Conservative Management of Severe Cerebral Trauma

Christoph Castellani and Hans-Georg Eder

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Abstract

Traumatic brain injury (TBI) is a common cause for death in children and adolescents. The underlying brain injury can be categorized into primary lesions caused by the immediate effects of the trauma and secondary lesions due to inflammation, hypoxia, hypotension, hyperthermia, and other metabolic processes. Modern intensive care lies in the prevention of these secondary lesions by correct patient positioning, monitoring of intracranial pressure with rapid therapy of intracranial hypertension (deep sedation, osmotic therapy, barbiturates, liquor drainage), early neurosurgical intervention, and glucose and temperature control. This chapter summarizes current literature and guidelines for conservative management of TBI patients from shock room to advanced intensive care.

Keywords

Traumatic brain injury · Intracranial pressure · Intracranial hypertension · Intensive care · Neuromonitoring

Introduction

Traumatic brain injury (TBI) ranks among the most common causes of death and disability in childhood and adolescence. Modern intensive care, however, grants improvements in the survival rate of TBI patients. This chapter will focus on the conservative management of TBI patients in the ICU setting and pick out the most important issues concerning their management. Additionally, some important pathologies associated with TBI will be discussed.

Etiology

Regarding TBI etiology, falls are the predominant cause for TBI in all children aged 0–14 years (Bhalla et al. 2012). However, different mechanisms of injury have to be considered depending on patient age: inflicted TBI (shaken baby syndrome or child abuse) are possible causes in infants and younger children (Duhaime et al. 1998). School-aged children often sustain bicycle-related injuries. With increasing age, the rate of motor vehicle- and sports-related traumas and assault increases (Langlois et al. 2005). Although the mortality of TBI has decreased within the past 30 years, its incidence has more than tripled (Bhalla et al. 2012). Both sports- and vehicle-related accidents open a field for accident prevention. In this regard recent biomechanical examinations of human skulls could clearly demonstrate an 87% reduction of acceleration forces experienced during force impact by bicycle helmets advocating the use of bicycle helmets as important preventive tool to reduce severity of associated TBI (Mattei et al. 2012, McLean et al. 2017).

Pathophysiology

Brain injury in patients with TBI can be categorized into a primary and a secondary lesion. The primary injury is a direct result of the trauma itself and is caused by acceleration-deceleration or rotational forces resulting in skull fractures, brain contusion, intracranial hemorrhage, hematoma, or diffuse axonal injury (Bhalla et al. 2012; Greve and Zink 2009). Since the primary lesion is a direct result of the initial trauma, it is not accessible to any therapeutic measures. The outcome of
TBI patients, however, is also influenced by the secondary lesion resulting from inflammatory and excitotoxic processes with edema and further increase of intracranial pressure (ICP), hypotension, hypoxemia, hypo- or hypercarbia, and hypo- or hyperglycemia (Chesnut et al. 1993; Hardcastle et al. 2014; Werner and Engelhard 2007). Compared to adults, children exhibit important anatomical differences: the head-to-torso ratio is larger, the neck is more unstable and immature, and the skull is more compliant. Furthermore, it is speculated that children react to inflammation with a more significant edema compared to adults (Kochanek 2006). The prevention of this secondary injury lies in the focus of modern intensive care medicine specifically targeting cerebral perfusion, ICP/edema management, and adequate ventilation.

Classification

The severity of TBI is classified according to the Glasgow Coma Scale (GCS):

- Mild TBI: GCS 13–15
- Moderate TBI: GCS 9–12
- Severe TBI: GCS <9

This chapter will exclusively focus on the conservative management of severe TBI (sTBI). It is important to note that the following strategies rely on sTBI guidelines already published in the literature (Bhalla et al. 2012; Hardcastle et al. 2014; Kochanek et al. 2012). Despite numerous articles in the literature, the evidence levels of most of the recommendations published lie between II and III.

Initial (Shock-Room) Management

Children with isolated sTBI or polytraumatized patients should be referred to a specialized center providing pediatric intensive care medicine, trauma surgery, and neurosurgery as soon as possible. Due to differences in primary healthcare, some of the measures addressed below may be covered by healthcare professionals at the site of the accident or during transport. Briefly, in this sensitive phase, care should be taken to grant adequate ventilation (especially avoiding hypoxemia as well as hypo-/hypercarbia) and cardiocirculatory support avoiding hypotension.

In our institution, the primary shock-room team consists of a general pediatric surgeon, a pediatric trauma surgeon, a pediatric anesthesiologist, a nurse with shock-room training, and an anesthesiology nurse. This team grants initial management, stabilization, and diagnostics – further specialists (e.g., neurosurgeon, cranio-maxillo-facial surgeon, ophthalmologist, ear-nose-throat specialist) are called in depending on the results of trauma imaging (usually blood sampling, FAST sonography, and head or polytrauma CT scan).

Patients with sTBI have a high risk of developing progressive cerebral edema (Davis et al. 2011), requiring immediate endotracheal intubation and respiratory support. Until proven otherwise, all (sTBI) patients should be considered to have a full stomach, and intubation should be carried out by rapid sequence induction. A gastric tube should be inserted for gastric decompression. In case of fractures at the base of the skull, nasogastric placement should be avoided to prevent intracranial malpositioning of the tube through the fracture line (Psarras et al. 2012).

Additionally, it has been shown that TBI patients have a higher incidence of cervical spine injuries than the general trauma population, especially with increasing severity (Holly et al. 2002). Thus, every TBI patient should be suspected to have cervical spine injuries until proven otherwise, and the cervical spine should be protected by (manual) stabilization during intubation whenever possible (Tobias 1998).

For the induction of anesthesia, various drugs are available. Etomidate has a limited effect on the mean arterial pressure (MAP), decreases the cerebral metabolic rate for oxygen (CMRO₂), and thereby decreases the ICP (Bramwell et al. 2006). Etomidate may only be used as bolus for induction (for dosage recommendations, see Table 1). Although limited to patients with sepsis, even single doses of etomidate have been reported to
negatively influence adrenocortical performances (den Brinker et al. 2008). Overall, etomidate is a valuable agent for rapid sequence induction (in patients without sepsis) in TBI patients (Bhalla et al. 2012). Next to bronchodilatation, S-ketamine was found to increase heart rate and blood pressure due to release of endogenous catecholamines (Chernow et al. 1982). While past literature accused ketamine of increasing ICP (Schulte am Esch et al. 1978), newer data has shown that ketamine may even decrease ICP when used to prevent pain during invasive procedures (Bar-Joseph et al. 2009). Therefore, Hardcastle et al. suggest the use of ketamine to mitigate ICP increases during stressful procedures and treat refractory ICP elevations (Hardcastle et al. 2014). Neuromuscular blockade can be achieved by succinylcholine or rocuronium (Perry et al. 2008). Although hyperkalemia (Larach et al. 1997), fasciculations, and mild ICP elevations (Minton et al. 1986) are possible side effects of succinylcholine, there is no contraindication for its use in TBI patients (Hardcastle et al. 2014). In particular, if the antagonist sugammadex is available, rocuronium may be a valuable alternative (Bhalla et al. 2012). Due to their vasodilatatory and negative inotropic side effects, thiopental and propofol should be carefully considered in critically ill trauma patients.

A detailed description of ventilator support and hemodynamic stabilization can be found in the following sections.

Following stabilization and depending on the diagnosis, the patient is transferred from the shock room to either the operating room or directly to the intensive care unit. In recent years, evidence-based recommendations have provided guidance for the development of local protocols to treat pediatric patients with severe traumatic brain injury (Kochanek et al., 2019).

### Neuroimaging

Appropriate imaging is essential to determine the extent and severity of sTBI in children. Computed tomography (CT) is widely available and allows rapid detection of hematomas (subdural, epidural, intracerebral), acute hydrocephalus, and fractures. Although magnetic resonance imaging (MRI) is superior to CT in the detection of intracranial lesions (Pinto et al. 2012), it is currently not as easily available. Additionally, there is little evidence supporting MRI in influencing the management of patients with sTBI (Kochanek et al. 2012). Currently, there are studies reporting progressive lesions in 1–50% of TBI patients (Tabori et al. 2000). Progressive sub- or epidural hematomas (Fig. 1) may develop within hours or even days after the initial trauma. Therefore, repeated imaging might appear beneficial for sTBI patients. In a retrospective study, Da Silva et al. addressed this question and found out that unchanged or improving neurologic examination alone in children after moderate or severe TBI may be adequate to exclude the necessity of neurosurgical intervention (Da Silva et al. 2007; their findings were confirmed by another investigation in pediatric sTBI patients (Figg et al. 2006).

Additional to induction of malignomas (Brenner et al. 2001), ionizing radiation in childhood was demonstrated to cause long-term cognitive defects in adulthood (Hall et al. 2004). Considering these facts and the risks of transport (ICU to imaging) with possible deterioration of the patient, repeated imaging is reserved for selected cases and should be considered if (Hollingworth et al. 2007):

- There is no evidence of neurological improvement.
- Patients demonstrate persisting high or increasing ICP.

### Table 1 Dosage recommendations for rapid sequence induction

| Drug component | Dose recommendation |
|----------------|---------------------|
| Etomidate      | 0.15–0.3 mg/kg      |
| Propofol       | 1–2 mg/kg           |
| Rocuronium     | 0.6 mg/kg           |
| S-ketamine     | 0.5–1.0 mg/kg       |
| Succinylcholine| 1.0–2.0 mg/kg       |
| Sugammadex     | 2 mg/kg             |
| Thiopental     | 2–5 mg/kg           |

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There is an inability to assess the clinical status (sedation).

Monitoring and Thresholds for Cerebral Perfusion and Intracranial Pressure

Intracranial pressure (ICP) is a key variable in the development of secondary brain injuries (Sharples et al. 1995). Presently, many studies demonstrate a high incidence of elevated ICP in children with sTBI (Cruz et al. 2002; Pfenninger and Santi 2002; White et al. 2001) and relate elevated ICP (and systemic hypotension) to poor outcome or death (Chesnut et al. 1993; Jagannathan et al. 2008; Schoon et al. 2002; Wahlstrom et al. 2005). ICP monitoring is achieved by placing intraparenchymal or intraventricular catheters. Measurements of both methods have been shown to correlate (Exo et al. 2011). While the former has the advantage of less tissue damage, the latter allows liquor drainage in case of refractory ICP elevations. Continuous measurements of ICP and MAP allow the calculation of the cerebral perfusion pressure (CPP) as simple global measure for cerebral perfusion (Chambers et al. 2001).

\[
\text{CPP} = \frac{\text{MAP}}{\text{ICP}}
\]

Regarding complications, infections are rarely documented after catheter placement; neither seizures nor hemorrhage have been reported (Padayachy et al. 2010). As there is evidence that improved clinical outcomes are associated with successful control of intracranial hypertension (Alberico et al. 1987; Jagannathan et al. 2008), ICP monitoring is recommended for all sTBI patients (level of evidence: III (Kochanek et al. 2012)).

Invasive monitoring methods are the current gold standard for monitoring ICP; however, complications caused by their invasive nature are of concern. Of all the noninvasive methods based on the literature, transcranial Doppler and optic
nerve sheath diameter assessment are reported to be the best tools to monitor ICP in pediatric TBI. The promising results and developments of noninvasive ICP monitoring modalities with its ideal features of high sensitivity, diagnostic accuracy, and simple acquisition technique may make it the future of neurointensive monitoring in pediatric TBI (Narayan et al. 2018).

Maintaining CPP by controlling intracranial hypertension with elevated ICP is one of the key goals of intensive care medicine in sTBI patients. Investigations concerning cerebral autoregulation in children have shown that younger children appear to have less autoregulatory reserve than older children (Vavilala et al. 2003), probably requiring lower ICP targets in infants and younger children. Despite this knowledge, there are currently no published studies examining the impact of age-dependent ICP thresholds on outcome measures. Thus, current guidelines set the target ICP to 20 mmHg (Bhalla et al. 2012, Kochanek et al. 2012). With this target, brief ICP increases >20 mmHg returning to normal within 5 min may be insignificant. However, elevations persisting longer than 5 min warrant treatment (McLaughlin and Marion 1996).

Both systemic hypotension and intracranial hypertension have negative influences by reducing the CPP leading to cerebral ischemia and secondary damage. CPP is the pressure gradient for the cerebral blood flow (CBF), which is coupled to CMRO2 and underlies autoregulation (Kochanek et al. 2012). While the relationship between systemic hypotension and reduced CBF was found to be inconsistent, clear evidence exists that increased ICP is related to low CBF (Allen et al. 2014). Since MAP, CBF, and CMRO2 depend on patient age, age-related thresholds for CPP are also suggested (Kochanek et al. 2012). An investigation by Allen et al. (Allen et al. 2014) addressed this question and defined the following CPP thresholds:

- Children/infants 0–5 years old: >40 mmHg
- Children/adolescents 6–17 years old: >50 mmHg

This study also found entrance in the anesthesiology guidelines for the management of sTBI (Hardcastle et al. 2014).

**Advanced Neuromonitoring**

Children after TBI may have abnormal hemodynamics, cerebral hypoxia, altered electrophysiology, and impaired autoregulation (Kochanek et al. 2012). These effects may be regionally different throughout the brain leading to focal hypoxia with consecutive ischemic events, despite adequate ICP and CPP and adherence to therapy guidelines (Figaji et al. 2009; Lang et al. 2007; Rohlwink et al. 2012; van den Brink et al. 2000). The problem with these effects lies in their diagnosis. Methods such as positron emission tomography (PET) or xenon-enhanced computed tomography can identify altered cerebral blood flow (Bouma et al. 1992; Vespa et al. 2005). However, despite showing good spatial resolution, these methods have the disadvantage that they represent a snapshot with poor temporal resolution and they require transport of the patient (Padayachy et al. 2012). In contrast, ICU-based methods such as brain tissue oxygenation (PbtO2), near-infrared spectroscopy (NIRS), and jugular venous oxygenation (SvjO2) have good temporal but poor spatial resolution (Padayachy et al. 2012). Studies in adult patients demonstrated poor outcomes in the case of jugular venous desaturation (<50%) and low values for PbtO2 (Kochanek et al. 2012). Similar results could be shown for PbtO2 decreases in pediatric TBI, where poor outcome was associated with a reduced PbtO2 (Rohlwink et al. 2012). Moreover, the authors demonstrated a variable correlation between PbtO2 and ICP, based on complex interactions (Figaji et al. 2009, Rohlwink et al. 2012). Currently, it is recommended to keep PbtO2 above 10 mmHg in children (level III) (Kochanek et al. 2012). However, up to now it remains unclear how to react in a case of desaturation, especially in cases with normal ICP and/or CPP (especially in association with their low spatial resolution).
Although promising, there is still very limited data of these methods in pediatric TBI, especially regarding their use to guide therapy (Kochanek et al. 2012).

**General Remarks on ICU Treatment of TBI Patients**

**Positioning**

Positioning of the head influences the venous drainage of the head and brain. Flexion or rotation in the cervical spine or Trendelenburg position can impair venous drainage and lead to significant ICP increases (Hung et al. 2000; Ng et al. 2004). Therefore, patients with TBI should be positioned with slight elevations of the head (15–30°), with the head in midline position (Bhalla et al. 2012).

**Fluid Management**

Hypotension has been shown to worsen outcome of TBI patients. As hypovolemia may be a cause for hypotension, TBI patients should initially receive volume resuscitation aiming at euvoolemia (Bhalla et al. 2012; Kochanek et al. 2012). In patients with normal ICP, isotonic fluid should be chosen. It is important to note that the sodium concentration of Ringer’s lactate is below serum levels, leading to a decrease in serum sodium and osmolarity when compared to physiologic saline solution (Williams et al. 1999). Similar effects result from administration of semi-isotonic solutions (e.g., Elomel®) and solutions containing glucose (e.g., Elomel-OPG®). In the initial management, solutions containing glucose should be reserved for patients with serum glucose levels <70 mg/dl (Bhalla et al. 2012). Further management of the sTBI patient requires an individually tailored parenteral nutrition, depending on lab parameters. Albumin data from adult patients with sTBI has shown higher mortality in patients receiving albumin (Investigators et al. 2007). Thus, current guidelines suggest using isotonic solutions (e.g., NaCl 0.9% or Elomelisoton®) for initial fluid management (Bhalla et al. 2012).

**Analgesia and Sedation**

In the current guidelines, there is little information regarding the continuous sedation required in intubated TBI patients. It is evident that patients require analgesia, sedation, and eventually neuromuscular blockade (the last has already been addressed above). While continuous use of propofol(R) in the ICU setting is prohibited by the FDA (Food and Drug Administration 2015), there are numerous strategies for analgesia and sedation. Table 2 gives an overview of the different agents used in our center in various combinations.

All of our patients are equipped with continuous BIS monitoring (Infinity® BISx® SmartPod® by Draeger), allowing the determination of the bispectral index as a measure for the depth of narcosis. In cases of elevated ICP, the aim of sedation is to achieve burst suppression (usually BIS levels 15–30); analgesia and sedation should be adapted accordingly.

**Glucose Control**

Various studies have demonstrated that (early) hyperglycemia is associated with poor outcome after TBI (Cochran et al. 2003). Additionally, persisting hyperglycemia has been shown to be a powerful predictor for mortality in children and adults with TBI (Seyed Saadat et al. 2012).

| Drug       | Purpose              | Dose recommendation |
|------------|----------------------|---------------------|
| Midazolam  | Sedation             | 0.03–0.2 mg/kg/h    |
| Clonidine  | Sedation             | 0.5–1.0 mcg/kg/h    |
| Fentanyl   | Analgesia            | 0.35–1.8 mcg/kg/h   |
| Morphine   | Analgesia            | 10–40 (~60) mcg/kg/h|
| S-ketamine | Sedation and analgesia| 0.2–0.5 (~1.5) mg/kg/h|
Anti-seizure Prophylaxis

Early (within 7 days) post-traumatic seizures (EPTS) are possible complications in patients with TBI. EPTS increase cerebral metabolic demands and cerebral blood flow with consecutive increase of the secondary damage (Arndt et al. 2013). An investigation by Arndt et al. (2013) has shown an increased risk of EPTS in younger children (especially those <1 year) and after abusive head trauma. Of their cohort, 16.1% suffered clinical and subclinical seizures and 6.9% subclinical seizures only (corresponding risk factors were younger age, abusive head trauma, and intra-axonal bleeding). This data allows the conclusion that in 7% of their cohort, seizures would have been missed in the absence of continuous EEG monitoring. By recommending prophylactic treatment with phenytoin, the current guidelines pursue a different approach to EPTS (Kochanek et al. 2012). Recent data from adult studies, however, questions the use of phenytoin prophylaxis to prevent EPTS in TBI patients and suggests suppressed functional outcomes in the prophylaxis group (Bhullar et al. 2014). Where there are clear benefits in continuous EEG monitoring to detect (and treat) subclinical seizures (especially in cases with risk factors), there is limited evidence for the benefit of anticonvulsive prophylaxis in TBI patients.

Treatment of Intracranial Hypertension

Hyperosmolar Therapy

Investigations in the early twentieth century proved pressure changes in the cerebral spinal fluid, after administration of hypertonic solutions (Weed and McKibben 1919). Current therapy focuses on the application of mannitol and/or hypertonic saline solutions.

Mannitol

The reduction of ICP by mannitol is based on two different mechanisms: (1) transient reduction of blood viscosity leading to reflex vasoconstriction with decreased cerebral blood volume but maintenance of CBF (Muizelaar et al. 1984, 1986) and (2) mannitol exhibiting an osmotic effect shifting water from the parenchyma into blood vessels (James 1980). In cases of disturbed blood-brain barrier (as found in the region of cerebral lesions), mannitol was suggested to accumulate in the parenchyma leading to a reversed osmotic effect and possible ICP increases (Kaieda et al. 1989) – a phenomenon described especially after repeated use of mannitol (Kaufmann and Cardoso 1992). Additionally, investigations in adult patients suggest acute tubular necrosis and renal failure in cases of mannitol administration, when serum osmolarity was >320 mosmol/l (The Brain Trauma Foundation et al. 2000). Additional side effects include natriuresis, osmotic diuresis, hypervolemia, and hypotension (Hardcastle et al. 2014).

Despite being one of the most commonly used agents in the management of intracranial hypertension, there are no controlled clinical trials comparing mannitol versus placebo or other agents in children (Kochanek et al. 2012). Moreover, a Cochrane review of mannitol in adults could not reach any conclusions concerning its efficacy compared to placebo or any other therapy (Schierhout and Roberts 2000). Thus, current guidelines (Hardcastle et al. 2014; Kochanek et al. 2012) state that there is currently insufficient evidence to propagate or refute the use of mannitol in children with TBI.

Hypertonic Saline Solutions

Similar to mannitol, hypertonic sodium affects blood viscosity and exerts osmotic effects. Additionally, it has been postulated to restore resting membrane potentials, stimulate the secretion of atrial natriuretic peptide, inhibit inflammation, and increase inotropy (Arjamaa et al. 1992; Bhalla et al. 2012; Qureshi and Suarez 2000). Possible side effects mentioned in the guidelines (Bhalla et al. 2012; Kochanek et al. 2012) include ICP rebound, central pontine myelinolysis, renal impairment, subarachnoid hemorrhage, natriuresis, osmotic diuresis, hyperchloremic acidosis, and masking of the beginning of diabetes insipidus (Qureshi and Suarez 2000). For therapy,
thresholds of 145–160 mmol/l serum sodium and 360 mosmol/l serum osmolarity have been recommended (Dominguez et al. 2004; Himmelseher 2007; Khanna et al. 2000). Generally, a 3% solution is applied, without evidence for beneficial effects of higher concentrations (Kochanek et al. 2012), with effective bolus doses reported between 6.5 and 10.0 ml/kg (Fisher et al. 1992); additionally, beneficial effects for continuous infusion of a 3% sodium solution at a rate between 0.1 and 1.0 ml/kg/h have been reported (Peterson et al. 2000) (Table 3). Despite the lack of evidence for benefits of concentrations higher than 3%, we prefer to use a 10% solution (but apply the recommended amount of sodium/bolus) to save volume.

Temperature Control

Hyperthermia

Hyperthermia is defined as a core body temperature <35.0°C. Hyperthermia decreases the cerebral rate of oxygen consumption (CMRO₂) leading to vasoconstriction and thus decrease of cerebral blood flow (CBF) and consecutively ICP (Bhalla et al. 2012). Additionally, stabilization of the blood-brain barrier and decreases in the release of excitatory transmitters, inflammation, cell death, and lipid peroxidation are discussed (Adelson 2009; Adelson et al. 1997; Clark et al. 1996; Mansfield et al. 1996; Metz et al. 1996). A study investigating the effect of short (24 h) moderate hypothermia (32–33°C) and rapid rewarming at a rate of 0.5–1.0°C/h showed good ICP control in the phase of hypothermia, but rebound ICP increases in the rewarming phase (Hutchison et al. 2008). Additionally, the hypothermia group had a trend toward higher morbidity and mortality as well as higher incidence of hypotension demanding cardiovascular support (Hutchison et al. 2008). Studies with longer duration (48 h) of hypothermia and slower rewarming showed more favorable outcomes with reduced mortality (Adelson et al. 2005). Current guidelines recommend avoidance of short hypothermia with rapid rewarming. They state that moderate hypothermia, beginning within 8 h after the trauma for up to 48 h, with slow rewarming may be considered (level II) (Kochanek et al. 2012). Since the release of these guidelines, the results of the “cool kids” trial were published (Adelson et al. 2013). This trial had to be terminated early for futility – the interim data analysis showed no improvements in mortality or functional outcome in pediatric patients with sTBI by hypothermia for 48 h with slow rewarming (Adelson et al. 2013). This data is summarized in a review stating that there is still a lack of evidence to recommend hypothermia as first tier therapy in children or adults with sTBI (Sandestig et al. 2014).

Hyperventilation

Hyperventilation leads to a reduction in the arterial partial pressure of carbon monoxide (paCO₂)
and causes hypocapnia-induced vasoconstriction. Besides ICP reduction, this may also cause a decrease in cerebral oxygenation and may induce ischemia thus increasing secondary damage (Muizelaar et al. 1991; Skippen et al. 1997). Despite its retrospective character, a large study in 464 patients showed a strong association between severe hypocarbia and poor outcome (Curry et al. 2008). Thus, the 2012 guidelines recommend avoidance of (prophylactic) severe (<30 mmHg) hypocarbia (in the first 48 h). If refractory hypertension is treated by hyperventilation, advanced neuromonitoring should be considered to evaluate cerebral oxygenation (Kochanek et al. 2012).

**Liquor Drainage**

Drainage of cerebrospinal fluid (CSF) reduces intracranial volume and subsequently decreases ICP. Both continuous and intermittent approaches have been reported (Shore et al. 2004). Drainage can be achieved by placing either an intraventricular catheter (which may also be used for ICP measurement) or lumbar drainage (Baldwin and Rekate 1991; Jagannathan et al. 2008; Levy et al. 1995; Shapiro and Marmarou 1982). CSF drainage can be associated with an increased risk of hemorrhage and cerebral malpositioning (Kochanek et al. 2012). Presently, studies report effective ICP control in 60–87.5% of cases (Baldwin and Rekate 1991; Levy et al. 1995). Also, three of these studies confirm that refractory intracranial hypertension is associated with 100% mortality (Baldwin and Rekate 1991; Jagannathan et al. 2008; Levy et al. 1995). Resulting from this data, the 2012 guidelines give a level III recommendation for the use of CSF drainage for ICP control (Kochanek et al. 2012). Furthermore, a lumbar drain (only in conjunction with a cerebral drain) may be considered in cases of refractory intracranial hypertension (in patients with open cisterns and without mass lesions or shift) (Kochanek et al. 2012).

**Barbiturate Coma**

Children with severe TBI may experience refractory intracranial hypertension with an incidence of up to 43% (Guerra et al. 2010). In cases with intracranial hypertension, refractory to other measures (i.e., adequate positioning, deep analgesia, and sedation with neuromuscular blockade and hyperosmolar therapy), high-dose barbiturate therapy may be considered in hemodynamically stable patients (Kochanek et al. 2012). Barbiturates lower ICP by coupling blood flow to metabolic demands with higher brain oxygenation, lower CBF, and decreased ICP (Chen et al. 2008). Additionally, reduced lipid peroxidation and excitotoxicity have been postulated (Goodman et al. 1996). Barbiturates lead to severe cardiovascular side effects with reduced cardiac output, hypotension, and increased intrapulmonal shunting (Kasoff et al. 1988). Thus, patients subjected to high-dose barbiturates have to be equipped with continuous arterial monitoring. A large proportion of patients (up to 90%) undergoing this treatment will require cardiovascular support (Kasoff et al. 1988). Dose recommendations are listed in Table 4. However, there is evidence that barbiturate levels correlate poorly with electrical activity (Turcant et al. 1985) and guidelines recommend EEG monitoring to achieve burst suppression (Kochanek et al. 2012). Overall, there is very little data on the use of high-dose barbiturates in children (Kochanek et al. 2012). There seems to be evidence that barbiturates effectively lower the ICP in cases of refractory intracranial hypertension; nevertheless, there is no proof for beneficial effects on improved survival or outcome (Kochanek et al. 2012).

**Table 4 Barbiturate dose according to the literature**

| Source                | Bolus     | Continuous infusion |
|-----------------------|-----------|---------------------|
| Kasoff et al. (1988)  | 4–7 mg/kg | 1–4 mg/kg/h         |
| Pittman et al. (1989) | 5 mg/kg   | 1–2 mg/kg/h         |
Corticosteroids

Corticosteroids have demonstrated beneficial aspects in a variety of neurological conditions, such as brain tumors and meningitis. Currently, only dexamethasone has been investigated in the setting of pediatric TBI (Kochanek et al. 2012). Similar to adult studies, dexamethasone at 1 mg/kg/d for 3 days did not influence ICP, CPP, and 6-month Glasgow Outcome Scale. However, there were a suppression of endogenous cortisol production and a trend toward increased rates of bacterial pneumonia in the dexamethasone group compared to placebo (Fanconi et al. 1988). Due to this data, corticosteroids are not recommended to improve outcome or reduce ICP in children with sTBI, in the current guidelines (Kochanek et al. 2012).

Other Pathologies Associated with TBI

Hyponatremia and TBI: Syndrome of Inappropriate Antidiuresis and Cerebral Salt Wasting Syndrome (CSWS)

Hyponatremia is a common disorder in patients after TBI (Harrigan 1996). Two different pathologies may lead to hyponatremia in this context: SIADH (Ishibashi and Yokokura 1999) and CSWS (Nelson et al. 1981) – both are differentiated by the volume status of the patient (Palmer 2003).

SIADH (SIADH) is a volume-expander state due to renal water retention by inadequately high levels of vasopressin (=adiuretin). It is characterized by hyponatremia, inappropriately concentrated urine, increased urine sodium levels, and slightly increased intravascular volume (hypervolemic hyponatremia) (Palmer 2003). Additionally, there is a tendency toward diminished uric acid and urea nitrogen due to reduced renal reabsorption (Palmer 2003), although this proved inconsistent and unreliable in differentiating between these two entities in an analysis by Lohani et al. (Lohani and Devkota 2011).

| Parameter                  | CSWS    | SIADH |
|----------------------------|---------|-------|
| Extracellular fluid volume | Decreased| Increased |
| Hematocrit                 | Increased| Normal |
| Plasma albumin             | Increased| Normal |
| Plasma urea nitrogen/creatinine ratio | Increased| Decreased |
| Plasma potassium           | Normal/increased | Normal |
| Plasma uric acid           | Normal/decreased | Decreased |

In contrast, CSWS results from renal salt wasting, but the underlying mechanism is poorly understood. Either disruption of the neural input to the kidney or central elaboration of circulating natriuretic factors (atrial natriuretic peptide, ANP, or brain natriuretic peptide, BNP) is postulated (Palmer 2003). CSWS leads to increased sodium secretion in the urine followed by decreased blood volume (hypovolemic hyponatremia). This causes an appropriate (in contrast to SIADH) release of vasopressin as response to volume depletion (Palmer 2003).

The differentiation between these two syndromes (Table 5) is essential as SIADH is managed by fluid restriction and CSWS by vigorous salt replacements (Jimenez et al. 2006; Palmer 2003).

Diabetes Insipidus (DI) After TBI

DI is caused by insufficient production (hypothalamus) or secretion (posterior hypophysis) of vasopressin (=adiuretin). This leads to polyuria and increases of serum sodium and osmolarity in combination with decreased urine sodium and osmolarity (hypovolemic hypernatremia). When the abovementioned findings raise suspicion, it is possible to administer vasopressin and wait for the response (desmopressin test) and/or to determine serum levels of copeptin (the C-terminal part of the arginine-vasopressin precursor peptide (Dong et al. 2011)), to prove the diagnosis. DI, after TBI, is uncommon and almost always occurs in the early (up to 30 days) post-traumatic...
If diagnosed, DI may be a poor prognostic factor (Barzilay and Somekh 1988). For the therapy of DI, nasal, oral, and intravenous desmopressin are available. However, there is a wide variation of dose requirements and dosing intervals (Ooi et al. 2013). In the literature, a median nasal dose of 0.7 (range of 0.4–1.4) mcg/kg/d in 2–3 doses and a median oral dose of 9.5 (range of 4.2–17.0) mcg/kg/d in 2–3 doses have been reported (Ooi et al. 2013). In any case, the dose should be titrated and adapted to fluid input, diuresis, and sodium levels (Oiso et al. 2013). The authors prefer intravenous continuous vasopressin because this attenuates fluctuations in serum sodium and diuresis frequently seen in repeated boluses. For a continuous infusion, 4 mcg vasopressin is diluted to 50 ml and started at a rate of 1 ml/h (=0.08 mcg/h). The dose is then adjusted according to serum sodium and diuresis, taking care that urine output stays above 1 ml/kg/h.

Conclusions and Future Directions

Overall, the management of children with severe traumatic brain injury is challenging. There is no level I evidence for any of the therapies mentioned in this chapter. Much research will be required to gain this knowledge in the different approaches for the treatment of TBI.

First-line management in our department consists of adequate positioning, deep analgesia and sedation (if required additional neuromuscular blockade), ICP and CPP monitoring, avoidance of hyperglycemia, hyperthermia and incidental hyperventilation, and hyperosmolar therapy. Additionally, CSF drainage can be considered.

In case of refractory intracranial hypertension, neurosurgeons are involved in the decision for decompressive craniectomy (see chapter “Surgical Treatment of Severe Head Trauma”). Furthermore, a barbiturate coma is initiated when tolerated by the patient.

Hyperventilation is reserved for patients in whom all other measures fail. Hypothermia is currently not considered due to lacking evidence for benefits and possible side effects.

Cross-References

- Anesthesia and Pain Management
- Facial Trauma
- Fluids and Electrolyte Balance in Infants and Children
- Principles of Pediatric Surgical Imaging
- Surgical Treatment of Severe Head Trauma

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