3. Intensive care and neuromonitoring of the patients with severe TBI

Basic life support is needed: recovery and support of respiration (restoration of airway patency and correction of hypoventilation disorders, such as hypoxemia and hypercapnia) and blood flow (correction of hypovolemia, hypotension and anemia) (standard care).

3.1 Monitoring (guidelines)

Rational intensive care needs to be based on monitoring vital functions. Neuromonitoring, monitoring of blood flow, respiration, arterial and cerebral oxygen saturation should be performed in patients with suppressed wakefulness (GCS score ≤8). The optimal measures include continuous monitoring of intracranial pressure (ICP) and cerebral perfusion pressure (CPP), monitoring of cerebral oxygen saturation (measuring brain tissue oxygen tension, cerebral oximetry in the para-infrared range, or measuring hemoglobin oxygen saturation in the jugular vein bulb through a catheter placed retrograde), monitoring arterial pressure (invasive procedure is preferred), pulse oximetry, monitoring carbon dioxide concentration in respiratory gas and heart rate).

Where possible, these primary diagnostic measures should be expanded by ultrasonography of the cerebral vessels, monitoring central venous pressure, systemic hemodynamics, evaluation of the acid–base balance of arterial and venous blood, and tissue microdialysis [1—9].

3.2. Respiratory support

Patients with disorders of awakening (GCS score ≤10, soporose and comatose state) require tracheal intubation and respiratory support to prevent aspiration complications and ensure normal oxygen saturation of arterial blood and correct hypercapnia (standard care).

The trachea should be intubated with minimum flexion or extension of the cervical spine: (either nasotracheal intubation or orotracheal intubation with the spinal axis maintained). In case of a soporose or comatose state, patients undergo assisted or volume-controlled ventilation with an oxygen–air mixture with oxygen content of at least 40—50%. Proper selection of ventilation modes or the use of short-acting muscle relaxants and sedatives is required to prevent the episodes of non-synchronism between the respirator and the patient’s respiratory attempts during ventilation, which abruptly increase ICP. PaCO2 needs to be maintained at 36—40 mm Hg and oxygen hemoglobin saturation in blood outflowing from the brain, at ≥60%. To prevent cerebral hypoxia, all the manipulations related to interruption of the contour of the medical ventilation apparatus need to involve pre- and post-oxygenation with 100% oxygen. Hyperventilation and hyperventilation-induced hypocapnia should be prevented during mechanical ventilation. Long-term hyperventilation (PaCO2 <30 mm Hg) has to be avoided during the first 5 days if patients with severe TBI show no signs of intracranial hypertension (standard care).

Preventive hyperventilation (PaCO2 <35 mm Hg) during the first 24 h after injury should also be avoided because there is a risk of worsening of cerebral perfusion during the period of reduced volumetric cerebral blood flow (recommendations).

Short-term hyperventilation can be used in case of sudden worsening of the neurological status or during a longer time if intracranial hypertension persists despite using the sedatives, muscle relaxants, CSF drainage from cerebral ventricles, and the use of hyperosmolar solutions. If hyperventilation is used in patients with PaCO2 <30 mm Hg, oxygen hemoglobin saturation should be measured in the jugular vein bulb, the arteriovenous oxygen difference should be determined and/or oxygen tension in cerebral tissue should be evaluated [1, 6, 10—13] (options).
3.3. Correction of arterial hypotension (recommendations)

The CPP value needs to be maintained at a level of at least 60 mm Hg in order to correct cerebral perfusion disorders. At all the stages of rendering medical aid (at the injury site, during transportation, and under inpatient treatment), arterial hypotension (systolic blood pressure <90 mm Hg) needs to be immediately and meticulously prevented or corrected. Mean blood pressure should be maintained above 90 mm Hg during the whole duration of intensive care. Severe TBI is one of the few pathologies when arterial hypotension requires administration of sympathomimetic agents parallel to infusion therapy to increase CPP. Today, there are no convincing literature data demonstrating that a certain sympathomimetic agent is superior to other ones. Depending on the state of systemic hemodynamics and the clinical presentation, long-term intravenous infusion is used: noradrenaline (0.01—3 μg/kg/min), dopamine (1—2 μg/kg/min — affects D-receptors, usually stimulates urine production, 2—10 μg/kg/min — also affects b-receptors and increases cardiac output, >10 μg/kg/min — additionally affects a1-receptors and causes vasoconstriction), mesatone (0.4—5 μg/kg/min), and in rare cases, dobutamine (0.5—20 μg/kg/min). Infusion of colloid and crystalloid solutions should be performed in case of hypovolemia. Osmolarity and plasma sodium concentration need to be monitored. Low osmolarity (<280 mOsm/L) and sodium concentration (<135 mmol/L) are corrected towards higher values. Hyposmotic solutions (e.g., 5% glucose solution) are not used in therapy of acute TBI [1, 6, 7, 8, 9, 14].

3.4. ICP monitoring

ICP monitoring is indicated for patients with severe TBI (GCS score ≤ 8) and a pathology proved by CT scanning (hematoma, contusion focus, edema, or compressed basal cisterns). It is reasonable to monitor ICP in comatose patients showing no pathological alterations in CT scans and having one of the following characteristics: over 40 years old, unilateral or bilateral decerebration, systolic blood pressure <90 mm Hg. Measuring ventricular pressure is the most accurate and reliable ICP monitoring method. This procedure also allows one to remove cerebrospinal fluid (CSF) in therapeutic purpose [6—9, 14—19] (recommendations).

Kocher's point at the subdominant hemisphere is the preferred site for inserting an external ventricular drain. When the dominant hemisphere cannot be identified, the drain is preferably placed on the right side at Kocher's point [20] (options).

Before the drain is installed, the entire system should be filled with sterile normal saline. This manipulation needs to be performed by two physicians: a surgeon who directly places the drain and his/her assistant who helps to maintain sterile conditions [20] (options).

Special care is needed when performing external ventricular drainage in patients who have a subtentorial mass effect because of the risk of developing paradoxical dislocation due to the emergence of a pressure gradient and in patients with the mass effect of contralateral drainage because of the risk of dislocation worsening [20] (standard care).

In case of sanitation of the tracheobranchial tree or using a purgative enema, the external ventricular drainage needs to be temporarily closed to prevent undesired hyperdrainage. Sedation is recommended in patients with external ventricular drainage before these procedures [20] (options).

If intrahospital transport of patients with external ventricular drainage is needed, the drainage should be closed during the manipulation to prevent hyperdrainage [20] (options).

To prevent errors by medical personnel during intravenous administration of medications, the external ventricular drainage port needs to be clear marked in a way differing from that used for the intravascular insertion ports [20] (options).

ICP monitoring using a sensor inserted intraparenchymally is commonly used in clinical practice for patients with severe TBI, since it is difficult to make a ventricular puncture to measure the intraventricular pressure for the ventricular system narrowed and displaced.

3.5. Indications for correction of ICP

Correction of ICP should be started at ICP values higher than the threshold of 20 mm Hg registered for 5 min and longer [6—9, 14, 21] (recommendations).

3.6. CPP monitoring and the optimal CPP levels

In the daily intensive care routine, maintenance of CPP in patients with cerebral edema is ensured by moderate arterial hypertension using catecholamines and infusion solutions. The desired CPP values lie within the range of 50—70 mm Hg. A short-term increase in CPP may occur in patients with intact autoregulation of the cerebral blood flow without any significant aggravation of the injury outcomes. Auxiliary monitoring of the cerebral blood flow, oxygen saturation, and metabolism makes it easier to choose the optimal CPP parameters.

Aggressive attempts to maintain cerebral perfusion pressure above 70 mm Hg using infusion therapy and catecholamines should be avoided because of the risk of developing edema and acute pulmonary lesion (recommendations).

The CPP value below 50 mm Hg should be prevented (options).

3.7. Monitoring of autoregulation of cerebral blood flow (options)

The use of induced arterial hypertension in patients with disturbed autoregulation of the cerebral blood flow is fraught with intracerebral complications: blood–brain barrier disturbance, development of vasogenic cerebral edema and induced intracerebral hypertension. Development of extracerebral complications during CPP-oriented therapy, such as myocardial dysfunction and pulmonary lesion accompanied by development of edema and acute pulmonary lesion has been confirmed. These complications significantly increase the mortality among TBI patients and counterbalance the initial efficacy of the CPP protocol [7]. The therapeutic strategy aimed at maintaining CPP is an aggressive method of intensive care; some authors believe [22] that it should be focused on the status of autoregulation of cerebral blood vessels. Monitoring the pressure reactivity index (PRx) is one of the reliable and safe methods for continuous assessment of autoregulation of cerebral vessels [22]. The method does not require any function tests and is based on analyzing wave-like fluctuations in blood pressure and ICP. Furthermore, the method allows one to calculate the optimal CPP, providing a
landmark for targeted CPP therapy [22]. The optimal CPP value should correlate with the minimal PRx value.

### 3.8. Treatment of Intracranial Hypertension

Therapy of intracranial hypertension is classified into background (preventive) and urgent therapy.

#### 3.8.1. Background (preventive) therapy

Background (preventive) therapy is aimed at preventing and correcting the factors that can aggravate or accelerate the development of intracranial hypertension. Specific factors that may result in increased intracranial pressure include disturbed venous outflow from the cranial cavity (improper positioning of patient’s head, psychomotor agitation, increased intrathoracic and abdominal pressure), respiratory failure (airway obstruction, hypoxia, hypercapnia), hyperthermia, arterial hypo- and hypertension, and convulsive disorder [1, 6—10, 14, 23, 24]. To provide the optimal venous outflow from the cranial cavity in patients with severe TBI, the head end of the bed is raised by 30—40° and the head is positioned medially. Abdominal pressure is reduced by administering drugs that increase intestinal peristalsis and normalize the gastrointestinal function, as well as by inserting a gastric and/or intestinal tube to evacuate the stomach and intestines contents. Short-term drugs are preferred for judging psychomotor agitation, since they allow one to assess patient’s neurological status if necessary. Various antipyretic medications and/or physical methods of cooling are used to correct hyperthermia.

#### 3.8.2. Urgent therapy of intracranial hypertension

If preventive measures to correct intracranial pressure above 20 mm Hg prove inefficient, the stepwise algorithm for reducing ICP is used.

##### 3.8.2.1. CT of the brain is performed to rule out the reasons for intracranial hypertension requiring surgical correction (standard care).

##### 3.8.2.2. If an intraventricular catheter was inserted, controlled CSF drainage is used. An absolute indication for controlled drainage of CSF is intracranial hypertension caused by disturbed CSF flow in patients with occlusive hydrocephalus (standard care).

##### 3.8.2.3. Hyperosmotic solutions in treating intracranial hypertension

The use of hyperosmotic solutions is the most common methods for nonsurgical correction of intracranial hypertension. Nowadays, 15% mannitol solution is most often used in Russia. Bolus injections of mannitol at a dose of 0.25—1.0 g per kilogram body weight are used. The daily dose of administered mannitol should not be higher than 140—180 g. It is reasonable to administer mannitol before ICP monitoring if a patient has signs of trastentorial herniation or neurologic worsening unrelated to extracranial factors [1, 6, 7, 21, 25] (recommendations). The osmolality of blood plasma needs to be constantly monitored when using hyperosmotic solutions and the therapy should be stopped once the osmolality of 320 mOsm/L is reached.

Acute kidney failure is a complication of the therapy using hyperosmotic solutions. The risk of developing acute kidney failure rises when plasma osmolality increases to 320 mOsm/L and above and/or at hyponatremia >160 mmol/L [26, 27]. In patients with cardiopulmonary disorders, hyperosmolar therapy may cause the overload of the lesser circulation and pulmonary edema; rapid administration of hyperosmotic agents may be accompanied by arterial hypotension because of reflex transient decrease in the total peripheral resistance. Mannitol-induced osmotic diuresis may also contribute to arterial hypotension, especially in patients initially presenting with hypovolemia. When using mannitol, intracranial pressure can even increase above the original level after the initial decrease (the so-called rebound effect) [28, 29]. The development of the rebound effect is attributed to the delayed change between the osmolarities of blood plasma and the cerebral interstitial space [29]. A serious complication of using hypertonic sodium chloride solution in patients with the initial chronic hyponatremia is central pontine myelinolysis (rapid movement of fluid from the pontine cells into the vascular bed caused by hyperosmolality of blood plasma). Hypertonic solutions must be administered very slowly to prevent this condition in patients with chronic hyponatremia.

##### 3.8.2.4. The use of barbiturates in treating intracranial hypertension

Therapeutic anesthesia with high-dose barbiturates can be used in patients with severe TBI with stable hemodynamics and intracranial hypertension resistant to the maximally aggressive conservative and surgical treatment methods [1, 6, 7] (recommendations).

When using therapeutic anesthesia with barbiturates, it is reasonable to control the arteriovenous oxygen difference, since there is a risk of developing cerebral oligemic hypoxia (options).

The drug at a dose of 10 mg/kg during 1 h is initially administered followed by infusion of 3 does (5 μg/kg during 1 h) and maintaining the achieved plasma barbiturate concentration using an automated infusion pump (1 mg/kg during 1 h). Monitoring of sedation depth and choosing the optimal drug dose to suppress cerebral metabolism should be performed by electroencephalography or BIS monitoring.

##### 3.8.2.5. Artificial hypothermia in treating intracranial hypertension

Moderate reduction of brain temperature suppresses cerebral metabolism, which in turn may reduce cerebral blood flow, intracranial blood volume, and ICP. Moderate hypothermia modes (up to 32—35°C) are used [1, 6, 7, 14, 30, 31].

Cooling of the patient to the required temperature should be performed quickly (within 30—60 min), while heating should be slow (0.2—0.3°C per 1 h). Cooling of the patient can be accompanied by serious complications: hypocoagulation, increased diuresis, electrolyte imbalance, insufficient moistening of the incoming air, and infectious complications (options). The possible adverse effects of hypothermia are most typical of uncontrolled and deep hypothermia (patient’s body temperature less than 30°C).

##### 3.8.2.6. The use of hyperventilation in treating intracranial hypertension

Hyperventilation is a temporary measure for reducing increased intracranial pressure (e.g., when a patient is transported to the operating room if all the conservative measures for correcting intracranial hypertension proved inefficient). When using hyperventilation, one should monitor whether oxygen supply to the brain is sufficient by measuring blood oxygen saturation in the jugular vein. SvO2 indices lying within 55—75% are considered normal, provided that oxygenation of arterial blood is sufficient. The normal PbrO2 is 25—35 mm Hg at oxygen tension in the arterial blood of 80—100 mm Hg [1, 6, 7] (recommendations).

Hyperventilation can be an efficient method for correcting
intracranial hypertension caused by cerebral hyperemia [18, 32].

3.9. Role of glucocorticoids in the acute phase of severe TBI

Since 2000, the use of glucocorticoids to treat the acute phase of severe TBI has not been recommended, since according to the results of a number of class I and II studies, these agents do not reduce ICP and do not improve the outcome in patients with severe TBI (standard care). A randomized study carried out in 2004 in patients with severe TBI (CRASH) showed higher mortality among the patients who received high-dose methylprednisolone compared to those who received placebo. A meta-analysis published by the Cochrane Community shows that the patients had an increased risk of gastrointestinal bleeding after receiving glucocorticoid therapy.

The use of glucocorticoids is reasonable in patients with diencephalic damage and hormonal insufficiency caused by it.

3.10. Infectious complications in patients with severe TBI

3.10.1. Prevention and treatment of pulmonary complications

3.10.1.1. Prevention of aspiration of the oropharyngeal and gastric contents

Early tracheal intubation and maintaining the required pressure (20–25 cm H2O) in endotracheal tube cuffs is required. Continuous supra-cuff suction is used to prevent pulmonary aspiration. Tracheostomy is needed for mechanical ventilation lasting more than 5 days [10] (standard care).

To prevent gastroesophageal reflux, the patients should be positioned to his/her side on the bed with the head end elevated and receive enteral feeding through a nasojejunal tube (standard care). At late stages of treating severe TBI, percutaneous endoscopic gastrostomy can be performed in patients with signs of dysphagia (recommendations).

3.10.1.2. Prevention of cross-contamination and colonization through personnel hands (recommendations)

Mechanical ventilation equipment and fibrobronchoscopes should be meticulously cleaned; regular monitoring of bacteriological contamination of mechanical ventilators after sterilization should be performed. The order of individual use of aspiration equipment should be maintained and repeated use of sanitation catheters should be prevented. If possible, specialized closed systems for sanitation of the tracheobronchial tree and combination breathing filters should be used. A person performing sanitation of the tracheobronchial tree needs to wear sterile gloves. After any manipulations with the patient, one should wash his/her hands and gloves with special alcohol-based disinfectants. Hands should be washed with running water and dried with disposable paper towels or napkins.

When prescribing antibacterial therapy, one should take into account the pharmacokinetic properties of antibiotic drugs, choose dosage with allowance for the minimally suppressive concentrations, and performed scheduled drug rotation [1].

3.10.2. Prevention and treatment of intracranial suppurative complications

Antimicrobial prophylaxis that takes into account the microbiological status of the inpatient unit is indicated for scheduled and emergency neurosurgical interventions.

Failure to comply with the aseptic/antiseptic rules when manipulating the external ventricular drainage is the most common cause of intracranial infection. The risk of developing intracranial pyoinflammatory complications increases during long-term external CSF drainage [20] (recommendations). CSF drainage for more than 14 days is associated with the high risk of developing intracranial infection.

To reduce the risk of intracranial pyoinflammatory complications during external CSF drainage, the medical personnel needs to be trained to handle the drainage system and collect biological samples for analysis. Routine replacement of any elements of the drainage system should be avoided unless absolutely necessary. The system needs to remain closed as well as air- and watertight during the entire duration of CSF drainage. CSF can be collected for the analysis only through a special port that prevents system’s unscealing and detachment of its pieces. If accidental detachment of any elements of the system occurs, all the elements connected to the external ventricular drainage system need to be replaced. Samples can be collected from the drainage system only when strictly adhering to the aseptic and antiseptic techniques. Before sample collection, it is recommended that the sample port is treated with solutions of monomer- and polybasic alcohols (e.g., 70% ethanol solution, chlorhexidine/ethanol solution) for 3 min that are allowed to be used for treating the surgical field, or polyvidone–iodine solution for 30 s [20] (options).

CSF flow along the drainage system towards the fluid collector should be maintained during the entire duration of CSF drainage, which reduces the risk of infection ascending along the drain [20] (recommendations).

One should avoid retrograde flow of CSF from the fluid collector as the risk of ascending infection increases in this case [20] (options).

Routine replacement of the fluid collector should be avoided because of possible unscealing of the entire drainage system. The fluid collector should be replaced only after it is more than three quarters full [20] (recommendations).

Wound cleaning that includes hair removal and treatment with aseptic and antiseptic solutions in the site where the external ventricular drainage is placed and the contraincision should be performed at least every 48 h. A dressing consisting of adhesive moisture- and air-tight plaster bandage is recommended [20] (options).

Clinical signs of meningitis (rigidity of occipital muscles, decreased consciousness, developing cranial nerve dysfunction, elevated body temperature (including occasionally) in patients with an external ventricular drain are the absolute indications for CSF analysis that involves bacterial testing, in addition to the general CSF analysis [27] (recommendations).

The following laboratory data attest to the high probability of intracranial pyoinflammatory complications: cytosis >500/μL, the number of neutrophils with different degrees of decay >80%; low CSF glucose/plasma glucose ratio <0.4; increased CSF protein >0.6% accompanied with high CSF lactate >4.0 mmol/L. The increased level of inflammatory response markers (procalcitonin, >2.0 μg/L) should be additionally taken into account. In complicated diagnostic cases, PCR analysis of CSF to detect DNA of the most plausible
causative agents with allowance for the microbiological situation in the inpatient unit can be performed.

Analysis of CSF should be conducted shortly after it was collected because CSF is hypomolar and cell count decreases by 35% during the first hour and up to 50% during the second hour. Analysis of CSF should involve cell counting and morphological classification of cell composition, determining the protein, glucose, and lactate levels. In case of external ventricular drain infection, the drain should be removed [20, 33]. In case of shunt-dependent condition, the drain should be placed again through the non-infected tissues via a subcutaneous tunnel (>5 cm). In patients with pyoinflammatory complications caused by multidrug-resistant Acinetobacter, refusal of drain replacement is associated with increased mortality rate [20, 33] (options).

It is mandatory to obtain the CSF culture results and determine antimicrobial resistance when treating intracranial pyoinflammatory complications. Empiric antibiotic therapy is required if lumbar puncture cannot be performed or CSF cannot be collected from the ventricular drain, as well as before CSF culture results are obtained. The preferred empirical therapy is the therapy with parenteral administration of Ceftriaxone (2 g every 12 h) or Cefotaxime (2 g every 6 h). The alternative empiric therapy regimen includes Meropenem (2 g every 8 h) combined with Vancomycin (60 mg per kilogram bodyweight per day — long-term infusion). This empiric therapy regimen is preferred in inpatient units with the high incidence rate of penicillin-resistant and/or cephalosporin-resistant hospital-acquired infection [26]. In particular instances, antimicrobial drugs can be administered intrathecally in patients with aggravated course of meningitis and in the absence of contraindications. Intrathecal administration of specially adjusted antibiotic salts: vancomycin (10—20 mg/day), gentamicin (4—8 mg/day), tobramycin (5—20 mg/day), amikacin (50—30 mg/day), polymixin B (5 mg/day), and colistin (10 mg/day) [33]. After intrathecal administration of antibiotics, the external drain should be kept closed for at least 1 h [20]. Patients receiving intrathecal antibacterial therapy should permanently undergo monitoring for neurotoxic events, such as aggravation of meningeal symptoms, suppression of consciousness, partial or generalized seizures [20, 33] (options).

3.11. Nutrition in patients with severe TBI

The TBI patients in critical state should receive early nutritional support satisfying his/her needs for protein and energy. The basal metabolic rate in patients with severe TBI is 20—25 kcal/kg per day. Indirect calorimetry should be used to accurately assess the energy demand of patients. If no metabolograph is available, the energy demand of patients is calculated using formulas. Both enteral and parenteral nutrition can be given. The advantages of enteral feeding over the parenteral one include the lower risk of developing hyperglycemia and infectious complications. A nasogastric or an orogastric tube is inserted to provide enteral feeding. If the gastric feeding variant for 2 days proves inefficient, a small-bowel feeding tube is inserted. In this case, specialized semi-elemental formulas should be used to feed the patients. A gastrostomy tube can be placed if long-term enteral tube feeding for more than 4 weeks is required [1, 26, 34—36] (recommendations).

3.12. Anticonvulsant therapy

TBI is the main cause for developing epilepsy in middle-aged patients. Posttraumatic seizures include single or repeated seizures that first manifested after the TBI. Seizures can be classified as acute-phase (manifesting within the first 12 h), early (within 7 days), and late (more than 1 week) posttraumatic epilepsy. Other potential reasons for developing epilepsy should be ruled out (especially in the acute phase of the injury): electrolyte imbalance, alcohol intoxication, the past medical history of epilepsy, etc. Epilepsy can be diagnosed based on the clinical presentation of a seizure (according to the evidence by eyewitnesses or a video of a seizure) confirmed by routine EEG recording, video-EEG monitoring for 24—72 h and monitoring plasma prolactin level during the first hours after the seizure.

Status epilepticus is the generalized seizure lasting longer than 5 min or a series of seizures between which the patient remains unconscious. Status epilepticus requires immediate alleviation by administering anticonvulsants. Alleviation of seizures should be started with intravenous injection of drugs. If an agent is unavailable in an intravenous form, it is administered through a gastric tube. A combination of anticonvulsants should be used if monotherapy proves to be inefficient. Myorelaxants are not anticonvulsants; they alleviate only the muscular component of seizures and are used temporarily if a patient needs to be synchronized with the mechanical ventilation system.

Results of class I studies have proved that preventive therapy with phenytoin, carbamazepine, phenobarbital, or valproates is inefficient for preventing late posttraumatic seizures (standard). Anticonvulsants (phenytoin and carbamazepine) are indicated for patients with high risk of developing early seizures during the acute-phase TBI. The risk factors include the presence of foci of cortical contusion, depressed skull fractures, intracranial hematomas, penetrating head injury, and development of a seizure within 24 h after injury (options). Anticonvulsant therapy is prescribed to patients diagnosed with posttraumatic seizures, which can be stopped gradually provided that seizures have not occurred for two years (an option).

3.13. Neuroprotective therapy in the acute phase of severe TBI

As opposed to the experimental studies, there is very little evidence for the effectiveness of neuroprotective drugs in clinical practice. Molecules with different biochemical activity have been considered among the possible neuroprotective agents: inactivators of free radical mechanisms (polyethylene glycol superoxide dismutase — PEG SOD, α-tocopherol, melatonin, etc.), inactivators of carboxyl groups (D-penicillamine, carnosine, aminoguanidine), activators of glutathione synthesis (N-acetylcysteine, gamma-glutamylcysteine ethyl ester), steroids (progesterone, methylprednisolone), calcium channel blockers (Nimodipine), immunosuppressants (cyclosporine A), and modulators of excitotoxicity.

Only few of the aforesaid molecular agents have been tested in clinical trials in patients with severe TBI. PEG-SOD was one of the first agents to be studied; phase II trials demonstrated that it exhibited a positive effect on reduction of the frequency rate of unfavorable outcomes (a persistent vegetative state and death) compared to placebo; however, this
effect has not been confirmed in the phase III trials. In the phase II trials (SYNAPSE), progesterone has shown good effectiveness in reducing the mortality rate and improving the outcomes according to the SCG score 3 and 6 months after injury compared to the placebo group; however, results of the phase III study (PROTECT III) revealed no intergroup difference. The phase II study of cyclosporine A has also yielded promising results; however, the phase III study will be finished only in 2018. A meta-analysis performed by the Cochrane Community for Nimodipine has found that this agent can be used to reduce the risk of fatal outcome only in the group of patients with subarachnoid hemorrhage. Efficacy of the Bradykinin antagonists (Deltibant), modulators of excitotoxicity (dexamabnil), magnesium sulfate and its analogue, Sellichtol, has been refuted by clinical trials.

Hence, none of the few neuroprotective agents that have made their way to phase III clinical trials has shown efficacy in actual clinical practice. The remaining agents require planning new, conducting multi-center, randomized, placebo-controlled trials. However, the extremely narrow therapeutic range is a significant limitation of their application that is difficult to overcome.

Authors declare no conflict of interest.

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