

Case report

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Safety of Extended Sedation with Sevoflurane in Patients with Severe Traumatic Brain Injury

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RELEVANCE In conditions of increased sensitivity of damaged brain tissue to disruption of homeostasis, it is important to achieve stabilization of the vital functions of the body as soon as possible. Given the excess afferent impulse, adequate sedation and analgesia are an integral component of intensive care for patients with traumatic brain injury. The use of halogenated anesthetics is associated with a lower risk of complications associated with long-term sedation with intravenous drugs. In the example of two patients with severe traumatic brain injury, the effectiveness and safety of sevoflurane for prolonged inhalation sedation was noted. This study was approved at a meeting of the Local Ethics Committee of the Federal Scientific and Clinical Center for Resuscitation and Rehabilitation, an extract from protocol No. 5/21/1 dated December 23, 2021, as well as at a meeting of the LEC of the N.V. Sklifosovsky Research Institute for Emergency Medicine of the Moscow Health Department, meeting No. 1-2022 dated January 11, 2022.

AIM OF STUDY To demonstrate the safety of inhalation sedation in patients with traumatic brain injury using clinical observations as an example.

MATERIAL AND METHODS An analysis of two clinical observations of patients with severe traumatic brain injury was carried out. The effectiveness and safety of prolonged inhalation sedation was assessed by indicators: intracranial pressure, dynamics of mean arterial pressure and blood saturation in the jugular vein bulb, as well as the total duration of artificial ventilation and stay in the intensive care unit.

Clinical observation No. 1.

Patient B, 41 years old, was admitted with cerebral insufficiency (GCS 8) with damage to the soft tissues of the head. As a result of the examination, the patient was diagnosed with "Closed craniocerebral injury." Fracture of the bones of the vault and base of the skull. Severe brain contusion. Traumatic subarachnoid hemorrhage, acute subdural hematoma in the left frontotemporal region 3 cm³. Considering the size of the trauma (65 cm³) and the life-threatening dislocation syndrome, the patient underwent surgical intervention: "Decompressive craniotomy, removal of contusion areas. Installation of a ventricular intracranial pressure sensor." The early course of the postoperative period was complicated by the development of infectious complications, which led to the need for prolonged sedation in the intensive care unit. On the 3rd day, a lower tracheostomy was performed. The total time of sedation was 3 days, and the duration of artificial ventilation was 10 days. On the 21st day, the patient was decannulated and transferred to a specialized department.

Clinical observation No. 2.

Patient K, 42 years old, was admitted to the hospital with a depressed level of consciousness (GCS 6). Based on the results of the examination, a diagnosis was made: "Penetrating traumatic brain injury with severe brain contusion, a focus of crush contusion in the right temporal lobe, acute subdural hematoma of the right frontal-temporo-parietal region 100 cm³ and a fracture of the bones of the vault and base of the skull, facial skeleton, micropneumocephaly". Considering the size and location of the hematoma, the patient underwent surgery including decompressive craniotomy, removal of an acute subdural hematoma, and a Spiegelberg intracranial pressure sensor was installed. In the early postoperative period, severe hemodynamic instability associated with vascular insufficiency of central origin was noted. The use of inhalational sedation sevoflurane did not lead to the development of intracranial hypertension and escalation of vasopressor therapy. The total time of use of sevoflurane was 36 hours. Spontaneous breathing was restored by the 18th day. The patient's stay in the ICU was 31 bed days.

CONCLUSION Based on the data obtained, we may conclude that the use of inhalation sedation in this category of patients is safe, as well as the absence of a significant effect of sevoflurane on the level of intracranial pressure and central hemodynamic parameters. However, secondary complications that developed in patients do not allow us to draw an unambiguous conclusion about the effect of this method of sedation on the duration of artificial ventilation and stay in the intensive care unit. Only the accumulation of a sufficient volume of clinical material will reveal all the advantages and disadvantages of this method.

Keywords: inhalation sedation, AnaConDa, extended sedation, traumatic brain injury, jugular oximetry

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ALV — artificial lung ventilation
 BP — blood pressure
 CNS — central nervous system
 CRP — C- reactive protein
 CT — computed tomography
 GCS — Glasgow Coma Scale
 HR — heart rate
 ICH — intracranial hypertension
 P/F — respiratory index

ICP — intracranial pressure
 MAP — mean arterial pressure
 MRV — minute respiratory volume
 ORIT — intensive care unit
 SAH — subarachnoid hemorrhage
 SDH — subdural hematoma
 SMAT — strategy for managing antimicrobial therapy
 TBI — traumatic brain injury

INTRODUCTION

Traumatic brain injury (TBI) is one of the most important problems of modern healthcare, related to the three leading causes of death in the world [1]. For anesthesiology and resuscitation, the issue of

intensive care of patients with traumatic injuries, including brain injuries, is of particular relevance [2]. In Russia, about 600,000 cases of TBI are registered annually. In case of mild and moderate injuries, the mortality rate can be from 1.5 to 3.5%, in severe

forms 15-25%, and in extremely severe cases it reaches 60% [3]. A high degree of disability (about 100-150 people per 100,000 population) [4], as well as high mortality mainly among people of working age, is an important socio-economic problem that requires a search for relevant and modern solutions [5].

The course of TBI is often complicated by the development of respiratory failure. Damaged brain tissue is extremely sensitive to hypoxia and hypercapnia [6], which can lead to secondary hypoxic injury. In order to prevent this complication, it is recommended to immediately perform respiratory function replacement [7]. Artificial lung ventilation (ALV) implies the beginning of sedative therapy to ensure the comfort of the victim. Also important points are the reduction in the use of opioid analgesics, relief of psychomotor agitation, reduction in the metabolic needs of the brain and safe procedures. It has been proven that compliance with these conditions can reduce the impact of damaging factors and improve the outcomes of traumatic disease in victims in the intensive care unit (ICU) [8].

Traditional intravenous sedatives include propofol and midazolam [9, 10], but their long-term use is associated with a number of problems that can negatively affect patient treatment [11–13]. The ability of propofol to negatively affect nervous tissue has already been proven since 2016 [14], but the lack of clear instructions on the method of sedation in the recommendations of the Ministry of Health of the Russian Federation leaves the question of drug choice open [15, 16]. Among modern drugs, dexmedetomidine can also be noted, used for moderate sedation in a wide range of pathologies [17, 18]. However, when it comes to the need for total myoplegia and maintaining deeper levels of sedation (*BIS* <60), the effectiveness of Dexdor is significantly inferior to earlier drugs [19]. It is worth noting separately that the use of sedatives to correct intracranial hypertension (ICH) is a method with a very weak evidence base, and the level of sedation has a greater impact on ICP indicators than the effect of a particular drug [20, 21].

Since the early 2000s, the *AnaConDa* (*The Anaesthetic Conserving Device*) inhalation sedation device has been certified in Europe and later in the Russian Federation, allowing comfortable and safe use of inhalation anesthetics in intensive care settings [22]. However, the results of using halogenated drugs in neuroreanimatology at this stage are not unambiguous. Thus, in patients with massive subarachnoid hemorrhage (SAH) due to a ruptured cerebral aneurysm (*Fisher IV*), there was no significant increase in ICP against the background of prolonged isoflurane sedation in the postoperative period. On the contrary, improved regional cerebral blood flow and reduced cerebral oxygen demand in the acute period had a beneficial effect on the course of the disease with the development of cerebral vasospasm [23, 24]. In their work published in 2015, *J.C. Purruker et al.* It is not without reason that attention is drawn to the difficulty in interpreting increased ICP in patients with intracranial hemorrhages due to the presence of various factors influencing human vital signs [25].

A distinctive feature of inhalation anesthetics is the implementation of organoprotective properties due to phosphorylation of the active enzyme glycogen synthase kinase β (GSK- β) [26, 27]. Studies on experimental animals prove a reduction in the area of brain damage due to the use of volatile anesthetics in induced cerebral damage [28, 29]. Of course, the use of inhalation anesthetics is not a complete alternative to classical intravenous drugs, but as a method of safe prolonged sedation, inhalation anesthetics certainly deserve the right to be considered.

Clinical observation No. 1

Patient B., 41 years old. He was found unconscious on the street and taken to the hospital via ambulance. Upon admission, severe cerebral insufficiency with suppression of the level of consciousness to 8 points on the Glasgow Coma Scale (GCS), as well as respiratory disorders were noted. In order to protect the respiratory system and prevent possible secondary brain damage and aspiration, the patient underwent orotracheal intubation of the trachea with transfer to mechanical ventilation. Complex intensive therapy was

carried out, aimed at stabilizing the vital functions of the body and correcting the increasing intracranial hypertension. Despite this, the development of Cushing's triad was noted: systemic hemodynamics with a tendency to hypertension up to 170/100 mm Hg, heart rate (HR) with a tendency to bradycardia from 50 to 60 per minute, the development of tachypnea and asynchrony with the respirator.

Based on the results of instrumental diagnostics, including computed tomography (CT) of the brain (Fig. 1), X-ray and ultrasound examinations, the following diagnosis was made: "Closed TBI. Fracture of the bones of the vault and base of the skull. Severe contusion of the brain. Traumatic subarachnoid hemorrhage, acute subdural hematoma in the left frontal-temporal region 3 cm³ with contusions of the left frontal, parietal and temporal lobes (65 cm³), fracture of the vault and base of the skull, traumatic SAH, acute subdural hematoma (SDH) in the left frontal-temporal region 3 cm³". When calculating the integrative scales: *SOFA* score 6 points, *APACHE II* score 18 points (predicted mortality 25%).



Fig. 1. Results of computed tomography of the brain before surgery. A—areas of contusion; B—acute subdural hematoma

Given the nature of the injury, in order to prevent the development of life-threatening dislocation and cerebral edema, the patient was given an indication for emergency surgical intervention in the amount of decompressive craniotomy, removal of contusion foci and free plastic surgery of the dura mater (Fig. 2). Intraoperatively, a ventricular ICP sensor "*Spiegelberg*" was installed (ICP at the end of the operation was 9 mm Hg).

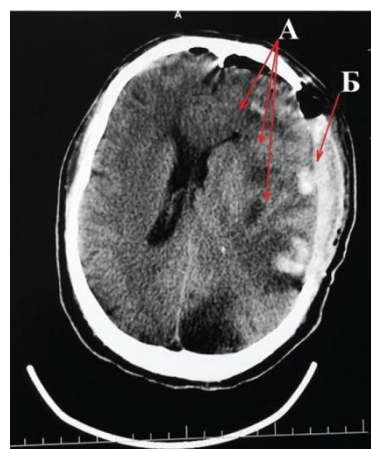


Fig. 2. Results of computed tomography of the brain after surgery. A - perifocal edema; B - hemorrhagic contents

On admission to the intensive care unit for neurosurgical patients, the patient's general condition was assessed as severe, mechanical ventilation was performed with a minute ventilation of 8.5 l/min, FiO₂ 50% (SpO₂ 100%). Hemodynamics with a tendency to hypotension, accompanied by moderate sinus tachycardia up to 100-110 per minute. Minimum blood pressure (BP) values 100/50 mm Hg, which was regarded as an additional risk factor for the progression of cerebral edema, due to which an infusion of norepinephrine solution was started at a calculated rate of 0.2 µg/kg/min. Against the background of the therapy, relative stabilization of hemodynamics was noted, and the average BP level reached target values 80-100 mm Hg.

Intraoperative anesthesia was performed using sevoflurane, with intravenous bolus administration of propofol to ensure adequate sedation at the time of transportation. In the intensive care unit, already in the first hours after admission, a marked increase in ICP (25-26 mm Hg) was recorded, in connection with which anti-edema therapy was initiated (15% Mannitol solution 0.5 g/kg and moderate deepening of inhalation sedation), as well as positional correction methods. Against the background of the measures taken, it was possible to achieve stabilization of ICP at a level of 15-17 mm Hg. The use of sevoflurane with an end-expiratory concentration of 0.8-1.3 vol.% (0.4-0.6 MAC) and awakening every 4-6 hours did not lead

to a significant increase in ICP. Taking into account the current recommendations [20], effective conservative correction and stable reduction of ICP below 20 mm Hg allowed not to resort to more aggressive methods. Another monitored indicator of the effectiveness of the sedation was the oxygen extraction coefficient of the brain. The calculation of this indicator was performed using the formula:

$$K = SpO_2(a) - SpO_2(v),$$

where K is the extraction coefficient, $SpO_2(a)$ is the saturation of arterial blood, $SpO_2(v)$ is the saturation of blood from the jugular bulb.

Normal values of the oxygen extraction coefficient for the brain are 25–45% (provided there is adequate SpO_2 in the bulbs of the jugular vein). However, it is important to understand that these deviations of SpO_2 in the “retro-vein”, and, accordingly, the values of the oxygen extraction coefficient are acceptable in the presence of a massive contusion focus and developed edema–ischemia of the brain (Table 1).

On the 2nd day from the moment of admission to the intensive care unit, negative dynamics were observed due to the development of meningitis with the development of infectious and toxic complications. The laboratory parameters showed pronounced leukocytosis. A significant increase in the levels of C-reactive protein (CRP) and procalcitonin was also noted (Fig. 3), which fully corresponded to the addition of bacterial complications. The patient continued to undergo inhalation sedation with sevoflurane, and empirical broad-spectrum antibacterial therapy was prescribed according to the SMAT program (antimicrobial therapy management strategy). Confirmation of secondary meningitis during the control of laboratory and instrumental studies and cultures of media (*pan-culture*): inflammatory changes in the clinical analysis of cerebrospinal fluid and the growth of microorganisms in the cerebrospinal fluid. It is worth noting that the use of inhalation sedation did not lead to uncontrolled hemodynamic instability and did not affect cerebral perfusion parameters.

Table 1

Dynamics of data during sedation sevoflurane in the intensive care unit

Time from operation, h	pH		pCO ₂ , mmHg		pO ₂ , mmHg		P/F	Lac, mmol/L		SpO ₂		MAP, mmHg	ALV
	a.	retro-v.	a.	retro-v.	a.	retro-v.		a.	retro-v.	a.	retro-v.		
12	7.32	7.28	54.7	61.7	173	82.9	346	1.3	1.3	99.9	88.7	111	FiO ₂ 50%, MV 8.6 l/min
24	7.44	7.42	44.2	45.7	90.3	57.3	180	1.5	1.3	99.9	86.2	93	FiO ₂ 50%, MV 10.1 l/min
36	7.50	7.45	36.0	34.1	169	52.7	423	1.2	0.9	99.9	88.4	90	FiO ₂ 40%, MV 10.0 l/min
48	7.58	7.51	27.4	25.1	177	50.0	442.5	1.3	0.9	99.9	88.2	85	FiO ₂ 40%, MV 9.2 l/min
60	7.49	7.46	33.3	34.9	126	54.6	420	1.5	1.5	99.9	85.9	107	FiO ₂ 30%, MV 9.5 l/min
72	7.51	7.49	30.7	32.5	156	57.1	445.7	1.2	1.4	99.9	81.7	110	FiO ₂ 35%, MV 8.9 l/min

Notes: ALV – artificial lung ventilation; MV – minute volume; a. – indicators in arterial blood; Lac – blood lactate; MAP – mean arterial pressure; P/F – respiratory index; pH – hydrogen index (acidity indicator); pCO₂ – blood carbon dioxide tension; pO₂ – blood oxygen tension; retro-v. – indicators in the jugular vein bulb; SpO₂ – saturation of hemoglobin with oxygen

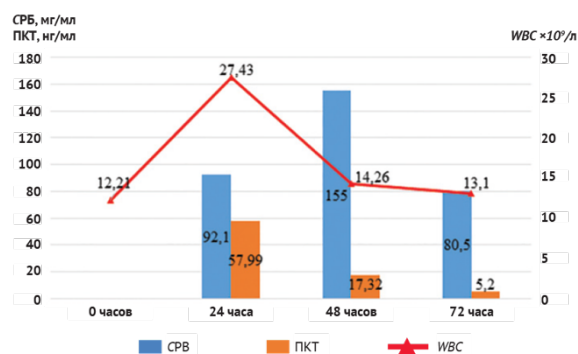


Fig. 3. Dynamics of biochemical markers of inflammation
Notes: CRP - C-reactive protein; PCT - procalcitonin; WBC - white blood cells

Against the background of specific and non-specific therapy, by the 3rd day, fever regression and a decrease in inflammation markers were noted, as well as the absence of a significant increase in ICP, which, according to the time intervals and the clinical picture, made it possible to initiate the refusal of further sedation and stop using sevoflurane. Also, in the course of ICH regression, hemodynamic stabilization was noted with a gradual decrease in the doses of vasopressor support, a complete refusal of which, due to the addition of septic complications, became possible only by the 7th day (Fig. 4). However, due to the severity of cerebral dysfunction (the level of wakefulness is 9 points according to the GCS and 9 points according to *the FOUR*), a decision was made to conduct extended mechanical ventilation with a temporary tracheostomy. By the 10th day, against the background of cerebral dysfunction regression, decreased inflammation intensity, and stabilization of vital functions and blood gas parameters (Fig. 5), the patient's planned weaning from mechanical ventilation was initiated. On the 20th day, after the necessary methods for assessing the swallowing and respiratory function were performed, successful decannulation was performed and activation was continued. The patient was transferred to a specialized department for the next stage of rehabilitation after 21 days of stay in the ICU. The level of consciousness at the time of transfer was assessed as clear, with elements of sensorimotor aphasia and right-sided hemiplegia (GCS score 3, extended GCS score 4).

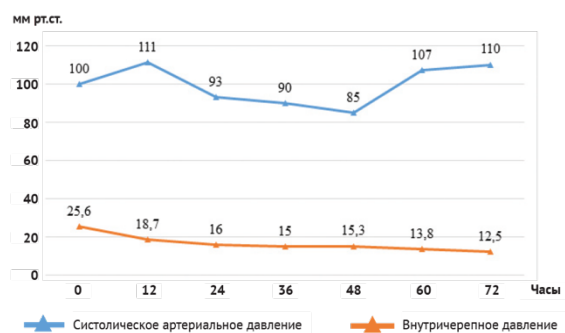


Fig. 4. Dynamics of systolic blood pressure and intracranial pressure during sedation with sevoflurane

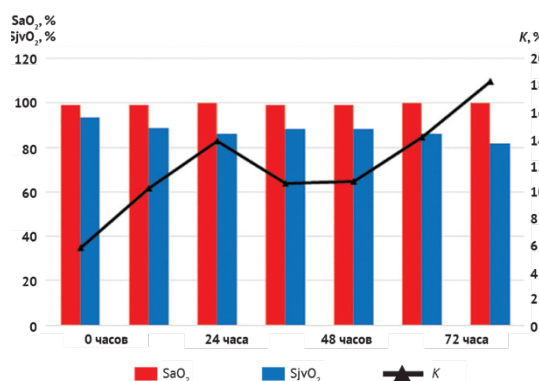


Fig. 5. Indicators of oximetry and oxygen extraction
Notes: SaO₂ – arterial blood saturation; SjvO₂ – blood saturation in the jugular vein bulb; K – oxygen extraction coefficient

Clinical observation No. 2

Patient K., 42 years old. Delivered to the intensive care unit in an extremely serious, unstable condition with the diagnosis of "Closed TBI with contusion of the brain, soft tissues of the head and periorbital hematoma on the left". The severity of the condition is due to severe cerebral insufficiency with depression of the level of consciousness up to coma (GCS score 6) and respiratory failure (saturation 78%, acrocyanosis, RR up to 8 per minute). Given the severity of the condition, a decision was made to transfer the victim to mechanical ventilation. The respirator parameters are set with a minute ventilation volume of 8.7 l/min and FiO₂ 50% (SpO₂ 100%). Initial hemodynamics with a tendency to hypertension with maximum blood pressure values of

145/110 mm Hg. and sinus tachycardia up to 130 per minute. Neuroimaging revealed penetrating TBI with acute SDH in the right frontal-parietal-temporal region, a focus of contusion and crushing of the right temporal lobe, a fracture of the bones of the vault and base of the skull, facial skeleton, micropneumocephalus, complicated by life-threatening dislocation of the brain (Fig. 6). Emergency surgery was performed: decompressive craniotomy, removal of acute SDH 100 cm³ and installation of the "Spiegelberg" ICP sensor.

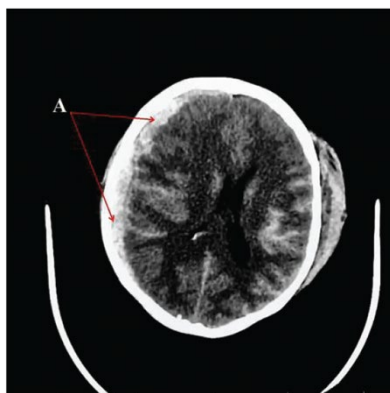


Fig. 6. Results of computed tomography of the brain before surgery. A – subdural hematoma

After the surgery, the patient was taken to the intensive care unit, where mechanical ventilation was continued with a minute ventilation of 8.5 l/min, FiO₂ 50% (SpO₂ 100%) (Fig. 7). During the surgery, as well as in the early postoperative period, hemodynamic instability was noted, which required the initiation of vasopressor therapy with norepinephrine at an estimated rate of 0.3–0.45 µg/kg/min. Given the patient's condition, a decision was made to use prolonged drug sedation with sevoflurane. Intraoperative anesthesia was also performed using this drug, and ICP did not exceed 8–9 mm Hg. After stabilization of hemodynamic parameters and achievement of adequate sedation depth in the

intensive care unit, the ICP value was 7 mm Hg. Against the background of the therapy, the patient's condition was assessed as stable severe, respiratory support parameters were adjusted according to the blood gas composition, and vasopressor therapy was adjusted according to hemodynamic parameters. When assessing the severity of the condition according to the integrative scales: *SOFA score* 8, *APACHE II score* 19 (predicted mortality 25%).

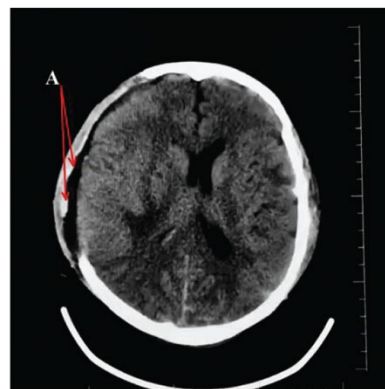


Fig. 7. Results of computed tomography of the brain after surgery. A – postoperative subflap contents

At the same time, a retrograde catheter was inserted into the jugular bulb for dynamic assessment of cerebral oxygenation. Inhalation sedation was performed with an end-expiratory anesthetic concentration of 0.6–1.25 vol.% (0.3–0.6 MAC). Considering the severity of the injuries sustained, as well as for the purpose of better care and further mobilization of the patient, a decision was made to perform a tracheostomy early. To ensure a stable condition of the patient, including analgesia, sevoflurane was continued in combination with nonsteroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics as needed. In 36 hours, inhalation sedation was switched off, and during its administration, stability of ICP and cerebral oxygen metabolism was noted (Table 2).

Table 2

Dynamics of data during sedation sevoflurane in the intensive care unit

Time from operation, h	pH		pCO ₂ , mmHg		pO ₂ , mmHg		P/F	Lac, mmol/L		SpO ₂		MAP, mmHg	ALV
	a.	retro-v.	a.	retro-v.	a.	retro-v.		a.	retro-v.	a.	retro-v.		
12	7.27	7.31	31.1	33.4	133	47.9	332.5	14.3	15.7	98.8	76.8	94	FiO ₂ 40%, MV 14.5 l/min
24	7.34	7.30	31.5	36.8	140	49.1	350	11.8	10.8	98.9	77.7	85	FiO ₂ 40%, MV 12.4 l/min
36	7.46	7.42	37.9	44.3	169	60.8	422.5	3.8	4.3	99.6	90.0	87	FiO ₂ 40%, MV 11.2 l/min

Notes: ALV – artificial lung ventilation; MV – minute volume; a. – indicators in arterial blood; Lac – blood lactate; MAP – mean arterial pressure; P/F – respiratory index; pH – hydrogen index (acidity indicator); pCO₂ – blood carbon dioxide tension; pO₂ – blood oxygen tension; retro-v. – indicators in the jugular vein bulb; SpO₂ – saturation of hemoglobin with oxygen

Already after the cessation of inhalation sedation (Fig. 8), by the 3rd day, the course of the injury was complicated by the development of post-traumatic cerebral angiospasm, which required a change in the tactics of monitoring and maintaining cerebral perfusion pressure. The opposite dynamics of oxygen extraction indices in the 1st and 2nd clinical observations is associated with autoregulation disorders and with the predominance of the angiospastic component on the first day in patient No. 1, while in patient No. 2, a decrease in O₂ consumption by 36 hours was associated with the "switching off" of the focus with irreversible damage from metabolism (Fig. 9). Also on the 5th day, an increase in body temperature to 39.3° C and inflammation markers (CRP 215 mg/l) were noted. In order to exclude a CNS infection, a diagnostic lumbar puncture was performed, based on the results of which a diagnosis of "Meningitis" was established (cytosis 853 cells in 1 µl, lactate 5.6 mmol/l, glucose 2.3 mmol/l). Antibacterial therapy was adjusted according to the SMAT program. Against the background of conservative therapy, the patient's condition showed positive dynamics, and by the 13th day there was no data for meningitis. On the

18th day, the patient was transferred to independent breathing through a tracheostomy tube. Against the background of restoration of the level of wakefulness to clear consciousness, partial regression of left-sided hemiparesis and stabilization of vital functions of the body after assessment of the swallowing function, tracheal decannulation was performed, and the next day the patient was transferred to a specialized department. The total time of stay in the intensive care unit was 31 bed-days (GCS score 3, expanded GCS score 6).

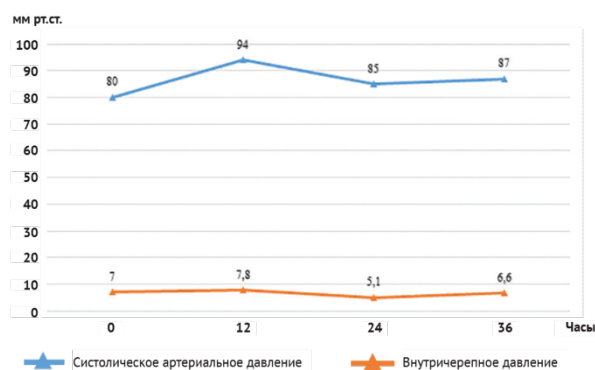


Fig. 8. Dynamics of systolic blood pressure and intracranial pressure during inhaled sedation with sevoflurane

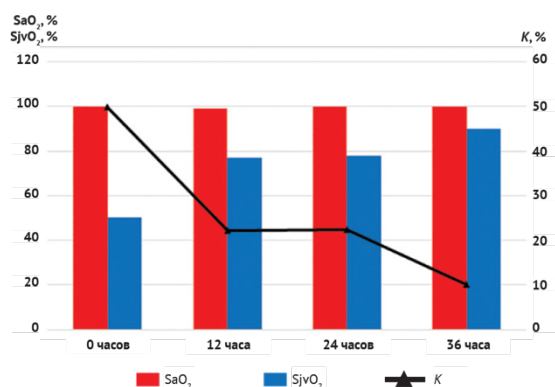


Fig. 9. Indicators of oximetry and oxygen extraction

Notes: SaO₂ – arterial blood saturation; SjvO₂ – blood saturation in the jugular vein bulb; K – the oxygen extraction coefficient

DISCUSSION

The results of using sevoflurane as a prolonged sedative therapy are shown using two patients with severe TBI. Such important parameters as ICP, systemic hemodynamics, and cerebral oxygen metabolism were considered for dynamic monitoring. In the first clinical observation, even in the presence of initial ICH, which required drug correction, the use of an inhalation anesthetic for 72 hours did not lead to a significant increase in ICP. In the patient of the second clinical observation, against the background of sevoflurane inhalation for

36 hours, the initially low ICP remained within the reference values. No negative effect of inhalation sedation in patients in the early postoperative period with secondary infectious damage to the central nervous system on systemic hemodynamics was detected. The parameters of gas exchange of nervous tissue in both cases, although not within the physiological norm, corresponded to the changes characteristic of the course of these diseases. Patients were transferred from the intensive care unit to further stages of rehabilitation in a stable condition with significant regression of neurological disorders.

CONCLUSION

Based on the data obtained, it is possible to conclude that inhalative sedation can be used in this category of patients, and also to note the absence of a negative effect of sevoflurane on the level of intracranial pressure and central hemodynamic parameters. However, secondary complications that developed in patients do not allow us to make an unambiguous conclusion about the effect of this sedation method on the duration of artificial ventilation and their stay in the intensive care unit. Only the accumulation of a sufficient volume of clinical material will allow us to identify all the advantages and disadvantages of this method.

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