USA) was developed for extracorporeal binding of endogenous toxins with molecular weight less than 55 kDa. This feature allows the removal of medium molecular weight substances, which include various interleukins and other cytokines, pathogen-associated and damage-associated molecular patterns (PAMP and DAMP). The CytoSorb device can effectively eliminate substances with a high concentration. At the same time the efficiency of their elimination decreases as their concentration in blood falls. This effect is due to the physical and chemical sequelae of hydrophobic interactions, which prevent complete removal of some mediators from the bloodstream [70, 75, 76]. Based on the above properties, selective hemoadsorption using the CytoSorb device has been most widely used in sepsis and septic shock. The majority of published works is devoted to this use of hemoadsorption [77]. However, given the molecular weight of myoglobin, which is 17.8 kDa, selective hemoadsorption using the CytoSorb device can lead to a clinically effective removal of myoglobin from blood and theoretically improve treatment results. Thus, in the last few years, publications on clinical observations of the use of the CytoSorb adsorption device for selective hemoadsorption in rhabdomyolysis started to appear. One of them reports the results of treatment of a patient with traumatic rhabdomyolysis complicated by AKI. Extracorporeal detoxification started with prolonged RRT using an ultrahigh permeability hemofilter. The chosen strategy was not successful in reducing the manifestations of disease. Due to the lack of improvement, selective hemoadsorption was added to the intensive therapy, which resulted in blood myoglobin reduction amidst persisting tissue ischemia [78]. A team of researchers from India described rhabdomyolysis with AKI, which developed as a result of fever induced by influenza B and enterovirus infection. Treatment with selective hemoadsorption using the CytoSorb device was successful [79]. We also found a case report of a patient with 3,4-methylenedioxymethamphetamine poisoning complicated by rhabdomyolysis and multiple organ failure. Selective hemoadsorption performed on the CytoSorb adsorption device was associated with a significant decrease in the levels of intoxicating agent, myoglobin, and interleukin-6. Treatment of this patient also had a favorable outcome [80].

One of the largest published studies on this subject was conducted by a team of German researchers. It included 43 patients with severe rhabdomyolysis. The inclusion criteria were AKI with anuria, blood myoglobin level above 5,000 ng/ml before selective hemoadsorption which was done

using CytoSorb adsorption device for at least 90 min. Serial assessment of the blood myoglobin concentration was performed 24–36 hours before hemoadsorption, immediately before the ECD session and 12–24 hours after the start of perfusion. The results of the study showed a significant decrease in blood myoglobin level during selective hemoadsorption. The median myoglobin content was reduced by 29% [81].

The literature data on selective cytokine hemoadsorption using the CytoSorb device in rhabdomyolysis complicated by AKI indicate a fairly high efficiency of this ECD method, which is primarily due to efficient elimination of myoglobin from the systemic circulation. These mechanisms can also contribute to nephroprotective effect, consisting in the prevention of further progression of renal damage and / or in the regression of the existing AKI. Despite these results, the effectiveness of selective hemoadsorption using the CytoSorb device cannot be considered confirmed, since the body of evidence on the subject consists mainly of individual clinical observations. In addition, a large published study on this problem has several flaws due to the lack of a control group [81]. Based on the available data, it is difficult to make a definitive conclusion about the impact of including selective cytokine hemoadsorption on the outcome of patients with rhabdomyolysis complicated by AKI.

In addition to CytoSorb, other adsorption devices for selective hemoadsorption have been developed that can potentially eliminate myoglobin from the bloodstream. Such devices include Desepta (Hemos-DS, Russia), Efferon CT (Efferon, Russia), HA330 (Jafron Biomedical, PRC). These devices were registered in Russia and have been used in practical medicine. However, there are no data on the effectiveness of these devices for selective hemoadsorption in patients with rhabdomyolysis complicated by AKI in the literature so far.

Conclusion

Based on the literature review on rhabdomyolysis, we can see that treatment of patients with rhabdomyolysis, especially severe, remains a challenging issue to date. The greatest interest of researchers is focused on using various methods of ECD along with the other intensive therapy options, for effective elimination of myoglobin, the main factor of endogenous intoxication and AKI development in rhabdomyolysis, from the circulation. Available research results do not provide the necessary evidence of the effectiveness of plasma replacement techniques of ECD. Techniques based on mass exchange devices with high cut-off point are considered to be the most effective. Most authors recognize hemodiafiltration as the most effective of RRT methods. Studying the effectiveness of combined use of RRT and selective hemoadsorption appears to be a promising area of research.

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Все, что нужно знать об

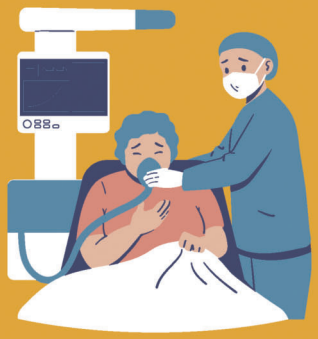
INVERSE

30-40%

составляет летальность при ОРДС средней степени тяжести

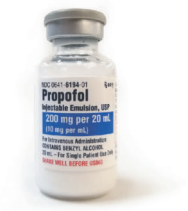
Гипотеза исследования

Севофлуран предотвращает развитие эндотелиальной дисфункции, которая является неотъемлемой частью патогенеза острого респираторного дистресс-синдрома.



Цель исследования

Оценить влияние метода седации у пациентов с ОРДС средней степени тяжести на исходы лечения.



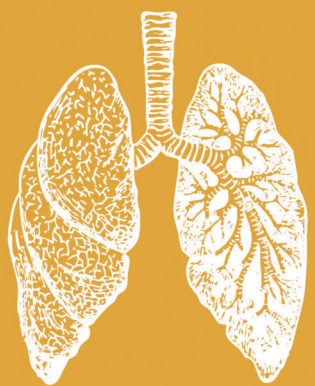
Пропофол

VS

Севофлуран

Дизайн исследования

Многоцентровое рандомизированное активно-контролируемое двойное слепое исследование



Продолжение на последней странице обложки

310 пациентов

Рассчитанный объем выборки для получения статистически достоверного результата относительно первичной конечной точки.

72 часа

Максимальное время от появления первых респираторных симптомов до момента рандомизации. Мы предполагаем, что в таком случае будет зафиксирован максимальный эффект от методов седации.

28 дней

Максимальное время соблюдения статегии седации, которая была определена для пациента по результатам рандомизации.

1 год

Максимальная длительность наблюдения за пациентами от момента рандомизации. В рамках исследования состояние пациентов определяется в 3-х временных точках: 28 дней, 6 месяцев и 1 год после рандомизации.

4 центра

Количество центров, которые принимают участие в исследовании INVERSE. Наша главная задача - увеличить количество центров, чтобы создать большое многоцентровое РКИ.

3 вида анализа

В рамках исследования будет проведено 3 вида анализа: Intention-to-treat, Per-protocol и As-treated. Данные виды анализа позволят проанализировать и наиболее полно определить влияние метода седации на исходы лечения пациентов.

2 стратегии

В исследовании изучаются 2 стратегии. Экспериментальная стратегия - седация севофлураном. Контрольная - седация пропофолом. Обе стратегии в настоящее время разрешены к использованию в палатах реанимации и интенсивной терапии.

1 результат

По итогам исследования будет получен однозначный ответ на вопрос: является ли стратегия седации севофлураном лучше, чем стратегия седации пропофолом для пациентов с острым респираторным дистресс-синдромом средней степени тяжести.

Будем рады сотрудничеству!

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