Received: 10 December 2018 / Accepted: 12 January 2019 / Published online: 30 April 2019

UDC: 616.714.1+616.831-001

MODERN TENDENCY IN TREATMENT OF PATIENTS WITH SEVERE TRAUMATIC BRAIN INJURY. LITERARY REVIEW

Marat K. Syzdykbayev [1], https://orcid.org/0000-0002-0561-4111
Marat B. Temirgaliev [1], https://orcid.org/0000-0001-8151-8538
Alexander A. Prokazyuk [1], Anton Sheinin [2],
Daulet S. Tokenov [1], Adlet M. Mamayev [1]

[1] University hospital of Semey Medical University, Semey, The Republic of Kazakhstan;
[2] Tel-Aviv University, Sagol School of Neuroscience, Tel-Aviv, Israel.

Summary

Relevance: Carrying out of intensive therapy at severe traumatic brain injury is a complex of measures aimed on saving of the brain tissues and maintaining its functions. To achieve this goal, it is necessary to do timely diagnostics and monitoring of critical parameters - intracranial pressure and cerebral perfusion pressure; pathogenetically based therapy and nutritional support for critically ill patients.

Aim: The goal of this review was to find evidences of admissibility of use for such methods as control of cerebral perfusion pressure and intracranial pressure, anti-edematous therapy, brain hypothermia and nutritive support at severe traumatic brain injury.

Materials and methods: we have reviewed all available works that met inclusion criteria for mentioned aims, that were published on PubMed, Cochrane Library and Scopus within the period from 1970 till 2018.

Results and Summary: Current topics is narrow-specified, so there is lack of information and available researches in reviewed fields of neurotrauma. Additional qualitative research works on this topics should be done.

***Key words**: neurotrauma, resuscitation, intracranial pressure, nutritional support, mannitol, hypertonic saline solution.*

Резюме

СОВРЕМЕННЫЕ ТЕНДЕНЦИИ В ЛЕЧЕНИИ БОЛЬНЫХ С ТЯЖЕЛОЙ ЧЕРЕПНО-МОЗГОВОЙ ТРАВМОЙ. ОБЗОР ЛИТЕРАТУРЫ

Марат К. Сыздыкбаев [1], https://orcid.org/0000-0002-0561-4111
Марат В. Темиргалиев [1], https://orcid.org/0000-0001-8151-8538
Александр А. Проказюк [1], Антон Шейнин [2],
Даулет С. Токенов [1], Адлет М. Мамаев [1]

[1] Университетский госпиталь НАО «Медицинский университет Семей», г. Семей, Республика Казахстан;
[2] Университет Тель-Авива, Школа нейробиологии им. Сагола, г. Тель-Авив, Израиль.

Актуальность: Проведение интенсивной терапии при тяжелой черепно-мозговой травме – это комплекс мероприятий, направленных на спасение головного мозга и поддержание его функций. Для достижения поставленной задачи необходимо проведение своевременной диагностики и мониторинга критически важных параметров – внутричерепного давления и церебрального перфузионного давления; патогенетически обоснованная терапия и нутритивная поддержка критически больного.

Цель: Целью данного обзора являлся поиск доказательств допустимости применения таких методов, как контроль церебрального перфузионного и внутричерепного давления, противоотечной терапии, гипотермии головного мозга и питательной поддержки при тяжелой черепно-мозговой травме.

Материалы и методы: нами были изучены все доступные работы, которые подошли под критерии включения для выше упомянутых целей, опубликованные в PubMed, Cochrane Library и Scopus за период 1970-2018 гг.

Результаты и выводы: Данная тема узко-специфична, и имеется дефицит качественных исследований в указанных областях нейрореанимации. Необходимо провести дополнительные качественные исследования по данным темам.

***Ключевые слова**: нейротравма, реанимация, внутричерепное давление, нутритивная поддержка, маннитол, гипертонический солевой раствор.*

Түйіндеме

АУЫР БАС-МИ ЖАРАҚАТЫ БАР НАУҚАСТАРДЫ ЕМДЕУДЕГІ ЗАМАНАУИ БАҒЫТТАР. ӘДЕБИЕТТІК ШОЛУ

Марат К. Сыздыкбаев [1], https://orcid.org/0000-0002-0561-4111
Марат В. Темиргалиев [1], https://orcid.org/0000-0001-8151-8538
Александр А. Проказюк [1], Антон Шейнин [2],
Дайлет С. Токенов [1], Адлет М. Мамаев [1]

[1] «Семей медицина университеті» КеАҚ Университеттік госпиталь, Семей қ., Қазақстан Республикасы;
[2] Тель-Авив Университеті, Сагол ат. Нейробиологияның мектебы, Тель-Авив қ., Израиль.

Өзектілгі: Ауыр бас ми жарақаты кезіндегі интенсивті терапия жүргізу – бас миын қорғау мен оның қызметтерін сақтап қалуға бағытталған шаралар жиынтығы. Бұл жағдайларда алдыға қойған мақсатқа жету үшін бассүйек ішілік қысым мен церебралды перфузионды қысымның аса маңызды көрсеткіштерін уақытылы анықтап, мониторинг жасау қажет; сондай-ақ науқастарға патогенез тұрғысынан негізделген терапия және нутритивті қолдау қажет.

Мақсаты: Шолудың негізгі мақсаты ауыр бассүйек-ми жарақаты кезінде церебральді және бассүйек ішілік қысымды, ісінуге қарсы терапия, ми гипотермиясы және қоректік демеуді бақылау болып табылады.

Материалдар мен әдістеро: біз 1970-2018 жылдар аралығындағы PubMed, Cochrane Library және Scopus басылымдарында жарық көрген, жоғарыда аталған мақсаттардың қосу критерийлеріне сәйкес келетін барлық жұмыстарды зерттедік.

Қорытындылар мен нәтижелер: Берілген тақырып ауқымы кіші маманданған, нейрореанимацияның көрсетілген бөлімдерінде сапалы зерттеулер жеткіліксіз болып табылады. Аталған тақырыптар бойынша қосымша сапалы зерттеулер жүргізілуі тиіс.

Негізгі сөздер: *Нейрожарақат, реанимация, бассүйекішілік қысым, нутритивті қолдау, маннитол, гипертониикалық тұзды ерітінді.*

Библиографическая ссылка:

Сыздыкбаев М.К., Темиргалиев М.В., Проказюк А.А., Шейнин А., Токенов Д.С., Мамаев А.М. Современные тенденции в лечении больных с тяжелой черепно-мозговой травмой. Обзор литературы // Наука и Здравоохранение. 2019. 2 (Т.21). С. 5-12.

Syzdykbayev M.K., Temirgaliev M.B., Prokazyuk A.A., Sheinin A., Tokenov D.S., Mamayev A.M. Modern tendency in treatment of patients with severe traumatic brain injury. Literary review. *Nauka i Zdravookhranenie* [Science & Healthcare]. 2019, (Vol.21) 2, pp. 5-12.

Сыздыкбаев М.К., Темиргалиев М.В., Проказюк А.А., Шейнин А., Токенов Д.С., Мамаев А.М. Ауыр бас-ми жарақаты бар науқастарды емдеудегі заманауи бағыттар. Обзор литературы // Ғылым және Денсаулық сақтау. 2019. 2 (Т.21). Б. 5-12.

Relevance

Craniocerebral trauma (CCT) or Traumatic brain injury (TBI) – are terms that embrace the different types and severity grades of damage to both the skull itself and intracranial structures: meninges, brain substance, cerebral vessels, cranial nerves. The modern classification of TBI is not ideal, since in some cases the same pathomorphological and pathophysiological changes can lead to different clinical manifestations. But despite this the following conditions are universally accepted as a serious craniocerebral trauma: brain contusion of severe degree, diffuse axonal injury and all kinds of acute compression of the brain (both traumatic and organic nature) [2].

At present there is no precise statistics on the incidence of CCT, but the approximate range figures from 800 people per 100,000 population each year for the underdeveloped countries, and up to 1,300 people in high-developed countries. Among which from 3 to 10% are heavy forms [28]. The problem of severe TBI doesn't lose its relevance due to the high incidences of mortality and disability in the post-traumatic period, which are affecting the workability and the professional suitability, social activities and the quality of life in general. This pathology directly affects the society, because the main contingent of sufferers are the people of working age.

Despite the high incidence among all injuries, severe TBI remains a nosology which has no common international protocol for patients' management. Nevertheless, from the position of evidence-based medicine, next gaining popularity diagnostic and treatment methods should be noted: control of the intracranial pressure and cerebral perfusion pressure, anti-edematous or dehydrating therapy, preventive hypothermia and nutritive support of patients.

Aim: The goal of this review was to find strong evidences of admissibility of use for such methods as control of cerebral perfusion pressure and intracranial

pressure, anti-edematous therapy, brain hypothermia and nutritive support at severe traumatic brain injury. If such are present to define indications and contraindications for this methods, to find optimal parameters that will bring profit nor harmful influence for patient.

Material and methods: This work was subdivided in subtopics: "Control of the intracranial pressure", "Control of cerebral perfusion pressure", "Anti-edematous therapy", "Prophylactic mild induced hypothermia" and "Nutritive support". For every subtopic there we made search keywords: severe traumatic brain injury, neurotrauma, intracranial pressure, cerebral perfusion pressure, monitoring, neuromonitoring, anti-edematous therapy, mannitol, hypertonic saline solution, brain hypothermia, nutrition, enteral feeding. By combinations of this keywords and with use of logic operators OR, AND, NOT we made search of research works on PubMed, Cochrane Library and Scopus that contained in title or abstract mentioned keywords. Another inclusion criteria were: all articles that were published during the period from 1970 till 2018 (wide range because of lack of studies); researches are made on adult human with severe traumatic brain injury with Glasgow score 3-8 points, N > 25, randomized controlled trials/meta analyses/retrospective reviews/observation reviews/systematic reviews/cohort trials. Also we were searching for such end-points as outcome, mortality, complications, in-hospital time, stay time at intensive care unit. Publication language English.

We have found 127 articles that met our inclusion criteria. Next stage was to read the abstracts and analyze involvement of article to reviewed topics. Finally we got 73 articles for final analysis.

Control of the intracranial pressure.

Weed L. and McKibben P.S. have proven [72] that the internal volume of the skull is always constant, and it's fluid media and the brain substance under normal conditions are in a state of volumetric equilibrium. When the volume of one of the components changes, an involuntary compensatory decrease in the volume of the other components occurs. The damage of these compensatory mechanisms leads to a single final result - an increase in intracranial pressure (ICP), that compress cerebral venous sinuses and blood flow is disturbed. In this turn ischemia and edema of the brain takes place. Critical brain tissue compression leads to a violation of consciousness, hemodynamics, external respiration, and most important - irreversible lesion of the brain cells. A generally accepted criterion for increased intracranial pressure is ICP more than 20 mmHg [14, 15].

The disturbed consciousness does not allow to adequately assess the whole scale of the catastrophe, and hinders to choose correctly the appropriate therapeutic plan. Such non-diagnosed crises of intracranial pressure lead to worse outcomes [7, 32, 33, 67]. In most modern clinics for diagnostic purposes special methods are used - computed tomography (CT) and magnetic resonance imaging (MRI). However, the use of these non-invasive methods is associated with some problems. The first - inability to make an examination "in situ". The second - absence of dynamic monitoring of volumes of intracranial mediums. An invasive measurement of intracranial pressure with constant monitoring is supposed to be as an alternative to these visual methods [49].

The use of intracranial sensors for ICP measurement is not an ubiquitous method of diagnostics because of its narrow focus, high cost and insufficient spread outside of specialized clinics [17, 30]. Another point is the neurosurgeon's decision on rationally of the sensor installing in a specific patient, since, the risk of surgery may often exceed the potential benefit of the method, or the patient has a cerebral injury that incompatible with life.

Nevertheless, the control of intracranial pressure in the first hours after trauma makes it possible to choose therapy effectively, and to correct it in a time, thereby it reduces mortality in the first day of hospitalization [32, 33, 67, 74]. In the later period of severe TBI treatment, the use of invasive monitoring does not bring practical benefit, but slightly improves the 30-days survival rate. Long-term monitoring in most cases leads to an increase in the number of patients requiring tracheostomy, so the number of days for ventilator therapy and stay in the ICU gets more than two times [7, 18]. Due to the longer period of artificial ventilation in the group of invasive ICP monitoring the development risk of ventilator-associated pneumonia is significantly higher [6, 46].

The main limitations for the routine use of ICP measurement are the recommended clinical criteria [14, 16]: depression of consciousness (coma, pre-coma), cerebral hernia on CT or volume lesion, systolic blood pressure <90 mmHg, that does not contribute to the formation of adequate cerebral perfusion pressure. In addition, it is necessary to have qualified personnel who can correctly assess the result of CT and / or MRI and correctly install the sensor in the required location. It should be remembered that the indiscriminate application of this diagnostic method doubles the incidence of complications. Most often occur infectious complications and thromboembolic processes [6].

Summarizing, the invasive measurement of intracranial pressure remains to be not fully investigated diagnostic method, which at improper application conceals a potential threat of intracranial complications.

Control of cerebral perfusion pressure

Cerebral perfusion pressure (CPP) - is defined as the pressure gradient between the inflow and outflow of blood in the cranial cavity. As an inflow it is accepted to take the mean arterial pressure (MAP), and as an outflow - pressure in the jugular vein. At craniocerebral trauma, intracranial pressure increases, which becomes higher than the pressure in the jugular vein (JVP). In this case, the CPP will be proportional to the gradient between MAP and mean ICP. So the change in the CPP is directly related with the inflow and outflow of blood [15, 70].

Taking into account the "Starling resistance", the formula for CPP calculation will be as following:

- If CPP> JVP
  CPP (mmHg) = MAP - ICP
- If the CPP <JVP
  CPP (mmHg) = MAP - JVP

It is necessary to distinguish the terms of CPP and perfusion. Perfusion is the rate of passage of one medium (blood) through another (brain tissue) per unit of time

(minutes). The physiological values of cerebral perfusion are varying depending on the zone of blood supply. A generally accepted average blood flow is 50 ml per 100 g of brain tissue per minute [1]. At critical decrease in CPP, a decrease in brain perfusion takes place, processes of oxidation-reduction are violating, hypoxia and irreversible lesion of neurons are developing.

Despite the importance of this parameter, the CPP remains to be an open question in the field of neuroreanimation. At the moment, there are no fundamental researches devoted to the studying and analysis of issues related to the target levels of perfusion pressure at traumatic brain injuries. However, there are several small studies in which authors take as the target CPP level the value of more than 70 mmHg [33, 37, 26].

The following of a specific protocol for the treatment of severe TBI with CPP control and selection of adequate therapy, based on received data, leads to a significant reduction in the two-week mortality rate [33].

Anti-edematous therapy

In the acute period of TBI, damage of the tissues and vessels leads to the movement of water and Na^+ ions into the intercellular space, from where they move into the cells causing intracellular edema, violation of cerebral blood circulation and cerebrospinal fluid circulation. Reduction of cerebral blood flow below 15 ml per 100 g of brain tissue leads to the development of irreversible lesion of neurons with the formation of zone of an infarct nucleus.

Dehydration therapy is ethiopathogenetic basis of therapy at cerebral edema. In the experiment [72], the effects of hypertonic and hypotonic saline solutions on brain tissue were demonstrated. It has been proven that the use of osmotically active drugs can cause dehydration of the brain substance by creating an osmotic gradient across the blood-brain barrier, which leads to a shift of the fluid from the intercellular space to the microcirculation, thereby reducing its edema [12, 55, 73].

This effect occurs within minutes and is observed up to several hours [14, 53, 54].

In the practice of intensivist currently are available two drugs for hyperosmolar therapy - mannitol and hypertonic saline solution (HS).

In European countries, for the purpose of dehydration therapy 3-4% of HS is mainly being used and injected as bolus [50, 61]. The use of 7.5%, 10% and 23.4% solutions is also acceptable [44], but it should be remembered that high-concentration of saline solutions in high doses can lead to a state of hypernatremia. However, such drugs can have the desired effect at mannitol-resistant ICP [25, 31, 45], with an additional improvement in cerebral blood flow and oxygenation. There are evidences that the saline solution, in comparison with mannitol, has a longer lasting effect, without the development of the “ricochet” effect [35, 36, 58, 71]. The negative effect of saline is the development of acute cardiac and / or renal failure in the state of hypernatremia.

The use of mannitol in a dosage from 0.25 g / kg to 1.0 g / kg of weight is also able to increase cerebral perfusion pressure and improve cerebral blood flow, but its effect is less expressed [63, 64]. Unlike HS, mannitol has an opposite effect on the volume of circulating blood, and its diuretic effect is not desirable in shock and hypotensive states. Similarly, the precipitation of mannitol in the renal tubules exacerbates the clinical course in patients with renal failure [50, 25, 40].

Treatment with hyperosmolar therapy reduces mortality in the first weeks after severe TBI and the time of stay in the ICU also decreases. [33]

Prophylactic mild induced hypothermia

Besides of stabilizing the critical state at severe TBI, therapy and prevention of so-called secondary brain damage are noted as the main aim. This occurs due to increased intracranial pressure, cerebral hypoxia and ischemia, metabolic and acid-base balance disorders. These consequences may develop as in the first hours, so in several hours or days after trauma [59]. From the non-pharmacological methods of therapy of these conditions, the so-called “Mild induced hypothermia” is the most widely used. Its idea is to provide therapeutic cooling of the body to a temperature of 32-35 °C. The study on animals of the neuroprotective properties of such cooling has shown its positive effects [47], however the transfer of this model to clinical practice has faced with a number of difficulties.

In the pathogenesis of brain lesion with the development of its edema, a key role is played by brain vessels damage and violation of venous outflow, resulting in ischemia and hypoxia of the brain tissue. The release of glutamate and other stimulating neurotransmitters takes place at ischemic conditions. Such increase in the glutamate level leads to the opening of calcium channels and Ca^{+2} ions flow into the cell where they activate some lipases and proteases, cause increase of the nitric oxide level and free oxidative radicals [56]. All these substances lead to the effect of so called “excitotoxicity” (derivate from “excitatory mediators”), – the damage of mitochondria and destruction of the neuron's DNA with the development of apoptosis and necrosis [9, 52].

The proven effects of moderate hypothermia are:

1. Decrease in oxygen consumption by the brain tissue for metabolic processes ($CMRO_2$ level) is about 6.5% for each lowered °C. Due to this effect there is sufficient extraction of oxygen from the blood at condition of reduced blood flow [11].
2. As a result of slow metabolism, glucose and energy consumptions are reduced [57, 66].
3. The low temperature affects the current of calcium ions into cells, thereby excitotoxicity is being reducing [24, 29].
4. Protection of the hemato-encephalic barrier from damaging by preserving of vascular endothelium and its functions, at states of vasogenic and cytotoxic brain edema. Hypothermia disrupts the formation of micro-thrombi by interrupting of hemostasis cascade at the level of the cell membranes [48, 59]. Hypothermia decreases blood inflow and swelling of the brain substance, respectively [65].
5. Inhibition of inflammatory processes by reduction of the free oxidation radicals amount [27, 69].
6. Decrease in epileptic activity of the brain [10, 43].

Moderate hypothermia applicable in the early period after trauma (before increase of intracranial pressure), is often named as "preventive". At present, this technique is done at critical states with cardiac arrest, with the goal of

neuroprotection in conditions of metabolic changes [8, 39]. In addition to the above described neuroprotective effects, hypothermia is able to reduce intracranial pressure, and is sometimes an alternative in the treatment of refractory ICP [65]. Such hypothermia is commonly called "therapeutic".

However, the overall body hypothermia has the risk of coagulopathy and immunosuppression development, and at deep hypothermia, it is possible to develop cardiac dysrhythmias that lead to death of patient [13]. In connection with this, in the hope of avoiding systemic side effects, some researchers suggest of local hypothermia use – cooling the patient's head with specialized cooling helmets, the so-called "selective brain cooling". At this method in the long term observations the patient's neurological status and quality of life is significantly better than at system cooling. [48]

There are published studies of hypothermia use in adults which mostly have controversy results. As the main endpoints in such publications, mortality and mark based on the Glasgow outcome scale (GOS) are chosen. In limited studies on small samples, there is a significantly lower (in twice) mortality and a better GOS score in six months, in comparison with the management of patients with normothermia [5, 41, 51, 74]. Systemic hypothermia, in contrast to selective brain cooling, is directly related to the risk of nosocomial pneumonia [60].

Other studies conversely report a lack of statistically significant differences [20, 22, 23], including two qualitative pediatric studies [4, 38]. It is worth noting that in one of these studies [23] patients with surgically removed hematomas had better outcomes in the hypothermic group.

Speaking about the speed of hypothermia, in the case of its use, preference should be given to rapid cooling (within 1.5 hours after removing of the intracranial hematoma). In such situation there are less complications [21]. Maintenance of cooling during 5 days is considered to be long-term, which results more favorably on the final outcomes. [42]

In summary, there are multiple potential effects, proven on experimental models. However, the lack of common indications, criteria and standards for the preventive and therapeutic hypothermia directly affects the results of published studies. There is no unambiguous answer about the expediency of this method using. So the issue of cooling for the purpose of neuroprotection leaves a great field for new, qualitatively thought-out studies.

Nutritive support

In extreme situations, the body loses a large amount of energy, this is also true for an acute period of traumatic brain injury. Being in a coma, the patient often does not receive adequate nutrition and the number of necessary calories, thereby showing a negative impact on the gastrointestinal tract, immunity and overall resistance of the body. Rapid utilization of glucose and stored glycogen under the influence of stress hormones leads to energy exhaustion [75], and the lack of proteins and fats adversely affects the growth and recovery of cells and tissues.

Early enteral feeding is recommended, if there are no combined injuries of the abdominal and gastrointestinal tract. It is necessary to introduce full-calorie feeding on the first day after the trauma [19, 68]. So the food introduced in the first week after the injury reduces the two-week mortality [62]. In addition to this early nutrition improves the endocrinologic background of the patient with TBI [34].

Enteral feeding with a probe in the duodenum has a protective effect due to a decrease in residual contents in the stomach, which in turn is manifested by a lower incidence of aspiration and a ventilator-associated pneumonia [3, 45].

Conclusion

Thus, timely monitoring of intracranial pressure and cerebral perfusion pressure in combination with hyperosmolar therapy significantly increases the chances of rapid recovery of patients with severe TBI. On the other hand, keep in mind that the late installation and improper care of an ICP sensor leads to infectious complications in patient. You should also pay attention to the patient's vollemic status, and choose a drug for dehydration of the brain with respect to blood circulation volume. In the case of refractory elevated ICP, it is appropriate to use highly concentrated hypertensive saline solutions, and selective hypothermia of the brain. In order to prevent the development of secondary increase in ICP and neuroprotective effect, it is permissible to use preventive selective hypothermia, which is preceded by the removal of intracranial hematomas. However, the effectiveness of this method is not reliably confirmed, nor is it refuted. And in the absence of effect, the only correct solution is decompressive craniotomy.

Neglecting of enteral and parenteral nutrition may be manifested by an energy deficit in an already weakened and vulnerable patient, which subsequently leads to the development of infections and worsening of the general condition of the underlying disease.

The authors of this manuscript assure that the work as a whole and some of its parts are sent to the publication at first. The manuscript was also not subjected to multiple dispatch to other print publications, thereby being unique.

Conflicts of interest:

The authors state that there are no conflicts of interest, no financial interests, no sponsorship and no biased presentation of the results.

References:

1. Oshorov A.V., Goryachev A.S., Popugaev K.A. et al. Monitoring tserebral'nogo perfuzionnogo davleniya v intensivnoi terapii (obzor literatury) [Monitoring of cerebral perfusion pressure in intensive care]. *Vestnik anesteziologii i reanimatologii* [Herald of anesthesiology and reanimatology]. 2013. T. 10, №2. pp. 52-59 [in Russian]

2. Smychyok V.B., Ponomareva E.N. Sovremennaya klassifikatsiya cherepno-mozgovoi travmy [Modern classification of traumatic brain injury]. *Meditsinskie novosti* [Medical news]. 2012. №1, pp. 17-23. [in Russian]

3. Acosta-Escribano J., Fernandez-Vivas M., Grau Carmona T., et al. Gastric versus transpyloric feeding in severe traumatic brain injury: a prospective, randomized trial. *Intensive Care Med.* 2010. PMID: 20495781 DOI: 10.1007/s00134-010-1908-3

4. Adelson P.D., Wisniewski S.R., Beca J., et al. Comparison of hypothermia and normothermia after severe traumatic brain injury in children (Cool Kids): a phase 3,

randomised controlled trial. *Lancet Neurol.* Jun 2013;12(6):546-553. PMID: 23664370.

5. Aibiki M., Maekawa S., Yokono S. Moderate hypothermia improves imbalances of thromboxane A2 and prostaglandin I2 production after traumatic brain injury in humans. *Crit Care Med. Dec.* 2000;28(12):3902-3906. PMID: 11153633.

6. Aiolfi A., Benjamin E., Khor D., Inaba K., Lam L., Demetriades D. Brain Trauma Foundation Guidelines for Intracranial Pressure Monitoring: Compliance and Effect on Outcome. World J Surg. 2017 Jun;41(6):1543-1549. doi: 10.1007/s00268-017-3898-6. *Erratum in: World J Surg*. 2017 Jun;41(6):1542. PubMed PMID: 28188356. DOI:10.1007/s00268-017-3913-y

7. Alali A.S., Fowler R.A., Mainprize T.G., et al. Intracranial pressure monitoring in severe traumatic brain injury: results from the American College of Surgeons Trauma Quality Improvement Program. *J Neurotrauma. Oct* 15 2013; 30(20): 1737-1746. PMID: 23731257. DOI:10.1089/neu.2012.2802

8. Arrich J., Holzer M., Havel C., Mullner M., Herkner H. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. *Cochrane Database Syst Rev*. 2012(9):1-40. PMID: 22972067.

9. Ashkenazi A., Dixit V.M. Death receptors: signaling and modulation. Science. 1998;281:1305–8

10. Atkins C.M., Truettner J.S., Lotocki G., et al. Post-traumatic seizure susceptibility is attenuated by hypothermia therapy. *Eur J Neurosci.* 2010;32:1912–20.

11. Bacher A., Illievich U.M., Fitzgerald R., et al. Changes in oxygenation variables during progressive hypothermia in anesthetized patients. *J Neurosurg Anesthesiol.* 1997;9:205–10.

12. Berger S., Schürer L., Härtl R., et al.: Reduction of post-traumatic intracranial hypertension by hypertonic/hyperoncotic saline/dextran and hypertonic mannitol. *Neurosurgery*. 37:98–108, 1995. PMID: 8587698. DOI: 10.1227/00006123-199507000-00015

13. Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, et al. Guidelines for the management of severe traumatic brain injury. *J Neurotrauma.* 2007;24 Suppl 1:S1-106. PMID: 17511554.

14. Bratton S.L., Chestnut R.M., Ghajar J., et al. Guidelines for the management of severe traumatic brain injury. II. Hyperosmolar therapy. *J Neurotrauma.* 2007;24 Suppl 1:S14- 20. PMID: 17511539. DOI: 10.1089/neu.2007.9994

15. Bratton S.L., Chestnut R.M., Ghajar J., et al.: Guidelines for the management of severe traumatic brain injury. VIII. Intracranial pressure thresholds. J Neurotrauma. 2007;24 Suppl 1:S55-8. Erratum in: *J Neurotrauma.* 2008 Mar;25(3):276-8. PubMed PMID: 17511546. DOI:10.7887/jcns.22.831

16. Carney N., Totten A.M., O'Reilly C., et al.: Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. *Neurosurgery*. 2017 Jan 1;80(1):6-15. PubMed PMID: 27654000. DOI: 10.1227/NEU.0000000000001432.

17. Chesnut R.M., Petroni G., Rondina C. Intracranial-pressure monitoring in traumatic brain injury. *N Engl J Med.* May 2013;368(18):1751-1752. PMID: 23635057. DOI: 10.1056/NEJMc1301076

18. Chesnut R.M., Temkin N., Carney N., et al. A trial of intracranial-pressure monitoring in traumatic brain injury. *N Engl J Med.* Dec 2012;367(26):2471-2481. PMID: 23234472. DOI:10.1056/NEJMx130056

19. Chourdakis M., Kraus M.M., Tzellos T., et al. Effect of early compared with delayed enteral nutrition on endocrine function in patients with traumatic brain injury: an open-labeled randomized trial. *J Parenter Enteral Nutr.* 2012;36(1):108-116. PMID: 21965459 DOI: 10.1177/0148607110397878

20. Clifton G.L., Allen S., Barrodale P., et al. A phase II study of moderate hypothermia in severe brain injury. J Neurotrauma. Fall 1993;10(3):263-271; discussion 273. PMID: 8258839.

21. Clifton G.L., Coffey C.S., Fourwinds S., et al. Early induction of hypothermia for evacuated intracranial hematomas: a post hoc analysis of two clinical trials. *J Neurosurg.* Oct 2012;117(4):714-720. PMID: 22839656.

22. Clifton G.L., Miller E.R., Choi S.C., et al. Lack of effect of induction of hypothermia after acute brain injury. *N Engl J Med.* Feb 22 2001;344(8):556-563. PMID: 11207351.

23. Clifton G.L., Valadka A., Zygun D., et al. Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): a randomised trial. *Lancet Neurol.* Feb 2011;10(2):131-139. PMID: 21169065

24. Colbourne F., Grooms S.Y., Zukin R.S., et al. Hypothermia rescues hippocampal CA1 neurons and attenuates down-regulation of the AMPA receptor GluR2 subunit after forebrain ischemia. *Proc Natl Acad Sci USA.* 2003;100:2906–10.

25. Cottenceau V., Masson F., Mahamid E., et al: Comparison of effects of equiosmolar doses of mannitol and hypertonic saline on cerebral blood flow and metabolism in traumatic brain injury. *J Neurotrauma* 28:2003–2012, 2011. PMID: 21787184. DOI: 10.1089/neu.2011.1929

26. Cruz J. The first decade of continuous monitoring of jugular bulb oxyhemoglobin saturation: management strategies and clinical outcome. *Crit Care Med.* Feb 1998;26(2):344-351. PMID: 9468174

27. Deng H., Han H.S., Cheng D., et al. Mild hypothermia inhibits inflammation after experimental stroke and brain inflammation. *Stroke*. 2003;34:2495–501.

28. Dewan M.C., Rattani A., Gupta S., Baticulon R.E., Hung Y.C., Punchak M., Agrawal A., Adeleye A.O., Shrime M.G., Rubiano A.M., Rosenfeld J.V., Park K.B. Estimating the global incidence of traumatic brain injury. *J Neurosurg.* 2018 Apr 27:1-18. doi: 10.3171/2017.10.JNS17352. [Epub ahead of print] PubMed PMID: 29701556.

29. Dietrich W.D., Bramlett H.M.: The evidence for hypothermia as a neuroprotectant in traumatic brain injury. *Neurotherapeutics*. 2010, 7:43–50.

30. Dubost C., Pasquier P., Merat S. Intracranial-pressure monitoring in traumatic brain injury. *N Engl J Med.* May 2013;368(18):1750-1751. PMID: 23635063. DOI: 10.1056/NEJMc1301076

31. Eskandari R., Filtz M.R., Davis G.E., Hoesch R.E.: Effective treatment of refractory intracranial hypertension

after traumatic brain injury with repeated boluses of 14.6% hypertonic saline. Clinical article. *J Neurosurg*. 119:338–346, 2013. PMID: 23706055. DOI: 10.3171/2013.4.JNS121541

32. Farahvar A., Gerber L.M., Chiu Y.L., Carney N., Hartl R., Ghajar J. Increased mortality in patients with severe traumatic brain injury treated without intracranial pressure monitoring. *J Neurosurg*. Oct 2012;117(4):729-734. PMID: 22900846. DOI:10.3171/2012.7.JNS111816

33. Gerber L.M., Chiu Y.L., Carney N., Hartl R., Ghajar J. Marked reduction in mortality in patients with severe traumatic brain injury. *J Neurosurg.* Dec 2013;119(6):1583-1590. PMID: 24098983. DOI:10.3171/2013.8.JNS13276

34. Hartl R., Gerber L.M., Ni Q., Ghajar J. Effect of early nutrition on deaths due to severe traumatic brain injury. *J Neurosurg.* Jul 2008;109(1):50-56. PMID: 18590432. DOI: 10.3171/JNS/2008/109/7/0050

35. Härtl R., Ghajar J., Hochleuthner H., et al. Hypertonic/hyperoncotic saline reliably reduces ICP in severely headinjured patients with intracranial hypertension. *Acta Neurochir Suppl.* 70:126–129, 1997 PMID: 9416299. DOI: 10.1007/978-3-7091-6837-0_39

36. Horn P., Münch E., Vajkoczy P., et al: Hypertonic saline solution for control of elevated intracranial pressure in patients with exhausted response to mannitol and barbiturates. *Neurol Res.* 21:758–764, 1999. PMID: 10596385. DOI: 10.1080/01616412.1999.11741010

37. Huang S.J., Hong W.C., Han Y.Y., et al. Clinical outcome of severe head injury using three different ICP and CPP protocol-driven therapies. *J Clin Neurosci.* Oct 2006;13(8):818- 822. PMID: 16908157

38. Hutchison J.S., Ward R.E., Lacroix J., et al. Hypothermia therapy after traumatic brain injury in children. *N Engl J Med.* Jun 5 2008;358(23):2447-2456. PMID: 18525042.

39. Ibrahim K., Christoph M., Schmeinck S., et al. High rates of prasugrel and ticagrelor nonresponder in patients treated with therapeutic hypothermia after cardiac arrest. *Resuscitation.* May 2014;85(5):649-656. PMID: 24555950.

40. Ichai C., Armando G., Orban J.C., et al. Sodium lactate versus mannitol in the treatment of intracranial hypertensive episodes in severe traumatic brain-injured patients. *Intensive Care Med.* Mar 2009;35(3):471-479. PMID: 18807008. PMID: 18807008 DOI: 10.1007/s00134-008-1283-5

41. Jiang J., Yu M., Zhu C. Effect of long-term mild hypothermia therapy in patients with severe traumatic brain injury: 1-year follow-up review of 87 cases. *J Neurosurg.* Oct 2000;93(4):546-549. PMID: 11014530.

42. Jiang J.Y., Xu W., Li W.P, et al. Effect of long-term mild hypothermia or short-term mild hypothermia on outcome of patients with severe traumatic brain injury. *J Cereb Blood Flow Metab.* Jun 2006;26(6):771-776. PMID: 16306933.

43. Karkar K.M., Garcia P.A., Bateman L.M., et al. Focal cooling suppresses spontaneous epileptiform activity without changing the cortical motor threshold. *Epilepsia.* 2002;43:932–5.

44. Kerwin A.J., Schinco M.A., Tepas J.J., et al.: The use of 23.4% hypertonic saline for the management of elevated intracranial pressure in patients with severe traumatic brain injury: a pilot study. *J Trauma*. 67:277–282, 2009. PMID: 19667879. DOI: 10.1097/TA.0b013e3181acc726

45. Koenig M.A., Bryan M., Lewin J.L., et al.: Reversal of transtentorial herniation with hypertonic saline. *Neurology.* 70:1023–1029, 2008. PMID: 18272864. DOI: 10.1212/01.wnl.0000304042.05557.60

46. Lepelletier D., Roquilly A., Demeure dit latte D., et al. Retrospective analysis of the risk factors and pathogens associated with early-onset ventilator-associated pneumonia in surgical-ICU head-trauma patients. *J Neurosurg Anesthesiol.* Jan 2010;22(1):32-37. PMID: 20027012. DOI: 10.1097/ANA.0b013e3181bdf52f

47. Liu L., Yenari M.A. Therapeutic hypothermia: neuroprotective mechanisms. Front Biosci. 2007;12:816–25

48. Liu W.G., Qiu W.S., Zhang Y., Wang W.M., Lu F., Yang X.F. Effects of selective brain cooling in patients with severe traumatic brain injury: a preliminary study. *J Int Med Res.* Jan-Feb 2006;34(1):58-64. PMID: 16604824.

49. Lundberg N., Troupp H., Lorin H. Continuous recording of the ventricular-fluid pressure in patients with severe acute traumatic brain injury. A preliminary report. *J Neurosurg.* Jun 1965;22(6):581-590. PMID: 5832775. DOI:10.3171/jns.1965.22.6.0581

50. Mangat H.S., Chiu Y.L., Gerber L.M., et al.: Hypertonic saline reduces cumulative and daily intracranial pressure burdens after severe traumatic brain injury. J Neurosurg. 2015 Jan;122(1):202-10. Erratum in: *J Neurosurg.* 2016 Jan;124(1):277. PubMed PMID: 25380107. DOI: 10.3171/2014.10.JNS132545.

51. Marion D.W., Penrod L.E., Kelsey S.F., et al. Treatment of traumatic brain injury with moderate hypothermia. *N Engl J Med.* Feb 1997;336(8):540-546. PMID: 9023090.48

52. Moquin D., Chan F.K. The molecular regulation of programmed necrotic cell injury. *Trends Biochem Sci.* 2010;35:434–41.

53. Muizelaar JP, Wei EP, Kontos HA, Becker DP. Cerebral blood flow is regulated by changes in blood pressure and in blood viscosity alike. *Stroke. Jan-Feb* 1986;17(1):44-48. PMID: 3080824. DOI: 10.1161/01.STR.17.1.44

54. Muizelaar J.P., Wei E.P., Kontos H.A., Becker D.P. Mannitol causes compensatory cerebral vasoconstriction and vasodilation in response to blood viscosity changes. *J Neurosurg.* Nov 1983;59(5):822-828. PMID: 6413661. DOI: 10.3171/jns.1983.59.5.0822

55. Nath F., Galbraith S.: The effect of mannitol on cerebral white matter water content. *J Neurosurg*. 65:41–43, 1986. PMID: 3086519. DOI: 10.3171/jns.1986.65.1.0041

56. Nilsson P., Laursen H., Hillered L., Hansen A.J. Calcium movements in traumatic brain injury: the role of glutamate receptor-operated ion channels. *J Cereb Blood Flow Metab*. 1996;16:262–70

57. Oddo M., Frangos S., Milby A., et al. Induced normothermia attenuates cerebral metabolic distress in patients with aneurysmal subarachnoid hemorrhage and refractory fever. *Stroke.* 2009;40:1913–6

58. Oddo M., Levine J.M., Frangos S., et al. Effect of mannitol and hypertonic saline on cerebral oxygenation in

patients with severe traumatic brain injury and refractory intracranial hypertension. *J Neurol Neurosurg Psychiatry.* 2009 Aug;80(8):916-20. Epub 2009 Mar 16. PubMed PMID: 19293171. DOI: 10.1136/jnnp.2008.156596.

59. Polderman K.H. Therapeutic hypothermia in the intensive care unit: problems, pitfalls and opportunities (review). Part 1: indications and evidence. *Intensive Care Med.* 2004;30:556–75.

60. Qiu W.S., Liu W.G., Shen H., et al. Therapeutic effect of mild hypothermia on severe traumatic head injury. *Chin J Traumatol.* Feb 2005;8(1):27-32. PMID: 15676086.

61. Qureshi A., Suarez J., Castro A., Bhardwaj A. Use of hypertonic saline/actate infusion in treatment of cerebral edema in patients with head trauma: experience at a single center J Trauma. 1999;47(4):659-665. PMID: 10528599. DOI: 10.1097/00005373-199910000-00009

62. Rapp R.P., Young B., Twyman D., et al. The favorable effect of early parenteral feeding on survival in head-injured patients. *J Neurosurg.* Jun 1983;58(6):906-912. PMID: 6406649. DOI: 10.3171/jns.1983.58.6.0906

63. Rockswold G.L., Solid C.A., Paredes-Andrade E, et al.: Hypertonic saline and its effect on intracranial pressure, cerebral perfusion pressure, and brain tissue oxygen. *Neurosurgery*. 65:1035–1042, 2009. DOI: 10.1227/01.NEU.0000359533.16214.04

64. Schatzmann C., Heissler H.E., König K., et al: Treatment of elevated intracranial pressure by infusions of 10% saline in severely head injured patients. *Acta Neurochir Suppl*. 71:31–33, 1998. PMID: 9779135. DOI: 10.1007/978-3-7091-6475-4_9

65. Schreckinger M., Marion D.W.: Contemporary management of traumatic intracranial hypertension: is there a role for therapeutic hypothermia? *Neurocrit Care*. 2009, 11:427–436.

66. Soukup J., Zauner A., Doppenberg E.M., Menzel M., et al. Relationship between brain temperature, brain chemistry and oxygen delivery after severe human head injury: the effect of mild hypothermia. *Neurol Res.* 2002;24:161–8.

67. Talving P., Karamanos E., Teixeira P.G., et al. Intracranial pressure monitoring in severe head injury: compliance with Brain Trauma Foundation guidelines and effect on outcomes: a prospective study. *J Neurosurg. Nov*. 2013;119(5):1248-1254. PMID: 23971954. DOI:10.3171/2013.7.JNS122255

68. Taylor S.J., Fettes S.B., Jewkes C., Nelson R.J. Prospective, randomized, controlled trial to determine the effect of early enhanced enteral nutrition on clinical outcome in mechanically ventilated patients suffering head injury. *Crit Care Med.* Nov 1999;27(11):2525-2531. PMID: 10579275. DOI: 10.1097/00003246-199911000-00033

69. Truettner J.S., Suzuki T., Dietrich W.D. The effect of therapeutic hypothermia on the expression of inflammatory response genes following moderate traumatic brain injury in the rat. *Brain Res Mol Brain Res.* 2005;138:124–34

70. Wagner E.M., Traystman R.J. Hydrostatic determinants of cerebral perfusion. *Crit Care Med.* May 1986;14(5):484-490. PMID: 3084172.

71. Ware M.L., Nemani V.M., Meeker M., et al.: Effects of 23.4% sodium chloride solution in reducing intracranial pressure in patients with traumatic brain injury: a preliminary study. *Neurosurgery*. 57:727–736, 2005. PMID: 16239885. DOI: 10.1093/neurosurgery/57.4.727

72. Weed L., McKibben P.S. Experimental alteration of brain bulk. *Am J Physiol.* 1919;48:531-558.

73. Wisner D.H., Schuster L., Quinn C. Hypertonic saline resuscitation of head injury: effects on cerebral water content. *J Trauma.* 30:75–78, 1990. PMID: 2296070. DOI: 10.1097/00005373-199001000-00011

74. You W., Feng J., Tang Q., Cao J., Wang L., Lei J., Mao Q., Gao G., Jiang J. Intraventricular intracranial pressure monitoring improves the outcome of older adults with severe traumatic brain injury: an observational, prospective study. *BMC Anesthesiol*. 2016 Jul 11;16(1):35. doi: 10.1186/s12871-016-0199-9. PubMed PMID: 27401211; PubMed Central PMCID: PMC4940906. DOI:10.1186/s12871-016-0199-9

75. Young B., Ott L., Dempsey R., et al. Relationship between admission hyperglycemia and neurologic outcome of severely brain-injured patients. *Ann Surg.* Oct 1989;210(4):466-472; discussion 472-463. PMID: 2679455. DOI: 10.1097/00132586-199008000-00066

Corresponding Author:
Syzdykbayev Marat Kelissovich - Head of Department Anesthesiology and Resuscitation Doctor of Medical Sciences, anesthesiologist-resuscitator of highest qualification category, assistant at chair of anesthesiology and resuscitation at State Medical University of Semey city.
address: 071400, The Republic of Kazakhstan, The East Kazakhstan region, Semey city, Abay Kunanbaev street, 103.
phone: +7(777)-633-47-57.
e-mail: fortunato74@mail.ru