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Sevoflurane in the Acute Phase of Severe Traumatic Brain Injury

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Summary

The aim of the study was to evaluate the usefulness and safety of sevoflurane in patients in the acute phase of severe traumatic brain injury (TBI).

Materials and methods. A prospective, randomized, pilot clinical trial was conducted at the Sklifosovsky Research Institute for Emergency Medicine (Moscow) in adults with acute severe TBI, aged 18 years and older, undergoing intensive intracranial pressure (ICP)-guided therapy. To achieve the desired sedative effect, the inhaled anesthetic sevoflurane was administered in the main group, and standard doses of intravenous propofol were administered in the control group. ICP and cerebral oxygen extraction fraction (OEF) were monitored in all patients. Hemodynamic and respiratory support parameters, transcranial Doppler ultrasound scan, brain bioelectrical activity, brain CT scan, laboratory parameters, markers of inflammation, patients' need for sedation and mechanical ventilation, and length of ICU stay were also evaluated.

Results. The use of inhalation sedation contributed to the reduction of ICP on day 2 (9.5 mmHg in the sevoflurane group and 17.3 mmHg in the propofol group, P=0.003) and day 3 (10 mmHg and 14.2 mmHg, respectively, P=0.005). BIS monitoring showed no significant difference in depth of sedation between groups on day 2 (60 vs. 48.5, P=0.070) and day 3 (61 vs. 46, P=0.095). Inhalation sedation reduced cerebral OEF on the injury side compared to propofol on day 2 (23.3 vs. 30.2%, P=0.006) and day 3 (22.7 vs. 31.2%, $P<0.001$). After 24 hours of sedation therapy, there was a significant difference in P/F (PaO_2/FiO_2) ratios between the groups. On days 1, 3, and 7, the sevoflurane group had P/F ratios of 340, 324, and 323 mmHg, while the propofol group had significantly lower ratios of 271, 278, and 275 mmHg ($P<0.001$). Pneumonia was documented in 9 cases in the sevoflurane group vs. 18 cases in the propofol group (P=0.028), and a similar trend was observed in the total number of infectious complications: 13 vs. 21 cases, respectively (P=0.046).

Conclusion. Sevoflurane in the acute phase of severe TBI was not only safe, but also improved several vital functions, including ICP, blood pressure, P/F ratio, and also slowed brain metabolism via reduced oxygen consumption without affecting the depth of sedation according to BIS monitoring data. All of the above suggests that inhalation sedation may improve the prognosis for patient recovery. However, multicenter randomized clinical trials are needed to identify and verify all positive and negative effects of inhalation sedation in this patient population.

Keywords: sevoflurane; propofol; inhalation sedation; AnaConDa; prolonged sedation; traumatic brain injury; neuromonitoring

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

Introduction

The primary goals of sedation and analgesia in the intensive care unit (ICU) are to control the pain syndrome, reduce patient anxiety and agitation, prepare the patient for various invasive and noninvasive manipulations, and prevent asynchrony during lung ventilation [1]. Sedation is often required in patients with severe brain injury to prevent or reduce elevated intracranial pressure (ICP) [2, 3]. The initial phase of treatment of acute brain injury and stabilization of vital functions is followed by a recovery and rehabilitation phase during which sedation is discontinued and the patient is mobilized. According to this concept, sedatives should not interfere with the recovery process. The ideal sedative for patients with severe brain injury should have a manageable and easily controlled sedative effect, few side effects, and a short half-life. The combination of these properties allows for rapid assessment of neurological status [4]. Propofol, administered intravenously (IV), is currently the most commonly recommended hypnotic agent [5]. Propofol has several advantages, including a relatively short half-life and the ability to potentiate the effects of analgesics while having virtually no analgesic effect [6]. However, there are certain risks associated with prolonged propofol sedation, such as hypotension due to vascular paralysis, transient apnea followed by hyperventilation, muscle tremors, visual disturbances, and hallucinations [7]. In addition, there is a risk of developing a life-threatening complication associated with its administration, called propofol infusion syndrome (PIS), which occurs more frequently in young patients when doses are escalated

above 4 mg/kg/hour over 48 hours. PIS also occurs in the elderly, even when lower doses are used [8]. The sedative potential of propofol is limited by its duration of its action and dose. If there is a need to increase the depth of sedation or if the safe time of propofol administration is exceeded, its combination with benzodiazepines or a complete switch to benzodiazepines is used. Benzodiazepines, in turn, have a relatively long half-life, which depends largely on the patient's medical condition [9]. In addition, their cumulative effect prolongs the time to awakening, the duration of mechanical ventilation (MV), and the patient's stay in the ICU, increasing the risk of complications such as delirium [10].

Inhaled anesthetics (IAs) such as isoflurane and sevoflurane are alternative anesthetic agents. They are easy to administer, easily controlled, metabolized to a small extent (about 5% by volume for sevoflurane and less than 1% by volume for isoflurane), and have a short half-life. Importantly, these drugs can have potent sedative and analgesic effects with relatively few adverse reactions [11–13]. The use of IAs outside the operating room has become possible with the miniature vaporizer AnaConDa (The anaesthetic conserving device; SEDANA Medical, Uppsala, Sweden), which is integrated into the breathing circuit instead of an antibacterial filter [14]. IAs have been shown to be safe for patients and medical staff in the ICU when the rules for their use are followed. In addition, their use reduces the time to awakening and tracheal extubation as well as the length of hospital stay [15, 16]. To date, IAs have been widely used throughout Europe, and in Germany they are recommended as an alternative sedative agent according to current guidelines [17]. Thus, IAs meet the criteria for the best sedatives for patients with severe traumatic brain injury (TBI). However, there is currently a lack of clinical evidence on the efficacy of IAs in neuroresuscitation to definitively support their use.

Aim of the study was to evaluate the feasibility and safety of sevoflurane inhalation in patients with acute severe TBI.

Materials and Methods

We conducted a prospective pilot randomized controlled clinical trial. This study was approved at the LEC meeting of the Federal Scientific and Clinical Center of Critical Care and Rehabilitology No. 5/21/1 of December 23, 2021, and at the LEC meeting of the N. V. Sklifosovsky Research Institute for Emergency Medicine No. 1/2022 of January 11, 2022.

Inclusion criteria:

- Diagnosis of intracranial trauma (ICD-10 codes S06.1, S06.3, S06.5, S06.6, S06.8);
- GCS score < 9 and/or need for sedation and mechanical ventilation;
- Feasibility of neuromonitoring;
- Initiation of sedation within the first day after trauma.

Exclusion criteria:

- Age less than 18 years;
- Terminal illness;
- Severe uncontrolled or decompensated comorbidities;
- Pregnancy;
- History of malignant hyperthermia or allergic reaction to IA or propofol in both the patient and close relatives;
- Persistent intracranial hypertension (ICP > 20 mm Hg) that cannot be corrected by hyperosmolar solution infusion for more than 5 minutes;
- Severe gas exchange disorders (PaO_2 < 60 mm Hg);
- Fraction of inspired oxygen (FiO_2) > 0.6 and PEEP > 10 cm H_2O;
- Combined injury.

From 2021 to 2023, 2637 patients diagnosed with severe TBI were studied at the N. V. Sklifosovsky Research Institute for Emergency Medicine (Department of Health Care, Moscow). Conservative hospital treatment was given to 2214 patients, 423 patients underwent surgery, and 50 patients underwent ICP sensor implantation.

After confirmation of the diagnosis of isolated severe TBI and surgical intervention with implantation of an intracranial pressure (ICP) sensor, patients were randomized into two groups according to the choice of sedation method, using the envelope method with «blinding» of patients and without «blinding» of medical professionals.

After admission to the ICU, patients in the intravenous sedation group (*N*=25) were started on a continuous propofol infusion at a dose of 2–4 mg/kg/hour (propofol group). In the inhalation sedation group (*N*=25), patients were sedated with inhaled sevoflurane at 4–12 ml/hr (0.4–0.7 MAC) (sevoflurane group).

Later in the study, 3 patients in the sevoflurane group were found to have combined trauma. These patients were excluded from the study.

Twenty-one patients in the sevoflurane group and 24 patients in the propofol group (because one patient in each group died within the first 12 hours after admission) were included in the analysis (Fig. 1).

The local protocol for the management of patients with severe TBI at the N. V. Sklifosovsky Research Institute of Emergency Medicine was consistent with the clinical guidelines of the Russian Ministry of Health and did not contradict international approaches to the management of patients with traumatic brain injury. According to the clinical guidelines of the Russian Association of Neurosurgeons on the management of patients with focal brain injury, propofol is recommended as a sedative to control ICP. However, there is no evidence that it reduces mortality and improves outcome 6 months

after injury, and the administration of high doses of propofol is associated with poor outcomes [18, 19].

ICP-guided therapy has also been recommended for patients with severe TBI documented by CT scan (hematoma, contusion lesion, edema, basal cistern compression).

In both groups, fentanyl solution was used for analgesia at a dose of 2 mcg/kg/hour. Respiratory support for all patients was provided in pressure mode according to the concept of «protective ventilation». The patient groups were comparable in terms of chronic comorbidities, type of trauma, extent of surgical procedures performed, and presence of alcohol intoxication prior to admission (Table 1).

Inhalational sedation was performed with a certified device (The Anaesthetic Conserving Device). ICP was measured invasively with a Spiegelberg transducer (Spiegelberg GmbH & Co. Hamburg, Germany). On admission to the ICU, all patients underwent central venous catheter (CVC) placement into the jugular bulb, followed by radiographic control.

One of the measured parameters of perfusion and metabolism was the cerebral oxygen extraction fraction (OEF). It was calculated using the formula

$$\mathbf{K = [SpO_2(a) - SpO_2(v)] / SpO_2(a),}$$

where K is the extraction fraction, **SpO_2(a)** is the arterial blood saturation, and **SpO_2(v)** is the blood saturation in the jugular bulb. Normal values of **K** for the brain are 25–45% (assuming adequate SpO_2 in the jugular bulb). However, it is important to note that variations in jugular bulb SpO_2, and therefore oxygen extraction fraction, are possible in the presence of a massive contusion lesion and edema with ischemia of brain tissue.

The Radiometer ABL800 analyzer was used to assess blood acid-base balance and gases. Hemodynamic and respiratory support parameters, ECG, transcranial Doppler ultrasound scan, brain bioelectrical activity, computed tomography (CT) of the brain, complete blood count and clinical chemistry parameters, blood gases, electrolytes and metabolites, inflammatory markers, duration of sedation, ventilation and ICU stay were also evaluated.

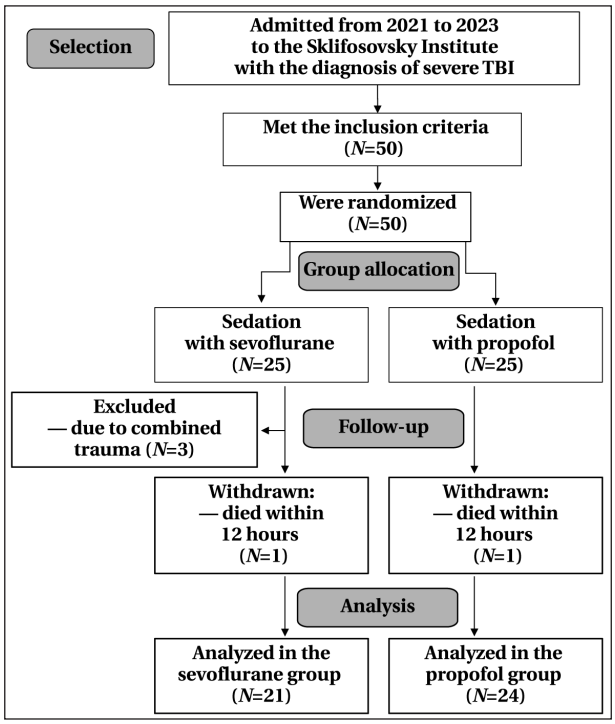

Fig. 1. Study flowchart.

Statistical analysis of the data was performed using SPSS Statistics software (IBM SPSS Statistics for Windows, version 27.0.1, Armonk, NY: IBM Corp) and MedCalc® Statistical Software version 20.305 (MedCalc Software Ltd, Ostend, Belgium). Microsoft Office Excel 2019 was used to generate dot plots (trend graphs) and data sheets.

The study protocol (per protocol analysis) was used to analyze the results. The Shapiro–Wilk test was used to assess the normality of the data distribution. Due to the non-normal distribution of most parameters, the non-parametric Mann–Whitney *U* test was used for determining the significance of differences between groups of quantitative independent variables. Frequency variables in independent groups were compared using the chi-squared test or Fisher's exact test (when the frequency of the outcome was less than 10%). Quantitative

Table 1. Characteristics of patients, *N* (%) or median *[Q1; Q3]*.

Parameter	Values in groups		*P*-value
	Propofol, *N*=24	Sevoflurane, *N*=21	
Male sex	18 (75.0)	14 (66.7)	0.538
Age, years	40 [33.0; 52,5]	41 [33; 43]	0.531
BMI	25.2 [23.1; 29.0]	26.6 [24.0; 29.2]	0.554
Hypotension on admission	6 (25.0)	6 (28.6)	0.787
Diabetes mellitus	2 (8.3)	1 (4.8)	0.632
Hypertension	7 (29.2)	2 (9.5)	0.100
Hyperventilation on admission (pCO_2 below 30 mmHg)	5 (20.8)	3 (14.3)	0.567
History of alcohol consumption	7 (29.2)	5 (23.8)	0.685
History of aspiration	5 (20.8)	6 (28.6)	0.547
SOFA on admission	8 [4.5; 10.0]	8 [6.0; 10.0]	0.592
APACHE II on admission	12.5 [9.5; 16.5]	16 [13.0; 19.0]	0.106
FOUR on admission	9.5 [8.0; 12.0]	7 [6.0; 10.0]	0.053

data were presented as *Me [Q1; Q3]*, where *Me* is the median, *Q1* is the first quartile (25th percentile), and *Q3* is the third quartile (75th percentile). Frequency data were reported as *N* (%), where *N* is the absolute number of observations in the group and % is the percentage of observations in the group. The strength of correlation between parameters was determined using Spearman's rank correlation coefficient. The critical two-sided significance level *(P)* was set at 0.05.

Results

Of 45 patients with isolated severe TBI, 14 men and 7 women received inhalational sedation with sevoflurane, and 18 men and 6 women received intravenous propofol. The type of brain damage according to CT scan and the extent of surgical intervention performed are summarized in Table 2.

The use of inhalational sedation contributed to a decrease in ICP with comparable depth of sedation. ICP values remained within normal limits in both groups during sedation therapy in the postoperative period. In addition, patients receiving inhalational sedation showed a more significant decrease in ICP on day 2 (9.5 mmHg vs. 17.3 mmHg, *P*=0.003) and day 3 (10 mmHg vs. 14.2 mmHg, *P*=0.005) compared to patients receiving propofol (Fig. 2, *a*). Meanwhile, there were no differences in depth of sedation between groups on day 2 (60 vs. 48.5, *P*=0.070) and day 3 (61 vs. 46, *P*=0.095) as measured by BIS monitoring.

Inhalational sedation decreased OEF on the lesion side. OEF was significantly lower in the sevoflurane group than in the propofol group on day 2 (23.3 vs. 30.2, *P*=0.006) and day 3 (22.7 vs. 31.2, *P*<0.001) (Table 3). The use of IAs also led to an improvement in the patients' hemodynamic parameters. Mean arterial pressure was significantly higher with sevoflurane than with propofol from day 1 to day 3 (Table 3). Furthermore, there was no significant difference in the dose of required vasoactive and inotropic support when calculating the vasoactive inotropic index (VIS) in the groups (Table 3).

After 24 hours of sedation, P/F (PaO_2/FiO_2) values differed significantly between groups. Initially, no significant difference was observed between the propofol group (P/F = 290 [268; 322] mmHg) and the sevoflurane group (P/F = 300 [254; 310] mmHg) (*P*=0.767). On day 1, a significant difference was found between the groups: P/F was 271 [254; 317] mm Hg in the propofol group and 324 [290; 355] mm Hg in the sevoflurane group (*P*=0.05). On days 3 and 7, the oxygenation index values in the propofol group were 278 [250; 301] mm Hg and 275 [221; 300] mm Hg, respectively, significantly lower (*P*<0.001) than in the sevoflurane group (P/F = 340 [320; 385] mm Hg and 323 [310; 350] mm Hg, respectively). At days 14 and 28, the difference between the groups was no longer significant (Fig. 2, *b*).

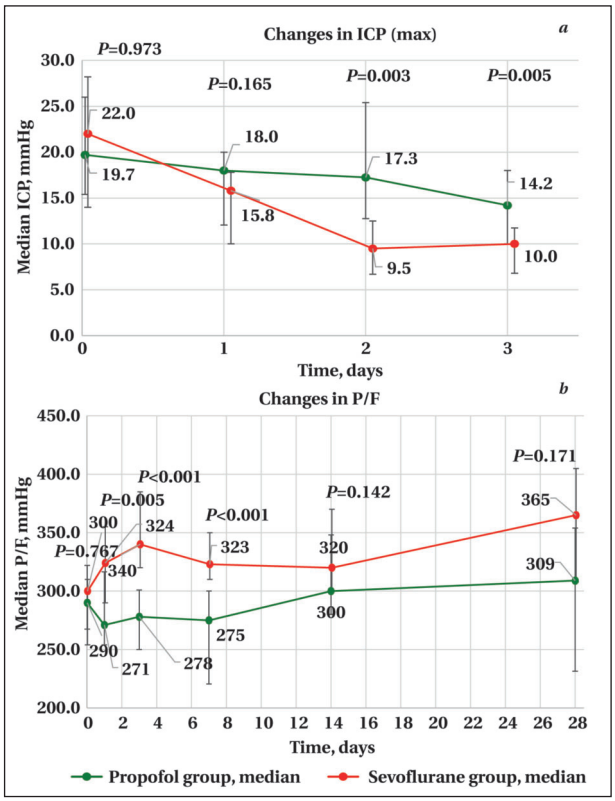

Fig. 2. Changes in intracranial pressure during the first 3 days *(a)* and P/F index during treatment in ICU *(b)*.

The pattern of complications was different between groups (Table 4). There was a significant decrease in the incidence of pneumonia development in the sevoflurane group with 9 cases versus 18 cases in the propofol group (*P*=0.028). The total number of infectious complications was also lower

Table 2. Type of brain injury and intervention in patients with severe TBI.

Parameter	Frequency of parameter in groups, *N* (%)		*P*-value
	Propofol, *N*=24	Sevoflurane, *N*=21	
Subdural hematoma	17 (70.8)	16 (76.2)	0.685
Epidural hematoma	7 (29.2)	9 (42.6)	0.338
Intracerebral hematoma	5 (20.8)	4 (19.0)	0.881
Focal contusion lesions	22 (91.7)	19 (90.5)	0.889
Severe subarachnoid hemorrhage	21 (87.5)	17 (80.95)	0.545
Cerebrospinal fluid leakage	4 (16.7)	5 (23.8)	0.550
Fracture of skull vault and skull base	20 (83.3)	14 (66.7)	0.194
Decompressive craniectomy	15 (62.5)	9 (42.9)	0,188

Table 3. Changes in the studied parameters during the first three days of treatment of patients with severe TBI in ICU, median *[Q1; Q3]*.

Parameter	Days	Values in groups		*P*-value
		Propofol, *N*=24	Sevoflurane, *N*=21	
Changes in intracranial pressure, mm Hg	0	19.7 [15.4; 26.0]	22.0 [14.0; 28.2]	0.973
	1	18.0 [12.1; 20.0]	15.8 [10.0; 17.8]	0.165
	2	17.3 [12.8; 25.4]	9.5 [6.7; 12.5]	0.003*
	3	14.2 [10.0; 18.0]	10.0 [6.8; 11.8]	0.005*
Oxygen extraction fraction, mm Hg	0	23.1 [15.0; 37.7]	38.5 [21.9; 47.1]	0.076
	1	28.3 [22.3; 33.3]	27.5 [22.7; 31.0]	0.633
	2	30.2 [22.0; 37.4]	23.3 [19.8; 25.5]	0.006*
	3	31.2 [25.2; 36.4]	22.7 [19.2; 24.6]	<0.001*
Changes in the mean arterial pressure, mm Hg	0	84.0 [76.0; 89.0]	84.0 [76.0; 89.0]	0.785
	1	80.0 [75.0; 85.0]	86.0 [82.0; 90.0]	0.003*
	2	81.0 [73.5; 88.0]	84.0 [80.0; 90.0]	0.033*
	3	80.0 [73.5; 82.0]	86.0 [82.0; 90.0]	<0.001*
Changes in VIS, points	0	25.0 [0.0; 60.0]	30.0 [0.0; 70.0]	0.855
	1	29.0 [0.0; 85.0]	20.0 [0.0; 50.0]	0.290
	2	21.0 [0.0; 95.0]	4.0 [0.0; 45.0]	0.185
	3	10.0 [0.0; 80.0]	10.0 [0.0; 60.0]	0.795
Changes in BIS, units	0	65.0 [45.0; 72.0]	57.0 [45.0; 61.0]	0.055
	1	47.5 [40.0; 56.0]	59.0 [47.0; 64.0]	0.094
	2	48.5 [37.5; 58.0]	60.0 [48.0; 67.0]	0.070
	3	46.0 [38.0; 68.0]	61.0 [53.0; 70.0]	0.095

Note. * — significant differences.

Table 4. Complications and duration of treatment, *N* (%) or median *[Q1; Q3]*.

Parameters	Frequency and treatment duration in groups		*P*-value
	Propofol, *N*=24	Sevoflurane, *N*=21	
Meningitis	8 (33.3)	9 (42.9)	0.511
Seizures	2 (8.33)	5 (23.8)	0.153
AKI	7 (29.2)	5 (23.8)	0.685
PE	4 (16.7)	2 (9.52)	0.482
ARDS	11 (45.8)	4 (19.1)	0.057
Pneumonia	18 (75.0)	9 (42.86)	0.028*
Mortality in the first 30 days	14 (58.33)	7 (33.3)	0.094
Days on lung ventilation	12 [8; 20]	14 [10; 19]	0.715
Days in ICU	18 [11; 25]	20 [12; 31]	0.681
Infectious complications in ICU	21 (87.5)	13 (61.9)	0.046*
Thrombotic complications	15 (62.6)	11 (52.4)	0.493
MOF (ARDS and AKI)	13 (54.2)	7 (33.3)	0.161
MACE	13 (54.2)	8 (38.1)	0.281
MACE with PE	14 (58.3)	10 (47.6)	0.472

Note. AKI — acute kidney injury; PE — pulmonary embolism; ARDS — acute respiratory distress syndrome; MOF — multiorgan failure; MACE — major adverse cardiac event. * — significant differences.

in the sevoflurane group: 13 cases versus 21 cases (P=0.046).

Correlation analysis revealed several significant correlations between patient parameters recorded on day 3 (Fig. 3, *a*). In accordance with the classical approach to interpreting Spearman correlation coefficient R values, some correlations were defined as strong: APACHE II score and SOFA score (P<0.001, R=0.747); APACHE II score and VIS score (P<0.001, R=0.636) (Fig. 3, *b*).

Discussion

Currently, the use of IAs in the ICU is not widespread in our country, despite the availability of all authorization documents. This is partly due to the lack of clear indications for the choice of this method of sedation, its cost, and possible safety issues for medical staff when prolonged inhalational sedation is used outside the operating room. There is also conflicting data on the safety of this method in patients with brain damage, which limits the use of IA despite its proven benefits. A study by Purrucker et al (2015) showed that in some patients with acute intracranial injury, the use of IAs caused an increase in ICP [20]. However, a year later, Badenes and Bilotta published an article in the British Journal of Anaesthesia commenting on the findings of Purrucker et al [21].

The authors suggested that the problems associated with elevated ICP could be explained by inadequate correction of arterial carbon dioxide pressure ($PaCO_2$). When the AnaConDa device is used, there is an increase in the dead space volume (approximately 50–150 mL) of the respiratory circuit. Increasing the tidal volume of ventilation in this case normalizes the level of CO_2 and thus the cerebral blood flow [21]. Often severe TBI is associated with subarachnoid hemorrhage (SAH), which can worsen

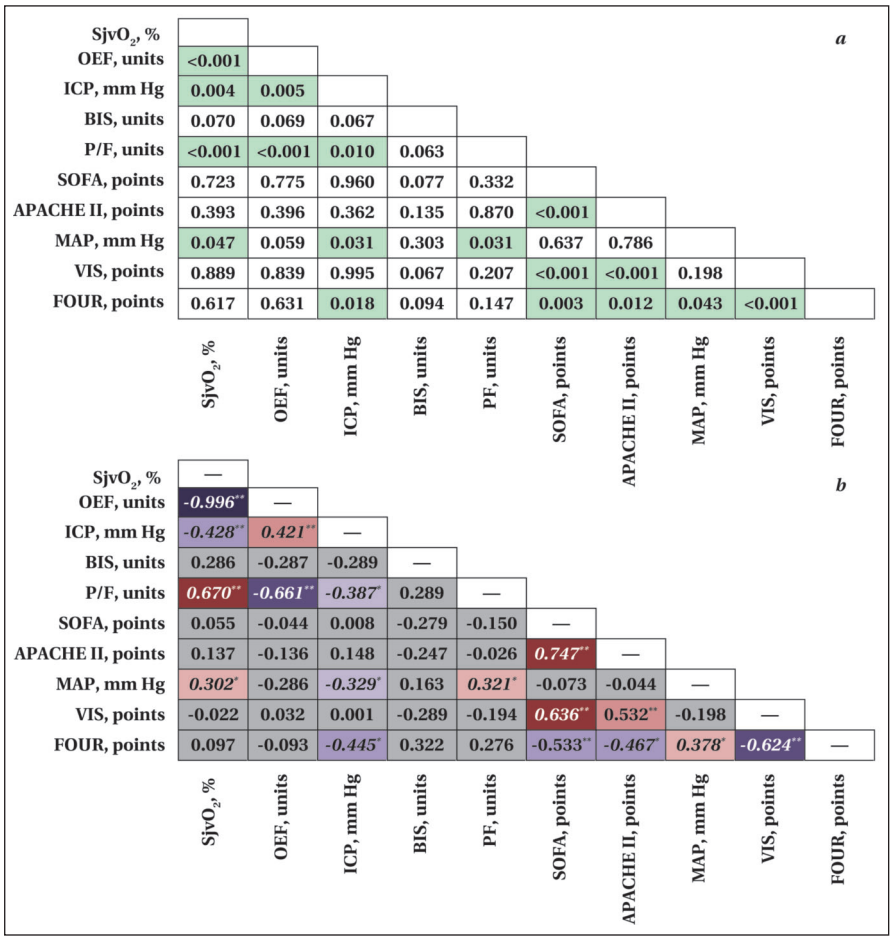

Figure 3. Correlation analysis of data obtained on day 3: Spearman correlation test *P* values *(a)* and Spearman *R* coefficient values *(b)*.

Note. Green cell shading — significant correlation ($P<0.05$). Warmer color — positive correlation; colder color — negative correlation; gray color — correlation is not significant; * — $P<0.05$; ** — $P<0.01$. Interpretation of correlation strength: 0–0.3 — very weak; 0.3–0.5 — weak; 0.5–0.7 — moderate; 0.7–0.9 — high; 0.9–1 — very high.

the disease due to cerebral angiospasm. Improvement of regional cerebral blood flow without significant increase in intracranial pressure is promising to prevent and reduce the severity of delayed ischemia. A similar effect has been observed in patients treated with inhalation sedation for aneurysmal SAH [22, 23]. To date, the non-anesthetic effects of inhaled anesthetics such as anesthetic pre- and postconditioning, glycocalyx protection are well known, and their anti-inflammatory and antioxidant properties imply a beneficial effect on clinical outcomes of neurotrauma [24]. However, a recent experimental study showed a negative effect of propofol on the course of brain injury in rats due to an increase in the intensity of neuronal cell apoptosis [25].

No significant adverse effects were found when using IAs for prolonged sedation in patients with severe TBI. In addition, there were no critically important increases in ICP throughout the sedation period. This fact alleviates concerns that the use of sevoflurane in this patient population may lead to an increase in ICP and progression of cerebral edema. The results of the administration of IAs at subanesthetic doses ranging from 0.4 to 0.7 MAC confirmed the experimental data on the reduction of ICP due to the suppression of cerebral metabolism and vasoconstriction [26]. They also showed a decrease in OEF, confirming the slowing of brain metabolism and the creation of appropriate conditions for maintaining brain tissue viability in the acute phase of brain injury.

The data obtained do not contradict those of other investigators [27]. Taking into account the results of BIS monitoring during the use of IAs, it can be assumed that deep sedation is possible if necessary, for example, in the treatment of refractory and super-refractory status epilepticus [28]. In the absence of indications for deep sedation, it is necessary to strive for its minimally sufficient effect on the bioelectrical activity of the brain. The results of BIS and ICP monitoring suggest that the use of IAs contributes to early rehabilitation without the risk of intracranial hypertension. The beneficial effect of IAs on pulmonary oxygenation, manifested as an increase in P/F from the first day of inhalation, cannot be underestimated. In severe hypoxemia, this leads to better oxygenation of the damaged, hypoxia-sensitive brain tissue [29]. The lesser effect of IA on mean arterial pressure compared to propofol contributes to the maintenance of the target cerebral perfusion pressure. Infectious and septic complications such as meningitis and pneumonia were significantly less frequent under IA than under propofol sedation, and no significant difference was found in the incidence of ARDS, seizures, and death.

Limitations. The authors state that the study protocol was not registered on ClinicalTrials.gov and note that this RCT is a pilot study. They also intentionally excluded two patients who died within 12 hours of randomization and three patients with combined thoracic trauma, thus performing a per-protocol analysis. The authors acknowledge that

the sample size of this pilot study is small to draw conclusions, and further multicenter randomized clinical trials are needed.

Conclusion

The use of sevoflurane in patients in the acute phase of severe TBI has demonstrated its safety, improved several vital parameters such as ICP, BP, P/F index, also reduced cerebral oxygen metabolism with no difference in the depth of sedation according to BIS monitoring. Considering the above, this method of sedation could improve the prognosis of patients' recovery.

Multicenter randomized clinical trials are needed to confirm all the positive characteristics and to identify the prospects for the use of inhalational anesthetics.

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Veno-Venous Extracorporeal Membrane Oxygenation in COVID-19-Associated ARDS: Predictors of Mortality

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Summary

The aim of the study was to identify factors associated with hospital mortality in patients with COVID-19-associated acute respiratory distress syndrome (ARDS) receiving veno-venous extracorporeal membrane oxygenation (VV-ECMO).

Materials and methods. The retrospective study included data from the medical records of 123 patients treated in the intensive care unit (ICU) № 7 of the City Clinical Hospital № 52 of Moscow Department of Health. ECMO was initiated in all patients for respiratory indications according to current recommendations. A number of factors potentially associated with mortality were systematized and analyzed. Statistical processing to identify predictors of death included univariate analysis and calculation of odds ratio (OR), ROC analysis with calculation of area under the ROC curve (AUROC).

Results. The resulting mortality rate was 87% (107/123), 11% (14/107) of all deaths occurred after weaning from ECMO. High VV-ECMO flow, delayed initiation of mechanical ventilation and ECMO therapy, and low pH at the time of ECMO initiation were identified as independent predictors of death in the study group. Low median albumin concentration and prolonged use of vasopressors were identified as predictors of death within 28 days of initiation of VV-ECMO. Development of acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT), septic shock and its recurrences, and the use of extracorporeal blood purification therapy for septic shock were found to be predictors of death during VV-ECMO therapy.

Conclusion. High-flow VV-ECMO regimen, delayed initiation of mechanical ventilation and ECMO support, hypoalbuminemia, prolonged need for norepinephrine infusion, development of AKI requiring CRRT, septic shock occurrence and the number of its recurrences requiring extracorporeal blood purification therapy during VV-ECMO support were identified as predictors of death in patients with COVID-19-associated ARDS after initiation of VV-ECMO therapy.

Keywords: veno-venous extracorporeal membrane oxygenation; COVID-19; acute respiratory distress syndrome; ARDS; predictors of mortality

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

Introduction

One of the most severe manifestations of COVID-19 is acute respiratory distress syndrome (ARDS), with a prevalence of 32.2% [1]. When protective lung ventilation fails to provide adequate blood gas parameters, veno-venous extracorporeal membrane oxygenation (VV ECMO) is the last option to maintain gas exchange, serving as a «bridge» to recovery and creating conditions for repair processes in the lung tissue. Despite the available expertise in the use of VV ECMO in respiratory failure of various etiologies, in-hospital mortality remains high, reaching 50% [2].

The respiratory support strategy in this group of patients involves «pulmonary rest» to maximize the reduction of secondary lung injury while achieving adequate gas exchange rates with VV ECMO.

The high economic cost, the need for human resources and the complexity of a multidisciplinary approach in the management of such patients require a thorough evaluation of indications and contraindications, as well as the identification of predictors of mortality for potential correction.

The aim of the study was to identify factors associated with in-hospital mortality in patients with COVID-19-associated ARDS undergoing VV ECMO.

Materials and Methods

Study design. We conducted a single-center retrospective cohort study of factors influencing mortality in ICU patients treated with VV ECMO for COVID-19 during the entire pandemic period in the ICU #7 of Moscow City Clinical Hospital #52 (March 2020-August 2022).

Inclusion criteria: age ⩾ 18 years, confirmed diagnosis of COVID-19 (U07.1; U07.2), initiation of VV ECMO for respiratory indications due to respiratory failure associated with ARDS.

Exclusion criteria: initiation of VV ECMO in other departments and medical institutions, death within 24 hours after vascular cannulation due to its complications, death due to septic shock within 48 hours after initiation of VV ECMO, baseline veno-arterial ECMO. The scheme of patient selection in the study is shown in Fig. 1.

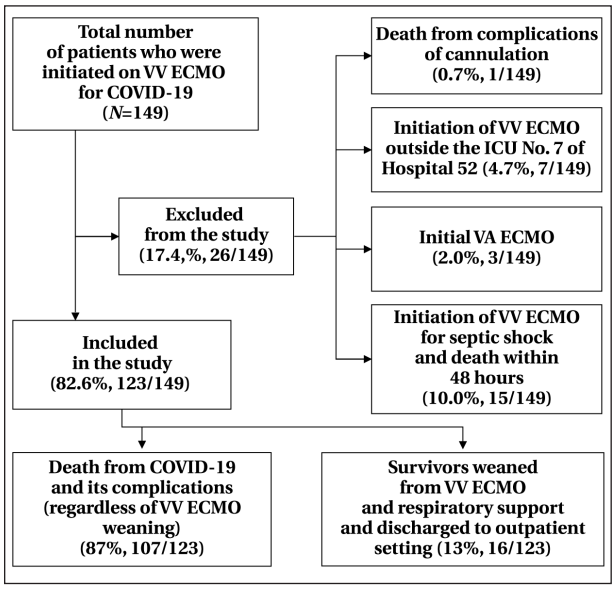

Fig. 1. Scheme of patient selection in the study.

The study was approved by the Ethical Committee of the Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology (No. 1/23/6, April 5, 2023). Informed consent was not obtained for this study.

Information was collected from paper and electronic versions of the ORBITA KIS and EMIAS KIS case histories using Microsoft Excel spreadsheet software (Microsoft Corp., USA). A number of parameters potentially associated with mortality were analyzed: age, body mass index, time points of decision (from onset of illness to transfer to mechanical ventilation and initiation of VV ECMO), duration of VV ECMO and its maximum flow rate, blood gas and acid-base status ($PaCO_2$, pH), P/F, norepinephrine dose and SOFA (Sequential Organ Failure Assessment) score at the time of VV ECMO initiation, and static lung compliance value after transition to protective ventilation parameters.

During the first 28 days of VV ECMO, the duration of norepinephrine use, mean albumin concentration, and number of blood component transfusions (fresh frozen plasma, erythrocyte suspension, platelet concentrate, and cryoprecipitate) were evaluated. During the entire period of VV ECMO, we evaluated recurrences of septic shock and their number, frequency of thrombotic events related to the ECMO machine circuit and to the patient, bleeding, use of renal replacement therapy (RRT) for renal indications, and methods of extracorporeal blood purification for septic shock.

Indications and contraindications for VV ECMO initiation and weaning were based on the current ELSO guidelines [3]. The adapted algorithm is shown in Fig. 2.

All patients underwent peripheral VV ECMO, primarily in a femoro-jugular configuration, with ultrasound guidance during vascular cannulation. All patients received protective ventilation in a prone position, recruitment maneuvers, and therapeutic bronchoscopy (if necessary). A puncture dilatation tracheostomy was performed within the first three days of starting lung ventilation. The anticoagulant used during VV ECMO was unfractionated heparin, which was monitored using measurement of APTT. In the event of hemorrhagic complications, anticoagulant therapy was de-escalated or discontinued. Thrombotic complications were categorized as either circuit-related (impeller or oxygenator thrombosis requiring circuit replacement) or patient-related (new thrombosis developing during VV ECMO).

Hemorrhagic complications were classified as major (any bleeding that necessitated the discontinuation of anticoagulation therapy or surgical hemostasis, such as intracranial/intracerebral, gastrointestinal, pulmonary, or bladder bleeding, or severe nosebleeds) or minor (bleeding from ECMO catheter and cannula sites, bleeding from pleural drainage sites, erosive gastritis, nasal bleeding), depending on severity.Patients were started on renal replacement therapy (RRT) for acute kidney injury (AKI) based on common indications like hyperkalemia, the need for rehydration, uremia, and uncorrected metabolic acidosis.

Statistical analysis. The data were analyzed using IBM SPSS Statistics 27. The data were checked for normality using the Shapiro–Wilk test. The results showed that parametric criteria were not applicable for all parameters due to the small number of outcomes. Mann–Whitney *U*-test was used to compare groups of quantitative data, Fisher's exact test was used for qualitative binary outcomes, and a Pearson's χ^2 test of agreement was used for ordinal outcomes. The null hypothesis was rejected at the significance level of 0.05. One-factor regression analysis (binary logistic regression) was used to search for predictors

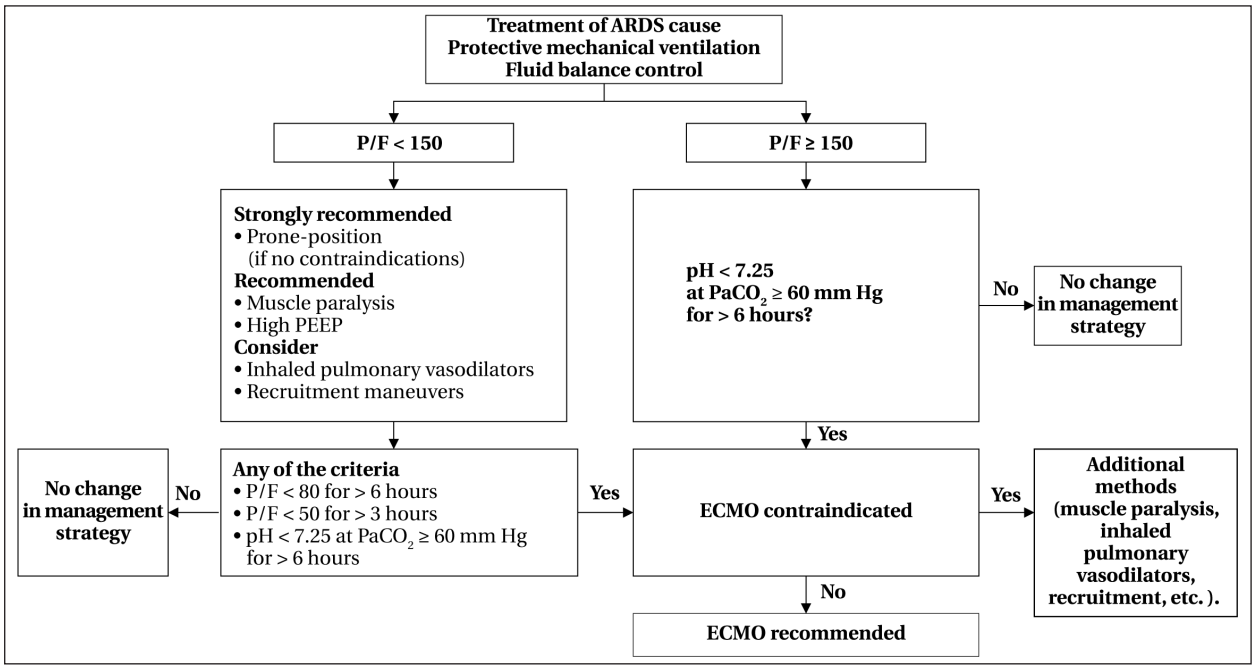

Fig. 2. Decision-making algorithm and indications for initiation of VV ECMO (ELSO) [2].

of mortality. The risk of poor outcome was estimated using the odds ratio and its 95% confidence interval.

Results

The hospital mortality rate was 87% (107/123); 11% of patients (14/123) died after weaning from VV ECMO, while 13% (16/123) were weaned from VV ECMO and respiratory support and discharged. Infectious complications resulting in septic shock and multiorgan failure were the leading causes of mortality.

Patients in both groups (non-survivors and survivors) were comparable in the main parameters (Table 1) and were predominantly male: the male-to-female ratio in the groups was similar (79/28 (73.8%/26.2%) in the non-survivor group and 12/4 (75%/25%) in the survivor group).

The comparative analysis revealed statistically and clinically significant differences between the groups in a number of parameters (Tables 1, 2).

The mean age of the non-survivors was higher than that of the survivors.

Table 1. Characteristics of patients.

Parameter	Values in groups		*P*-value
	Non-survivors, *N*=107	Survivors, *N*=16	
Demographic and anthropometric parameters			
Age, years	52.0 [42.0–59.0]	38.0 [35.25–50.75]	0.036*
BMI, kg/m²	30.86 [26.34–34.7]	32,76 [26.5–34.6]	0.913
Time points for management decisions			
Time from disease onset to ventilation, days	16.0 [12.0–21.0]	8.0 [7.0–11.75]	<0.001*
Time from disease onset to initiation of VV ECMO, days	18.0 [14.0–22.0]	11.0 [8.25–14.0]	<0.001*
Time from ventilation transfer to initiation of VV ECMO, days	1.0 [1.0–2.0]	1,5 [0.0–3.75]	0.692
Values at the time of initiation of VV ECMO			
$PaCO_2$ at the time of VV ECMO initiation, mmHg	78.5 [54.75–90.0]	52.5 [45.0–72.5]	0.035*
P/F at the time of VV ECMO initiation, mmHg	71.0 [59.0–87.53]	80.0 [71.25–92.5]	0.056
pH at the time of VV ECMO initiation	7.2 [7.1–7.3]	7.32 [7.17–7.4]	0.076
Norepinephrine dose at the time of VV ECMO initiation, μg/kg/min	0.1 [0.0–0.25]	0.1 [0.0–0.3]	0.451
SOFA at the time of VV ECMO initiation	8.0 [6.0–10.0]	6,5 [5.0–9.0]	0.230
VV ECMO characteristics			
Duration of ECMO, days	17.0 [9.0–30.0]	11.5 [7.0–25.5]	0.196
C_{stat} immediately after initiation of VV ECMO	21.3 [16.6–29.0]	28.5 [23.75–38.75]	0.035*
Maximum flow rate of VV ECMO, L/min	4.6 [4.2–5.2]	3.8 [3.5–4.0]	<0.001*
Duration of norepinephrine use in the first 28 days of VV ECMO, days	11.0 [5.0–19.0]	3.0 [1.0–10.0]	0.002*
Median albumin concentration in the first 28 days of VV ECMO, g/L	28.6 [25.7–33.0]	34.08 [29.18–37.68]	0.002*
Transfusions of fresh frozen plasma in the first 28 days of VV ECMO, doses	2.0 [0.0–6.0]	4.0 [0.0–9.5]	0.420
Cryoprecipitate transfusions in the first 28 days of VV ECMO, doses	6.0 [0.0–25.0]	18.0 [0.0–49.0]	0.149
Platelet concentrate transfusions in the first 28 days of VV ECMO, doses	5.0 [1.0–12.0]	3.0 [0.0–4.75]	0.049*
Red cell suspension transfusions in the first 28 days of VV ECMO, doses	5.0 [2.0–10.0]	5.0 [0.25–7.75]	0.317
Mean incidence of septic shock during VV ECMO	1.0 [1.0–2.0]	0.0 [0.0–1.0]	<0.001*

Notes. Shown are *Me [Q1; Q3]*. C_{stat} — static pulmonary compliance. * — significant differences ($P<0.05$).

Table 2. Complications in survivors and non-survivors (categorical parameters).

Parameter, *N*	Values in groups				*P*-value
	Non-survivors, *N*=107		Survivors, *N*=16		
	Present	Absent	Present	Absent	
Thrombotic complications					
ECMO circuit thrombotic events requiring circuit replacement	28	79	6	10	0.374
Thrombotic events in patients on VV ECMO	43	64	5	11	0.589
AKI, septic shock					
RRT for renal indications during the VV ECMO procedure	87	20	5	11	<0.001*
Septic shock during the VV ECMO procedure	95	12	6	10	<0.001*
Use of extracorporeal blood purification techniques during VV ECMO	65	42	5	11	0.032*
Hemorrhagic complications					
Bleeding during ECMO	Absent	Minor	Major	Absent	Minor	Major	0.256
	32	31	44	8	4	4	

Note. * — significant differences ($P<0.05$).

When blood gases were analyzed at the time of VV ECMO initiation, the P/F value was less than 100 mmHg in all patients, and significant differences between the groups were seen only in $PaCO_2$: more severe hypercapnia at the time of VV ECMO initiation was observed in the non-survivors.

The non-survivors had longer vasopressor support than the survivors, which was not due to drug sedation. In addition, the non-survivor group was characterized by a higher incidence of septic shock and AKI requiring initiation of RRT and a higher rate of extracorporeal blood purification.

Patients in the survivor group were placed on mechanical ventilation and subsequently on VV ECMO earlier. The median albumin concentration was higher in the survivors group.

In the survivor group, higher C_{stat} values on protective ventilation and lower maximum required flow rate of VV ECMO throughout the treatment period were observed.

Survivors received platelet concentrate transfusions less frequently than non-survivors.

There were no significant differences in other parameters between the groups.

Candidate predictors influencing outcome using single factor regression analysis and ROC analysis are shown in Table 3.

Discussion

Epidemiologic and anthropometric characteristics. The findings regarding the effect of patient age on COVID-19 outcome are consistent with previously published results. According to a large meta-analysis of the characteristics of patients undergoing VV ECMO for COVID-19-associated ARDS, age was an independent predictor of mortality and was lower in surviving patients [4, 5]. Other publications and data from large meta-analyses also demonstrated a significant decrease in survival and difficulty weaning from ECMO in patients older than 60 years [6–8].

In contrast, body mass index did not differ between groups. No differences in BMI between non-surviving and surviving patients have been previously reported [4,9–18], which is also true for patients with other etiologies of ARDS [19]. Excessive body weight in the context of VV ECMO may present difficulties in obtaining vascular access for cannulation, as well as requiring the implantation of larger diameter cannulae due to the potential need for a higher ECMO machine flow rate.

The results of large meta-analyses regarding the effect of patient sex on survival are mixed. There is evidence of both significant differences in mortality between the sexes and increased mortality in male patients [4, 7, 8]. In addition, mortality has been re-

Table 3. Predictors of outcome in COVID-19-associated ARDS.

Parameter	OR	95% CI	*P*-value	AUROC	Asymptotic significance
Maximum flow rate of VV ECMO, L/min	21.808	4.647–102.345	<0.001*	0.852	<0.001*
Time from disease onset to ventilation, days	12.840	3.399–48.500	<0.001*	0.849	<0.001*
Time from disease onset to initiation of VV ECMO, days	16.406	3.523–76.401	<0.001*	0.840	<0.001*
P/F at the time of VV ECMO initiation, mmHg	3.150	1.023–9.704	0.103	0.357	0.065
pH at the time of VV ECMO initiation	8.727	2.731–27.888	0.026*	0.315	0.018*
Median albumin concentration in the first 28 days of VV ECMO, g/L	14.182	1.808–111.212	0.003*	0.263	0.002*
Duration of norepinephrine use in the first 28 days of VV ECMO, days	25.750	6.354–104.350	0.010*	0.743	0.002*
Cryoprecipitate transfusions in the first 28 days of VV ECMO, doses	2.906	0.981–8.609	0.017*	0.392	0.163
RRT for renal indications during the VV ECMO procedure	9.570	2.990–30.635	<0.001*	0.750	0.001*
Use of extracorporeal blood purification techniques for septic shock during VV ECMO, cases	3.405	1.104–10.499	0.033*	0.647	0.058
Frequency of septic shock during the VV ECMO procedure	13.194	4.067–42.805	<0.001*	0.756	0.001*
Cases of septic shock during the VV ECMO procedure	13.194	4.067–42.805	0.001*	0.754	0.001*

Note. * — significant differences.

ported to be higher in patients with two or more comorbidities than in those with fewer than two comorbidities [7, 9, 20].

Time frame from disease onset to mechanical ventilation and initiation of VV ECMO. In a single-factor analysis, later time from disease onset to mechanical ventilation (OR: 12.840 [95% CI: 3.399–48.500], $P<0.001$; AUC=0.849 [95% CI: 0.759–0.939], $P<0.001$) and to initiation of VV ECMO (OR: 16.406 [95% CI: 3.523–76.401], $P<0.001$; AUC=0.840 [95% CI: 0.757–0.923], $P<0.001$) were found to be predictors of mortality. The time from onset of symptoms to initiation of VV ECMO was also an independent factor associated with mortality in previous studies. In particular, an increased risk of death has been shown on the 12th day or more after the onset of clinical symptoms [6, 8]. At the same time, no significant association was found between the time from initiation of mechanical ventilation and the start of VV ECMO, which is inconsistent with data available in the literature and may be due to insufficient sample size.

There is evidence of increased mortality as the time from placement on mechanical ventilation to initiation of VV ECMO increases [8, 21]. According to data from German ECMO centers, the survival rate of patients significantly decreased when VV ECMO was initiated on day 5 and later from the time of mechanical ventilation placement [22]. Data from a large multicenter study show a significantly shorter duration of mechanical ventilation before VV ECMO initiation in survivors compared to non-survivors (3 and 6 days, respectively) [22]. In another sample, this was the only parameter independently associated with mortality, with values of 1 and 6 days in the survivor and non-survivor groups, respectively [24].

The non-survivor group had lower static lung compliance values after the initiation of VV ECMO and placement on protective lung ventilation, which could be attributed to increased lung tissue damage. Lung compliance is not typically listed as an indication for VV ECMO. Previous studies have found no association between this parameter at the time of VV ECMO initiation and mortality [25].

Blood gases at initiation of VV ECMO. At the time of initiation of VV ECMO, hypercapnia, respiratory acidosis, and a severe (<100 mm Hg) decrease in P/F were observed, which was an indication for ECMO. The P/F value at the time of VV ECMO initiation did not predict a poor outcome which could be due to insufficient sample volume.

At the time of VV ECMO initiation, pH was slightly lower in the non-survivor group than in the survivor group (Table 1). However, lower pH at the time of VV ECMO initiation was a predictor of mortality (OR: 8.727 [95% DI: 2.731–27.888], $P=0.026$; AUC=0.315 [95% DI: 0.159–0.471], $P=0.018$). According to the literature, acidosis, hypercapnia and elevated blood lactate levels are associated with mortality. In particular, a pH below 7.23 significantly increased the risk of death in patients over 60 years of age, suggesting that VV ECMO should be initiated early, i. e. before the development of severe metabolic disturbances [9, 26].

At the time of VV ECMO initiation, the survivor group had a higher P/F and lower $PaCO_2$ than the non-survivors (Table 1), which is consistent with previous studies [7, 8, 25].

Performance of VV ECMO. Single factor analysis showed that a high flow rate of VV ECMO required to achieve target gas exchange values was a predictor of mortality (OR: 21.808 [95% CI: 4.647–102.345], $P<0.001$; AUC=0.852 [95% CI: 0.766-0.937], $P<0.001$). There were no significant differences in the duration of ECMO between the groups. The results of a previous study with a small sample showed a similar duration of VV ECMO in survivors and non-survivors of COVID-19 (11 days) [18]. In another study, the duration of VV ECMO in patients with COVID-19 was longer than in patients with other etiologies of respiratory failure [27].

Sepsis and multiorgan failure. Identification of septic shock during VV ECMO (OR: 13.194 [95% CI: 4.067–42.805], $P<0.001$; AUC=0.756 [95% CI: 0.609–0.904], $P=0.001$) and the number of its reported cases during this period (OR: 13.194 [95% CI: 4.067–42.805], $P=0.001$; AUC=0.754 [95% CI: 0.607–0.901], $P=0.001$) were predictors of adverse outcome. Septic shock during VV ECMO developed in 101/123 patients (82.1%) and was the leading cause of death regardless of ECMO weaning. The use of extracorporeal purification techniques for septic shock was also a predictor of mortality (OR: 3.405 [95% CI: 1.104–10.499], $P=0.033$; AUC=0.647 [95% CI: 0.505–0.790], $P=0.058$). Nosocomial infections increase the length of stay in the ICU for patients of any profile, and their negative impact can be fairly extrapolated to a cohort of patients with COVID-19 [28–30]. According to the literature, bacterial pneumonia was one of the most common (34.7%) complications after VV-ECMO initiation [19], and positive bacterial culture of ascitic or pleural fluid was associated with increased mortality [31].

In our study, sepsis and septic shock were the main causes of hemodynamic instability requiring vasopressor support. The duration of norepinephrine administration during the first 28 days of VV ECMO was a predictor of poor outcome (OR: 25.750 [95% CI: 6.354–104.350], $P=0.010$; AUC=0.743 [95% CI: 0.592–0.893], $P=0.002$). Norepinephrine was used longer in the non-survivor group than in the survivor group (Table 1).

Meanwhile, no significant differences were found between the groups regarding the dose of norepinephrine at the time of VV ECMO initiation.

The use of vasopressors in intensive care patients is often considered as one of the parameters indicating the severity of organ dysfunction (e. g., SOFA score). However, the need for vasopressor support may be due to the effects of drug sedation as well as respiratory acidosis due to hypercapnia, which in turn is an indication for VV ECMO. According to a systematic review, no differences in survival were found in relation to the use of vasopressors prior to VV ECMO initiation: of 13 studies, only 3 (in hematological patients) showed an association between the need for vasopressor support and decreased survival [19, 32, 33].

No significant differences in the severity of illness according to the SOFA scale at the time of VV ECMO initiation were found between the groups, which casts doubt on the reliability and representativeness of the scale in the assessment of such patients. Several recommendations include a SOFA score greater than 12 as a contraindication to ECMO [19]. Despite the very high accuracy of this scale in predicting mortality [33–35], there are currently only a few studies evaluating its use in patients with VV ECMO and COVID-19, where a score of more than 10 points is associated with increased mortality [37].

Single factor analysis showed that the development of AKI during VV ECMO requiring RRT was a predictor of mortality (OR: 9.570 [95% CI: 2.990–30.635], $P<0.001$; AUC=0.750 [95% CI: 0.611–0.890], $P=0.001$). Renal dysfunction can be associated with life-threatening electrolyte abnormalities, promote the progression of secondary lung injury, lead to coagulopathy, and impair dehydration, which is critical in patients with ARDS. According to the literature, patients with COVID-19 and renal failure, including new-onset renal failure during hospitalization, had a significantly higher risk of death [38], and the use of RRT was associated with mortality [22], as was the fact of developing ARDS itself [38, 39].

Dehydration and normal pharmacokinetics and pharmacodynamics of drugs can be further exacerbated by hypoalbuminemia, which is more common in patients undergoing VV ECMO. The median albumin concentration values during the first 28 days of VV ECMO were lower in the non-survivor group compared to the survivor group (Table 1), which was a predictor of mortality (OR: 14.182 [95% CI: 1.808–111.212], $P=0.003$; AUC=0.263 [95% CI: 0.131–0.394], $P=0.002$), consistent with the results of sparse previous publications [40, 41].

Thrombotic and hemorrhagic complications. Among all blood component transfusions during the first 28 days of VV ECMO, only the number of cryoprecipitate doses was a predictor of mortality: survivors had more transfusions than non-survivors (OR: 2.906 [95% CI: 0.981–8.609], $P=0.017$; AUC=0.392 [95% CI: 0.234–0.549], $P=0.163$). Statistical data on the number of blood component transfusions and the impact of this parameter on outcome have been reported in a very limited number of studies. According to observational studies, an increased number of transfusions of red cell mass and fresh frozen plasma was associated with an unfavorable outcome, which may be explained by the need for massive blood transfusions in more critically ill patients, while a high number of platelet concentrate transfusions was associated with thrombotic complications of the ECMO circuit [42].

No significant association was found between mortality and the development of hemorrhagic complications or any thrombotic complications. Similarly, among patients with bleeding complications, no differences were found in the effect of different categories of bleeding (major or minor) on mortality. In a study with a similar number of patients surviving and a lower number of patients dying, the incidence of «major» bleeding complications was 42.5% of the total number of patients [43]. The results of other studies show a high incidence of both thrombotic and hemorrhagic complications in COVID-19 and VV ECMO patients [44–46]: an increased incidence of hemorrhagic complications and the need for blood transfusion in non-survivors has been demonstrated [16]. The results of an analysis of 620 patients with COVID-19 showed an association of hemorrhagic complications (mainly intracranial) with mortality, which was not true for thrombotic complications [47]. Furthermore, according to a large meta-analysis including 6878 patients, the incidence of intracranial complications in patients with COVID-19 was significantly higher than in patients with other etiologies of respiratory failure [48].

Study limitations. This is a retrospective, single-center cohort study with all the limitations associated with this type of design. The patient groups varied considerably in size, which may have influenced the statistical results. Given the multifactorial nature of the causes of death in this patient cohort, the list of parameters studied could be expanded to include several other characteristics potentially associated with mortality (echocardiographic features, development of right ventricular failure, sepsis, etc.) if adequate data collection were possible.

Conclusion

We identified a number of predictors of mortality during VV ECMO in COVID-19 patients. In selected patient groups, reducing the duration of non-protective respiratory support and initiating VV ECMO as early as possible, when indicated, before major gas exchange disturbances develop, may reduce secondary lung injury and promote lung repair. The development of AKI and septic shock, as well as hypoalbuminemia and duration of vasopressor support, are all associated with mortality in this patient population.

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Efficacy of Cytokine Hemoadsorption with Efferon CT in Severe Acute Pancreatitis

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Summary

The aim of the study was to evaluate the effect of cytokine hemoadsorption on clinical manifestations and laboratory parameters in patients with severe acute pancreatitis (SAP).

Materials and methods. The single-center, observational, controlled pilot study included 34 patients, 25 men (73.4%) and 9 women (26.4%), treated for severe acute pancreatitis (SAP) at the N. V. Sklifosovsky Emergency Care Research Institute from May 2022 to August 2023 (ClinicalTrials.gov ID NCT05695001). The mean age of the patients was 42.7±12.6 years. Participants were divided into two groups. In the main group (8 men and 1 woman], mean age 37.2±9.4 years), standard care was supplemented by selective cytokine hemoadsorption (SCH) and renal replacement therapy (RRT) using continuous veno-venous hemofiltration (CVVH) in the first 72 hours after the onset of abdominal pain syndrome (APS). In the control group (N=25, 18 men and 7 women], mean age 44.7±13.2 years), patients were managed similarly except for SCH.

Results. After 24 hours in the ICU, the study group had significantly lower levels of lactate (P=0.045) and IL-6 (P<0.001) than the control group. Lactate and IL-6 concentrations remained significantly different between groups at 72 hours (P<0.001 and P<0.05, respectively). ICU stay was significantly shorter in the study group, with a median of 6 days [95% CI, 4–25] before transfer to the general ward, whereas patients in the control group spent 37 days [95% CI, 22–73] in the ICU (P<0.001).

Conclusion. CVVH is an effective method of extracorporeal detoxification in the management of SAP, but it is less specific than cytokine adsorption in terms of elimination of proinflammatory markers. The data obtained provide sufficient evidence to consider the combination of these two modalities as the most effective approach for the management of SAP.

Keywords: acute pancreatitis, cytokine hemoadsorption, Efferon CT, organ failure, proinflammatory cytokines

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

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Introduction

Acute pancreatitis (AP) is a demarcation-type aseptic inflammation characterized by underlying pancreatic acinar cell necrosis and enzyme release, followed by extensive pancreatic necrosis and degeneration, damage to adjacent tissues, distant organs and systems, and secondary bacterial infection [1]. Approximately 10% of AP patients develop severe disease with local and systemic complications, including multi-organ failure, which is associated with a mortality rate of up to 42%. [2, 3]. Early acute pancreatitis is characterized by both local and systemic inflammation. Acinar cell damage can lead to overstimulation of the inflammatory cascade, including increased synthesis of pro-inflammatory cytokines such as interleukin-1β, 6, 8, 18 (IL-1β, IL-6, IL-8, IL-18), which can cause a «cytokine storm». The early release of IL-6 is critical for the propagation of pro-inflammatory signals that can promote disease progression. At the same time, IL-6 and C-reactive protein (CRP), which is produced in the liver in response to IL-6 stimulation, are prognostic markers of poor disease outcome [4–7]. Interruption of the rapid and uncontrolled inflammatory cascade seems to be a logical pathogenetic approach to eliminate the manifestations of multiorgan failure and to stabilize hemodynamics [8]. However, the use of pharmacological schemes to modulate the inflammatory response in AP has not yet yielded results, which can be explained by the delayed onset of action of immunomodulatory drugs [9, 10]. Over the last decades, the effect of non-selective removal of a wide range of inflammatory mediators during continuous venovenous hemofiltration (CVVH) without significant changes in their serum concentrations and clinical outcomes in patients in late AP with septic shock and acute renal failure has been studied [11–17].

Thus, immediate elimination of proinflammatory markers in early AP via cytokine adsorption may be the most promising alternative pathogenetic strategy. Several recent studies have shown that cytokine adsorption effectively eliminates inflammatory mediators such as IL-1β, IL-6, IL-8, IL-10, and

TNF-α [18–22]. Furthermore, the results of numerous studies show that cytokine adsorption improves systemic hemodynamics and reduces mortality in patients with systemic inflammatory response syndrome (SIRS) and sepsis [23–32].

The aim of this study was to determine the effect of cytokine hemoadsorption on clinical manifestations and laboratory parameters in patients with severe acute pancreatitis (SAP).

Materials and Methods

A single-center, observational, controlled study included 34 patients, 25 men (73.5%) and 9 women (26.5%), who were treated at the N.V. Sklifosovsky Research Institute of Emergency Medicine of Moscow Health Department between May 2022 and August 2023 with a diagnosis of SAP (ClinicalTrials.gov ID NCT05695001).

Patients ranged in age from 25 to 80 years. The mean age was 42.7±12.6 years.

Inclusion criteria for the study were age 18–70 years, documented episode of SAP without signs of infection, diagnosed according to the criteria approved in the Russian Clinical Guidelines 2020, time no more than 72 hours from the onset of the pain attack before the start of extracorporeal detoxification.

Exclusion criteria were a history of chronic pancreatitis (exacerbated chronic pancreatitis), active surgical infection, terminal renal failure requiring chronic dialysis, the use of other methods of extracorporeal elimination of inflammatory mediators, including hemofilters with highly permeable and surface-modified membranes, inability to achieve or maintain a minimum mean arterial pressure ⩾65 mmHg despite vasopressor and infusion therapy within 24 hours, acute pulmonary embolism, blood transfusion reaction, severe congestive heart failure, myocardial infarction in the previous 4 weeks, oncologic disease not in remission, severe granulocytopenia (less than 500 cells/mm^3) or severe thrombocytopenia.

To assess the efficacy of therapy, patients were divided into two groups: prospective main group and retrospective control group. Disease severity in both groups was assessed using the SOFA (Sequential Organ Failure Assessment), BISAP (Bedside index for severity in acute pancreatitis), Ranson (scale for objective assessment of severity and mortality in patients with acute pancreatitis), SAPSII (Original Simplified Acute Physiology Score), APACHE II (Acute Physiology and Chronic Health Evaluation II) scales (Table 1).

The main group included 9 patients (8 men (88.9%) and 1 woman (11.1%), mean age 37.2±9.4 years) who were treated with standard conservative therapy according to the national clinical guidelines for acute pancreatitis (2020) and local protocols of the Moscow Health Department «Management of intestinal failure with underlying infected pancreatic necrosis» with additional administration of cytokine hemoadsorption (HA) on the Efferon CT device during 72 hours after the onset of abdominal pain (Fig. 1).

Efferon CT (AO Efferon, Moscow, Russia) is a device for extracorporeal blood purification by direct hemoperfusion. Detoxification is performed by adsorption of cytokines and other endogenous toxins on a super cross-linked highly porous sorbent. The range of absorbed molecules is from 0 to 55 kDa.

Cytokine hemoadsorption was performed in combination with renal replacement therapy in a single extracorporeal circuit with a blood flow rate of 140 mL/min (120; 150) and a duration of 10 hours (8; 15). The exchange rate was 2500–3300 mL/hour. Mortality in the main group was 11.1% (*N*=1).

To establish a comparison group, we retrospectively reviewed the case histories of 90 patients with SAP (Fig. 1). The detailed analysis revealed that in 30% (*N*=27) of the patients, the time of continuous CVVH initiation exceeded 72 hours from the onset of abdominal pain, 2.2% (*N*=2) refused inpatient treatment, 8.9% (*N*=8) were diagnosed with severe comorbidity that later influenced the outcome of the hospitalization, and 31.1% (*N*=28) did not have results of the required laboratory parameters at the specified time points.

Thus, the control group included 25 patients (18 males (72%) and 7 females (28%)) with a mean age of 44.7±13.2 years. They received standard therapy supplemented with CVVH during the first 72

Table 1. Demographic characteristics and baseline severity assessment of patients with SAP.

Parameter	Values in groups		*P*-value
	Main, *N*=9	Control, *N*=25	
Mean age, years	37.2±9.4	44.7±13.2	0.468
Sex			0.403
Female	1 (11.1%)	7 (28%)	
Male	8 (88.9%)	18 (72%)	
SOFA	4.1±2.8	4.3±2.6	0.684
BISAP	2.2±1.2	2.5±1.0	0.631
Ranson	3.5±1.2	3.8±1.4	0.599
SAPSII	18.0±5.3	17.5±4.7	0.742
APACHE II	12.9±2.5	13.6±2.0	0.708

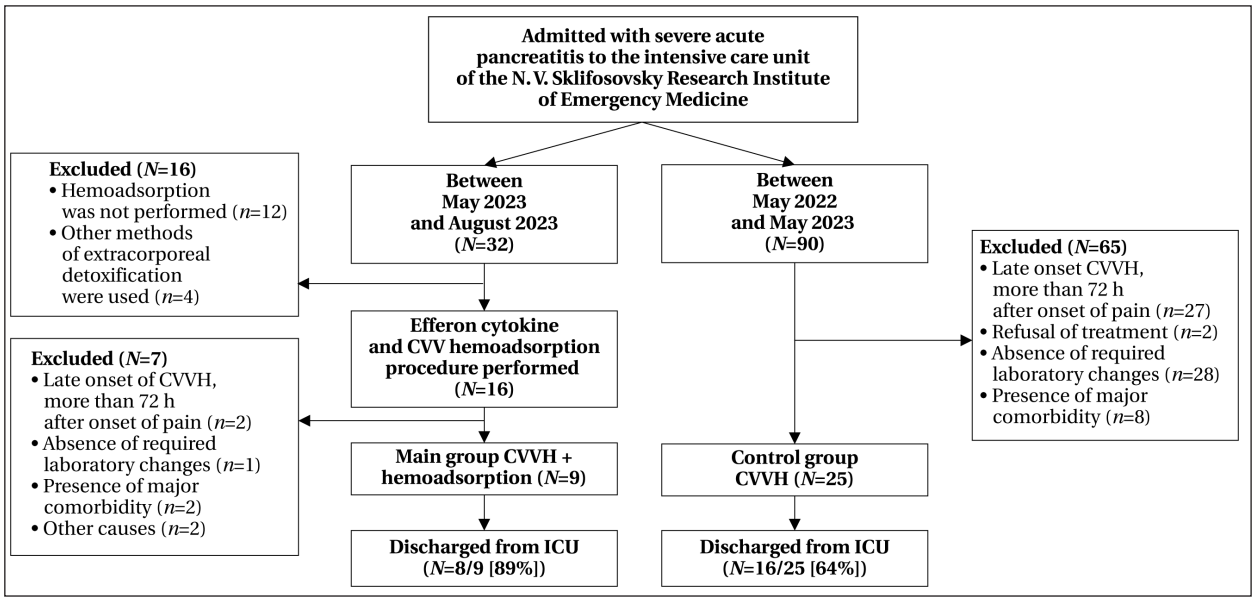

Fig. 1. Study flowchart.

hours after the onset of abdominal pain. The blood flow rate was 140 mL/min (120,150) and the duration was 18 hours (14,24). The exchange rate ranged from 2500 to 3300 mL per hour. The mortality rate in the control group was 36% (*N*=9).

Table 1 shows a comparison of the groups based on demographics and disease severity.

To evaluate the efficacy of non-selective cytokine adsorption, blood was collected on admission to the ICU and 24 and 72 hours later.

Complete blood counts were analyzed using Advia 2120i hematology analyzer (Siemens, Germany). Biochemical blood analysis was performed on an OLYMPUS AU 2700 analyzer (Japan) using reagents from Beckman Coulter, USA. The coagulation study was performed on an automatic coagulometer «ACL TOP-700», Instrumentation laboratory (USA), using reagents from Instrumentation laboratory (USA).

In order to prevent thrombotic complications due to baseline elevated levels of procoagulants and decreased levels of natural anticoagulants in patients with SAP [33], cytokines were adsorbed using the «Efferon CT» column with citrate-calcium anticoagulation and control of ionized calcium levels on the analyzer «ABL 800» (Radiometer, Denmark) in arterial or mixed venous blood.

The obtained data were processed using RStudio 2023 software. For all characteristics, we calculated the mean *(M)* and standard deviation *(±SD)* for normally distributed variables, and the median *(Me)* with 1st and 3rd quartiles *(Q1; Q3)* for variables with nonparametric distribution. The Shapiro–Wilk test was used to determine the type of distribution. Student's *t*-test was used to compare groups according to age and severity scales, and Fisher's exact test was used to compare gender characteristics. The Mann–Whitney *U* test between groups was used to analyze laboratory data, and the Wilcoxon signed-rank test was used to compare values at 24 and 72 hours versus 0 time point. ICU length of stay was analyzed using Kaplan–Meier curves and the log-rank test. The *P* value <0.05 was set as the threshold for assessing the significance of differences and changes. This was a pilot study and no adjustment for multiplicity was made.

Results and Discussion

On admission to the ICU, patients in both groups had elevated white blood cell counts and serum levels of lipase, triglycerides, lactate, CRP, D-dimer (Table 2), procalcitonin, and IL-6 (Fig. 1).

After a full course of treatment including CVVH, patients in the control group showed a decrease in APTT (*P*=0.047) 24 hours after admission to the ICU, and a decrease in neutrophils (*P*=0.005), lipase (*P*<0.001), creatinine (*P*=0.007), and APTT (*P*=0.004) 72 hours later. Meanwhile, in patients of the main group in which non-selective cytokine adsorption was used for extracorporeal detoxification, a decrease in leukocyte count (*P*=0.039), neutrophil count (*P*=0.031) and IL-6 level (*P*=0.032) was observed 24 hours after the start of the study (Fig. 2). After 72 hours, patients in this group showed a further decrease in WBC count (*P*=0.027), neutrophils (*P*=0.039), increase in lymphocytes (*P*=0.024), decrease in total bilirubin (*P*=0.007), CRP (*P*=0.034) (Table 2), IL-6 (*P*=0.035) and procalcitonin (*P*=0.015) (Fig. 2).

Significant differences between the groups were observed 24 hours after admission to the ICU, including

Table 2. Laboratory parameters of patients in the study groups. ***Me (Q1; Q3).***

Parameter	Hour in the ICU	Main group	P_1-value	Control group	P_1-value	P_c-value
Leucocyte count, 10^9/L	0	14.7 (13.0; 18.5)		12.6 (10.2; 16.6)		0.335
	24	10.4 (7.6; 11.8)	0.039	11.8 (9.8; 15.0)	0.470	0.441
	72	8.3 (6.8; 8.5)	0.027	10.2 (6.7; 15.7)	0.131	0.187
Neutrophils, %	0	89.8 (84.9; 90.8)		86.7 (82.9; 88.1)		0.162
	24	80.9 (79.7; 84.9)	0.031	81.6 (74.9; 87.5)	0.152	0.969
	72	75.6 (73.6; 85.3)	0.039	80.3 (74.0; 84.7)	0.005	0.938
Lymphocytes, %	0	6 (5.4; 7.3)		8.1 (6.2; 9.5)		0.175
	24	13 (6.5; 14.0)	0.308	8.0 (5.2; 11.7)	0.617	0.441
	72	11 (8.6; 14.7)	0.024	9 (5.9; 12.6)	0.429	0.419
Lactate, mmol/L	0	1.9 (1.0; 2.6)		2.2 (1.6; 3.4)		0.117
	24	1.3 (0.9; 2.3)	0.863	2.3 (1.7; 2.6)	0.787	0.045
	72	0.9 (0.8; 1.3)	0.135	1.9 (1.3; 2.1)	0.080	<0.001
Glucose, mmol/L	0	8.1 (6.9; 9.7)		7.9 (6.7; 8.7)		0.513
	24	6.6 (5.0; 7.7)	0.093	8.1 (7.1; 9.0)	0.429	0.093
	72	7.6 (6.1; 10.7)	0.796	7.4 (6.2; 9.9)	0.938	0.908
Lipase, U/L	0	731 (320; 1337)		592 (407; 966)		0.877
	24	256 (113; 410)	0.257	438 (304; 885)	0.246	0.218
	72	79 (34; 121)	0.064	202 (110; 400)	<0.001	0.053
Triglycerides, mmol/L	0	2.2 (1.3; 5.4)		2.4 (1.3; 4.0)		1.000
	24	1.5 (1.4; 1.9)	0.755	2.6 (1.9; 4.2)	0.441	0.222
	72	1.8 (1.7; 2.6)	0.833	3.2 (1.8; 4.5)	0.599	0.291
Creatinine, μmol/L	0	80 (70; 102)		98 (78; 123)		0.369
	24	82 (60; 93)	0.604	79 (67; 122)	0.246	0.369
	72	90 (62; 104)	0.730	74 (61; 87)	0.007	0.796
Urea, mmol/L	0	5.8 (4.7; 6.3)		5.3 (4.6; 6.9)		0.889
	24	4.1 (2.7; 9.8)	0.340	5.4 (3.9; 10.6)	0.926	0.289
	72	5.7 (4.7; 8.3)	0.730	5.3 (4.3; 8.3)	0.616	0.920
Total bilirubin, μmol/L	0	22.1 (18.2; 38.7)		17.9 (9.7; 29.8)		0.369
	24	18.6 (10.7; 31.1)	0.666	20.9 (13.6; 25.1)	0.991	1.000
	72	12.3 (9.3; 15.5)	0.007	19.4 (11.6; 23.8)	0.924	0.064
APTT, s	0	27.2 (26.6; 34)		23.4 (21.1; 30.8)		0.052
	24	28.6 (27.1; 34.4)	0.888	30.1 (26.2; 31.8)	0.047	0.740
	72	26.1 (25.5; 26.9)	0.002	29.8 (27.5; 35.0)	0.004	0.052
TT, s	0	15.5 (14.9; 20.2)		17.0 (16.4; 18.3)		0.519
	24	14.3 (14.1; 16.9)	0.276	17.6 (16.1; 18.9)	0.957	0.159
	72	20.1 (17.1; 60.8)	0.235	16.7 (15.7; 19.6)	0.789	0.090
INR	0	1.3 (1.1; 1.3)		1.3 (1.1; 1.4)		0.591
	24	1.2 (1.1; 1.2)	0.297	1.3 (1.2; 1.6)	0.441	0.054
	72	1.3 (1.1; 1.4)	0.814	1.3 (1.3; 1.5)	0.056	0.135
D-dimer, mg/L	0	3.9 (2.6; 5.5)		3.8 (3.0; 5.1)		0.955
	24	2.8 (2.3; 8.9)	1.000	4.8 (3.2; 6.6)	0.301	0.437
	72	3.3 (3.0; 4.9)	1.000	5.1 (4.0; 6.5)	0.161	0.210
CRP, mg/L	0	185 (144; 256)		209 (159; 282)		0.455
	24	168 (135; 249)	0.910	259 (147; 314)	0.499	0.174
	72	150 (138; 167)	0.034	168 (54; 252)	0.087	0.888

Note. P_1 — significance level of differences compared to day 1 of stay in ICU; P_c — compared to the control group; APTT — activated partial thrombin time; TT — thrombin time; INR — international normalized ratio; CRP — C-reactive protein.

a decrease in lactate (P=0.045) and IL-6 (P<0.001) levels. Similar changes were observed 72 hours after the start of the study, as evidenced by further decreases in several parameters (Table 2). There was also a trend towards a difference between groups in lipase (P=0.053) and total bilirubin (P=0.064) concentrations after 72 hours of treatment (Table 2).

In addition, changes in the levels of IL-6, IL-1β, IL-8, IL-10, IL-18 were evaluated in patients in the main group (Fig. 2).

The greatest specificity of cytokine adsorption using Efferon CT adsorbent appears to be with respect to IL-6, as no significant results were found when comparing changes in levels of other pro-inflammatory markers. Concentration of the anti-inflammatory IL-10 also remained relatively constant.

When analyzing the length of stay in the ICU, we found a trend toward shorter time for patients in the main group. The median time to ICU transfer for patients in the main group was 6 [95% CI, 4–25] days, while in the control group it was 37 days [95% CI, 22–73] (P=0.078) (Fig. 3). Mortality was 3.2 times lower in the main group (Fig. 3), suggesting that the addition of cytokine adsorption improves treatment outcomes.

Conclusion

Our results showed that CVVH is an effective method of extracorporeal detoxification in SAP patients, although it is less specific than cytokine ad-

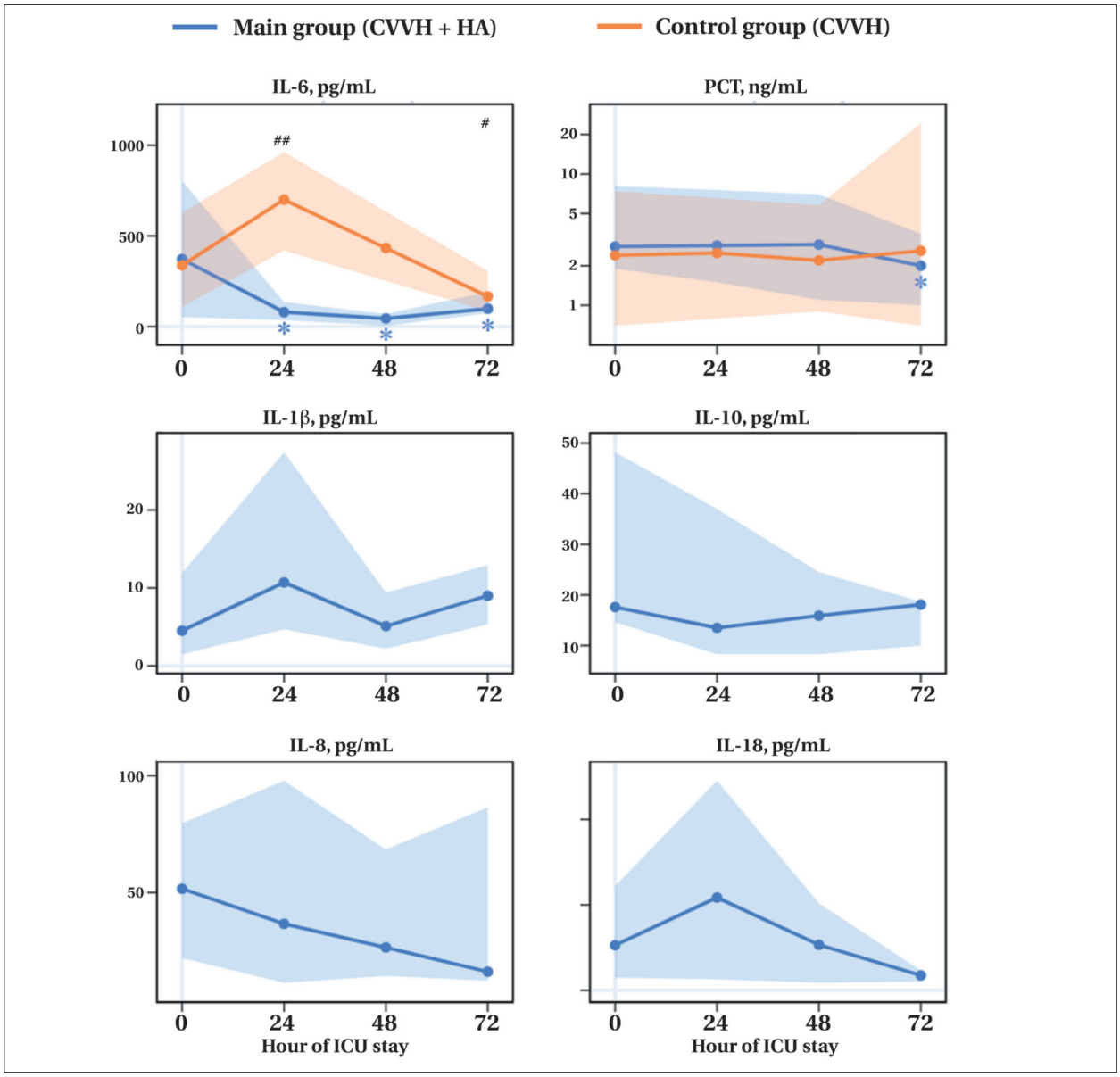

Fig. 2. Changes in interleukin and procalcitonin levels.
Notes. * — $P<0.05$ — within-group Wilcoxon test for differences from day 1 of ICU stay; # — $P<0.05$; ## — $P<0.001$ — between-group Mann–Whitney test. Shaded area (corridor) corresponds to interquartile range *(Q1; Q3)*. For Fig. 2, 3: CVVH — continuous veno-venous hemofiltration; HA — hemoadsorption.

sorption in terms of elimination of proinflammatory markers.

The use of cytokine hemoadsorption is associated with rapid elimination of IL-6, as evidenced by a significant decrease in its level after 24 hours of treatment, as well as a trend toward shorter ICU stays and lower mortality.

Based on the results of the study, we believe that the combination of the two indicated therapeutic approaches will provide the best efficacy in SAP patients.

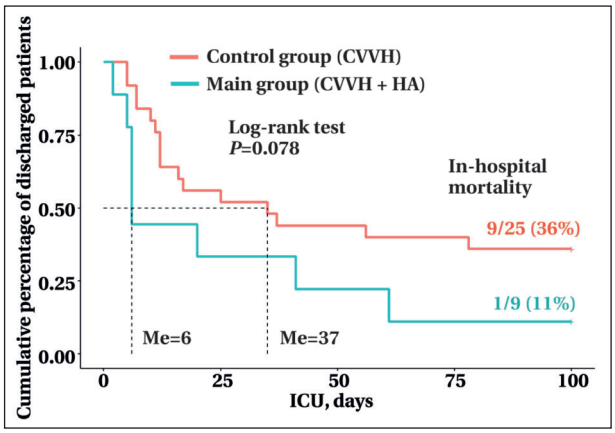

Fig. 3. Cumulative curves of ICU length of stay and mortality.

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The Effect of Hemoadsorption with CytoSorb on Severe COVID-19 Complications

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Summary

The aim of the study was to assess the effect of hemoadsorption with CytoSorb on the inflammatory response, respiratory failure, and mortality in patients with severe novel coronavirus infection.

Materials and methods. A retrospective single-center cohort comparative study of hemoadsorbtion using the CytoSorb therapy included data from 124 COVID-19 ICU patients. Patients were divided into two groups: the study arm with hemoadsorption (group 1, *N*=93) and the control arm without hemoadsorption (group 2, *N*=31). Patients in group 1 had more severe respiratory failure at baseline, but were otherwise comparable to patients in group 2 in terms of clinical and demographic parameters.

Results. After hemoadsorption, group 1 patients showed significant improvement in 9 of 13 monitored clinical, instrumental, and laboratory parameters: fever (P=0.005), lactate dehydrogenase (LDH) ($P<0.001$), C-reactive protein (CRP) ($P<0.001$), and IL-6 ($P<0.001$) levels, as well as an increase in SpO_2/FiO_2 ratio ($P=0.041$), leukocyte count ($P<0.001$) and lymphocyte count ($P=0.003$), as well as no significant changes in SOFA score ($P=0.068$). The only improvement seen in group 2 patients was a reduction in fever ($P=0.003$). Other significant changes in group 2 were unfavorable, such as a decrease in SpO_2/FiO_2 ratio ($P=0.002$), an increase in inspiratory oxygen fraction FiO_2 ($P=0.001$), leukocyte count ($P<0.05$), LDH ($P=0.038$), procalcitonin ($P<0.001$), and IL-6 ($P=0.005$), as well as an increase in SOFA score from 3.0 to 7.0 (95%CI, 3.0–9.0) ($P=0.001$). The all-cause hospital mortality rate was 37.63% in group 1 and 74.20% in group 2.

Conclusion. The use of hemoadsorption with CytoSorb as a pathogenetic therapy targeting the hyperinflammatory response in the management algorithm of ICU patients with severe COVID-19 complications resulted in resolution of the inflammatory response and respiratory failure, as well as a significant reduction in mortality.

Keywords: hemoadsorption; hemoperfusion; CytoSorb; COVID-19; cytokines; hyperimmune response; inflammatory response; cytokine storm; multiorgan failure; respiratory failure

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

Introduction

Because of the high mortality rate among intensive care unit (ICU) patients with severe COVID-19, developing adjuvant techniques to improve the efficacy of routine ICU care for acute respiratory distress syndrome (ARDS) is still relevant today. COVID-19 is known to cause hyperactivation of the immune system and uncontrolled cytokine production [1]. In recent years, there has been increasing evidence for the role of pro-inflammatory cytokines in the pathogenesis of COVID-19 and its complications [2–4].

Studies have convincingly demonstrated that acute respiratory distress syndrome (ARDS) in COVID-19 is caused by an exaggerated immune response rather than viral load [5–7].

Taking into account the responses involving IL-6, which have traditionally been used to characterize the severity of the inflammatory response [8–10], it is possible to assess its role in pathophysiological gas exchange disturbances and increased pulmonary dysfunction. After production and binding to the receptor, the IL-6/sIL-6R complex binds to the membrane protein gp130, causing dimerization and activation of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway. Given the expression of gp130 in various cells, high levels of IL-6/sIL-6R and the consequences of JAK/STAT3 activation result in hyperproduction and release of various cytokines into the circulation, including IL-8, IL-6, vascular endothelial growth factor (VEGF), MCP-1, and E-cadherin. VEGF and E-cadherin increase vascular permeability and promote capillary leakage syndrome, leading to pathophysiological gas exchange disturbances and pulmonary dysfunction [11].

Tumor necrosis factor (TNF)-α, a cytokine that causes bronchial hyperreactivity, contributes to the progression of lung failure. TNF-α reduces airway diameter and promotes neutrophil migration into

the epithelium. In addition, this cytokine has the ability to directly degrade the airway epithelium, resulting in increased production of pro-inflammatory cytokines such as GM-CSF, IL-8 and intercellular adhesion molecules (ICAM). TNF-α stimulates neutrophils to release MMP-9. All of these events cause irreversible changes in lung tissue, leading to the development of pulmonary fibrosis [12]. IL-17A and TNF-α have been associated with lung injury in obese patients with COVID-19 [13]. Given the importance of elevated cytokine levels in the development, pathogenesis and outcome of lung injury in COVID-19 with severe complications, control and reduction of inflammatory mediator levels appears to be a clinically and pathophysiologically relevant intervention.

Steroid hormones are the primary inpatient anti-inflammatory therapy. When primary anti-inflammatory therapy fails, anti-cytokine therapy is prescribed to block the isolated receptors of a target cytokine. However, because many cytokines have duplicated mechanisms of action as well as pleiotropic and overlapping functions, monoclonal antibodies targeting only one of the pathways are insufficient to affect the mechanisms of hyperinflammatory response development [14].

Hemoadsorption is an adjuvant method for controlling cytokine hyperproduction and can be used as escalating anti-inflammatory therapy in COVID-19 patients. Hemoadsorption removes a wide range of substances from the patient's whole blood that contribute to the exacerbation of the hyperinflammatory response and the development of organ and tissue damage without the need for plasma separation. A number of large studies [15–17] have demonstrated the safety of hemoadsorption with the CytoSorb adsorber, and its use in the treatment of COVID-19 patients is associated with improved clinical outcomes [18–26] according to several international and Russian studies [27]. Given the proven safety of CytoSorb hemoadsorption, the high biocompatibility of the column, and the potential benefits of its use, this therapy deserves a place in the ICU armamentarium. However, because hemoadsorption is not currently included in ICU guidelines (except in a few European communities [28, 29]), it is not commonly used in severe COVID-19 complications. However, hemoadsorption allows pathogenetic treatment of the hyperinflammatory response that causes organ dysfunction in these patients.

Adsorption techniques have been extensively discussed in the scientific literature, but definitive conclusions about their applications have not been reached, and debates continue to this day. The authors of «Adsorption: The New Frontier in Extracorporeal Blood Purification», edited by Ronco and Bellomo, have concluded that as much research as possible is needed to enhance data accumulation on hemoadsorption and its role in critical care [30].

The aim of our work was to determine the effect of hemoadsorption on inflammatory response, respiratory failure and hospital mortality in patients with severe complications of COVID-19.

Materials and Methods

A single-center retrospective cohort comparative study was conducted at the V. P. Demikhov State Clinical Hospital of the Voronovskoye Moscow Clinical Center for Infectious Diseases.

The study included 124 ICU patients with severe COVID-19 and clinical and laboratory evidence of hyperimmune response admitted between January 1 and December 31, 2021.

Inclusion criteria were laboratory-confirmed COVID-19, ICU stay, age over 18 years, specific lung damage according to computed tomography; SpO_2/FiO_2 ratio < 200 mmHg and hemoadsorption in hemoperfusion mode using CytoSorb adsorber.

Patient exclusion criteria: hemoadsorption in combination with prolonged renal replacement therapy (RRT) or in combination with ECMO, or the use of other adsorption systems.

During 2021, 5293 patients diagnosed with COVID-19 were admitted to the ICU. Of these, 136 patients received extracorporeal therapy with the CytoSorb adsorber in the ICU (N=136). 43 patients were excluded based on the exclusion criteria (use of hemoadsorption in the RRT circuit and lateral flow ECMO). Thus, the main group was reduced to 93 patients (group 1). The control group (group 2) included 31 patients consecutively admitted to the ICU with progressive respiratory failure with underlying hyperinflammatory response.

The primary endpoint was to evaluate the effect of hemoadsorption on the inflammatory response and respiratory failure in patients with COVID-19, and the secondary endpoint was to compare in-hospital mortality between the study groups.

Patient examination, diagnosis of underlying disease, complications, comorbidities, and assessment of severity were performed according to the Interim Guidelines for the Prevention, Diagnosis, and Treatment of Novel Coronavirus Infections (COVID-19), versions 8 and 9, in effect at the time of the study.

In the hospital, patients in both groups received primary anti-inflammatory therapy according to interim treatment guidelines. Methylprednisolone or dexamethasone was used as the primary anti-inflammatory therapy. If the primary anti-inflammatory therapy failed, anticytokine drugs (tocilizumab, levilizumab, or olokizumab) were administered.

After admission to the ICU, patients in group 1 were started on the next stage of hyperinflamma-

Table 1. Severity of lung injury based on CT.

Group	Frequency of degree				*P*-value
	1 (<25%)	2 (25–50%)	3 (50–75%)	4 (>75%)	
1 (main)	1	19	45	28	<0.001
2 (control)	8	9	4	10	

tory response therapy, hemoadsorption, within 48 hours.

For hemoadsorption in group 1, we used the Cytosorb adsorber of substances from whole blood, which is considered the most widely studied and used adsorption detoxification system in the world, according to the manual published by the world authorities in extracorporeal methods, Ronco and Bellomo, in 2023 [29]. Hemoadsorption was performed in the hemoperfusion mode, using the long-term renal replacement therapy device MultiFiltrate (Fresenius Medical Care AG, Germany) as a blood pump, and the CytoSorb adsorber was added to the circuit. The duration of a hemoadsorption session was 24 hours. Group 1 patients had an average of 2.67±1.3 hemoadsorption sessions each.

Group 2 patients did not receive hemoadsorption.

The groups were similar in terms of demographics (sex, age, BMI) and Charlson comorbidity index (Fig. 1).

The number of patients with different degrees of lung injury according to CT was found to differ significantly between groups (Table 1), which is typical in comparative studies with retrospective comparator groups and does not preclude comparison.

Data were collected at two time points: on admission to the ICU prior to hemoadsorption in group 1 (time point T_0) and on day 7 of hospitalization in the ICU after completion of hemoadsorption in group 1 (time point T_1).

When comparing the parameters at T_0, patients in group 1 had more severe respiratory failure, as evidenced by a lower SpO_2/FiO_2 ratio (Table 2). At the same time, body temperature was higher in group 2. There were no other significant differences between the groups.

Thus, patients in groups 1 and 2 were similar in 9 out of 13 clinical parameters, with patients in group 1 having more severe respiratory failure than patients in group 2 (Fig. 2).

All patients underwent the same series of laboratory, clinical and biochemical analyses, as well as analysis of blood acid-base balance and gases.

Traditionally, the IL-6 level has been used to assess the severity of the hyperinflammatory response, as it reflects the current immune status and is associated with the severity of inflammation [8–10]. IL-6 levels were measured using an enzyme-linked immunosorbent assay (Vector Best technology, Russia). Throughout the study, instrumental parameters were collected and recorded using Mindray N15 bedside monitors (Mindray, China).

Data collection and primary analysis were performed in Microsoft Excel spreadsheet editor, and comparative statistical analysis was performed using IBM SPSS Statistics 27.0 software package. Data samples were characterized using descriptive statistics (minimum, maximum, mean, 25th percentile, 50th percentile (median), 75th percentile, and standard deviation). Data visualization included the construction of box plots and bar graphs to illustrate the differences between the samples.To clarify the applicability of parametric methods, we assessed the normality of the data distribution using the Kolmogorov–Smirnov test with Liliefors correction. We found that due to the small number of outcomes, parametric criteria were not applicable for all parameters, so we used the nonparametric Wilcoxon test for comparative within-group analysis of related samples. The nonparametric Kruskal–Wallis *H* test (for quantitative parameters) and Pearson's χ^2 test (for categorical and binary parameters) were used for between-group comparisons. The log-rank test was used to assess statistically significant differeces in time to a specific outcome/event (death). The significance level used to reject the noll hypothesis of no differences between the groups studied for different treatments was set at 0.05.

When significant differences were found, the nonparametric Mann–Whitney *U* test with Bonferroni–Holm correction for multiple comparisons (for quantitative parameters) and Pearson's χ^2 test with Bonferroni–Holm correction (for categorical and binary parameters) were used. The significance level was set at 0.05 and 0.017 using the Bonferroni–Holm correction.

Results

Positive evolution of several parameters in Group 1 was observed both over time and in comparison with Group 2, including mortality. Thus, significant changes of 9 parameters out of 13 monitored ones were noted: decrease in body temperature (P=0.005), levels of lactate dehydrogenase (LDH) (P<0.001), C-reactive protein (CRP) (P<0.001) and IL-6 (P<0.001), as well as an increase in SpO_2/FiO_2 ratio (P=0.041), increase in the lymphocyte count (P=0.003) and leukocyte count (P<0.001), no changes in the SOFA score (P=0.068) compared to the values before hemoadsorption (Table 2). The mortality rate in group 1 was 37,63%.

Group 2 patients without hemoadsorption experienced positive changes in body temperature (P=0.003). Other parameters, however, showed unfavorable changes, including decreased SpO_2/FiO_2

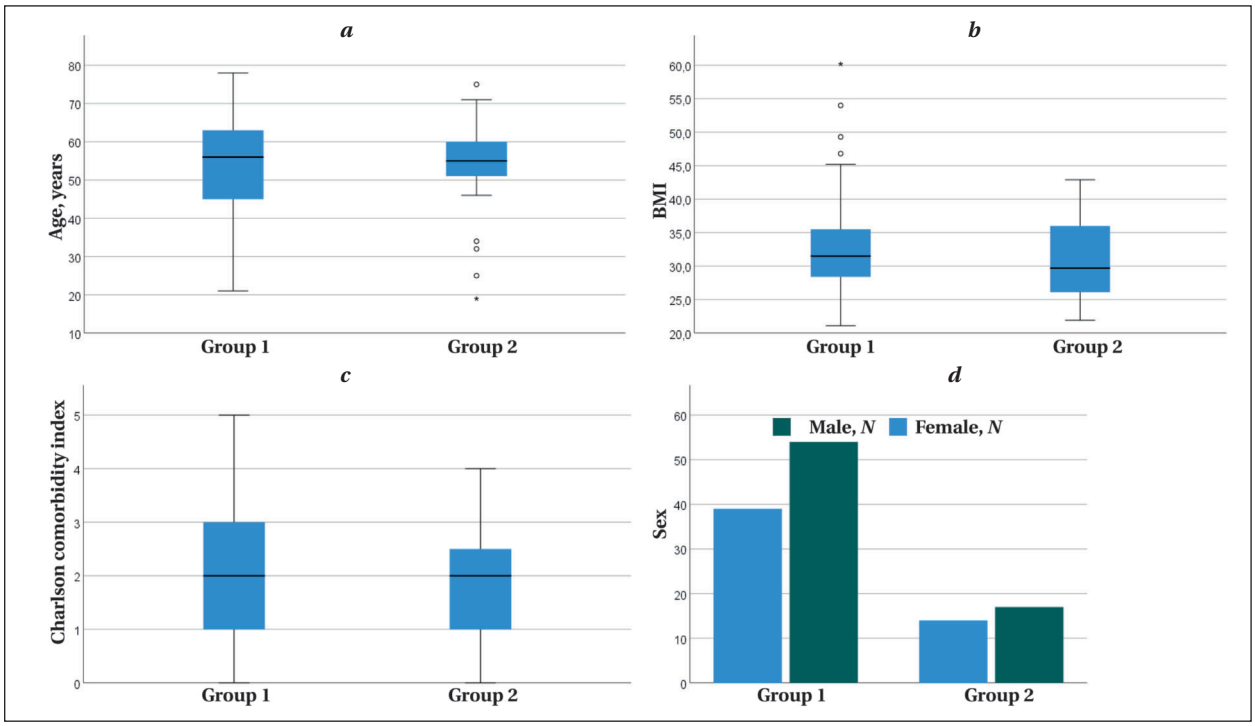

Fig. 1. Demographics and comorbidity index of groups 1 (main) and 2 (control).

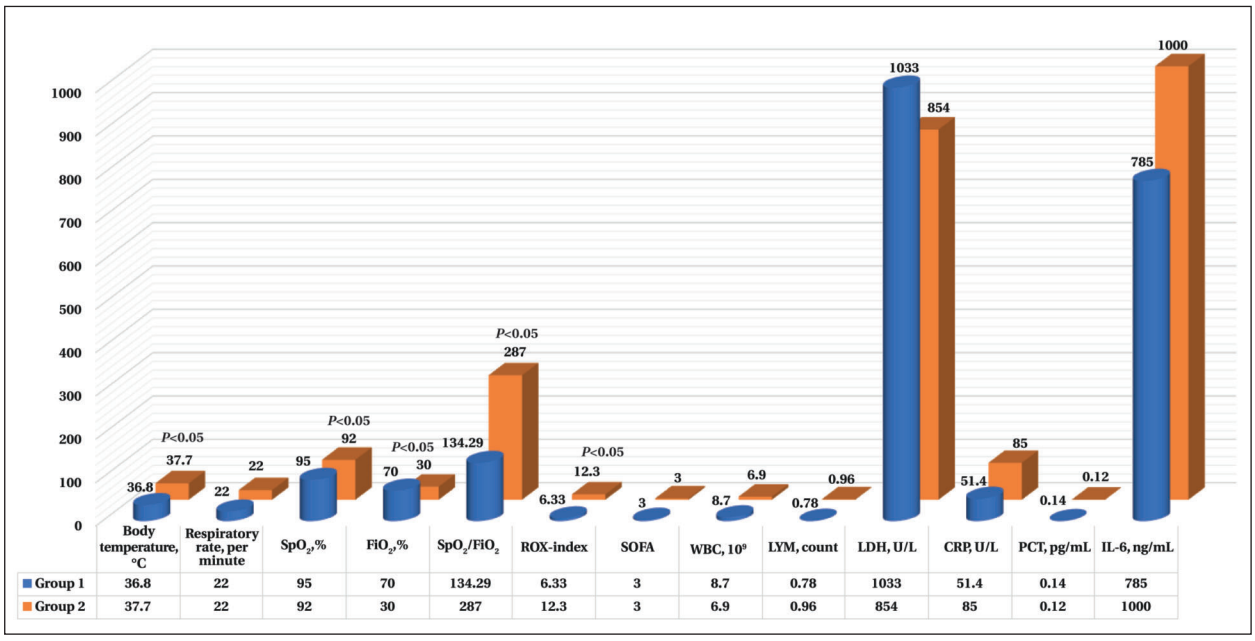

Fig. 2. Clinical characteristics of groups 1 and 2 at T_0.

ratio (P=0.002) and ROX index (P=0.001), as well as increases in leukocyte count (P<0.001), LDH (P=0.038), PCT (P=0.001), and IL-6 (P=0.005).

The SOFA score increased significantly from 3.0 to 7.0 (3.0; 9.0) (P=0.001), indicating that organ dysfunction had progressed in this group (Table 3). The mortality rate in Group 2 was 74.20%.

Comparing to group 2 on day 7, group 1 had significantly higher values of SpO_2 (P=0.003), SpO_2/FiO_2 ratio (P<0.001), ROX index (P<0.001), lower body temperature (P<0.001), and FiO_2 level (P<0.001) (Tables 2, 3).

Significantly lower levels of CRP (P<0.001) and IL-6 (P<0.001) were revealed in group 1 vs group 2. Pattern of secondary bacterial complications was more common in group 2 vs group 1, as evidenced by higher leukocyte counts (11.5×10^9 [9.1; 22.98], P<0.001), PCT levels (2.9 pg/mL [0.3; 9.1], P=0.001),

Table 2. Changes of studied parameters in patients of group 1 during 7 days of treatment in ICU.

Parameter	Values at different time points		*P*-value
	T_0	T_1	
Body temperature, °C	36.80 (36.65; 37.45)	36.7 (36.55; 36.95)	0.005
Respiratory rate, per minute	22.00 (20.00; 22.5)	22.0 (20; 23.5)	0.272
SpO_2, %	95 (93.0; 96.0)	96.0 (94.0; 97.0)	0.082
FiO_2, %	70 (60.0; 80.0)	70 (55.0; 80.0)	0.056
SpO_2/FiO_2	134 (117.5; 161.67)	137.14 (120.00; 175.45)	0.041
ROX index	6.33 (5.23; 7.64)	6.45 (5.19; 10.14)	0.024
SOFA	3.0 (2.0; 3.0)	3.0 (3.0; 4.0)	0.068
WBC, 10^9	8.7 (5.95; 11.30)	10.30 (8; 15.0)	<0.001
LYM, count	0.78 (0.56; 1.09)	0.91 (0.67; 1.28)	0.003
LDH, U/L	1033 (812.5; 1288.5)	898.0 (694; 1225.75)	<0.001
CRP, U/L	51.4 (12.75; 103.9)	10.40 (3.5; 36.08)	<0.001
PCT, pg/mL	0.14 (0.12; 0.23)	0.17 (0.12; 0.44)	0.051
IL-6, ng/mL	785 (54.55; 1000)	186.0 (31.0; 1000)	<0.001

Table 3. Changes of studied parameters in patients of group 2 during 7 days of treatment in ICU.

Parameter	Values at different time points		*P*-value
	T_0	T_1	
Body temperature, °C	37.7 (37.1; 38.6)	37.0 (36.6; 37.5)	0.003
Respiratory rate, per minute	22.0 (20.0; 24.0)	20.0 (18.0; 24.0)	0.168
SpO_2, %	92.0 (88.0; 96.0)	93.0 (88.0; 96.0)	0.927
FiO_2, %	30 (30.0; 70.0)	80.0 (30.0; 90.0)	0.001
SpO_2/FiO_2	287 (138.0; 316.70)	116.3 (103.5; 287.0)	0.002
ROX index	12.03 (5.83; 15.1)	5.88 (4.31; 15.71)	0.090
SOFA	3.0 (2.0; 4.0)	7.0 (3.0; 9.0)	0.001
WBC, 10^9	6.90 (5.5; 10.0)	11.5 (9.1; 22.98)	<0.001
LYM, count	0.96 (0.53; 1.18)	1.16 (0.54; 1.8)	0.115
LDH, U/L	854 (596.0; 1368.0)	1131 (703.0; 1612.0)	0.038
CRP, U/L	85 (34.9; 150.8)	53.0 (23.0; 166.6)	0.468
PCT, pg/mL	0.12 (0.12; 0.3)	2.9 (0.3; 9.1)	0.001
IL-6, ng/mL	1000 (500.6; 1000)	1000 (1000; 1000)	0.005

CRP levels (53.0 U/L [23.0; 166.6], *P*=0.468), and IL-6 concentrations (1000 ng/mL [1000; 1000], *P*=0.005).

Mortality in group 1 was 36.57% (1.97 times) lower than in group 2, *P*=0,017 (Fig. 3).

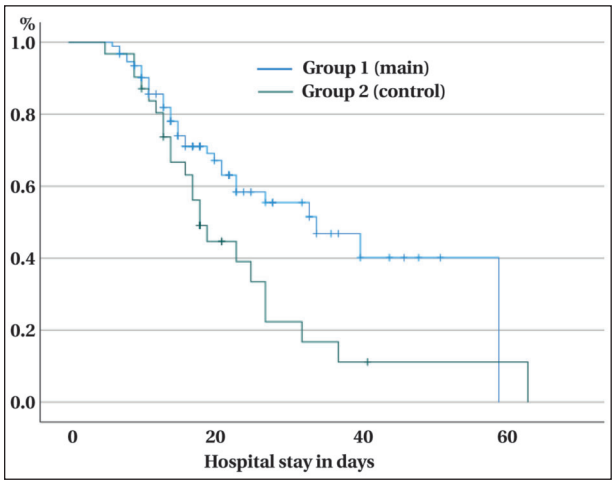

Fig. 3. Mortality rate and hospital stay.

Discussion

Our results show that hemoadsorption has a significant beneficial effect on hyperinflammatory response, severity of acute respiratory failure, and hospital mortality in patients with severe COVID-19 complications, both after within-group analysis and after between-group comparison.

The use of hemoadsorption allowed more effective control of proinflammatory cytokine concentrations, whereas the absence of hemoadsorption in the intensive care algorithm was associated with increased proinflammatory cytokine levels and organ dysfunction. Due to the duplicative mechanisms of cytokine action [31], monoclonal antibodies are not always capable to completely stop the development of the inflammatory response, resulting in the progression of COVID-19-induced ARDS and a number of other complications causing irreversible changes in the body.

Therefore, if primary anti-inflammatory treatment is not fully effective and hemoadsorption is not performed in the ICU, the patient will not receive true causal therapy for COVID-19 [6, 7].

High levels of proinflammatory cytokines are known to contribute to the development of secondary immunosuppression and the pattern of secondary infectious complications in patients with COVID-19.

E. A. Coomes et al. found that 86.8% of hospitalized patients with COVID-19 complications had significantly higher IL-6 concentrations than patients

with uncomplicated COVID-19, and 22.9% had more than a tenfold increase in plasma concentrations of this cytokine [9]. A. Alharthy et al. studied COVID-19 complications and showed that IL-6 concentration in ICU patients was a prognostic marker for mortality [31, 33].

The timely implementation of hemoadsorption in the management of patients with severe COVID-19 complications has been shown to effectively control IL-6 levels, which correlate with the severity of the inflammatory response. Several studies [16, 34, 35] and an experimental study by A. Jansen et al. (2023), using a standardized, highly reproducible technique, demonstrate a significant decrease in TNF (–58%, $P<0.0001$), IL-6 (–71%, $P=0.003$), IL-8 (–48%, $P=0.02$), and IL-10 (–26%, $P=0.03$) *in vivo* using the same sorption system as in our study [17].

A significant decrease in CRP in the hemoadsorption group indicated adequate control of the inflammatory response. Similar effects were described in a study by F. Hawchar et al. that evaluated the outcomes of over 1400 patients receiving hemoadsorption [15], with the concomitant decrease in CRP serving as additional evidence of the reduction in acute inflammation.

We attribute the observed strong positive effect of hemoadsorption on respiratory failure to a reduction in the severity of the hyperinflammatory response and cytokine concentration, as well as a limitation of their secondary damaging effects on lung tissue and gas exchange.

Similar findings were reported by S. David et al., in a large review by A. Akil et al., in a study by A. Alharty et al., and in our previous research [32, 36–39].

A. Supady et al. found that hemoadsorption had no beneficial effect on gas exchange [40]. However, in this study, hemoadsorption was performed during extracorporeal membrane oxygenation (ECMO), which was initiated significantly later than recommended by EuroELSO (after 11 days of ventilation versus the recommended 3 days), so these findings cannot be used as conclusive evidence for the absence of effects of adjuvant therapy in general.

In a pseudorandomized study of 19 pairs of patients, C. Sharf et al. found no differences in clinical parameters between those who received hemoadsorption and those who did not [41]. However, the indications for including hemoadsorption in the management of the patients described in this paper were extremely heterogeneous: some patients were undergoing organ transplantation, others were admitted with polytrauma, some patients developed ARDS as a result of other diseases, some patients were diagnosed with sepsis and septic shock, and the duration of the hemoadsorption session (90 minutes) did not seem sufficient to achieve positive changes [42].

The significantly lower mortality we observed in group 1 is consistent with the findings of Hayanga et al. in a registry of ECMO in patients with COVID-associated ARDS, as well as the results of D. Jarszak et al. who reported a higher survival rate in patients with severe COVID-19 complications when hemoadsorption was used (11 of 12 patients survived in the hemoadsorption group, 6 of 12 patients survived in the standard therapy group) [18, 43]. In a review of publications on the use of hemoadsorption as adjuvant therapy for COVID-19, J. C. Ruiz-Rodriguez et al. observed a trend toward decreased mortality in several of the studies reviewed by the authors [23]. J. He et al. found that the use of hemoadsorption in the pre-ECMO phase of COVID-19 treatment resulted in a significant increase in survival [44]. After reviewing data from over 500 patients on the timing of initiation of hemoadsorption, K. Kogelmann et al. concluded that early initiation of such therapy has a strong positive effect on survival, with each hour of delay increasing mortality by 1.5% ($P=0.034$) [16].

Thus, the initiation of hemoadsorption within the first two days from the patient's admission to the ICU was guided by the above considerations, as well as by the conclusions of the most important contemporary studies on this topic published in 2023 and 2024, such as the study by B. Einollahi et al. [45], which included 578 patients with COVID-19, a large review by Tomescu et al [46], the work by Calamani et al, where the researchers reported higher survival rates with a shorter delay in the initiation of hemosorption [47], and several other studies [48–52].

The findings of this study add to the growing body of knowledge regarding the role of hemoadsorption in treatment of severe COVID-19 complications.

Conclusion

As a result of the study, we found that timely introduction of hemoadsorption into the management of patients with hyperinflammatory response due to COVID-19 allows effective control of cytokine levels, has a strong and significant positive effect on respiratory failure, leading to its regression, as well as helps to reduce mortality in patients with severe complications of COVID-19.

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The Main Effects of the Original Oral Care Protocol Implementation in Patients on Invasive Mechanical Ventilation

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Summary

Respiratory infection is the most common nosocomial infection found in intensive care units (ICUs). Dental plaques and oral mucosa can be colonized by respiratory pathogens within a few days after tracheal intubation. Oral care plays an important role in reducing the incidence of ventilator-associated infections.

Aim of the study. To evaluate clinical effectiveness of the original oral care protocol in ICU patients on invasive mechanical ventilation (IMV).

Materials and Methods. A multicenter, open-label, randomized, prospective, controlled study was conducted in 55 surgical ICU patients on long-term mechanical ventilation. Oral care for patients in the study group (group 1, *N*=30) included brushing with disposable toothbrushes and rinsing with an aqueous solution of 0.05% chlorhexidine digluconate three times daily. In the control group (group 2, *N*=25), patients' oral care was performed twice a day using sterile cotton swabs soaked in 0.05% aqueous chlorhexidine digluconate solution. The results were statistically processed using IBM SPSS Statistics 21. The relative risk (RR) of events was calculated with a 95% confidence interval (95% CI). The 95% CIs for event density parameters such as incidence rate (IR) and incidence rate ratio (IRR) were calculated using the exact Poisson test.

Results. The incidence of ventilator-associated pneumonia (VAP) was 13.6 cases [95% CI: 4.4; 31.7] per 1,000 ventilation days in group 1 and 23.6 cases [95% CI: 7.7; 55] per 1,000 ventilation days in group 2. The incidence of VAP was 1.74 times lower [95% CI: 0.4, 7.54] in group 1 vs. group 2 (*P*=0.398). The identity of oral and tracheal flora on day 7 was 20% in group 1 and 50% in group 2, RR=0.4, 95% CI: 0.165–0.973, *P*=0.037. Serum C-reactive protein levels were significantly lower in group 1 on day 7 of ventilation compared to group 2 (*P*=0.04).

Conclusion. The original oral care protocol, based on toothbrushing 3 times daily with a set of disposable toothbrushes and 0.05% aqueous solution of chlorhexidine digluconate, is associated with a tendency to lower VAP incidence per 1000 days of ventilation, significantly lower similarity between oral and tracheal flora, and lower serum C-reactive protein levels on day 7 of IMV. Further research on various aspects of oral care in ICU patients is needed, especially in the absence of complete clinical guidelines and clearly effective strategies for the prevention of ventilator-associated infections.

Keywords: oral care; mechanical ventilation; infectious complications; ventilator-associated pneumonia; disposable toothbrushes; cotton swabs

Conflict of interest. The authors declare that the study was supported by the Intersurgical Company, which provided oral care supplies and conducted a series of educational seminars for nurses to train them in oral care techniques for mechanically ventilated patients prior to initiation of the study.

Introduction

Respiratory infections are the most common nosocomial infections in intensive care units [1]. Approximately 60–65% of ICU patients require mechanical ventilation as a result of acute or decompensated chronic respiratory failure [2]. In some cases, ventilatory support is used not only to increase blood oxygenation and normalize lung ventilation, but also to keep the airway open and prevent aspiration. Ventilator-associated pneumonia (VAP) is one of the most common nosocomial infections, accounting for at least 25% of all nosocomial infections in the ICU, depending on the unit profile [3, 4].

Maintaining the upper airway with an endotracheal tube compromises the protective function of the airway mucosa, allowing various microorganisms to enter the lower airway directly or via silent aspiration [5]. Pathogenic microorganisms

such as *Pseudomonas* and *Escherichia coli* can enter the lower respiratory tract directly through the endotracheal tube (ET) or its leaky cuff, resulting in tracheobronchitis and pneumonia due to compromised natural immune defenses caused by critical illness. As a result, the overall risk of VAP associated with endotracheal intubation is highest during the first week of a patient's ICU stay [6]. Mucus accumulation in the supra-cuff space, mouth opening and dryness of the oral mucosa, impaired cough reflex, difficulties in removing secretions through the mouth and larynx, and poor oral hygiene can all contribute to the development of VAP [7]. Aspiration of microorganisms from the gastrointestinal tract is another important mechanism for oropharyngeal colonization during mechanical ventilation, which becomes an important source of opportunistic bacteria in the hypoxia associated with critical illness [8].

The use of systemic or inhaled antimicrobial chemotherapy alone may not be the most effective way to reduce VAP. N.Beloborodova et al. conducted a pilot study in 2021 that demonstrated the safety and comparable clinical efficacy of inhaled phagotherapy in neurological intensive care patients with recurrent nosocomial pneumonia [9].

Tracheal intubation is known to cause mechanical trauma to the oral mucosa, xerostomia and changes in plaque and oral flora, all of which increase the risk of respiratory infections [10, 11]. Potential respiratory pathogens can colonize dental plaque and oral mucosa within days of tracheal intubation. During this time, the spectrum of oral microorganisms gradually shifts from gram-positive to gram-negative species and yeasts, mainly due to a decrease in fibropectin, which regulates the activity of phagocyte-binding streptococci [12, 13]. Genetically identical pathogens have been isolated from plaque samples and bronchoscopic specimens from long-term ventilated patients suffering from various types of nosocomial respiratory infections, including tracheobronchitis and pneumonia [14, 15]. The mechanisms underlying this «microbial shift» are unclear, but could be attributed to both the physical presence of ET and other invasive procedures, as well as medication side effects. Plaque composition is known to be diverse and dynamic, with many microbial strains adapting to their environment [16]. Any change in saliva production or composition may affect the microbial composition of plaque. The presence of ET in critically ill patients with compromised immune status on antibiotics and other drugs causes significant changes in the salivary proteome [17].

Over the past decade, various mechanical and pharmacological methods have been used in clinics to reduce the «microbial load» of the oral mucosa and dental plaque. For example, a study conducted by Russian scientists found that combined multispectral decontamination of the upper respiratory tract, including the subligamentous space, with octenidine antiseptic and bacteriophage can reduce the risk of VAP and influence the respiratory tract microbiome [18].

Numerous randomized trials have shown that regular (at least every 12 hours) oral treatment with 0.2% aqueous chlorhexidine solution can reduce the risk of VAP [19, 20]. However, practical application of these recommendations has shown that the recommended concentration of chlorhexidine causes significant damage to the patient's oral mucosa.

Observational studies on the efficacy of toothbrushing in patients on prolonged mechanical ventilation show a decrease in the titer of microorganisms in the oral mucosa and dental plaque, but data on the incidence of VAP are somewhat contradictory [21]. Recently, there has been an increase in the use of various dental treatment modalities in ICU patients, which could be attributed to the development of new technological solutions to improve the quality of oral care. However, prospective randomized controlled trials have produced conflicting results regarding the effect of toothbrushing procedures in patients undergoing prolonged ventilation on the incidence of nosocomial respiratory infections [22, 23].

In the nursing literature, recommendations of low level of evidence for tooth brushing in adult patients with intubated trachea can be found. In contrast, current clinical and national guidelines for the prevention of VAP do not mention tooth brushing [24–26]. Surveys of nurses indicate that tooth brushing is time consuming and that nurses would like to receive specific training in this technique because it is «not as easy as it seems at first glance» [27, 28].

It should be recognized that current approaches to oral care and tooth brushing in ICU patients on prolonged mechanical ventilation are diverse and often defined by traditional approaches, which seems to be due to the lack of a clearly better technique or technology. Therefore, the issue of clinical efficacy and safety of new methods for prevention of nosocomial respiratory infections in patients undergoing prolonged mechanical ventilation requires further investigation.

Aim of the study was to evaluate the clinical efficacy of the original oral cavity treatment protocol based on the use of a set of disposable toothbrushes and chlorhexidine digluconate 0.05% aqueous solution in mechanically ventilated intensive care patients.

Materials and Methods

We conducted a multicenter, prospective, open-label, controlled study in patients in the surgical intensive care units of the Almazov National Medical

Research Center of the Ministry of Health of Russia (St. Petersburg, Russia), the Petrovsky Russian Scientific Center of Surgery (St. Petersburg, Russia), and the City Clinical Hospital No. 17 (Moscow, Russia).

The study was approved by the local ethics committee of the Almazov National Medical Research Center of the Ministry of Health of the Russian Federation, protocol No. 11–21 dated November 03, 2021.

Surgical intensive care unit patients on mechanical ventilation in the early postoperative period were randomized to one of two groups to evaluate the clinical efficacy of the original oral treatment protocol.

Randomization. The principal investigator generated the randomization table using the resource www.randomizer.org.

According to the table, all patients were randomized into two groups: main (*N*=30, group 1) and control (*N*=25, group 2).

Inclusion criteria for the study (all criteria were mandatory):

1. Patients of both sexes between 18 and 80 years of age.
2. Mechanical ventilation for more than 24 hours
3. Orotracheal intubation
4. Expected duration of mechanical ventilation of at least 72 hours
5. Informed consent of the patient to participate in this study, signed prior to surgery.

Study exclusion criteria (at least one criterion):

1. Prehospital aspiration
2. Antimicrobial therapy 14 days prior to surgery
3. Community-acquired pneumonia on admission
4. Chronic obstructive pulmonary disease (COPD)
5. Thoracic trauma
6. Missing teeth
7. Fat embolism
8. Decompensated chronic renal failure
9. Decompensated chronic liver failure
10. Pregnancy or lactation
11. Use of corticosteroids
12. Chemotherapy less than 6 months prior to study entry
13. Any other condition that the investigator deemed inappropriate for participation in the study.

Other exclusion criteria:

1. Mechanical ventilation for less than 72 hours
2. Development of pulmonary embolism
3. Hemothorax
4. Pneumothorax
5. Acute gastrointestinal bleeding
6. Failure to monitor clinical and laboratory parameters
7. Tracheostomy during the first 5 days of treatment
8. Erroneous inclusion in the study
9. Patient refusal to participate in the study
10. On investigator's decision in order to ensure patient safety
11. Violation of the protocol that may affect the outcome of the study and/or increase the risk to the patient.

Oral cavity treatment methods. From day 1 (the moment of tracheal intubation) to day 10 of ventilation, oral cavity treatment and teeth cleaning of patients were performed by nurses who had received prior in-person training. Patients in group 1 (main group) had their oral cavity cleaned three times a day with a set of disposable toothbrushes «OroCare-Q8» and chlorhexidine digluconate 0.05% aqueous solution. Patients in group 2 (control) had their oral cavity treated twice a day with a sterile cotton swab moistened with chlorhexidine bigluconate 0.05% aqueous solution.

In both groups, standard methods for prevention of nosocomial respiratory infections were used, such as closed suction systems, regular pressure control in the cuff of the endotracheal tube, elevation of the head end of the bed by 30 degrees and more, regular cleaning of the supra-cuff space, as well as timely transition to other modes of ventilation and minimization of sedation [29].

Patients' oral status was assessed daily using the Beck Oral Assessment Scale (BOAS). This scale, which is most appropriate for assessing oral mucosa and plaque, included five criteria, including inspection and assessment of the lips, gums and oral mucosa, tongue, teeth, and saliva. Each criterion was scored from 1 to 4, for a total score of 5 to 20. No changes were scored as 5 points, mild changes were scored as 6–10 points, moderate changes were scored as 11–15 points, and severe changes were scored as 16–20 points [30, 31].

Each patient underwent chest radiography, registration of sex and age, assessment with the Acute Physiology and Chronic Health Evaluation (APACHE) II and SOFA (Sequential Organ Failure Assessment) scales, measurement of body temperature, white blood cell count, blood C-reactive protein, procalcitonin levels, PaO_2/FiO_2, routine biochemical parameters, assessment of duration of mechanical ventilation and ICU stay. 28-day mortality was also evaluated. Ventilator-associated infectious events (VAP, VAT, asymptomatic airway colonization) were recorded by microbiological monitoring and serial assessment using the Clinical Pulmonary Infection Score (CPIS) [32]. VAP was diagnosed when the CPIS score exceeded 6 points.

Microbiological examination of tracheobronchial tree and oral cavity secretions was performed on days 3, 7, and 10 from the time of tracheal intubation. Samples were collected early in the morning before the next antiseptic and tracheal hygiene treatment. A colony forming unit (CFU)

titer $\geqslant 10^5$ was considered diagnostically significant and a titer $\geqslant 10^3$ was considered colonization [33].

The primary endpoint of the study was the incidence of VAP at day 10 of mechanical ventilation. Secondary endpoints were the incidence of pulmonary infiltrates, identity of oral and tracheal flora, oral cavity status as assessed by the BOAS scale, and laboratory parameters of systemic inflammatory response on day 7 of ventilation.

Statistical analysis. Statistical analysis was performed with IBM SPSS Statistics 21. Normality of distribution was tested using the Shapiro–Wilk criterion. In the case of normal distribution, data were presented as *M*±*SD* (95% CI) (*M* — arithmetic mean, *SD* — standard deviation, 95% CI — confidence interval), and in the case of non-normal distribution, as median with interquantile range of 25 and 75 percentiles. Pearson's χ^2 and Fisher's exact test were used to compare qualitative variables. Student's *t*-test was used to analyze normally distributed quantitative variables. In case of non-normal distribution, the Mann–Whitney test was used. The critical level of significance was considered to be *P*=0.05. We also calculated the relative risk (RR) of the event with 95% confidence intervals (CI 95%) and the number needed to treat (NNT) values. The 95% confidence intervals (95% CI) for incidence rate (IR) and incidence rate ratio (IRR) were estimated using the exact Poisson method [34]. The exact two-sided test with mid-P correction was used to test the null hypothesis of equality of incidence rates in the two groups [35].

Results and Discussion

From December 2021 to June 2023, 55 patients on mechanical ventilation in surgical intensive care units were evaluated. 8 patients were excluded for the following reasons: erroneous inclusion — 5 patients, protocol violation that could affect the results of the study — 3 patients. Initially, the groups did not differ in age, sex, APACHE II, SOFA, body and blood temperature (Swan–Ganz catheter thermosensor), blood biochemistry, white blood cell count, and blood C-reactive protein concentration. No significant differences in SOFA, CPIS and BOAS scores, body temperature, blood leukocyte count and serum procalcitonin (PCT) levels were found between the compared groups during the 10-day follow-up period. However, the level of serum C-reactive protein was significantly lower (*P*=0.04) in the main group on day 7 from the time of patient enrollment. There were no significant differences in parameters such as duration of mechanical ventilation and ICU length of stay between the groups (Table 1).

There was a trend toward a decreased incidence of pulmonary infiltrates in the main group on day 7 of the study (36% of cases in the main group and 59.1% in the control group) (Table 2).

The frequency of oral and tracheal flora identity on day 3 of ventilation did not differ between groups (*P*>0.05) (Fig. 1), on day 7 it was 20% in the main group and 50% in the control group (RR=0.4; 95% CI, 0.165–0.973; *P*=0.037) (Fig. 1, Table 3).

The incidence rate (IR) of infectious events per 1000 ventilation days was 13.6 cases of VAP [95% CI, 4.4–31.7] in the main group and 23.6 cases of VAP [95% CI, 7.7–55] in the control group. There was a trend toward a lower incidence of VAP in group 1, which was 1.74 times lower than in group 2 [95% CI, 0.4–7.54; *P*=0.39].

Poor oral hygiene in ICU patients undergoing prolonged mechanical ventilation is one of the main factors leading to plaque accumulation and subsequent excessive colonization by pathogens. According to various authors, the percentage of positive plaque cultures in ICU patients ranges from 23 to 60% [36, 37].

Respiratory pathogens isolated from the lungs are often genetically identical to strains of the same species isolated from dental plaque and the patient's tongue [38]. Therefore, it seems logical that improved oral hygiene could reduce the risk of ventilator-associated infections.

In this regard, many authors have investigated the feasibility of oral decontamination with antibacterial or antiseptic agents [38, 39]. Regarding oral decontamination with chlorhexidine solution in critically ill patients, some studies have reported a decrease in the frequency of positive bacterial cultures from plaque samples, and a number of meta-analyses have found a decrease in the incidence of VAP with its use [40, 41].

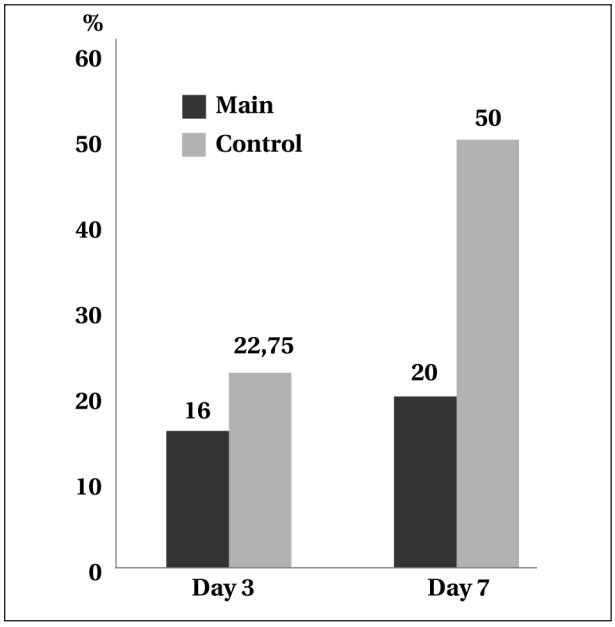

Fig. Frequency of oral and tracheal flora identity on days 3 and 7 of lung ventilation.

Table 1. Changes in clinical, laboratory, and paraclinical parameters in the groups during the study.

Parameter	Values in groups		*P*–value
	Group 1, *N*=25	Group 2, *N*=22	
Age, years	65 (53.5; 72)	70 (65; 74)	0.66**
APACHE II, points	13.05 (9.6–16.4)	13.1 (8.6–17.5)	0.98*
SOFA, points	8.33 (6.10–10.56)	7.64 (5.6–9.6)	0.65*
	Day 0		
Blood temperature, °C	37.4 (37.1; 37.8)	37.4 (37; 38)	0.78**
Body temperature, °C	36.85 (36.5; 37.3)	37.05 (36.7; 37.5)	0.5**
White blood cells, thousands per mm³	13.37 (11.3–15.4)	13.76 (11–16.5)	0.81*
CRP, mg/L	129.5 (90–169.1)	167.83 (100.3–235.3)	0.27*
BOAS , points	6 (5; 9)	8 (6; 11)	0.47**
CPIS , points	4.2 (3.1–5.4)	4.28 (2.9–6)	1.0*
	Day 1		
SOFA, points	7.5 (5; 13)	8.5 (5; 11)	0.95**
Blood temperature, °C	37.5 (37.2–37.8)	37.63 (37.2–38)	0.73*
Body temperature, °C	36.6 (36.5; 37.5)	37 (36.7; 37.6)	0.53**
White blood cells, thousands per mm³	13.5 (11.2–15.8)	13.55 (11.01–16.08)	0.99
CRP, mg/L	135 (105.5; 235.6)	195.4 (119; 273.4)	0.3**
BOAS , points	7.28 (6.05–8.5)	8.35 (6.5–10.2)	0.3*
CPIS , points	4.21 (3.3–5.08)	4.57 (3.2–5.8)	0.61*
	Day 3		
SOFA, points	8 (6–10.03)	7.2 (5–9.4)	0.6*
Blood temperature, °C	37.45 (37; 37.8)	37.4 (37.2; 37.6)	0.8**
Body temperature, °C	37 (36.7; 37.1)	37 (36.7; 37.3)	0.52**
White blood cells, thousands per mm³	12.2 (10.02–14.4)	12 (10.1–13.6)	0.83*
CRP, mg/L	129,6 (90,5–149,6)	147.67 (94.7–200.6)	0.3*
PCT, pg/L	0.7 (0; 10)	0.4 (0; 5.1)	0.88**
BOAS, points	7 (5; 8)	7 (5; 9)	0.74**
CPIS, points	5 (2; 6)	5 (3; 6)	0.66**
Pulmonary infiltrates, number and percentage of patients	7 (28.0 %)	7 (31.8%)	0.5***
	Day 5		
SOFA, points	8.4 (5.5–11.2)	6.8 (4.5–9.2)	0.36*
White blood cells, thousands per mm³	12.7 (10.1–15.3)	10.8 (9.6–12.1)	0.17*
CRP, mg/L	119.3 (81.6–157.04)	125.6 (81.06–170.2)	0.81*
BOAS, points	6.8 (5.1–8.6)	7.6 (6.6–8.7)	0.43*
CPIS, points	4.8 (3.4–6.2)	4.7 (3.3–6.2)	0.95*
	Day 7		
SOFA, points	7.4 (5.0–9.8)	6.4 (3.2–6.5)	0.56*
Blood temperature, °C	37.2 (37.1; 37.4)	37.5 (37.2; 37.8)	0.3**
Body temperature, °C	37 (36.8; 37.8)	37.05 (36.5; 37.2)	0.44**
White blood cells, thousands per mm³	12 (8.5; 14.4)	12.1 (9.7; 14)	0.8**
CRP, mg/L	75 (45; 184)	130.6 (33; 155.2)	0.04*
PCT, pg/L	1.4 (0; 14.2)	2.6 (0; 16.6)	0.3**
BOAS, points	7 (5.2–8,7)	8.1 (6.8–9.4)	0.36*
CPIS, points	5.05 (3.6–6.4)	4.5 (3.3–5.6)	0.55*
Duration of lung ventilation, days	15.5 (6; 20)	10 (4; 12)	0.2**
Length of stay in the ICU, days	19.6 (15.5–25.8)	14.9 (9.8–16.2)	0.65*

Note. Data are reported as *M* (95% CI) or as *Me (Q1; Q3)*. * — Student's *t*-test; ** — Mann–Whitney test; *** — Fisher's exact test; **** — Pearson's χ^2 test.

Table 2. Frequency of pulmonary infiltrates in groups on day 7 of lung ventilation.

Group	Patients, *N* (%)		Relative risk (RR)	95% CI	*P*-value	NTT
	Without infiltrates	With infiltrates				
1, *N*=25	16 (64)	9 (36)	0.61	0.325–1.141	0.113*	4.33
2, *N*=22	9 (40.9)	13.0 (59.1)				

Table 3. Frequency of oral and tracheal flora identity in the groups on day 7 of lung ventilation.

Group	Patients, *N* (%)		Relative risk (RR)	95% CI	*P*-value	NTT
	With non-identical flora	With identical flora				
1, *N*=25	20 (80)	5 (20)	0.4	0.165–0.973	0.037*	3.33
2, *N*=22	11 (50)	11 (50)				

Note. * — Fisher's exact test.

There is now strong evidence that oral care with chlorhexidine reduces the risk of VAP. However, there is no evidence that brushing has an additional beneficial effect.

Cohort studies conducted between 2006 and 2009 [42, 43] found that oral care with antiseptics and toothbrushing reduced the incidence of VAP compared with no care. Important limitations of these studies were the comparison of historical and prospective cohorts, which made it impossible to isolate the effect of toothbrushing on the incidence of infectious complications.

Analyzing the effect of oral care with and without a toothbrush, L. Lorente et al. [21] demonstrated that the clinical effects of using a chlorhexidine-impregnated gauze swab and a soft toothbrush with chlorhexidine were not significantly different. In this study, care was provided every 8 hours and, in addition to the above measures, patients' oral mucosa was irrigated with 10 ml of 0.12% aqueous chlorhexidine solution.

C. F. De Lacerda Vidal et al. [44] found a higher incidence of VAP in the group of patients using chlorhexidine-impregnated swabs than in the group using a brush impregnated with chlorhexidine gel. There was also a significant reduction in the duration of mechanical ventilation and ICU length of stay when the toothbrush was used.

In mechanically ventilated patients, we compared the use of two oral care protocols (traditional and original) that did not differ in the type and duration of antiseptic use (0.05% aqueous chlorhexidine solution) on the incidence of ventilator-associated infections.

We observed a 1.7-fold reduction in the incidence of VAP with triple brushing using disposable brushes with an aspiration system in combination with oral cavity treatment with 0.05% aqueous chlorhexidine solution. There was also a trend toward a decreased incidence of pulmonary infiltrates on day 7 of the study.

In a systematic review, L. de Camargo et al. showed that the addition of toothbrushes to the patient care program had no significant effect on reducing the incidence of VAP. However, L. de Camargo et al. analyzed studies in which tooth brushing was part of the oral care program and did not consider the similarities or differences in other interventions that affect the likelihood of developing ventilator-associated infections. They also compared the effectiveness of mechanical interventions and did not mention brushing frequency [45].

A study by J. Ory et al. [46] found a higher incidence of VAP with chlorhexidine-impregnated swabs compared to toothbrushes and chlorhexidine treatment. However, this study also did not examine the frequency of brushing during the day.

In our study, three treatments with disposable aspiration brushes combined with oral mucosal irrigation with 0.05% aqueous chlorhexidine solution resulted in a significant reduction in the incidence of identical oral and tracheal flora in the main group on day 7 of the study.

Limitations. The study had several limitations. First, the presence of caries and periodontal disease was not preassessed. We also did not compare the incidence of complications of the treatment procedure itself in the groups, such as wounds and bleeding of the oral mucosa, or the incidence of accidental removal of the endotracheal tube. The technique for diagnosing VAP was non-invasive, using only tracheal aspirate samples rather than culture of bronchoalveolar lavage fluid. Limitations also include both the open nature of the study, due to the obviousness of the manipulations, and the lack of a priori calculation of sample size.

Conclusion

The use of the original oral care protocol based on triple brushing with a set of disposable toothbrushes and 0.05% chlorhexidine digluconate aqueous solution is associated with significantly lower oral and tracheal mucosal flora identity and serum C-reactive protein on day 7 of invasive ventilation.

Further research on various aspects of oral care, especially in the absence of comprehensive clinical guidelines, and the development of effective methods to prevent ventilator-associated infections are needed.

Authors' contributions. All authors were equally involved in the design of the article, acquisition and analysis of the evidence, drafting and editing of the manuscript, and review and approval of the text.

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Methodology for Evaluating the Performance of a New Pulse Oximeter Model and Pulse Oximetry Algorithm in Neonates in a Clinical Trial (Exploratory Study)

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Summary

While evaluating a new domestically produced pulse oximeter model in clinical practice, we discovered a lack of references in Russian-language publications on clinical trial methodologies to assess device reliability and performance.

The aim of the study is to create a methodology for conducting a multicenter, prospective, cohort, non-randomized, controlled clinical trial evaluating a domestic pulse oximeter.

Methods. Measurements were performed on 20 preterm infants in the neonatal intensive care unit with a mean birth weight of 2340 [1250; 3125] g and a gestational age of 35 [30; 37] weeks using a new model pulse oximeter simultaneously with the reference monitor. Multiple oxygen saturation measurements of varying duration were taken alternately from the upper and lower limbs, and the number of false desaturation alarms was recorded. Pulse oximeter saturation data were evaluated for correlation with clinical findings.

Results. Attachment of sensors to the infant's feet was found to be optimal in terms of ease of use, minimal artifact generation, and minimal interference with routine medical procedures and neonatal care. To reduce motion-induced artifacts and false alarms, the optimal period of SpO_2 monitoring to detect desaturations and bradycardia was determined to be 120 min. Due to the high variability of pulse rate (PR) and saturation in neonates, two-second intervals were determined to be optimal for comparing records from the two monitors. Matching of ECG HR and pulse oximeter PR was required to eliminate artifacts. A mathematical software model required for accelerated analysis of data collected from all sensors during the study was approved.

Conclusion. The data analysis supported the proposed methodology for conducting a clinical trial to evaluate the performance and reliability of new pulse oximetry devices.

Keywords: pulse oximetry; neonates; neonatal pulse oximetry algorithm; Sensorex oximeter

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

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Introduction

Monitoring of vital signs, including pulse oximetry, is the foundation of the diagnostic process in the intensive care unit (ICU). The search for more advanced monitoring methods enables modernization and adaptation of treatment strategies, as well as shorter hospital stays and improved patient quality of life [1]. The timeliness of medical care depends largely on the reliability of medical equipment.

Pulse oximetry is a method of assessing arterial blood oxygen saturation (SpO_2) using photoplethysmography (PPG), which measures the increase in light absorption caused by an increase in arterial blood volume during myocardial systole [2]. Pulse oximetry is one of the most commonly used methods for continuous monitoring of vital signs in the ICU because of its ease of use and high data accuracy. Although some aspects of pulse oximeter performance can be evaluated using simulation, the pulse oximetry process involves numerous physical and optical interactions (light absorption by tissues, venous blood, etc.), so the pulse oximeter is classified as a device that requires empirical clinical studies for development, calibration, and validation [3, 4].

While preparing a protocol for clinical validation and testing of a new model of the Russian pulse oximeter «Sensorex», developed by the Ural Optical and Mechanical Company named after E. S. Yalamov, our Laboratory of Industrial Design and Re-engineering of Medical Equipment (LIDRME) faced the challenge of finding a methodology suitable for evaluating and comparing the performance of pulse oximetry devices in neonatal care in the Russian-language literature. Such a methodology was needed to list the advantages and shortcomings of a tested device in an understandable way.

As a result, it was decided to conduct an exploratory clinical trial to develop a methodology for future studies. The study determined basic parameters such as:

1. The scheme for connecting the control and tested pulse oximetry devices to the patient
2. The duration of each episode in the measurement
3. Recorded parameters
4. Automated workstation (AWS) scheme.

After reviewing the literature, we decided to use the Masimo SET® pulse oximetry monitor as the reference monitor. This decision was supported by the available studies, which provided compelling evidence of the clinical effectiveness advantage of this algorithm.

In one study, Masimo SET® pulse oximetry detected 86% fewer false alarms of SpO_2 and heart rate in neonates and detected more true episodes of hypoxia and bradycardia than pulse oximetry monitors with other algorithms (Nellcor N-200, Nellcor N-395, Novametrix MARS, Philips Viridia 24C). [5]. Because neonatal ICU patients typically have active limb movements, it was critical to maintain pulse oximetry accuracy during motor activity. Laboratory testing of pulse oximetry accuracy during active patient arm movement showed that the Masimo SET® pulse oximeter outperformed 20 other devices tested, including the Agilent Viridia 24C, Agilent CMS, Datex-Ohmeda 3740, Nellcor N-395, Criticare 5040, and others [6].

In addition, pulse oximetry using the Masimo SET® algorithm resulted in significantly faster acquisition of a steady signal after the sensor was placed on the body in neonates requiring resuscitation. Comparing Radical-7 (Masimo) and Biox 3700, the mean time to a stable reading was 20.2±7 and 74.2±12 seconds, respectively (P=0.02). When comparing Radical-7 and Nellcor N-395, the time to stable measurements from the start of monitoring was 20.9±4 and 67.3±12 seconds, respectively (P=0.03) [7].

Recent studies of the characteristics of pulse oximetry during extremity motion have shown a continuing trend of decreasing accuracy of data acquisition [8, 9]. Several studies have shown that virtually all pulse oximeters studied during movement tests showed an increase in mean square error to values above the recommended threshold of 3% [8, 9]. In this context, we also decided to match the episodes of sensor measurements to the clinical presentation, since the use of even a reference pulse oximetry monitor could lead to measurement errors in the presence of increased motor activity.

The growing need to create a consortium of domestic medical equipment manufacturers to replace foreign equipment that is difficult to import due to sanctions or disruptions in logistics chains [10] is of strategic importance and requires the development of validated testing methods. This will allow medical organizations to optimize their supply of equipment, as well as identify defects and flaws in tested equipment more quickly.

Aim of the study was to develop the methodology of the upcoming clinical study under the R&D program «Clinical testing of Sensorex pulse oximeter and developing algorithms for newborns».

The objectives of the study were:

- to determine the patient population according to the inclusion and exclusion criteria;
- to obtain informed consent from each patient's legal representative to test a new medical device (Sensorex pulse oximeter);
- to evaluate the safety of the Sensorex pulse oximeter during a single 180-minute test measurement;
- to perform a series of measurements with the Sensorex pulse oximeter;
- to determine the parameters necessary for measurement in a full-scale, multicenter clinical trial;
- to determine the optimal connection scheme of the pulse oximetry sensors of the Sensorex device under study and the reference control monitor;
- to determine the optimal duration of measurements;
- to design the automated workstation based on the data obtained;
- to formulate technical specifications for the development of software to process the array of data obtained.

Materials and Methods

This article is a publication of the study protocol.

Study design. Prospective, cohort, non-randomized, controlled study.

Allocation of patients to groups. Study (main) group. There was no control group.

Inclusion criteria. Neonatal intensive care unit patients (newborns).

Exclusion criteria.

- Participation in the study would interfere with diagnostic and therapeutic measures or routine patient care.
- Refusal of the legal representative of the child to participate in the clinical trial.

Location and period of the study. Ekaterinburg Perinatal Clinical Center from 01.10.2023 to 30.10.2023.

Study participants. Intensive care physicians of the neonatal intensive care unit.

General study principles. During the study, measurements were made using a Sensorex heart rate monitor and a reference monitor with a built-in Masimo SET® algorithm that is used daily in the newborn intensive care unit (NICU).

In the NICU, patients received routine interval care every three hours, which included repositioning, feeding and hygiene procedures. These activities took 30 to 50 minutes. We chose a study time of no more than 120 minutes between care procedures,

which has been shown in practice to influence the number of artifacts in pulse oximetry and thus the accuracy of the results obtained.

Transmission-type pulse oximetry sensors (control and study monitor) were placed on the child's extremities.

The start time of the study was confirmed using the control and study monitors. Values were manually recorded on a trend chart every 10 seconds.

At the end of the study, the investigator manually transferred each patient's data from the trend chart to an Excel spreadsheet. The time interval for data recording was set to 10 seconds.

If episodes of SpO_2 reduction of less than 85% and episodes of more than 20 min^{-1} difference between the device heart rate readings were recorded within the specified intervals, the clinical concordance of heart rate (HR) and SpO_2 reduction was recorded by marking «+» for concordance and «–» for discordance on the trend chart.

Depending on the study group, the extremities for the pulse oximetry sensors were changed at the specified interval.

If treatment interference occurred, the study was stopped early and not marked as completed.

The study was divided into three phases: determining the best location for the sensors on the patient, the best time to perform the study, and the use of the reference ECG channel.

Statistical analysis. The study materials were analyzed using both parametric and nonparametric analysis methods. The original data were collected, corrected, and organized, and the results were visualized using the developed trend chart and Microsoft Office Excel 2016 software. IBM SPSS Statistics v.26 software (developed by IBM Corporation) was used for statistical analysis. The Kolmogorov-Smirnov test was used to determine the normality of the distribution of quantitative parameters. The distribution of most parameters was not normal. Numerical parameters were described by median *(Me)* and lower and upper quartiles *[Q1; Q3]*. Categorical data were described by absolute values and percentages. The Mann–Whitney *U* test was used to compare the different conditions. Pearson's χ^2 test was used to compare categorical data. When analyzing four-way tables with an expected phenomenon and a value in at least one cell less than 10, the χ^2test was calculated using Yates' correction. A two-tailed value of $P<0.05$ was used to determine the statistical significance of differences.

Results

The study yielded a total sample of patients distributed over several phases (total *N*=20). The median body weight was 2340 [1250; 3125] g, the median gestational age was 35 [30; 37] weeks, and the median number of days after birth was 4 [2; 5].

Phase 1: Determination of optimal sensor placement on the patient. Two-hour measurements were performed on four patients.

During the first hour of the measurement, the pulse oximeter sensors were placed on the feet, and 30 minutes after the start of pulse oximetry, the location of the sensors was changed from one foot to the other. Sixty minutes after the start of the measurement, the sensors were moved to the wrists, and after 30 minutes, the sensors were moved to a different wrist. A total of 16 measurements of 30 min each were performed — 8 on the feet and 8 on the wrists.

The target parameter of the first phase of the study was the ratio of the number of measurements with artifacts (false bradycardia and hypoxemia in the absence of clinical manifestations) to the number of measurements without artifacts, and the correlation between this ratio and the location of the sensor (wrist or foot).

During the 30-minute foot and wrist measurements, the number of measurement with artifacts differed significantly for both the Sensorex pulse oximeter (7 vs. 3, *P*=0.039) and the reference monitor (6 vs. 2, *P*=0.046), as did the total number of artifacts for the two pulse oximetry monitors (13 vs. 5, *P*=0.005). The results are shown in Table 1.

Phase 2: Determination of the optimal study period. Before the study, the patients were divided into 3 subgroups according to the planned study time:

1. Subgroup with total study time of 30 minutes, with limb change after 15 minutes (5 patients);
2. Subgroup with total study time of 60 minutes, with limb change after 30 minutes (5 patients);
3. Subgroup with total study time of 120 minutes, with limb change after 60 minutes (5 subjects).

The target parameter of the second phase of the study was the number of patients who did not have any episodes of deviation from reference values during the study period.

Thus, in the 30-minute subgroup of the study, 3 (60%) patients had no abnormal episodes, and in the 60-minute subgroup of the study, 2 (40%) patients

Table 1. Comparative analysis of the number of measurements with artifact when pulse oximetry was performed at the wrists of the hands and feet for 30 minutes.

Monitor	Number of measurements with artifacts		*P*-value
	Wrists	Feet	
Sensorex, *N*=8	7	3	0.039*
Reference, *N*=8	6	2	0.046*
Total, *N*=16	13	5	0.005*

Note. Here and in the Table 3: * — significant differences.

had no abnormal episodes. In the 120-minute subgroup, at least one abnormal episode was observed in every patient.

The results are presented in Table 2.

Phase 3: Use of Reference Electrocardiographic Channel. In Phase 3 of the study, the quality of the reference pulse oximeter signal was evaluated by the correspondence of the pulse oximeter pulse values to the electrocardiography (ECG) sensor heart rate values, rather than by clinical presentation to the observer's judgment. The signal from the reference monitor's pulse oximeter sensor was considered true if the pulse rate matched the heart rate from the ECG sensors (a difference of no more than 20 min^{-1}).

The frequency of true episodes of hypoxemia and bradycardia recorded by the pulse oximeters (when the pulse rate matched the data from the ECG sensors) was compared with the mean number of episodes of hypoxemia and bradycardia obtained from the pulse oximeters that the observers considered consistent with the clinical presentation in studies without ECG sensors (Phase 2). The results are presented in Table 3.

Table 2. Matching the number of patients without episodes of pulse oximetry abnormalities to the duration of the study.

Study subgroup	Patients without abnormalities, *N* (%)
30 minutes, *N*=5	3 (60)
60 minutes, *N*=5	2 (40)
120 minutes, *N*=5	0 (0)

Discussion

Phase 1 of the study. From a clinical point of view, it is preferable to measure capillary blood saturation on the right arm, taking into account the need to determine preductal oxygenation in newborns (with a functioning patent ductus arteriosus, blood saturation values on the right and left arms may differ) [12], including pulse oximetry in the delivery room according to the Methodological Letter of the Ministry of Health of Russia «Resuscitation and Stabilization of Newborns in the Delivery Room» dated March 4, 2020 [13], as well as screening examination of all newborns before discharge from the maternity hospital for congenital heart disease [14, 15]. Meanwhile, differences in pre- and post-ductal saturation at the right and left wrists for physiological reasons may bias the results of the data analysis of the target study. In addition, the study procedure should not interfere with routine and unscheduled medical procedures and child care activities. For example, systemic blood pressure is measured at least once every 3 hours, primarily in the upper extremities, which will affect the pulse oximeter readings when the sensor is placed on the wrist and reduce the power of the study.

During the study, fewer artifacts were detected on the feet, in part due to more intense motor activity of the upper extremities. Therefore, the feet were determined to be the optimal location for the sensors during the study in terms of reducing the impact on the neonate's medical care and reducing the frequency of artifacts.

Phase 2 of the study. A total measurement time of 2 hours is optimal for assessing the clinical performance of the pulse oximeter in an individual patient. A shorter measurement period increases the risk of missing episodes of abnormalities and measurement errors. Prolonged placement of the pulse oximeter sensor on the limb increases the likelihood of adverse effects on the child's skin (compression, pressure sores) without a significant increase in information value [16]. Also, if the duration of measurement is increased, the influence of therapeutic and hygienic measures performed every 3 hours on the recorded events is inevitable. Thus, the maximum possible duration of measurement while minimizing the impact on treatment is 120 minutes.

Phase 3 of the study. The next step was to manually enter the data into a spreadsheet for further processing. When comparing the parameters of the study and reference pulse oximeters, the lack of a mechanism to control false values and the reduced accuracy of the signal from the reference pulse oximeter became significant.

In addition, determining whether pulse oximetry data correspond to the clinical presentation to detect erroneous values is not always a reliable method in neonates, since episodes of moderate SpO_2 reduction (up to 80–85%) may occur without significant changes in the patient's clinical condition [13].

Heart rate data obtained from ECG sensor readings can be an effective criterion for determining study objectives and serve as a reference channel for comparison and analysis.

Summary of the three phases of the study. During the study it became obvious that the input of large amounts of numerical data significantly prolongs the study time, introduces a certain number of misprints and errors, which negatively affects the reliability of the calculated parameters. It is

Table 3. Frequency of events considered true with and without ECG sensors.

Study phase	Number of episodes of hypoxemia and bradycardia		*P*-value
	Based on oximetry, *N*	Recorded, *N* (%)	
2. Clinical, without ECG sensors, *N*=5	47	16 (34)	0.029*
3. Based on ECG, *N*=1	9	6 (62.5)	

technically possible to record parameters manually no more often than once every 10 seconds. In order to reduce the influence of the human factor on the results, we decided to develop a special software that allows to extract and process the trend data of the tested monitors.

Comparison of monitor data with the frequency of their recording every 10 seconds is not very meaningful because episodes of significant variation in heart rate and SpO_2 may occur in a shorter time interval and the fact of their recording is critical to determining the clinical effectiveness of the pulse oximeter.

As a result, the recommended time interval for trend recording was 2 seconds, which is the minimum possible time for averaging the values of the two monitors used in the study.

It is impossible to perform the study with a sufficient level of accuracy and statistical significance while observing the limitation of the interval of recording parameters to 2 seconds manually. Therefore, it is necessary to develop specialized software capable of extracting, recording and processing data from the tested monitors.

Simultaneous connection of pulse oximetry sensors of the control and the tested device is critical for comparing their performance and clinical effectiveness.

We decided to use the ECG sensors of the control monitor as a reference for additional control of the accuracy of the signal received from the pulse oximetry sensors and to exclude episodes of unreliable data recording due to sensor displacement on the patient's foot.

Based on the obtained data, we developed an automated workstation (AWS) scheme.

We determined the data necessary for statistical analysis, developed schemes and algorithms for evaluation of four main target parameters for the upcoming clinical trial, which include:

- frequency and duration of episodes of false bradycardia and tachycardia (deviation of heart rate according to pulse oximetry sensor data by $\geqslant$25 min^{-1} from ECG sensor readings);
- frequency and duration of episodes of false hypoxemia (decrease in SpO_2 below 85%, not correlated with reference monitor readings);
- frequency and duration of episodes of true bradycardia (according to ECG monitor data), accuracy of pulse oximeter trend correspondence with ECG monitor data;
- frequency and duration of true hypoxemia episodes (SpO_2 drops below 85%, correlated with reference monitor readings).

Based on the obtained results, we prepared technical specifications for the development of analytical software for processing trends obtained from the tested and reference monitors.

Safety assessment. Transcutaneous pulse oximetry is a standard, noninvasive and safe method of monitoring vital signs. The devices were used in accordance with the instructions for use regarding safety measures (3601.00000000 RE) and on the basis of the technical characteristics. No complications or adverse effects of pulse oximetry with the Sensorex device on the patient's body were observed.

Study limitations. A limitation of the study is the lack of sample size calculation.

Conclusion

During the exploratory study, we formulated the principles and methodology for conducting a full-scale multicenter clinical trial of a new model of pulse oximetry device and pulse oximetry algorithm.

In this case, as a result of the forthcoming study, the performance of the device will be expressed in clear numerical values, and the obtained data will help to formulate a set of proposals for improving the device and algorithm of pulse oximetry in newborns.

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Short communication

On June 26, 2024, a meeting of the Chronic Critical Illness Research Club (hereinafter referred to as the Club) was held in Arkhangelsk during the Tenth White Sea Symposium. Three reports were presented, which provoked a lively discussion.

1. The three-steps model of critical conditions development: a new concept.

V. V. Likhvantsev, L. B. Berikashvili, M. Y. Yadgarov, A. A. Yakovlev, A. N. Kuzovlev. (Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology, Moscow, Russia).

The study used the eICU database (USA), which contains data on more than 200,000 hospitalizations in 335 intensive care units in the USA. All adult patients from day 2 to day 21 of hospitalization were evaluated for the presence of ICIS (inflammation, catabolism and immunosuppression) syndrome using biomarkers. The percentage of patients with ICIS was 6.7%, with peak incidence on days 2–3 and 10–12. The risk of developing ICIS by day 21 was 22.5%. A new three-steps model of critical condition with acute, prolonged, and chronic phases was proposed. The peaks of ICIS detection coincide with the time of transition from acute to extended phase (1) and from extended to chronic phase (2). Patients with the ICIS triad had a 2.5-fold higher risk of fatal outcome (P=0.009) and were twice as likely to use vasopressors (P=0.008).

The material was published as an article by *Likhvantsev, V.V.; Berikashvili, L.B.; Yadgarov, M.Y.; Yakovlev, A.A.; Kuzovlev, A.N.* The Tri-Steps Model of Critical Conditions in Intensive Care: Introducing a New Paradigm for Chronic Critical Illness. J. Clin. Med. 2024, 13, 3683. https://doi.org/10.3390/jcm13133683

2. Immune status in chronic critical illness.

E. V. Grigoriev (Research Institute of Complex Problems of Cardiovascular Diseases, Kemerovo, Russia).

Any critical illness is characterized by a systemic inflammatory response, including hyperinflammation and induced immunosuppression (IIS). In the early phase, with a rapid decrease in trigger concentrations, the immune balance is quickly restored without causing organ failure or secondary infections. In the late phase of critical illness, there is an increased likelihood of developing IIS, accompanied by peaks in the pro-inflammatory response. IIS results from disturbances in both innate and acquired immunity and is characterized by the release of anti-inflammatory cytokines, death of immune cells, and excess of immunomodulatory cells. Innate immunity is monitored through measurements of neutrophil function, monocyte antigen presentation, and cytokine production. Adaptive immunity monitoring includes an assessment of lymphocyte and T-cell counts, as well as their functional characteristics. The IIS monitoring algorithm involves identification of patients at risk for IIS, diagnosis of IIS, initiation of treatment and evaluation of its efficacy.

3. Development of concepts of chronic critical illness: a clinical observation.

A. V. Shchegolev (S. M. Kirov Military Medical Academy, St. Petersburg, Russia).

The development of concepts of chronic critical illness continues to this day, as evidenced by the growing number of publications. There is reason to believe that chronic critical illness should be diagnosed at least 14 days after the onset of acute critical illness complicated by multiorgan failure syndrome. When a pathological condition becomes chronic, the direct relationship between the severity of the patient's condition and the underlying cause, which can be treated intensively, is lost. Prognosis is an important aspect of chronic critical illness because the patient may develop a new pathophysiological state that requires intensive care unit treatment. It is essential to investigate the mechanisms underlying this development, as well as ways to mitigate the negative effects of intensive care and to develop early rehabilitation strategies. The cost-effectiveness of ongoing intensive care is also important.

After discussion, it was decided

1. To recognize the three-steps concept of critical illness development proposed by Prof. V. V. Likhvantsev and his team and to support future research in this area.

2. To establish the Club under the auspices of the All-Russian public organization «Federation of Anesthesiologists and Reanimatologists». The Club was founded by professors E.V. Grigoriev, A.N. Kondratyev, V.V. Likhvantsev, M.V. Petrova, G.P. Plotnikov and A.V. Shchegolev.

3. To schedule the next meeting of the Club for November 2024 in Moscow, during the «Life Support in Critical Illnesses» conference.

Prepared by Valery V. Likhvantsev, MD, PhD, Professor (Federal Scientific and Clinical Center of Intensive Care Medicine and Rehabilitology, Moscow, Russia)

Instructions for Authors of the General Reanimatology Journal

Based on the «Brief author guidelines for preparing and formatting scholarly papers in journals indexed in international scientific databases'edited by Olga Kirillova under the ASEP (Association of Scientific Editors and Publishers) and RRIEPL (Russian Research Institute of Economics, Politics and Law in Science and Technology) published in 2019, the CSE's White Paper on Promoting Integrity in Scientific Journal Publications, 2012 Update, **ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (December 2016)**, and the European Association of Scientific Editors (EASE) Guidelines for Authors and Translators (available at **https://ease.org.uk/guidelines-toolkits/**).

Version Dated February 2023

When submitting a manuscript to the General Reanimatology journal, the authors guarantee that:

— the manuscript has not been previously published in another journal;

— the manuscript is not currently reviewed for publication in another journal;

— the manuscript does not contain any confidential information;

— all co-authors agree with publication of the current version of the article.

Instructions for the Authors Before Submitting the Manuscript

Before submitting a manuscript for review, make sure that the file contains all the necessary information in Russian or English, lists all sources of information (references), has a full set of figures and tables, all citations are properly formatted.

The editorial board of the «General Resuscitation» journal recommends that authors use the following checklists and charts developed by international health organizations in preparing manuscripts and other materials (**EQUATOR, Enhancing the Quality and Transparency of Health Research, https://www.equator-network.org/reporting-guidelines/; SWIHM, Scientific Writing in Health & Medicine https://www.swihm.com/course/**):

When preparing papers reporting the results of randomized clinical trials, **«CONSORT 2010 checklist of information to include when reporting a randomized trial»**, **https://www.equator-network.org/reporting-guidelines/consort/**, should be used.

When preparing papers reporting the results of non-experimental research, **«The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies»**, **https://www.equator-network.org/reporting-guidelines/strobe/**, should be used.

When preparing a systematic review, **«PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)»**, **https://www.equator-network.org/reporting-guidelines/prisma/**, should be used. Additionally, we recommend the following outline for the abstract (summary): scope of the problem (1–3 sentences from the introduction); aim of the review (the same wording in the summary and in the introduction); number of sources, criteria and databases of source selection; specific issues considered according to the highlighted subheadings in the body of the review); limitations of the research on the topic; conclusion (an abridged version of the conclusion from the body of the review).

When preparing a clinical case report/series, **«The CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development»**, **https://www.care-statement.org/checklist/**, or **SWIHM** 2019 recommendations should be used. Russian language form can be found at **www.reanimatology.com** → Section «Authors Guidelines» → Case Report Writing Template for Authors.

When preparing papers reporting the results of qualitative research, **SRQR (Standards for reporting qualitative research)**, **https://www.equator-network.org/reporting-guidelines/srqr/**, should be used.

Full version at www.reanimatology.com

Main information for the manuscript submission

PARAMETER	INSTRUCTIONS
Limitations	
Initial submission	One file in the Word format in Russian for Russian-speaking authors in English for non-Russian-speaking authors, including: — the title of the paper; — full names of all authors; — affiliations of all authors; — IDs of profiles in the scientific databases for each author; — the text of all sections of the paper; — tables, figures, photos with captions and notes; — references; — conflict of interest; — information of study funding; — acknowledgements (optional); — authors' contribution (preferably)
The length of the manuscript	Original manuscript — about 40,000 characters with spaces; Short communication — should not exceed 2,500 words; Review, meta-analysis — 25,000–40,000 characters with spaces
Front page information	
Title of the paper	Should not exceed 15 words
Information about authors	Full name (Peter A. Johnson), author profile ID in the research database(s) for each author (e-Library/RSCI (Rus), ORCID, Scopus, WoS researcher ID if available)
Affiliations	Full name and postal address of the organizations with zip code
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The paper outline and references	
Summary (abstract)	250–300 words. Sections: scope of the problem (introduction/background), aim, material and methods, results, conclusion
Highlights (main messages as text or infographics, an optional section following the summary)	1–3 messages in graphic or text form (no more than 40 words per each text message)
Key words	6–8 words listed with a semicolon (;), without a dot at the end
Body of the paper	Sections: introduction (background), material and methods, results, discussion, conclusion
Supplementary information sections	Conflict of interest, funding of the study should follow the Keywords paragraph. Acknowledgements (optional) and authors' contribution (preferably) should be placed at the end of the paper
Illustrations, including tables	Original paper — up to 8; Short communication — no more than 3; Review — up to 8
References	Dating: 70% should be published within the last 5 years, of them at least 30% within the last 3 years. Number: Original paper – 25–45; Short communication — 10–25; Review — 80–120. Format: please see the «References Formatting» section, www.reanimatology.com
Formatting	
Font	Times New Roman, 12 points. The section titles should be typed in bold
Spacing and Indentation	Line spacing — 1.5; Interval before and after the paragraph — none; Interval between sections — one extra spacing; First line indent — 1.25 cm
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Page numbering	In the lower right corner

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