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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.

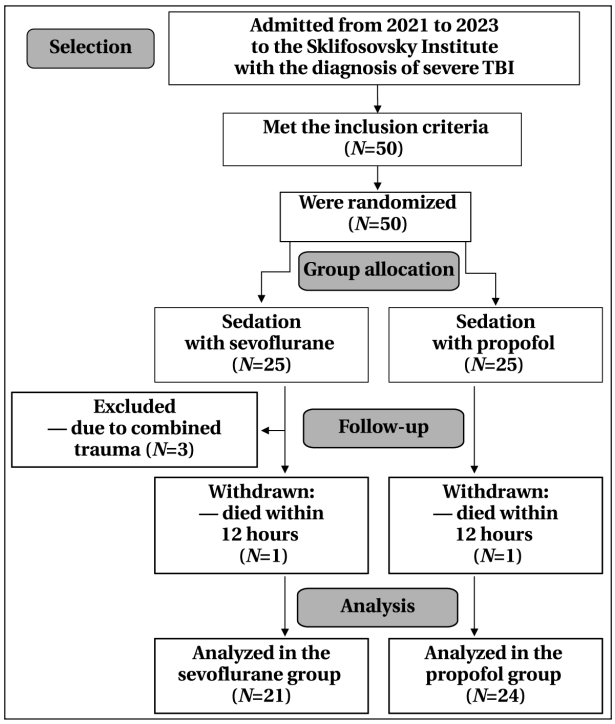

Fig. 1. Study flowchart.

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*).

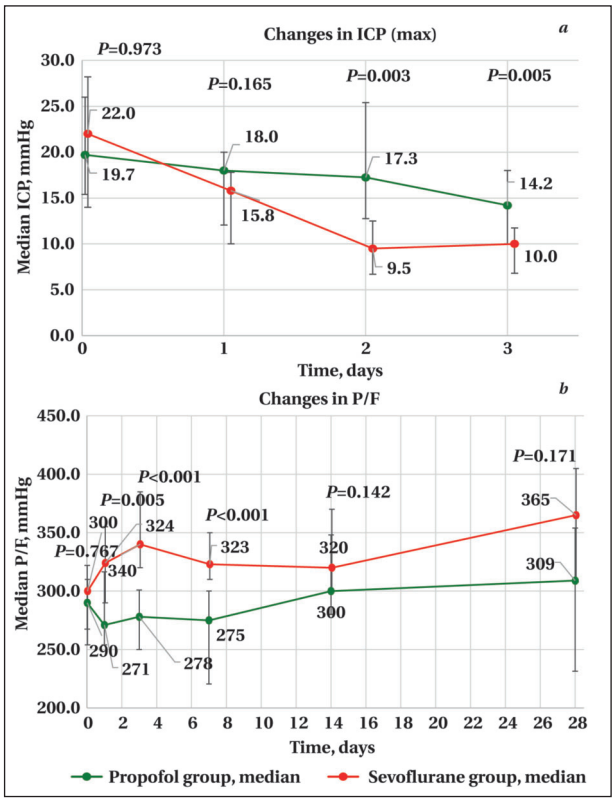

Fig. 2. Changes in intracranial pressure during the first 3 days *(a)* and P/F index during treatment in ICU *(b)*.

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

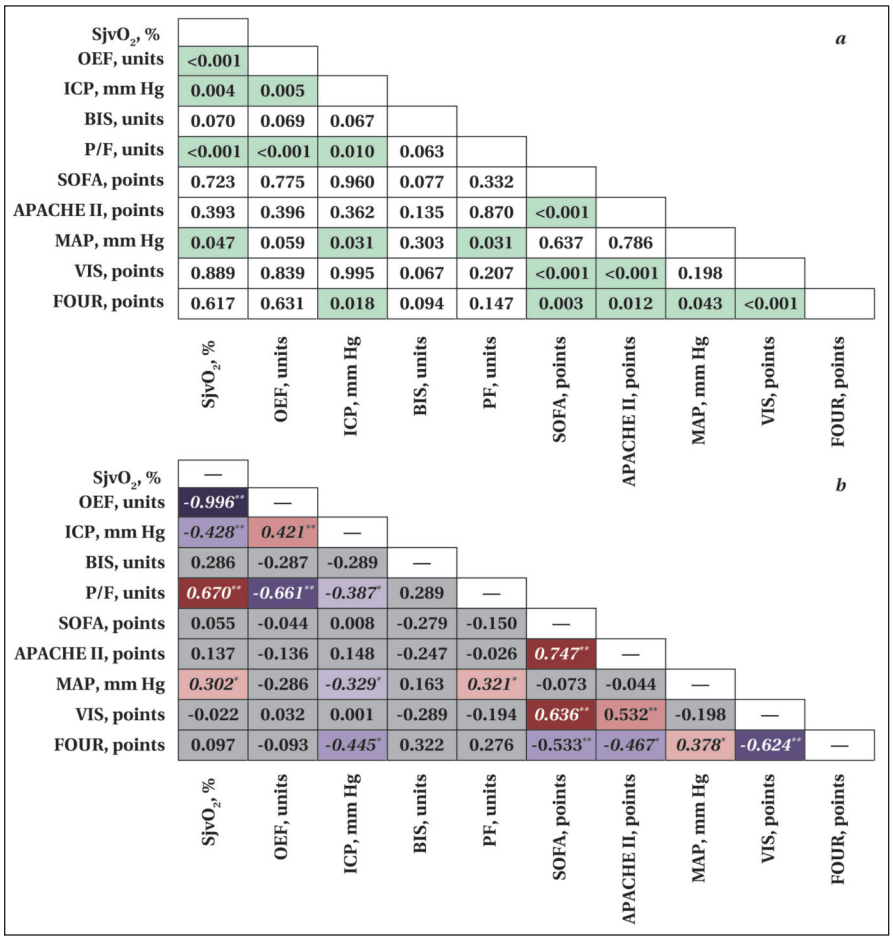

Figure 3. Correlation analysis of data obtained on day 3: Spearman correlation test *P* values *(a)* and Spearman *R* coefficient values *(b)*.

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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