Perioperative management of the pediatric patient with traumatic brain injury

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Introduction

The National Center for Injury Prevention and Control estimates that over 510,000 traumatic brain injuries (TBI) occur annually in children, 0–14 years of age in the United States (1). Of these, there are 35,000 hospitalizations and 2000–3000 deaths. Men are 1.5 times more likely to sustain TBI than women (2). Although falls are the leading cause of TBI when considering all children from 0 to 14 years of age, there are etiological variations between age groups. Nonaccidental trauma (shaken baby syndrome or child abuse) should always be in the differential diagnosis in infants and young children (3). Motor vehicle accidents and assault become more prevalent with increasing age. Among motor vehicle-related injuries in this age group, motor-pedestrian injuries are more common than motor vehicle occupant injuries (4,5). School-aged children exhibit a rise in bicycle-related injuries, whereas adolescents experience a rise in motor vehicle injuries, sports-related injuries, and assault (6). When compared with data from the 1980s, although the mortality of TBI has decreased, its total incidence has more than tripled, possibly due to the increased population, recognition of diagnosis, and presentation to emergency departments (7).

With an improved understanding of the pathophysiology of TBI, refinements of monitoring technology, and ongoing research to determine optimal care, the prognosis of TBI continues to improve. In 2003, the Society of Critical Care Medicine published guidelines for the acute management of severe TBI in infants, children, and adolescents. As pediatric anesthesiologists are frequently involved in the perioperative management of such patients including their stabilization in the emergency department, familiarity with these guidelines is necessary to limit preventable secondary damage related to physiologic disturbances. This manuscript reviews the current evidence-based medicine regarding the care of pediatric patients with TBI as it relates to the perioperative care of such patients. The issues reviewed include those related to initial stabilization, airway management, intraoperative mechanical ventilation, hemodynamic support, administration of blood and blood products, positioning, and choice of anesthetic technique. The literature is reviewed regarding fluid management, glucose control, hyperosmolar therapy, therapeutic hypothermia, and corticosteroids. Whenever possible, management recommendations are provided.

Summary

TBI and its sequelae remain a major healthcare issue throughout the world. With an improved understanding of the pathophysiology of TBI, refinements of monitoring technology, and ongoing research to determine optimal care, the prognosis of TBI continues to improve. In 2003, the Society of Critical Care Medicine published guidelines for the acute management of severe TBI in infants, children, and adolescents. As pediatric anesthesiologists are frequently involved in the perioperative management of such patients including their stabilization in the emergency department, familiarity with these guidelines is necessary to limit preventable secondary damage related to physiologic disturbances. This manuscript reviews the current evidence-based medicine regarding the care of pediatric patients with TBI as it relates to the perioperative care of such patients. The issues reviewed include those related to initial stabilization, airway management, intraoperative mechanical ventilation, hemodynamic support, administration of blood and blood products, positioning, and choice of anesthetic technique. The literature is reviewed regarding fluid management, glucose control, hyperosmolar therapy, therapeutic hypothermia, and corticosteroids. Whenever possible, management recommendations are provided.
management of such patients including their stabilization in the emergency department, familiarity with these guidelines is necessary to limit preventable secondary damage related to physiologic disturbances. This manuscript aims to provide an up-to-date summary of recommendations for the management of pediatric TBI as relevant to the field of anesthesia.

Pathophysiology of TBI

The pathophysiology and subsequent sequelae of TBI involve both primary and secondary injuries to the brain. Primary injury is caused by the initial trauma. It involves the physical impact to the brain tissue from acceleration to deceleration or rotational forces and may result in skull fracture, brain contusion, intracranial (intraparenchymal, epidural, and subdural) hematoma, or diffuse axonal injury (DAI) (11).

DAI refers to the widespread axonal damage caused by the shearing forces that occur with rapid acceleration and deceleration of the head. Motor vehicle accidents are the most frequent cause; however, falls, assault, and nonaccidental trauma are also implicated. Occurring in approximately half of all patients with TBI, it is a common injury with devastating effects. Patients with DAI frequently do not regain consciousness after their injury, leading to persistent vegetative state. Patients who do recover have severe residual impairment of cognitive function. Imaging may reveal multiple white matter lesions, although as microscopic injury may be more prevalent than macroscopic injury, even MRI may miss DAI. Its presence can be inferred when areas of punctate hemorrhage are visible in the corpus callosum or the cerebral cortex. As well as the primary injury, axonal damage in DAI may also result from secondary biochemical cascades, leading to a delayed onset or a clinical deterioration in a patient.

Recent attention has focused on the significance of secondary injury and its effect on the eventual outcome of patients with TBI. Inflammatory and excitotoxic processes following injury result in further edema formation, increases in intracranial pressure (ICP), and reduced cerebral perfusion pressure (CPP) (12,13). Secondary injury may also result from physiologic changes after the initial injury including hypoxemia and hypotension. The adult literature have demonstrated that the two major factors that result in secondary injury in patients with TBI are hypotension defined as a systolic blood pressure ≤90 mmHg and hypoxemia (PaO₂ ≤ 60 mmHg) (13).

A challenge specific to the pediatric population is the increased severity of cerebral edema as well as its diffuse nature, when compared with adults (14). The anatomic differences in the pediatric trauma patient include an immature or unstable neck, a larger head-to-torso ratio especially in infants, and a more compliant skull. These characteristics may result in more profound consequences from acceleration–deceleration injuries. Additionally, as there is limited brain atrophy in children in comparison with adults, there is little room to compensate for edema in the rigid skull. The immature brain also has a high water content and lacks complete axonal myelination. Finally, inflammatory mediators in the developing brain likely lead to more significant edema when compared with adult patients (15).

Initial stabilization and resuscitation

Given the potential for poor outcomes of TBI and the significant impact of secondary insults, treatment strategies are aimed not only at assessment and stabilization, but also early therapeutic interventions to decrease secondary injuries. Thus, the cornerstones of modern TBI management are field resuscitation, expeditious triage, emergent surgical evacuation of mass lesions, control of ICP, support of CPP, multimodal monitoring, and optimization of physiologic environment. The anesthesia provider is likely to be faced with such patients either in the emergency department when called upon for airway management or as these patients are urgently transported to the operating room for evacuation of space occupying lesions. As secondary injury is preventable and treatable, the perioperative period remains a key time to initiate interventions that may improve the outcome of TBI. Additionally, alterations in physiologic function induced by anesthetic care or the surgical intervention may result in secondary injury. The key components of perioperative management include rapid evaluation, ongoing resuscitation, early surgical intervention, intensive monitoring, and anesthetic planning.

The initial assessment and stabilization of the patient with TBI is usually achieved in the emergency department. Following the initial assessment, resuscitation, and stabilization, the patient is likely going to be transported to the computed tomography (CT) scanner and then to the operating room. As in many cases, there are no family members available and the patient is unable to provide any information, the anesthesia provider will have limited historical data on which to base their anesthetic care. Upon arrival, the anesthesia team performs a rapid assessment of the patient. The assessment should always begin with airway, breathing, and circulation, followed by a rapid assessment of neurologic status (GCS and papillary response) and
associated extracranial injuries. Information about the time and mechanism of injury can be valuable. Associated injuries involving the thorax, abdomen, pelvis, and long bones may be stable or evolve during the perioperative period. Should intra-operative decompensation occur, the potential impact of these associated injuries must be considered when attempting to determine the etiology of new onset hemodynamic instability, anemia, or ventilator difficulties.

**Airway management**

Patients with TBI requiring surgery will invariably require endotracheal intubation. The decision to perform endotracheal intubation is not only determined by the patient’s respiratory status or the need for an operative procedure, but more importantly by their Glasgow Coma Scale at the time of presentation. Current trauma guidelines recommend immediate endotracheal intubation for patients with a GCS <9 based on the high probability that such an altered level of consciousness is indicative of a brain injury of such severity that progressive cerebral edema is likely to occur (16,17).

Airway management is complicated by a number of factors including the urgency of situation with upper airway obstruction or preexisting hypoxia, uncertainty of cervical spine status, uncertainty regarding the airway because of the presence of blood, vomitus, debris in the oral cavity or laryngo-pharyngeal injuries, a full stomach, intracranial hypertension, and uncertain volume status. Although many of the tenets of airway management are the same regardless of the clinical scenario, all TBI patients should be considered to have a full stomach and an underlying cervical spine injury (CSI). Additionally, as patients may not be able to effectively cooperate with a physical examination that is key in ruling out a CSI by identifying neurologic deficits or point tenderness in the neck, the airway is managed with the assumption that their may be a CSI with a RSI and manual inline stabilization (18,19). Such initiatives are imperative as the recent data in the adult population suggest that an associated CSI is not infrequent in patients with TBI. Although it had been previously suggested that TBI patients had an incidence of CSI similar to that of the general trauma population, a higher incidence of CSI has been noted in patients with TBI especially those with increasing severity of injury as determined by low GCS score and unconsciousness (20–22).

Of equal importance is the choice of agents used for sedation/analgesia and neuromuscular blockade during RSI. Sodium thiopental, etomidate, and propofol are commonly used in the operating room to induce anesthesia before endotracheal intubation. All these agents decrease the systemic hemodynamic response to intubation, blunt increases in ICP, and decrease the cerebral metabolic rate for oxygen (CMRO2). However, thiopental or propofol may not be appropriate for critically ill patients given their vasodilatory and negative inotropic effects that are exaggerated by co-morbid conditions (23,24). In the trauma scenario, alternative agents such as etomidate or ketamine are frequently chosen (25). To date, the data regarding the potential deleterious effects of etomidate on outcome are limited to patients with presumed sepsis (26–28). Outside of that scenario, there are no data to demonstrate a deleterious effect on outcome despite the fact that adrenal suppression does occur. Given that etomidate has a limited effect on MAP and effectively decreases the CMRO2, thereby decreasing ICP, the net effect is maintenance or an increase in CPP, thereby making it a potentially valuable agent for patients with TBI.

Ketamine’s popularity in the trauma setting relates to its beneficial effects on cardiac and respiratory function. Ketamine generally increases heart rate and blood pressure as well as provides bronchodilatation because of the release of endogenous catecholamines (29). *In vitro* and animal studies suggest ketamine has direct negative inotropic properties (30,31), although clinically the indirect sympathomimetic effects from endogenous catecholamine release are generally overriding. The controversy with ketamine surrounds its effects on ICP and whether it is contraindicated in patients with TBI and altered intracranial compliance. Although the literature from the 1970s and 1980s suggested that ketamine increased ICP and was contraindicated in patients with altered intracranial compliance (32), more recent evidence has suggested no effect or even that ketamine may decrease ICP when used to prevent pain from invasive procedures (33–35).

Given the need to achieve rapid neuromuscular blockade and optimal conditions for endotracheal intubation, the choices for the neuromuscular blocking agent for RSI are succinylcholine and rocuronium (36). Although succinylcholine may mildly increase ICP (37–40), increases in ICP secondary to hypoxia and hypercarbia are well documented and much more likely to be clinically important. Therefore, rapid endotracheal intubation and control of oxygenation and ventilation are of paramount importance and far outweigh the risk of the mild increase in ICP from succinylcholine. If sugammadex is locally available, rocuronium may be a more feasible option. Although frequently considered as an adjunct to endotracheal
intubation of patients with increase ICP, there is no evidence-based medicine to show the efficacy of lidocaine (41). In the pediatric population, the process of endotracheal intubation with laryngoscopy in a patient with increased ICP may result in bradycardia. Although there are limited data to support its use, pretreatment with atropine is generally suggested (18,19). The incidence of bradycardia is further magnified by associated hypoxemia, hyperthermia, and the administration of succinylcholine.

**Intra-operative anesthetic care**

The perioperative period may provide an opportunity to either continue ongoing resuscitation or correct the preexisting secondary insults that have not been adequately addressed because of the urgency to get patients to the operating room. Furthermore, surgery and anesthesia may predispose the patient to the onset of potentially new secondary injuries (such as intraoperative hypotension because of surgical blood loss or the effect of anesthetic agents, hyperglycemia because of stress response), which may impact outcome. The primary goals of anesthetic management can be summarized as follows: (i) provide adequate anesthesia and analgesia; (ii) optimize surgical conditions; (iii) avoid secondary insults including hypotension, hypoxemia, hypocarbia, hypercarbia, hypoglycemia, and hyperglycemia; (iv) maintain an adequate CPP; and (v) avoid increases in ICP.

**Respiratory support and mechanical ventilation**

The basic tenets of ventilator support for the trauma patient are the same as for all patients in the OR. These include the provision of adequate oxygenation and ventilation while limiting the potentially deleterious effects of mechanical ventilation on cardiovascular function.

The goal of oxygenation is to maintain the PaO2 ≥ 60 mmHg (PaO2 ≥ 8 kPa) as CBF, CBV, and ICP increases linearly with PaO2 values ≤ 60 mmHg (PaO2 ≤ 8 kPa). Although PaO2 levels are routinely ≥60 mmHg (≥8 kPa) during anesthetic care, values above this level have no impact on CBF, CBV, or ICP. If adequate oxygenation cannot be maintained at inspired oxygen concentrations (FiO2) of 0.5–0.6, the usual practice is to increase positive end expiratory pressure (PEEP). However, it must be remembered that as PEEP increase, it may impact the overall CPP because of its effects not only on cardiovascular function, but also its effects on ICP. Based on lung compliance, PEEP is transmitted to the intracranial vault and may impact ICP (42,43). Therefore, in patients with TBI, it may be better to attempt to increase mean airway pressure and augment oxygenation by first increasing the inspiratory time, FiO2, and peak inflating pressure rather than PEEP.

Although practiced routinely in the past for patients with TBI, hyperventilation is generally avoided unless there is a precipitous increase in ICP with impending herniation (44,45). Prehospital ventilation has been shown to have a significant impact on outcome with increased in-hospital mortality in patients presenting with either hypocarbia or hypercarbia (46). Others have demonstrated a similar negative impact of in-hospital hyperventilation on outcomes (47). Although hyperventilation induces hypocapnia which causes cerebral vasoconstriction and a reduction in CBF and CBV and a corresponding decrease in ICP, there is a disconnect between CBF and CMRO2 as hypocarbia decreases CBF without effect CMRO2, thereby potentially exposing the patient to ischemia especially during the trauma period where there may be preexisting alterations in CBF and autoregulation. Skippen et al. (48) demonstrated a relationship between hypocarbia and frequency of cerebral ischemia. Given this information, hyperventilation should be used judiciously intra-operatively for short-term control of ICP and to facilitate surgical exposure during craniotomy. Prior to dural closure, normocarbia should be restored to avoid tension pneumocephalus. In situations where hyperventilation is necessary, it may be beneficial to increase the FiO2 as this may avoid the deleterious effects of hypocarbia on CBF and cerebral tissue oxygenation (49). Given the inaccuracy of ETCO2 monitoring and the importance of PaCO2 control in these patients, direct monitoring of arterial PaCO2 is recommended (50,51).

**Summary:**

1. Maintain PaO2 ≥ 60 mmHg (PaO2 ≥ 8 kPa)
2. PEEP may increase ICP
3. Hyperventilation should only be used if impending herniation
4. Avoid intra-operative hypoxemia

**Hemodynamic support**

As noted earlier, the role that hemodynamic support may play in prevention of secondary injury cannot be overemphasized. In both the adult and pediatric population, data demonstrate that even a single perioperative episode of hypotension can impact outcome (52,53). A meta-analysis of 8721 patients (IMPACT study) emphasizes the importance of secondary impact and its effect on outcome (54). The study noted that
both hypotension and hypoxemia were significantly associated with unfavorable 6-month outcome. Intraoperative hypotension can be equally as devastating. Pietropaoli et al. demonstrated that intraoperative hypotension increased the incidence of mortality by a factor of three (55). Additionally, the duration of intraoperative hypotension was also inversely associated with functional outcome. Intraoperatively if problems arise with the control of ICP, a slight elevation of the MAP may be effective in ameliorating such issues. With intact autoregulation, as the MAP is increased, there is a secondary cerebral vasoconstriction to maintain CBF at baseline. The cerebral vasoconstriction results in a decrease in CBV that may decrease ICP in patients with altered intracranial compliance. This relationship further demonstrates the need to effectively control the intraoperative MAP. Three small prospective, crossover trials have compared norepinephrine with dopamine to treat hypotension and maintain MAP (56–58). There were no differences in mean cerebral flow velocity, cerebral oxygenation, or cerebral metabolism. However, the authors reported that norepinephrine had a more predictable and consistent effect while dopamine resulted in a higher ICP. A recent single-center retrospective study of patients with severe TBI who received phenylephrine, norepinephrine, or dopamine reported that phenylephrine resulted in the maximum increase in CBV and CPP from baseline (59).

Summary:
1. Effective control of intraoperative MAP
2. A single intraoperative episode of hypotension can effect outcome
3. Maintain optimal CPP

Anesthetic agents

There are significant differences when comparing the effects of intravenous anesthetic agents and the volatile agents in regard to their effects on CBF, CBV, and CMRO2. However, to date, there are no evidence-based data to demonstrate a significant difference in outcome when comparing these two groups of agents. The intravenous agents including thiopental, propofol, and etomidate reduce CMRO2, which results in cerebral vasoconstriction and a decrease in CBF, CBV, and ICP. However, agents such as thiopental and propofol may result in significant hypotension and a reduction in CPP. Additionally, with intact autoregulation, the decrease in MAP is compensated for by cerebral vasodilatation to maintain CBF, which results in an increase in CBV and may increase ICP. A similar effect has been observed following the administration of fentanyl and sufentanil although these agents have no direct effect on the cerebral vasculature (60,61). This effect can be treated by the administration of a vasoactive agent such as phenylephrine to restore the MAP back to baseline.

All of the volatile anesthetic agents (isoflurane, sevoflurane, and desflurane) decrease CMRO2 and may cause cerebral vasodilatation, thereby increasing CBF, CBV, and ICP. These effects are generally minimal at exhaled concentrations of <1 minimum alveolar concentration. Therefore, they may be used in low concentrations in patients with TBI (62,63). However, nitrous oxide should be avoided as it can increase CMRO2 causing cerebral vasodilatation and increased ICP (63). As far as choice of neuromuscular blocking agent, the issues related to succinylcholine and its potential effects on ICP have been previously discussed. The nondepolarizing agents have no direct effect on ICP and can be used as needed to provide surgical relaxation and ensure immobility in critically ill patients. Although neuromuscular blocking agents decrease oxygen consumption and may transiently decrease ICP as they eliminate thoracic skeletal tone and increase venous drainage; postoperatively, their use is generally not recommended (64). The adult literature clearly demonstrates no outcome benefit and increased adverse effects including infection and prolongation of hospitalization (65).

Summary:
1. No significant difference in outcomes comparing intravenous and inhalational anesthetic agents
2. Avoid nitrous oxide, increases CMRO2 and possible increase in ICP
3. NMB are generally not recommended postoperatively, but are routinely used intraoperatively

ICP Monitoring

Preventing and treating intracranial hypertension that would lead to deleterious secondary injury is vital to the care of patients with TBI. While in common practice, monitoring of ICP for this purpose is presented as an option rather than a guideline for children with severe TBI (GCS < 8), because of insufficient evidence in the pediatric population (8). Typically the choice of monitor is between an intraparenchymal device and an intraventricular device connected by catheter to an external drain gauge. Correlation between the two has been shown (66), and while the former may result in less local tissue damage, the later allows CSF drainage and is the suggested device in adult TBI guidelines (67). An ICP greater or equal to 20 mmHg warrants treatment in children. CPP should be maintained.
of brain tissue oxygenation using invasive devices (73–75). Noninvasive transcranial doppler pulsatility index as an indicator of ICP is controversial, however may be useful on admission, having high sensitivity to predict ICH and abnormal CPP (72). Another alternative to direct ICP monitors is ocular ultrasound, which has been suggested to detect ICH in adults.

Although not standard of care or in routine practice, as the technology improves, perioperative cerebral monitoring may become more commonplace (73–75). Such technology may be particularly relevant in patients receiving more aggressive systemic interventions to manage refractory ICH, such as hyperventilation. Jugular venous oxygen saturation (SjvO2), measured by retrograde placement of a catheter from the internal jugular into the jugular bulb (73), gives a measure of cerebral oxygen delivery. In adults with TBI, episodes of decreased SjvO2 have been associated with poor neurologic outcome. Cerebral oximetry via near infrared spectroscopy (NIRS) monitoring has been shown to correlate with SjvO2, and in many centers, NIRS-based cerebral oximeters are used routinely for children undergoing repair of congenital heart defects. Other monitoring technologies to considered in the perioperative period that may help in adjusting therapies include transcranial Doppler ultrasonography to evaluate middle cerebral blood flow and direct measurement of brain tissue oxygenation using invasive devices (73–75).

Summary:
1. ICP ≥ 20 mmHg warrants intervention
2. CPP should be maintained at > 40 mmHg
3. Monitoring ICP helps to avoid further secondary injury

Positioning
As the patient is moved and positioned on the operating room table, the head position is generally mandated by the surgical procedure to be performed. However, several studies have demonstrated the potential impact of head positioning and head elevation on ICP. Whenever feasible, the patient’s head should remain in neutral and midline position to avoid jugular venous obstruction. Flexion of the head, rotation of the head to the right or the left, or lowering the patient into the Trendelenburg position can significantly increase ICP especially in patients with altered intracranial compliance (76–78). A more controversial issue that relates primarily to the ICU care of these patients is whether head elevation should be routine. While elevation of the head of the bed has been shown to lower ICP by promoting venous drainage, some studies have shown that a decrease in CPP may also occur. Furthermore, rebound autoregulatory responses to reduced CPP involve lowering of CBR to increase CBV, which may actually predispose these patients to episodes of intracranial hypertension and more problematic control of ICP (79). Overall, it has been suggested that a moderate elevation of 15–30° is an appropriate measure to lower ICP as long as adequate CPP is vigilantly maintained and the degree of elevation titrated to the individual based on ICP and CPP measurements (8). Head elevation has the added benefit of minimizing ventilator-associated pneumonia.

Summary:
1. Head of bed should be maintained at 15–30°
2. Reverse Trendelenburg may improve venous drainage, but may induce rebound increase in ICH
3. Patients head should remain neutral and midline

Fluid management including glucose control
Given the risks of hypovolemia and hypotension, patients with TBI should receive initial volume resuscitation to achieve a normovolemic state. Although significant fluid restriction was previously the acceptable standard for patients with TBI, the current trend has evolved to suggest that euvoemia is the optimal end-point. In the consideration of fluid therapy, the issues to be addressed include the type of fluid to be used and the control of serum glucose. Issues related to hyperosmolar therapy are discussed in the next section.

For the vast majority of patients, an isotonic fluid should be chosen. Although lactated Ringers (LR) is commonly used during the perioperative period, it must be remembered that the sodium concentration of 130 mEqL⁻¹ is less than that of the serum sodium concentration. When compared with the administration of normal saline, patients receiving LR will have a decrease in the serum sodium level and osmolarity (80). Given this information, normal saline should be used for the initial resuscitation and then the ongoing provision of maintenance and replacement fluids for the majority of patients with TBI. When comparing the potential advantages and disadvantages of
crystalloid vs colloid, recent data from an adult trial suggest that resuscitation with albumin containing fluids may impact outcome (81). In the posthoc analysis of a larger trial, the authors reported that the risk of death was increased in patients who received albumin compared with those who received normal saline. Among patients with severe brain injury (GCS 3–8), 61 of 146 patients in the albumin group died (41.8%) as compared with 32 of 144 in the saline group (22.2%, relative risk of 1.88) (81).

Although hypertonic fluids have been shown to be effective in the treatment of increased ICP (see below), there are few data to demonstrate their superiority over normal saline for the initial resuscitation of patients with TBI. Prehospital hypertonic saline resuscitation has been shown to be associated with a reduction in serum biomarker levels (S100B, neuron-specific enolase and membrane basic protein) (82). However, a prospective and randomized trial comparing prehospital resuscitation of TBI patients with hypotension found no difference in neurologic outcome when comparing resuscitation with hypertonic saline or standard fluid resuscitation protocols (83).

Another controversial issue regarding care of patients with TBI is the association of hyperglycemia with a poor outcome. As such, there remains some divergence in the opinions regarding the need to aggressively treat hyperglycemia in this population. Causes of hyperglycemia after TBI include an increase in gluconeogenesis and glycogenolysis from catecholamine response, cortisol release, and glucose intolerance (84–86). Hyperglycemia is more prevalent after severe TBI and in patients under 4 years old (84). Secondary brain injury from hyperglycemia can occur, leading to an increase in glycolytic rates as shown by increased lactate/pyruvate ratio, resulting in metabolic acidosis within brain parenchyma, overproduction of reactive oxygen species, and ultimately neuronal cell death through alterations in immune, inflammatory, and mitochondrial function (87). Several studies in both children and adults support an association between hyperglycemia and a poor neurologic outcome following TBI; however, there are limited data to prove whether treatment of the hyperglycemia will improve outcome (88–90). In a retrospective review of pediatric patients admitted to the regional trauma center over a 1-year period, Cochrane et al. note that patients who died had significantly higher admission glucose values (mean of 267 vs 135 mg·dl⁻¹) and that a serum glucose on admission of >300 mg·dl⁻¹ (16.7 mm) was uniformly fatal (88). Lam et al. (89) noted that in severely injured patients with a GCS ≤8 that a serum glucose ≥200 mg·dl⁻¹ (11.1 mm) was associated with a worse outcome. Smith et al. (90) reported that in children with severe traumatic brain injury, hyperglycemia beyond the initial 48 h is associated with a greater likelihood of a poor neurologic outcome.

Intensive insulin therapy for the control of hyperglycemia in critically ill adult patients has received a lot of press in the literature following the report of Van den Berghe et al. (91) which reported that intensive insulin therapy (target blood glucose 80–110 mg·dl⁻¹) in critically ill patients was associated with lower mortality. However, subsequent work has demonstrated that this may not be that case and that there is an increased risk of hypoglycemia (92,93). In a prospective trial, Billotta et al. (93) randomized 97 adults with severe TBI to insulin therapy to maintain a blood glucose at 80–120 mg·dl⁻¹ (4.4–6.7 mm) or conventional insulin therapy to maintain a blood glucose concentration below 220 mg·dl⁻¹ (12.2 mm). They reported that both the groups had similar mortality and neurologic outcome at 6 months and a similar incidence of infectious complications. Although the more strict control of glucose resulted in a shorter duration of ICU stay, there was a higher incidence of hypoglycemia. Given the potential for an increased risk of hypoglycemia in children and its potentially devastating neurologic consequences if unrecognized and untreated, an aggressive approach to the control of perioperative glucose cannot universally be suggested in children with TBI. Additionally, when reviewing the data, the studies focus on ICU care and not the intraoperative management of such patients. Given these issues, it seems prudent to suggest that glucose containing fluids not be administered to the pediatric patient with TBI unless the serum glucose is ≤70 mg·dl⁻¹. Given the potential impact of both hyperglycemia and hypoglycemia, intermittent monitoring of blood glucose concentrations during intra-operative care is suggested. This can easily be accomplished using bedside, point-of-care testing devices. Moreover, the anesthesia provider may want to take into account that there may be differential effects of the individual anesthetic agents on blood and brain glucose concentrations (94,95).

Summary:
1. Intra-operative euvoelemia is optimal
2. Normal saline should be used as maintenance fluid
3. Glucose containing fluids should not be infused unless the serum glucose is ≤70 mg·dl⁻¹ (3.9 mm)

**Hyperosmolar therapy**

Mannitol remains the standard agent used in hyperosmolar therapy. The principle of hyperosmolar
therapy is based on establishing an osmotic gradient between the plasma and parenchymal brain tissue, thereby reducing brain water content and thus ICP. An intact blood–brain barrier is necessary for this process. In addition to its osmotic effect, a rapid decrease in ICP may be seen following its administration as mannitol improves blood rheology and thereby results in an increase in cerebral vascular resistance (cerebral vasoconstriction) with a decrease in CBV and ICP. Available as a 20% solution (standard solution bag) or a 25% solution (bottle), dosing regimens vary from 0.25 to 1 gm·kg⁻¹ and aim not to exceed serum osmolarity of 320 mOsm·l⁻¹ (96,97). The osmotic diuresis from mannitol can result in hypovolemia and hypotension, and concern has been expressed regarding adverse effects following mannitol administration if there is an intracranial collection of blood (epidural or subdural hematoma). It is postulated that a reduction in the brain volume may result in relief of the tamponade that is preventing ongoing bleeding. Therefore, it has been suggested mannitol not be administered until the blood has been evacuated.

More recently, there has been considerable interest and work performed with the use of hypertonic saline solutions. Generally, a 3% solution is used, although concentrations up to 23.4% have been studied (98). A serum sodium level of 145–160 mEq·l⁻¹ has been recommended, and while patients have tolerated a serum osmolality up to 360 mOsm·l⁻¹, caution above 320 mOsm·l⁻¹ is recommended (99,100). In addition to its effects on the brain, hypertonic saline has beneficial hemodynamic effects including the restoration of intravascular volume, increased inotropy, constriction of capacitance vessels, and a decrease in resistance vessels. These effects result in an increased MAP and CPP in the majority of patients. Studies in both the adult and pediatric population have demonstrated the efficacy of these solutions in treating refractory increases in ICP that have failed to respond to conventional therapy including mannitol (99–102). Vats et al. (103) retrospectively reviewed their experience with hypertonic saline (5 ml·kg⁻¹ of a 3% solution) or mannitol (0.5–1 gm·kg⁻¹) to treat increased ICP in a cohort of pediatric patients ranging in age from 9 months to 16 years. Fifty-six doses of mannitol were administered to 18 patients, while 82 doses of hypertonic saline were administered to 25 patients. Although both reduced ICP at 60 and 120 min, only hypertonic saline reduced the ICP at 30 min and increased the CPP at 60 and 120 min. Although the majority of studies comparing these agents have been performed in the ICU setting, the efficacy of hypertonic saline has also been demonstrated intra-operatively (104). In a prospective, blinded trial, adults scheduled for elective resection of a supratentorial brain tumor were randomized to receive 160 ml of 3% hypertonic saline or 150 ml of 20% mannitol. The surgeon was asked to judge the brain relaxation conditions as soft, adequate, or tight. Brain relaxation was better in the patients who received hypertonic saline than in the mannitol group. Serum sodium was higher in the hypertonic saline group, while urine output was greater in patients receiving mannitol. No difference was noted in fluid administered, length of ICU stay, or length of hospital stay. Despite the data suggesting improved efficacy with hypertonic saline, there are no data to demonstrate an improvement in outcome. As such, either agent should be considered intra-operatively when the treatment of ICP is necessary or to provide intra-operative brain relaxation. However, hypertonic saline should be considered in patients who fail to respond to conventional therapy including mannitol.

Summary:
1. Mannitol remains the standard for hyperosmolar therapy
2. Hypertonic saline, although efficacious, has not demonstrated improved neurologic outcome
3. Hypertonic saline should be considered for patients who may be refractory to mannitol therapy

Temperature control and therapeutic hypothermia

Moderate hypothermia decreases the cerebral metabolic rate of oxygen consumption (CMRO₂) resulting in cerebral vasoconstriction, a decrease in CBF/CBV and ICP. Additional potential benefits include an attenuation of the alteration in the blood–brain barrier related to TBI and a decrease in the release of excitatory neurotransmitters including lactate, which have been implicated in secondary brain injury (105). A recent meta-analysis in adults with TBI noted no statistically significant reduction in mortality although there was an increase in the favorable neurologic outcome in patients that received hypothermia, particularly when cooling was maintained for more than 48 h (106). However, the authors noted that the potential benefits of hypothermia may be offset by a significant increase in the risk of nosocomial infections including pneumonia. By contrast, the National Acute Brain Injury Study (NABIS: HII) failed to show benefit when investigating 108 adults post-TBI randomized to early induction of hypothermia (33°C within 4.4 h of injury) or normothermia (107). Similarly, the pediatric literature has shown no clear benefit from the use of
routine hypothermia following TBI (108). In fact, in the prospective trial of 225 children, there was a relative risk of mortality of 1.4 in patients that received hypothermia with a mortality rate of 21% in the hypothermia group and 12% in the normothermia group (108). There was an increased need for vasopressor use and an increased incidence of hypotension in the hypothermia group. Several adverse effects have been reported with hypothermia including hypotension, bradycardia, arrhythmias, sepsis, and coagulopathy (109,110). It has been suggested that the latter may negate any significant outcome impact noted by hypothermia. Despite these issues, other investigators have continued to demonstrate the safety of hypothermia with the suggestion that additional trials are needed in the pediatric population to determine whether there is an outcome benefit (111). The overall consensus from the most recent set of guidelines for the care of pediatric patients with TBI suggests that there is currently no published support for the use of therapeutic hypothermia in pediatric patients with TBI (8–10).

Summary:
1. No class I evidence of improved outcomes for induced hypothermia
2. There are potential adverse effects with induced hypothermia, including hypotension, bradycardia, arrhythmias, sepsis, and coagulopathy

Corticosteroids

Historically, corticosteroids were used as part of the pharmacological management of patients with TBI, based on literature reporting edema reduction and improved outcome in patients with brain tumors. However, trials that specifically evaluated the use of corticosteroids in patients with TBI have failed to show an improvement in outcome (112,113). More recently, the large multicenter CRASH study found an increased mortality or severe disability in adult patients with TBI who received methylprednisolone within 8 h of the event treated (114). Adverse effects related to the administration of corticosteroids to critically ill patients include adrenal suppression, increased risk of infection, and gastrointestinal bleeding. Although there are no data specific to the pediatric population, given the strength and size of the CRASH trial, corticosteroids should not be administered to pediatric patients with TBI.

Summary:
1. Steroids do not provide benefit in TBI patients
2. CRASH trial showed increased mortality in adults receiving methylprednisolone suffering from TBI

Blood product administration and coagulation function

Given the multisystem involvement of patients with TBI, anemia is a common component related to extracranial injuries. In adults with TBI, anemia has been shown to be associated with increased inhospital mortality and poor outcome in TBI (115–117). However, there are limited data to support guidelines regarding the use of blood products in patients with TBI. More recently, there has been significant attention in the literature regarding the potential deleterious effects of the use of blood products in critically ill patients including an increased risk of nosocomial infections, adult respiratory distress syndrome, and longer hospital/ICU stays (118–120). Although not specifically studied in the pediatric population with TBI, data from other clinical scenarios involving critically ill infants and children have demonstrated no benefit to a liberal transfusion practice (hemoglobin 10 g dl⁻¹) vs a restrictive transfusion practice (hemoglobin 7 g dl⁻¹) (121,122).

In addition to the need for packed red blood cells, transfusions of allogeneic blood products may be required to treat coagulation disorders. Tissue factor, which is released following brain injury, activates the coagulation cascade resulting in thrombin formation and depletion of coagulation factors. Coagulation function may be further compromised by hypothermia, acidosis, and hypocalcemia. Disturbances of coagulation function are a frequent occurrence in patients with TBI with a reported incidence of more than 30% in adults with TBI (123). Risk factors for coagulation disturbances associated with TBI include GCS ≤ 8, a higher severity of illness score, and anatomic features noted on CT imaging including cerebral edema, subarachnoid hemorrhage, and a midline shift (124). As in all critically ill pediatric patients, the use of blood products to treat coagulation disturbances should be based on laboratory parameters including the prothrombin time (PT), partial thromboplastin time, and platelet count. In addition to the use of blood products, both antifibrinolytic agents such as tranexamic acid and pro-coagulant drugs such as recombinant factor VII (rFVIIa) have been used in trials and case series in patients with TBI. Anecdotal evidence has suggested the efficacy of rFVIIa even in pediatric patients with TBI not only in the control of bleeding that is unresponsive to conventional therapy, but also as a means of allowing patients to be taken rapidly to the operating room instead of waiting for the administration of routine blood products to reverse the coagulation disturbances (125,126). A review from the
Cochrane database reported that their analysis of two randomized controlled revealed that the cohorts were too small to draw a conclusion regarding the effectiveness of rFVIIa for TBI patients (127). Although not performed solely in patients with TBI, but rather adult trauma patients in general; the CRASH-2 trial reported decreased mortality in patients who received tranexamic acid (128).

Summary:
1. There is no defined optimal transfusion endpoint
2. Treatment of clinical symptoms in conjunction with coagulation laboratory results should drive therapy

Anticonvulsant prophylaxis

When compared with the adult population, infants and small children are at an increased risk of posttraumatic seizures (PTS) compared with adults, because of increased excitability of the developing brain (129). The incidence has been reported between 12% and 40% for early PTS (within 7 days of injury) following moderate to severe TBI with the incidence being higher based on the severity of the injury and the age of the patient (130,131). Children who are <2 years of age are 2.5 times more likely to suffer PTS. PTS has been identified as a poor prognostic indicator of recovery in the pediatric population with TBI. Seizure activity may lead to an increase in CMRO₂ and ICP, excessive neurotransmitter release, and fluctuations in systemic blood pressure, factors that may contribute to secondary brain injury. The administration of phenytoin reduces the incidence of early PTS with no effect on late occurring PTS (7 days postinjury) or overall outcome (132). It is therefore recommended that prophylactic anticonvulsant therapy be considered only in the first week following severe TBI in patients at high risk of seizure activity including those with intraparenchymal blood.

Summary:
1. Children are at higher risk of suffering from posttraumatic seizures
2. Seizure activity may worsen secondary brain injury
3. Prophylactic anticonvulsant therapy should be given for the first 7 days posttrauma

Summary

TBI and its sequelae are a major healthcare issue throughout the world. With an improved understanding of the pathophysiology of TBI, refinements of monitoring technology, and ongoing research to determine optimal care, the prognosis of TBI continues to improve. Regardless of whether these children are in the Pediatric ICU or the operating room, knowledge of the guidelines from the Society of Critical Care Medicine regarding the acute management of severe TBI in infants, children, and adolescents may be useful in guiding therapeutic interventions. Of particular note over the past decade has been the increasing evidence of the importance of the prevention of secondary injury and its role in a favorable outcome. As such, meticulous attention to ventilatory and hemodynamic management is vital for these patients. Of prime importance during the perioperative period is attention to the hemodynamic status as even a single episode of hypotension has been shown to worsen outcome. One area that merits further investigation is the optimal CPP in the pediatric population. Although there is general consensus in the adult population that the CPP should be maintained at >70 mmHg, there are no specific data for the various ranges along the pediatric population (133). A lower limit of acceptability in the pediatric population has been set at a CPP of 40 mmHg; however, there are no age-specific guidelines (68). Additionally, the intra-operative focus in the care of these patients remains on correcting or preventing physiologic disturbances that may result in secondary injury to the brain including hypocarbia, hypercarbia, hypoxemia, hypoglycemia, and hyperglycemia. Additional perioperative goals are outlined in

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Intra-operative goals in the goal of TBI</th>
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<tbody>
<tr>
<td>Respiratory support</td>
<td>Maintain PaO₂ ≥ 60 mmHg and PaCO₂ at 35–40 mmHg. Hyperventilation with a PaCO₂ ≤ 30 mmHg is not recommended except for the treatment of impending herniation or to temporarily treat inadequate surgical relaxation of the brain</td>
</tr>
<tr>
<td>Hemodynamic</td>
<td>Avoid hypotension. Use vasoactive agents (phenylephrine) to treat hypotension. Invasive blood pressure monitoring. Maintain cerebral perfusion pressure at 40–70 mmHg depending on patient’s age</td>
</tr>
<tr>
<td>Hyperosmolar therapy</td>
<td>Mannitol (0.25–1 g·kg⁻¹) to treat elevated intracranial pressure (ICP). Consider hypertonic saline for elevated ICP that is refractory to treatment</td>
</tr>
<tr>
<td>Fluid therapy</td>
<td>Normal saline without glucose unless serum glucose ≤70 mg·dl⁻¹. Monitor serum glucose. Avoid albumin</td>
</tr>
<tr>
<td>Temperature</td>
<td>Avoid hyperthermia. No role for routine therapeutic hypothermia</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>No role in TBI</td>
</tr>
<tr>
<td>Blood products</td>
<td>Maintain hemoglobin at 7–10 g·dl⁻¹. Follow and treat coagulation function with blood products</td>
</tr>
</tbody>
</table>
Table 1. As much of the clinical practice and care of children with TBI continues to be extrapolated from the adult literature, future studies focusing on the care of children with TBI should be considered. With appropriate attention to the current recommendations perioperatively, the outcomes of TBI will continue to improve.

Conflict of interest
No conflicts of interest declared.

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