



Pediatric traumatic brain injury—a review of management strategies

Sung Shin Teng^{1,2}, Shu-Ling Chong^{1,2}

¹Department of Children's Emergency, KK Women's and Children's Hospital, Singapore 229899, Singapore; ²Duke-NUS Medical School, Singapore 169857, Singapore

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Correspondence to: Dr. Shu-Ling Chong, MBBS, MRCPCH (UK), MCI, MPH. Department of Children's Emergency, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899, Singapore. Email: Chong.Shu-Ling@kkh.com.sg.

Abstract: Management of traumatic brain injury (TBI) in children varies due to differing physician practices and availability of resources. Optimizing treatment to meet the physiologic demands of the wounded brain is crucial to achieve maximal recovery and minimize secondary injury. This review aims to discuss and update the different aspects of acute care in a child with TBI. A literature search for relevant original and review articles was carried out via PubMed. Relevant literatures from adult studies were included where there was a lack of pediatric data. Case reports and non-English articles were excluded. Acute airway management with carefully chosen sedative agents, appropriate ventilation and hyperosmolar therapy strategies are targeted at maintaining normal cerebral perfusion pressure (CPP). The goal of temperature control and glycemic control is to maintain normal ranges to optimize outcomes. Decisions for neuroimaging and initiation of anticonvulsants are weighed against potential complications. Achieving a beneficial neurological outcome for pediatric patients with TBI depends on effective management from the onset of injury. More high quality collaborative prospective research is required to develop individualized management strategies for our pediatric TBI patients in the acute setting.

Keywords: Pediatric; traumatic brain injury (TBI); management

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Introduction

Traumatic brain injury (TBI) in children may result in death, permanent neurological deficit, and dependence on caregivers for all activities of daily living (1-3). TBI-related deaths range from 1.9 per 100,000 children aged 5 to 14 years old, to 4.3 per 100,000 children aged 0 to 4 years old in the United States in 2009–2010 (4). Recent studies found that children with severe TBI (5,6), those younger than 7 years of age (7), and those with severe concomitant injuries are at higher risk for mortality (8). Studies looking at long term outcomes in children found an association between previous TBI and a decreased ability in daily

functioning (9), pronounced behavioral changes (10-12) and difficulty coping with mainstream academic demands (10). All these form a significant burden from a health economics perspective (13-15). Yet, TBI is under-recognized and under-studied, especially in many low- and middle-income countries (13,16).

When encountering a head-injured child, favorable neurological outcomes depend on prompt identification and treatment of raised intracranial pressure (ICP) together with swift and effective resuscitation.

In this narrative review, we aim to focus on the following areas in the acute management of pediatric TBI: (I) airway management with sedation and hyperventilation; (II)

utility of hyperosmolar agents; (III) effect of hypothermia; (IV) glycemic control; (V) indications for neuroimaging; (VI) role of ICP monitoring, and (VII) indications for prophylactic anti-epileptics.

Materials and methods

We searched PubMed with the following MeSH search terms: brain injuries; child; hypnotics and sedation; hypocapnia; hypertonic solution, saline; hypothermia; glycemia and hyperglycemia; neuroimaging; ICP monitoring and anticonvulsants. Both original research and review articles that were relevant to each area of focus were included. We chose to exclude case reports and non-English articles. Regarding specific treatment strategies, we included relevant references from the adult TBI literature for discussion.

Results and discussion

Airway management, sedation and ventilation strategies

Prompt endotracheal intubation in an unconscious TBI patient [Glasgow coma scale (GCS) score ≤ 8] or one with rapidly deteriorating GCS allows for airway control, concomitant management of raised ICP and prevents hypoxemia, an important cause of secondary injury to the brain (17). When managing the airway, concurrent decisions have to be made to select an appropriate sedative agent. The appropriate choice and dosage of sedative agents facilitate airway intervention (18), while maintaining both mean arterial pressure (MAP) and cerebral perfusion pressure (CPP) (17,19).

Benzodiazepines are readily used in many settings and have proven useful for their anxiolytic, amnesic and anti-convulsant properties (19). However, because of the risk of hypotension and secondary injury to the brain, care must be taken to ensure that the MAP does not drop significantly during induction. Respiratory depression must be avoided, bearing in mind that sedation may be prolonged from a build-up of metabolites (19). Benzodiazepines may also be useful for the purpose of ICP control, although a recent small retrospective cohort study demonstrated that bolus dosing of midazolam (together with fentanyl), was ineffectual in lowering ICP when used for *episodic* intracranial hypertension in children (20).

Etomidate is a useful sedative agent in children with severe TBI (21). It is especially relevant in the presence of

hemodynamic instability, when the use of benzodiazepines is contraindicated. Etomidate, however, should be avoided among children at risk of adrenal suppression due to the known risk for relative adrenocortical insufficiency (22).

Propofol has demonstrated favorable effects in maintaining cerebral blood flow (CBF) among brain injured adult patients (23-25). However, propofol is not recommended in the acute resuscitation of a child with trauma because it can cause hypotension and decrease the CPP, particularly in children with multiple trauma or those with hypovolemia. Users should also monitor for propofol infusion syndrome, recognized by arrhythmias, metabolic acidosis, rhabdomyolysis, myoglobinuria, hyperlipidaemia, and fatty liver enlargement (26,27).

Ketamine is associated with improve outcomes in patients with TBI, contrary to prior beliefs that ketamine exacerbates raised ICP. MAP is either maintained or increased with the use of ketamine, as opposed to other sedative agents (28-30). In a study of 30 pediatric patients with intracranial hypertension, a single dose of ketamine prevented further increase in ICP during stressful interventions and reduced ICP among children with refractory intracranial hypertension (31). However, a systematic review of adults with TBI reported no significant difference in CPP, mortality, duration of intensive care unit (ICU) stay, or functional outcomes, with the use of ketamine (32).

No single sedative agent has proven superior in the adult severe TBI population, either in terms of mortality, functional outcomes, or in the treatment of raised ICP (33). As such, in the absence of known adrenal insufficiency, etomidate may be the sedative of choice. For unstable or hypotensive TBI patients, ketamine can be considered. If benzodiazepines are used, measures must be instituted to prevent and correct hypotension.

After optimizing sedation and establishing a secure airway, effective ventilation is essential to minimize secondary brain injury. Hyperventilation should not be performed routinely for children with TBI. Hyperventilation leads to cerebral vasoconstriction, reduced CBF and cerebral oxygenation, resulting in brain ischemia (34). Brain ischemia correlates proportionately with the extent of hyperventilation (35). In a retrospective cohort study, the more frequent the occurrences of severe hypocarbia among children with TBI, the greater the likelihood of mortality (36). In another retrospective cohort study, children with TBI and an admission PaCO₂ between 36–45 mmHg were separately shown to have a

better discharge outcome compared to those with admission hypocarbia ($\text{PaCO}_2 \leq 35$ mmHg) (37).

Current evidence comes mainly from observational studies. Prophylactic severe hyperventilation to $\text{PaCO}_2 < 30$ mmHg should be avoided in the initial resuscitation of a child with TBI (38). If hyperventilation is to be considered among patients with refractory intracranial hypertension, cerebral ischemia should be pre-empted and advanced neuromonitoring instituted (38).

Patients with TBI are known to be at risk for lung injury, which can be worsened by the use of high tidal volumes (39,40). This has led to the emergence of protective ventilation with new ventilation strategies (41). However, there is no clear evidence that the use of protective ventilation reduces mortality or duration of mechanical ventilation for TBI patients (42). The main ventilation goals in managing the child with TBI are still to avoid hypoxia and hypocarbia (43).

Hyperosmolar agents

The choice of hyperosmolar agent, dose and therapeutic threshold in management of TBI children with raised ICP vary between centers (44). While mannitol was used frequently in the past and is useful to reduce ICP (45), it has not been demonstrated to reduce mortality or improve functional outcomes (46). Mannitol use is associated with diuresis, hypovolemia and renal failure, raising concerns about routine use in raised ICP (47).

Hypertonic saline is being used increasingly and demonstrates effectiveness in rapid resolution of raised ICP (48,49). Hypertonic saline increases MAP (50), raises serum osmolality, and reduces cerebral edema. In the context of TBI, hypertonic saline increases the CPP and dampens spikes in ICP (51,52). Hypertonic saline also treats hypernatremia, which in patients with TBI can result from cerebral salt wasting, syndrome of inappropriate anti-diuretic hormone or sodium losses from cerebral spinal fluid drainage (38). Potential side effects, though rare, include central pontine myelinolysis, electrolyte abnormalities, rebound in ICP, and renal impairment (53).

Besides effectively reducing ICP (54), one randomized controlled trial in children reported shorter ICU stays, fewer interventions and shorter mechanical ventilation times with the use of hypertonic saline (55). In a retrospective study looking at children with TBI treated with hypertonic saline (56), there was a higher than expected survival rate, based on Injury Severity Score. Importantly, none of these

patients developed adverse effects such as central pontine myelinolysis, pulmonary edema, renal impairment or rebound increase in ICP.

Hypertonic saline is recommended as part of standard therapy for children with raised ICP, in the management of TBI (38).

Therapeutic hypothermia

Therapeutic hypothermia was previously reported useful in the management of intracranial hypertension in TBI patients (57,58). Hutchison *et al.* (59) studied 225 children who were randomized either to hypothermia (32–33 °C for 48–72 hours) or normothermia, within 8 hours of injury. They found that the hypothermia group had an increased risk of hypotension and requirement for vasoactive agents especially in the rewarming period, and increased risk of mortality. However, there were concerns raised pertaining to the use of hyperventilation, and the speed of rewarming as part of the standard protocol.

In the phase III Cool Kids multicenter trial, patients younger than 18 years old were enrolled within 6 hours of injury and randomly allocated to either hypothermia (32–33 °C for 48–72 hours) or normothermia (60). There was no significant difference in mortality or global functional outcomes at 3 months. The study was terminated for futility (60). Subsequent meta-analyses suggest that hypothermia therapy is associated with increased risk of mortality when compared to normothermia (61,62). A recent Cochrane review included both adult and pediatric TBI studies with a cooling duration of at least 12 hours, but did not find evidence that that hypothermia therapy was associated with a favorable outcome (63).

Hypothermia also has an impact on drug metabolism. For example, therapeutic hypothermia slows down phenytoin elimination thereby increasing the exposure risk for drug toxicity (64).

Hence, normothermia should be maintained in the care of a child with TBI (62,65).

Glycemic control

Hyperglycemia is known to be associated with TBI. Multifarious causes increase glucose levels and also bring about transient insulin resistance. These include but are not limited to raised levels of stress hormones, activation of inflammatory cytokine pathways, hypothalamic-pituitary-adrenal axis and sympathetic autonomic nervous system,

pituitary and/or hypothalamic dysfunction (66). Undergoing anesthesia, procedures and major surgery can also worsen hyperglycemia.

A recent retrospective study on pediatric TBI patients found that the presence of hyperglycemia at admission is associated with increased risk of mortality (67). Early hyperglycemia in TBI especially in the first twenty-four has been associated with adverse outcomes such as increased length of stay in the ICU, increased duration of invasive ventilation, higher morbidity and mortality (67-70).

Although glycemic control is crucial to minimize secondary complications due to neuron toxicity, the impact of strict glycemic control and the optimal target range in the setting of TBI has yet to be delineated based on current available literature. However, a few recent pediatric studies have shown poorer outcomes associated with a blood glucose of more than 11 mmol/L in the initial 12 to 24 hours after sustaining pediatric TBI (67,69,71).

Urgent neuroimaging

Children with TBI may have variable symptoms and signs that are age-dependent. The physician managing an acute brain injury needs to decide which child requires urgent neuroimaging. Although a computed tomography (CT) scan of the brain is able to identify and locate an intracranial bleed, it is also associated with radiation. Cancer incidence is reportedly significantly higher in children and adolescents who are exposed to CT scans compared to unexposed individuals (72).

Published clinical prediction tools (CHALICE, PECARN and CATCH) guide the physician when making neuroimaging decisions for children with head injury (73-75). Prospective observational studies comparing these prediction tools demonstrate that PECARN performed with the best sensitivity (76,77). Implementation of the PECARN prediction rule and using computerized clinical decision support to provide risks of clinically important TBI resulted in modest but variable decreases in CT use (78). A period of close monitoring potentially leads to more discretionary neuroimaging (79,80). The overall advantage of prompt diagnosis needs to be weighed against the disadvantage of radiation exposure complications.

ICP monitoring

ICP monitoring is an important component of multi-modal neurological monitoring for children with severe TBI.

Although ICP monitoring is not prognostic of neurologic or overall outcome as compared to cranial imaging modalities, its use in guiding management has been regarded as standard of care (81-83). In actual practice however, there are varied practices in initiation and application of ICP monitoring (84). This is likely contributed by uncertainty regarding effectiveness of monitoring and insufficient data on survival benefit and impact on neurological outcomes (85-87).

There has yet to be high quality randomized studies focused on the effects of ICP monitoring especially in children with severe TBI (88). A recent national study in the United States found ICP monitoring to be associated with decreased mortality only for patients with initial Glasgow Coma Scale score of 3. However the same study showed ICP monitoring to also be associated with longer ICU stay, invasive ventilation, hospitalization, and inflated hospital bills (87). Some have suggested that a standardized ICP monitoring protocol may be associated with beneficial outcomes (84). Advancements in technology such as the development of a non-invasive transfontanelle monitor may encourage routine use of ICP monitoring when managing infants with moderate to severe TBI (89).

Prophylactic anti-epileptics

Post traumatic seizures (PTS) are often subtle (90) and are more likely to occur in younger children less than 24 months old (91), those with severe injury with GCS score lower than 8 (91) and non-accidental trauma (91-95). PTS are classified as early when they occur within 7 days of the head injury (96).

Although practice is variable (97,98), electroencephalographic (EEG) monitoring and the use of antiepileptic drugs (AED) are more common among children with known risk factors for PTS (99). The literature reporting on the efficacy of prophylactic AEDs has been controversial. A randomized controlled trial of 102 children showed that phenytoin did not reduce the PTS rate within 48 hours of head injury (100). However, this study had enrolment difficulties, significant lost to follow up, and an overall low seizure rate.

While randomized controlled trials remain the gold standard to generate evidence for TBI, it has been recognized that we currently lack sufficient understanding on many basic aspects of TBI to standardize the other areas of TBI management. This could contribute to negative or failed trials (101). Here we highlight a large observational study of 275 children with TBI, which found that the

Table 1 Table of Recommendations for children with traumatic brain injury (TBI)

Domain of TBI management	Clinical considerations	Recommendations
Choice of sedatives	Mean arterial pressure (MAP) must be maintained throughout induction for endotracheal intubation and other invasive procedures	Consider etomidate in the absence of adrenal insufficiency. Consider ketamine in the presence of hypotension or hypovolemia
Applicability of hyperventilation	Hyperventilation results in brain ischemia and poorer survival rates	Avoid hyperventilation to PaCO ₂ <30 mmHg
Utility of hyperosmolar agents	3% hypertonic saline may reduce the need for concomitant interventions to treat raised intracranial pressure (ICP) (49,50)	Use of 3% hypertonic saline is recommended
Temperature control	Hypothermia is associated with potential cardiac arrhythmias and increased mortality (91,97,99,100)	Normothermia is recommended
Glycemic control	Early hyperglycemia is associated with unfavourable outcomes (67-70)	Euglycemia is recommended
Indication for neuroimaging	PECARN (75) has been shown to perform with highest sensitivity. Patients with GCS 14–15 (79) should be monitored first	The PECARN clinical prediction rule can be used to aid clinicians in their decision for urgent neuroimaging
Intracranial pressure monitoring	–	No conclusive evidence to recommend the routine use of intracranial pressure monitor
Prophylactic anti-epileptics	Anti-epileptic drugs should be considered in the presence of risk factors for post-traumatic seizures	No conclusive evidence to recommend the routine use of prophylactic anti-epileptics

use of AEDs reduced the likelihood of early PTS (91). A randomized double-blind trial in adults also reported that phenytoin was associated with a significantly lower risk of early PTS (102).

Apart from phenytoin, levetiracetam has recently surfaced as an alternative for the prevention of PTS (103). However, in a prospective observational study, early PTS occurred frequently despite prophylaxis with levetiracetam. The authors cautioned against routine use before more studies conclude its effectiveness, particularly in young children and those suspected to have abusive head trauma (104). Thus, anti-epileptic prophylaxis in children with TBI cannot be routinely recommended until further conclusive evidence emerges. AEDs should still be considered if risk factors for PTS are present.

Conclusions

Many domains of pediatric TBI management are consensus driven and lack strong evidence (*Table 1*). Developing individualized strategies based on age, clinical presentation, presence of raised ICP, within the limitations of each healthcare resource setting, would enable emergency and critical care physicians to manage children with TBI more

effectively (105).

New treatment options are being explored (89,106). Priorities for future research (107-110) have been defined and will facilitate collaborations and larger studies (111). Comparative effectiveness research (101) has emerged as a powerful tool to harness heterogeneity in TBI management strategies across multinational centers and will likely be able to address some of these pressing clinical questions.

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Footnote

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