

Severe Pediatric Traumatic Brain Injury Treatment Approaches of Pediatric Intensivists in Turkey PICUs: National Survey Results

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What is already known on this topic?

- It is possible to prevent secondary injury and associated morbidity-mortality through the administration of guideline-centered treatment in pediatric severe traumatic brain injury (TBI).
- In order to establish a common treatment approach, the guideline for pediatric severe TBI was published in 2003 and 2012, and it was updated in 2019.

What this study adds on this topic?

- The results of the survey supported that the pediatric intensive care specialists in Turkey managed the treatment of severe traumatic brain injury (TBI) in line with the pediatric TBI guideline, which was updated in 2019.
- Guideline-centered treatment can lead to a good long-term prognosis in TBI.

ABSTRACT

Objective: In patients with severe traumatic brain injury, it is possible to obtain a good long-term prognosis, prevent secondary injury, and decrease morbidity and mortality with the administration of appropriate treatments in the acute period. This study aims to evaluate the approaches of the pediatric intensive care specialists in Turkey towards the follow-up and treatment of severe traumatic brain injury by using a survey that had been prepared in light of the current pediatric severe traumatic brain injury guideline.

Materials and Methods: The survey, which included 45 questions, was prepared on the SurveyMonkey® system sent by e-mail to the centers, which were members of the Turkish Society of Pediatric Emergency and Intensive Care Medicine.

Results: A total of 45 centers participated in the survey. In all centers, computed tomography of the brain was found to be the first choice as an imaging method for traumatic brain injuries. In terms of hyperosmolar therapy, 30 (66.6%) centers stated that they used 3% hypertonic saline, and 16 (35.5%) centers stated using 3% hypertonic saline+mannitol. Forty (86.96%) centers stated that they did not use prophylactic hyperventilation in the first 48 hours. A total of 44 centers (97.78%) stated that they administered prophylactic antiepileptic drugs in the first 7 days while the most preferred antiepileptic drug was levetiracetam.

Conclusion: The results of our survey supported that the pediatric intensive care specialists in Turkey planned a large percentage of the treatment for patients with severe traumatic brain injury in line with the published traumatic brain injury guidelines.

Keywords: Traumatic brain injury, pediatric intensive care, guideline, Turkey

INTRODUCTION

Head trauma is one of the most important causes of brain injury in children and can lead to mortality and lifelong physical, cognitive and behavioral morbidity. The authors of a pediatric traumatic brain injury (TBI) study conducted in Turkey reported the mortality rate as 12.5%.¹ Optimal acute care, early assessment by a multidisciplinary team, and rapid stabilization are required to limit post-traumatic secondary brain injury and associated mortality in children with TBI. Similar to the differences in many clinical conditions between children and adults, the head traumas in childhood are different from those in adulthood in many aspects.² Children are not small models of adults. The most important differences can be listed as follows: the inability to protect intracranial structures; the mechanism of injury and long-term prognosis especially due to the higher head/body ratio compared to adults; smaller facial bones and thinner skull bones; weaker neck structures, and thus, inability to restrict head movements. Therefore, in children, the probability of head injury in pediatric trauma is higher compared to adults. In addition to these structural differences, it is not easy to achieve cooperation in a physical examination in young children. This makes clinical evaluation and

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accurate assessment of Glasgow Coma Score (GCS) difficult. Children are also more susceptible to the development of multiple organ failure and shock compared to adults. For all these reasons, head traumas belonging to the pediatric age group should be evaluated separately from adults.²

Although there is a lack of pediatric data in the literature regarding TBI in children and newborns, a group of scientists published a guideline on pediatric severe head traumas in 2003 and 2012. Then, this guideline was updated in light of recent studies in 2019. The latest pediatric severe head injury guideline contains 22 suggestions in total. While there is no level I suggestion in this guideline, it includes 3 level II suggestions and 19 level III suggestions.³

As we know guideline-centered approach provides better clinical outcomes. In the present study, we aimed to evaluate the severe TBI treatment approaches and guideline compliance of the pediatric intensive care professionals in the pediatric intensive care units in Turkey. Also, we wanted to discuss the recommendations of the TBI guideline and draw attention to the importance of the guideline-centered follow-up approach.

MATERIALS AND METHODS

A multi-centered, descriptive survey was prepared. A questionnaire including 45 questions was prepared using the SurveyMonkey system, and it was sent to the member centers of the Turkish Society of Pediatric Emergency and Intensive Care Medicine by e-mail. Access to the questionnaire was enabled in July 2020. The questionnaire included questions related to the capacity of the participating centers and units, and the diagnosis, treatment, and follow-up approaches followed in critical pediatric patients with TBI by the pediatric intensive care professionals working in these units. The survey also included questions about neurological evaluation scores, neuromonitoring methods, prophylactic antiepileptic drug strategies, hyperosmolar treatment approach, prophylactic hypothermia approach, prophylactic hyperventilation approach, sedation-analgesia strategies of participated centers. Questions in the questionnaire were prepared based on the recommendations in the recent pediatric TBI guideline.

Ethics approval for the study was received from the Çukurova University Faculty of Medicine Clinical Research Ethics Committee (Date: July 3, 2020, Meeting Number: 101). The study was conducted in accordance with the Declaration of Helsinki. No statistical analysis methods were used. As the questions in the questionnaire did not request any personal data of the patients, patient consent was not received.

RESULTS

A total of 45 centers participated in the survey. All the units were tertiary pediatric intensive care units led by a pediatric intensive care specialist.

To the question about the scoring system they used for the neurological evaluation in the pediatric patient with TBI, all of the centers stated that they used the GCS, and 15 (33.3%) centers stated that they additionally used the 'Alert, Voice, Pain, Unresponsive' (AVPU) scoring (Table 1).

Table 1. General Treatment and Follow-up Strategies of Participant Centers in Pediatric Severe TBI Patients

	n	%
Neurological evaluation		
Glasgow coma scale	45	100
Alert, Voice, Pain, Unresponsive'	15	33.3
Cranial Imaging		
Brain computed tomography	45	100
Control computed tomography at the 6th hour	13	28.8
Intracranial pressure monitoring methods		
Brain computed tomography	45	100
Magnetic Resonance Imaging	20	44.4
Near Infrared Spectroscopy	19	42.2
Ultrasonographic Optic Nerve Sheath Diameter measurement	12	26.6
Transcranial Doppler	7	15.5
Intracranial Pressure monitoring placement (routinely)	1	2.2
Hyperosmolar treatment		
Hypertonic Saline alone	30	66.6
Hypertonic Saline +Mannitol	15	33.3
Decompressive craniectomy	37	82.2

TBI: traumatic brain injury.

In all centers, computed tomography (CT) of the brain is the primarily preferred imaging method in TBI cases. Thirteen centers (28.8%) stated that they also conducted routine cranial CT on the patient after 6 hours when the patient's cranial CT at the time of admission was normal and no increased intracranial pressure (ICP) findings were observed in the patient's clinic. Table 1 presents general treatment and follow-up strategies of participant centers in pediatric severe TBI patients. Methods used to monitor the increase in the ICP can be seen in Table 1.

Table 2 shows the timing of the magnetic resonance imaging (MRI) for the patient with TBI in the participating centers to obtain information about the secondary injury.

Forty-two centers (93.33%) stated that they were able to perform ICP monitoring in their pediatric intensive care unit (PICU). However, just one center reported that they routinely perform ICP monitoring in patients with severe TBI.

The most common sedative drug administered to TBI patients used in these centers was midazolam (97.7%) while the most common analgesic agent was fentanyl (78.5%). In terms of routine usage of the neuromuscular blocker agents in intubated patients with TBI, 10 (22.2%) centers stated that they used routine neuromuscular blockers and the most frequent

Table 2. Magnetic Resonance Imaging Timing After Traumatic Brain Injury for Secondary Brain Injury Evaluation

Time	n	%
24th hour	1	2.2
24-72 hour	13	28.8
72 hour-2 weeks	31	68.8

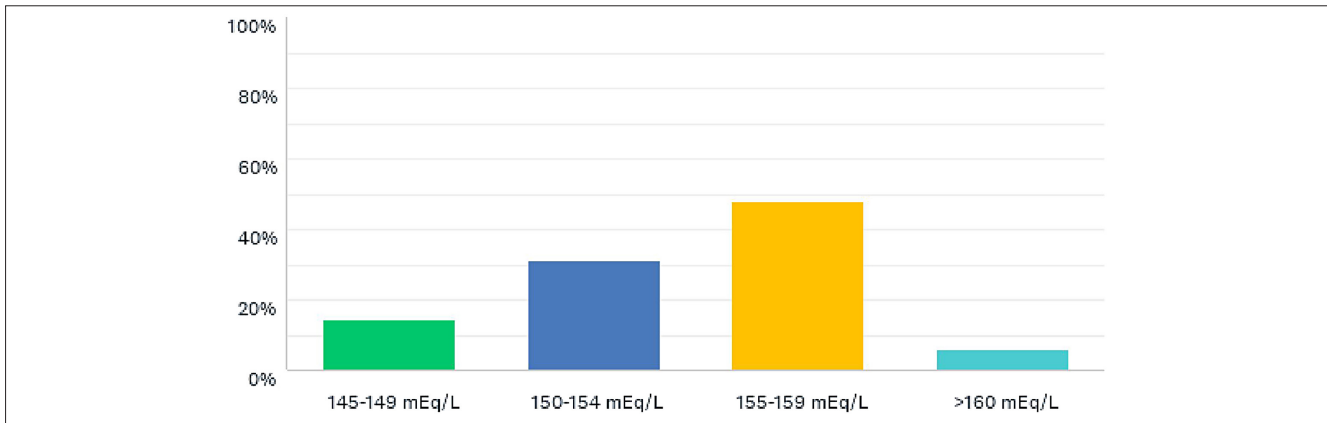


Figure 1. Target serum sodium levels with hyperosmolar treatment in pediatric TBI patients according to participating pediatric intensivists. TBI, traumatic brain injury.

neuromuscular blocker agent was rocuronium (71.7%). Also, 23 (51.1%) centers preferred the intravenous use of lidocaine for endotracheal intubation.

The choices of the centers for hyperosmolar treatment can be seen in Table 1. The targeted sodium levels with hyperosmolar treatment are given in Figure 1. The most common side effect resulting from the hyperosmolar state (HS) was natriuresis (Figure 2).

In the first 7 days after severe TBI, prophylactic antiepileptic drugs were administered in 44 centers (97.78%), and the most

frequently preferred antiepileptic drug was levetiracetam (82.61%). The number of centers with continuous electroencephalogram (EEG) monitoring capability was 13 (28.8%). Also, 26 (57.7%) centers stated that they applied barbiturate therapy in addition to invasive arterial monitoring in patients with severe TBI who were hemodynamically stable.

Forty (88.8%) centers said that they did not apply prophylactic hyperventilation in the first 48 hours. Table 3 presents the target partial arterial carbon dioxide pressure (PaCO₂) levels in hyperventilation of centers.

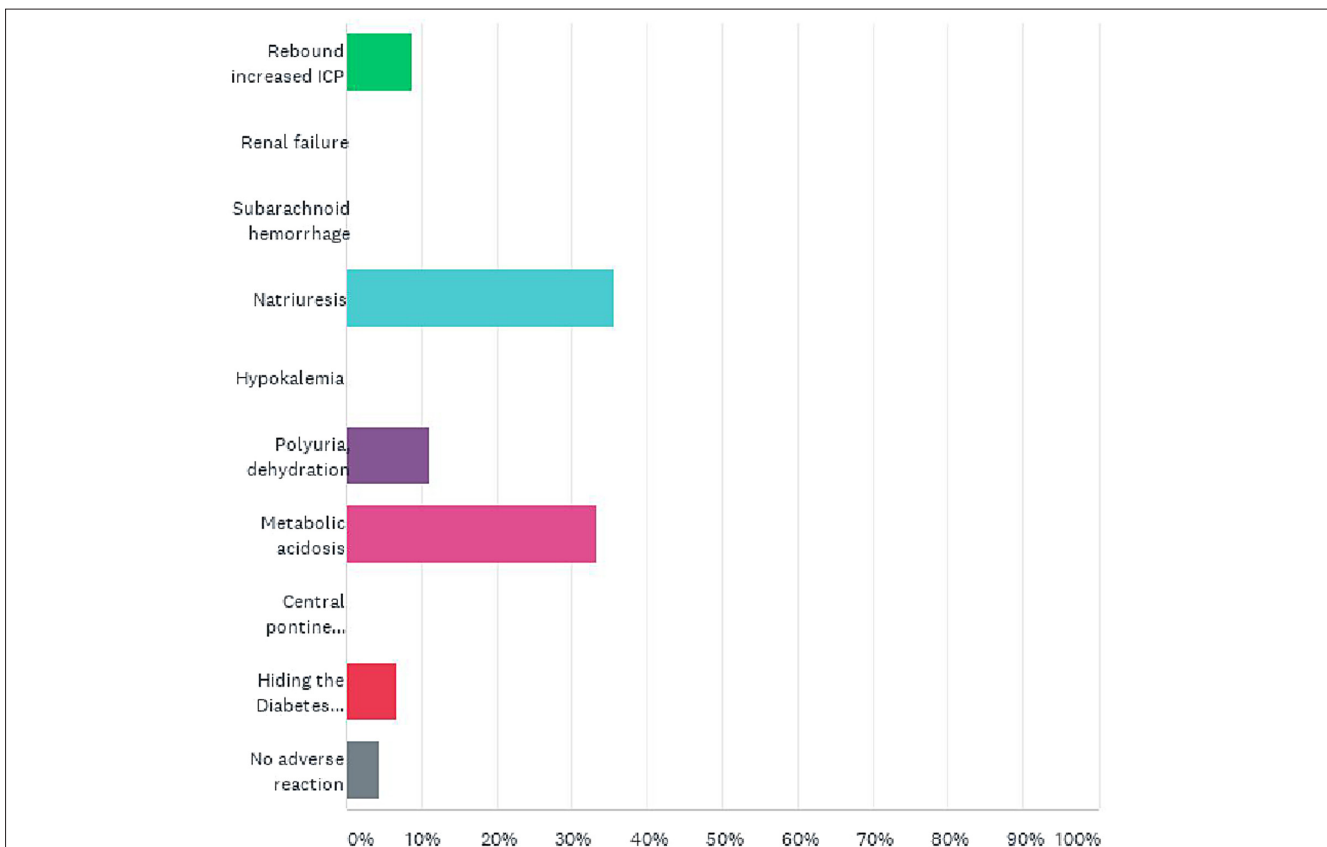


Figure 2. Side effects due to hypertonic saline treatment reported by participating pediatric intensivists.

Table 3. Target PaCO₂ Level in Hyperventilation

PaCO ₂	n	%
28-32 mmHg	5	11.1
30-35 mmHg	25	55.5
35-40 mmHg	15	33.3

Also, 39 (86.6%) centers stated that they applied prophylactic moderate hypothermia (32-33°C). However, 19 (42.2%) centers responded that they only hindered hypothermia to the question about the targeted body temperatures for this patient group.

It was found that 37 (82.2%) centers had decompressive craniectomy capability in intracranial hypertension resistant to medical treatment.

A total of 28 (62.2%) centers reported that the target serum glucose for the severe TBI patient group was 100-180 mg/dL. Also, 24 (53.3%) centers reported that the initiation time of enteral feeding was the first 48 hours.

DISCUSSION

It is important to use common terminology for evaluating the consciousness of a patient to eliminate interpretation differences resulting from the knowledge and experience of the clinician. Glasgow Coma Scale is one of the consciousness evaluation tools developed for this purpose. The verbal and motor parts of the GCS value were modified for the evaluation of infants.⁴ Alert, Voice, Pain, Unresponsive scale can be used as another scale that will enable neurological evaluation. In a study evaluating the correlation between pediatric GCS and AVPU scale with a large pediatric series of 302 patients, a strong correlation was found between the two scales, and it was found that the part of AVPU scale about the verbal response corresponds to 8 and above in GCS. Additionally, it was reported that the AVPU scale should be used widely, especially in prehospital and emergency services, because it is a quick and easy scale.⁵ All the centers that participated in our survey stated that they used GCS, and 15 centers stated that they also used the AVPU scale in addition to GCS.

Cranial CT retains its importance in the initial evaluation of TBI due to its quickness and superiority in evaluating the bone tissue and bleeding.⁶ Although the previous versions of the guideline suggested repeating the cranial CT 24-48 hours after the injury following severe head trauma, the latest version of the pediatric TBI guideline, which was published in 2019, does not recommend performing routine CT after 6 hours if the cranial CT is normal in the admission and there are no increased ICP findings in the patient's clinic. Moreover, if the patient does not have a neurological impairment or increased ICP findings, routine CT scans after 24 hours are not recommended for the decision of neurosurgical intervention.³ Accordingly, a decision should be made on the repetition of the brain CT according to the ICP and changes in the clinical examination. However, in our study, 13 (28.8%) centers stated that they performed routine cranial CT after 6 hours when the cranial CT of the patient was normal at admission and there were no increased ICP

findings in the patient's clinic, which is a noncompliance with the guideline.

Brain MRI is not the first imaging option due to reasons such as long imaging time in head trauma cases, difficulty in monitoring during imaging, unsuitability of ventilator and infusion pumps for use during MRI, the requirement of sedation, and high costs; however, the information it provides particularly about the secondary injury, such as diffuse axonal injury, contusions and microhemorrhages, and long-term prognosis might be very significant.⁷ In a study conducted with the participation of pediatric intensive care physicians, neurologists, and neurosurgeons from a total of 27 centers in the United States, United Kingdom, Spain, Netherlands, and India, 12 centers stated that they performed MRI on more than 95% of the patients with severe TBI. While 60% of the centers reported the timing of MRI was between 72 hours and 2 weeks, only 1 center answered as the first 24 hours after trauma, and 4 centers responded as between 24 and 72 hours.⁸ Similarly, in our survey, 31 (68.8%) centers reported that they performed MRI between 72 hours and 14 days, 13 (28.8%) centers in 24-72 hours, and only 1 (2.2%) center in the first 24 hours.

Intracranial pressure monitoring with a ventricular catheter is accepted as the most accurate, economic, and reliable method; also, the ability to perform cerebrospinal fluid drainage is a great advantage, because this is one of the implementations that can be performed in the first stage in the increased ICP treatment.⁹ Intracranial pressure monitoring is recommended in patients with TBI, children with abnormality in the first brain CT and an initial GCS of 3-8.³ Similar to the previous versions of the pediatric TBI guideline, the last version of it also suggests ICP monitoring, and it is recommended to keep the ICP below 20 mmHg as the treatment target.³ In our survey, 93.3% of the centers were observed to be able to perform ICP monitoring. However, since this result did not represent the actual case in Turkey, we needed to ask again about their ICP monitoring practices in PICU via a second e-mail. 93.3% of the centers responded that they were able to perform ICP monitoring but only one of these centers reported that they routinely perform ICP monitoring in patients with severe TBI.

Near-infrared spectroscopy (NIRS) is a noninvasive monitor which can detect regional brain tissue oxygenation, cerebral blood flow, and cerebral blood volume changes, and it provides continuous measurement.¹⁰ In a study conducted on pediatric patients with TBI, the researchers suggested that NIRS could reliably detect the changes in cerebral hemodynamics, and it could be used to better understand the etiology of the common cerebral edema observed after severe TBI. Not a single NIRS value but the general tendency of the NIRS values is important.¹¹ The disadvantages of NIRS monitoring include inadequate topographic resolution and dependence on superficial brain tissue while generating signals.¹² In our survey, 19 (42.2%) centers stated that they used NIRS in the follow-up of ICP.

Optic nerve sheath is the continuation of the dura mater, arachnoid mater, and pia mater. The optic nerve sheath diameter (ONSD) increases in line with the increase in the ICP, and the increase in ONSD is observed even before the development of papillae stasis.¹³ In a pediatric study, Rehman

Siddiqui et al.¹⁴ reported the limit for ultrasonographic ONSD measurement as >4 mm in the newborns, >4.71 mm in the children between 1 and 10 years of age, and >5.43 in those above 10 years of age (sensitivity 100%, specificity 60-66.7%). In the present study, 12 (26.6%) centers reported that they used ultrasonographic ONSD measurement in the follow-up of increased ICP.

A literature review study on the pediatric use of transcranial doppler (TCD) ultrasonography in head traumas suggested that TCD is a useful tool for evaluating autoregulation, vasospasm, and ICP after TBI.¹⁵ In our study, 7 (15.5%) centers stated that they used TCD in their clinical practices for patients with increased ICP.

Painful stimuli and stress lead to an increase in sympathetic tone, hypertension, and cerebral edema in the affected areas. The latest version of the pediatric TBI guideline suggests that specific indications, selection, and dosage of the analgesics, sedatives, and neuromuscular blocker agents should be left to the clinician who provides the treatment.³ Moreover, it is recommended to avoid bolus midazolam and/or fentanyl bolus administrations due to the risk of cerebral hypoperfusion during ICP increase crises, together with the use of multiple treatments for increased ICP and appropriate routine sedation analgesia treatment. In our survey, midazolam was found to be the most frequently used sedative agent, while fentanyl was found to be the most common analgesic agent. The number of the centers that administered routine neuromuscular blockers in intubated patients with TBI was 10 (22.2%), and rocuronium was found to be the most used neuromuscular blocker in PICUs in Turkey.

Endotracheal/intravenous lidocaine or intravenous thiopental can be used in ICP increases, which may occur during routine nursing care and endotracheal aspiration.³ In the present study, 23 (51.1%) centers stated that they preferred using intravenous lidocaine for endotracheal aspiration and nursing care.

Although mannitol is widely used in the treatment of increased ICP in pediatric trauma patients, no study was found to use as evidence or meet the inclusion criteria in the latest version of the pediatric TBI guideline. Thus, the guideline includes no suggestion for mannitol, and therefore, the use of HS has come into prominence since the 1990s.^{4,16} Yıldızdas et al.¹⁷ evaluated the efficiency of HS and mannitol in 67 pediatric patients with brain edema and the side effect profile, and they reported that the mortality was significantly lower in the patient groups given HS. When we questioned the hyperosmolar treatment approach of the centers participating in our survey, 30 (66.6%) centers reported using 3% hypertonic saline (HS), and 16 (37.78%) centers reported using 3% HS+mannitol. The sodium value targeted by 22 (48.8%) centers with hyperosmolar treatment was 155-159 mEq/L (Figure 1).

The latest version of the pediatric TBI guideline recommends the administration of 3% HS solution of 2-5 mL/kg 10-20 minutes (maximum 250 ml) if there is an increase in ICP. Possible side effects resulting from HS include increased ICP with a rebound effect, renal failure, subarachnoid hemorrhage, natriuresis, dehydration, hyperchloremic acidosis, central pontine myelinolysis, and diabetes insipidus when treatment

is discontinued.³ According to the results of the questionnaire, natriuresis was reported to be the most observed side effect caused by HS was natriuresis (Figure 2).

Studies reveal that the use of prophylactic antiepileptic drugs is protective against posttraumatic seizures.¹⁶ Intravenous phenytoin and levetiracetam are widely used in pediatric patients after a severe head trauma as prophylactic antiepileptic. The latest guideline suggests using prophylactic anticonvulsants to prevent posttraumatic seizures, particularly in the first 7 days.³ In the survey, 44 (97.7%) centers reported that they administered prophylactic antiepileptic drugs within the first 7 days, and the most frequently preferred antiepileptic drug was levetiracetam. The number of centers with the capability of continuous EEG monitoring was found to be 13 (28.8%).

The recent experimental studies and the studies on adults revealed that prophylactic hyperventilation after a severe head trauma caused neuronal death in the hippocampus and poor prognosis.¹⁹ The latest guideline suggests that prophylactic hyperventilation should be avoided by keeping the PaCO₂ level under 30 mmHg in the first 48 hours after the trauma. Hyperventilation with appropriate cerebral monitoring in the cases of refractory intracranial hypertension (PaCO₂ 30-35 mmHg) can be used as a treatment method.³ In our survey, 40 (88.8%) centers reported that they did not use the prophylactic hyperventilation approach for the PaCO₂ level in the first 48 hours in accordance with the suggestions of the guidelines.

Prevention of hyperthermia after TBI in children has been recommended.²⁰ In the light of the recent literature, the latest TBI guideline does not recommend applying prophylactic moderate hypothermia (32-33°C) to improve the clinical results; however, mild hypothermia is recommended for ICP control.³ For the question about prophylactic mild hypothermia (32-33°C) in our survey, 39 (86.6%) centers stated that they did not apply it. For the question about their targeted body temperatures for this patient group, 42.2% of the centers stated that they only hindered hyperthermia.

Barbiturates decrease ICP by reducing brain metabolism.²¹ Continuous EEG monitoring is necessary in cases where barbiturates are used in continuous intravenous infusion. Generally, pentobarbital or thiopental is used, and the dose of the drug is adjusted according to EEG and ICP.²² In the latest TBI guideline, high-dose barbiturate therapy is recommended in patients with refractory intracranial hypertension and stable hemodynamics despite maximum medical and surgical treatment. Barbiturates may cause hypotension since they may decrease cardiac output.²³ The guideline also suggests continuous invasive arterial blood pressure monitoring and cardiovascular support.² Our survey results revealed that 26 (57.7%) centers could perform invasive arterial monitoring and apply barbiturate therapy in patients with severe TBI who were hemodynamically stable.

The latest version of the pediatric TBI guideline suggests decompressive craniectomy in cases of neurological deterioration and no response to medical treatment.³ In our survey, 37 (82.2%) centers reported applying decompressive craniectomy in the increase in ICP resistance to medical treatment.

After severe head trauma, close glucose monitoring should be carried out. In these patients, the serum glucose level should generally be kept between 100 and 200 mg/dl by using insulin infusion when necessary.²⁴ For the question of serum glucose targets for this patient group, 28 (62.2%) centers stated the target of 100-180 mg/dL.

In a study conducted in Turkey on the association between admission hyperglycemia and clinical outcome in children with severe TBI, the authors stated that hyperglycemia could be considered as a marker of brain injury and, when present upon admission, could reflect extensive brain damage, frequently associated with mortality and poor outcome.²⁵

In the pediatric TBI guideline, early enteral nutritional support (within 72 hours after injury) is suggested as it decreases mortality and improves the clinical course. Using an immune modulator diet is not recommended.³ In the centers participating in our survey, the time to start enteral nutrition was reported to be the first 48 hours in 24 (53.3%) centers.

Limitations

The most important limitation of the present study is the possibility that the results point at the opinions of the participants of the survey rather than what is applied, as in all voluntary surveys. Besides, the number of the participating centers remained below the expectations.

CONCLUSION

Consequently, although it seems that clinicians in Turkey have not yet quit the habit of control cranial CT imaging after TBI, the results of our survey support that pediatric intensive care professionals in Turkey plan treatment in pediatric patients with severe TBI according to the guideline updated in 2019.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Committee Approval: This study was approved by Ethics committee of Çukurova University, (Approval No: 101, 3/7/2020).

Informed Consent: It is a survey study about treatment approaches. As the questions of the questionnaire did not contain any patient information patient consent was not obtained.

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