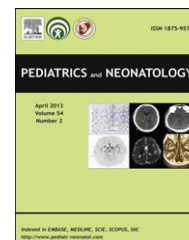


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REVIEW ARTICLE

Current Approaches to the Treatment of Head Injury in Children

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Head trauma is one of the most challenging fields of traumatology and demands immediate attention and intervention by first-line clinicians. Symptoms can vary from victim to victim and according to the victim's age, leading to difficulties in making timely and accurate decisions at the point of care. In children, falls, accidents while playing, sports injuries, and abuse are the major causes of head trauma. Traffic accidents are the main cause of disability and death in adolescents and adults. Injury sites include facial bones, muscles, ligaments, vessels, joints, nerves, and focal or whole-brain injuries. Of particular importance are cranial and intracranial injuries. A closed injury occurs when the head suddenly and violently hits an object but the object does not break through the skull. A penetrating injury occurs when an object pierces the skull and affects the brain tissue. Early diagnosis and proper management are crucial to treat patients with potentially life-threatening head and neck trauma. In this review, we discuss the different cases of traumatic brain injury and summarize the current therapies and neuroprotective strategies as well as the related outcomes for children with traumatic brain injury.

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1. Introduction

A head injury is any trauma that leads to injury of the scalp, skull, or brain, and it ranges from a minor bump on

the skull to serious brain injury. Traumatic brain injury (TBI) occurs when the brain is traumatically injured by an expected or unexpected external force.¹ TBIs can be grouped according to severity, mechanism, or specific features. The Department of Health reported that head injury is the third leading cause of death in Taiwan, and motor vehicle-related injuries ranked first among all forms of injuries. Head trauma poses a potentially devastating threat to a child's life, and international epidemiological surveys have shown that TBI is the leading cause of death

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among children of 5–15 years of age in industrialized countries.²

2. Epidemiology and Etiology

Age analysis shows a biphasic tendency; patients <5 years and those >60 years may have a higher risk of TBI.³ In general, gender distribution shows that men are more likely to have a TBI than women (2~2.8:1 in the USA). Similarly, the gender distribution of pediatric TBI in Taiwan is 1.69:1 (male:female).² TBI accounted for approximately 475,000 emergency department visits among children aged 0–14 years between 1995 and 2001,⁴ and 50,658 pediatric TBI-associated hospitalizations among children <17 years³ in the USA.

In an industrialized country such as the USA, estimates of the relative causes of TBI are as follows: motor vehicle accidents (45%), falls (30%), occupational accidents (10%), recreational accidents (10%), and non-accidental events (including child abuse, 5%).⁵ Among toddlers and the elderly, falls are more common causes of TBI, whereas motor vehicle accidents are more common among adolescents and middle-aged persons. In Taiwan, >70% of TBIs were reported to be caused by traffic accidents. In the 0–14 age group, TBI is the leading cause of death, and statistical records show that TBI accounted for 50% of deaths among children in 1993.² Since 2000, the enforcement of the motorcycle helmet law has increased the use of helmets in children in Taiwan from 1.0% to 40.2% ($p < 0.001$), but in comparison with adults (from 11.1% to 88.9%, $p < 0.001$), the situation is still far from optimal.²

3. Clinical Features of Childhood TBI

3.1. Concussion

Approximately 75–95% of TBIs have a mild clinical manifestation in the general population⁶ and pediatric mild TBI was reported to occur in 83.1% of children in one large study in Taiwan.² Concussion is the most common form of TBI. Although concussion is not usually accompanied by structural brain lesions or serious neurological residua, temporary disability because of symptoms such as nausea, headache, dizziness, and memory disturbances can occur.⁷

3.2. Seizures

Early post-traumatic seizures (EPTSs, Figure 1A) are those that occur within the first week after a head injury. These seizures are considered acute reactions and are not associated with epilepsy. In less severe TBI, the rate of EPTSs is <5%.

Evidence shows that approximately 50% of EPTSs occur within the first 24 hours after the injury, whereas approximately 25% of seizures occur in the first hour. In terms of seizure pattern after a head injury, the early onset of seizures is correlated with a generalized pattern; after the first hour, more than half are either simple partial seizures or focal with secondary generalization.^{8,9}

Early seizures cause a four-fold increase in the risk of post-traumatic epilepsy to >25%. Although anticonvulsants may be indicated in EPTSs, there is no solid evidence supporting the extended use of anticonvulsants for the prevention of post-traumatic epilepsy.^{9,10}

3.3. Contusions

Brain contusions (Figure 1B, C, and Figure 3A–D) are areas of bruising with associated localized ischemia, edema, and mass effect. They result from direct external contact forces or from the brain being slapped against intracranial surfaces with acceleration/deceleration trauma. Neurological deterioration is highly suggestive of an evolving intracranial hematoma, and usually occurs secondary to a tear in an intracranial artery or vein.¹¹

3.4. Other signs and symptoms

Early symptoms (within minutes to hours) include headache, dizziness, vertigo or imbalance, lack of awareness of surroundings, and nausea and vomiting. Over the next hours and days, affected children may also experience mood and cognitive disturbances, sensitivity to light and noise, and sleep disturbances (Figure 1D–F).^{12,13}

Occasionally, associated transient cortical neurological deficits, such as global amnesia or cortical blindness, can occur. These deficits are thought to be secondary to vascular hyperreactivity and may be trauma-induced, migraine-equivalent phenomena.¹⁴ Recently, a study by Eme showed that attention deficit-hyperactivity disorder (ADHD) after pediatric TBI is more common than the 30% rate suggested by the current literature, and guidelines for the assessment and management of ADHD associated with pediatric TBI have been provided.¹⁵

4. Neuroimaging

A systematic review estimated that the prevalence of computed tomography (CT) scan abnormalities in patients presenting to a hospital with a Glasgow outcome scale (GCS) score of 15 was 5%, and it was 30% for those presenting with a GCS of 13. Patients with mild TBI can be selected for CT scan based on the clinical criteria of the Canadian CT Head Rule,¹⁶ including a GCS <15 2 hours after injury, suspected open or depressed skull fracture, and any signs of basilar skull fracture, neurological deficit, or seizures.

Neurologically-normal patients with a normal CT scan are at low risk for subsequent neurological deterioration. In one study, of 542 patients admitted to the hospital with a 'mild' head injury and a normal initial CT scan, none showed subsequent deterioration, and none required surgery.^{17,18}

Compared with CT scanning, magnetic resonance imaging (MRI) is more sensitive for the detection of small areas of contusion or petechial hemorrhaging and axonal injury. In a case series of patients with mild TBI, abnormalities on MRI scans were reported in 30% of cases with normal CT findings.¹⁹ Diffusion tensor MRI may be more sensitive for detecting traumatic axonal injury. In one study, abnormalities on diffusion tensor MRI scan appeared to correlate with the severity of symptoms.²⁰

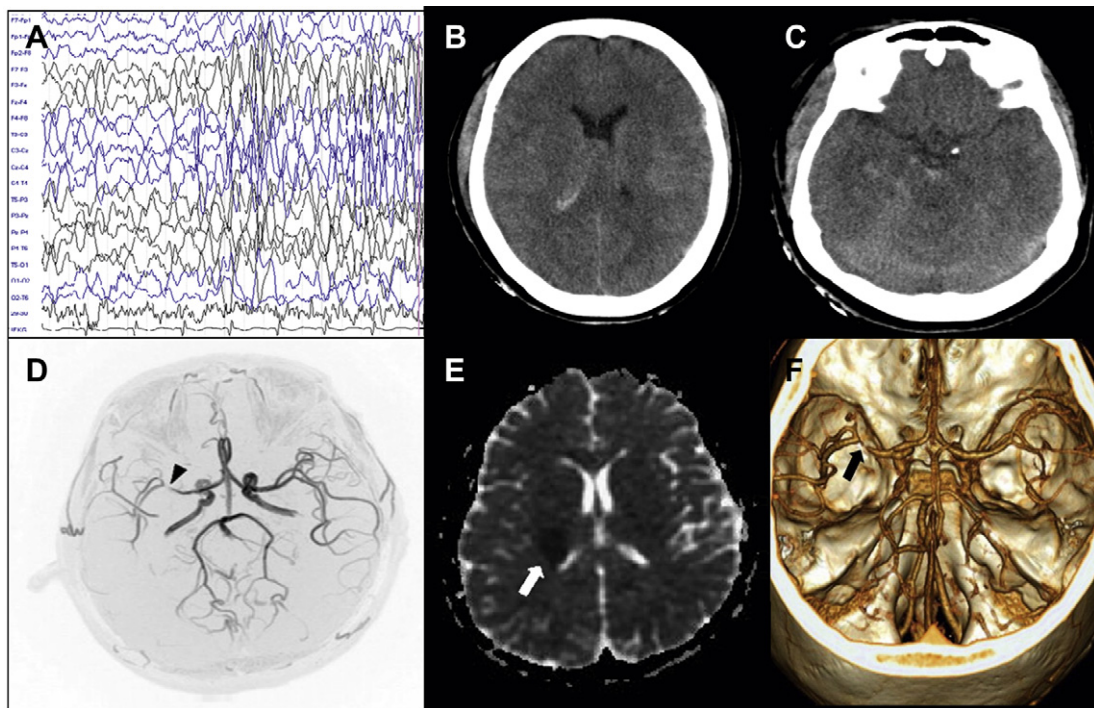


Figure 1 Brain injury with accelerated force. (A) An electroencephalography showing repetitive and active diffused epileptiform discharges in a 2-year-old boy with a subdural hemorrhage that occurred when he and his mother were hit by a car while riding a motorcycle. (B, C) Axial brain computed tomography scan showing diffused multiple hematomas in an 18-year-old girl hit by a truck. (D) Reconstructed magnetic resonance angiography results of the brain showing obvious stenosis with decreased flow at the right middle cerebral artery (black arrowhead) in a 15-year-old boy who presented with an acute and severe right-sided headache and left-sided paralysis after practicing backward somersaults. (E) The same case as in D. Apparent diffusion coefficient mapping showed a 2.4-cm low-signal area in the posterior limb of the right internal capsule, suggesting a hyperacute infarct (white arrow). (F) The same case as in D. Reconstructed computed tomography angiography of the brain depicting a narrowing of the right middle cerebral artery at the M1 section (black arrow) with decreased flow and many distal branches.

While CT is the test of choice for emergency department evaluation, MRI may have a more important role in the evaluation of patients with post-traumatic sequelae.

5. Classification

Head injuries are classified as open or closed based on the nature of the injury. Although many injuries are minor, both closed and open head injuries can result in TBI and severe damage, and may cause cognitive problems, loss of the senses such as hearing and vision, and other debilitating conditions. In the following sections, we describe each type of head injury and include images of pediatric cases.

5.1. Primary injury

5.1.1. Scalp injury

A scalp injury (Figure 2A, B) may indicate the presence of an intracranial lesion at the same site, but not able to rule out an intracranial injury if not seen.

5.1.2. Skull fracture

There are several types of skull fracture (Figure 2A, B). A vault fracture is a linear fracture that may lead to middle meningeal artery rupture and extradural hemorrhage

(EDH). A basilar fracture can cause subsequent meningeal tears and cerebral spinal fluid leakage.^{21,22}

5.1.3. Intracerebral hemorrhage

A cerebral hemorrhage is an intra-axial hemorrhage, which means that it occurs within the brain tissue. There are two types of intra-axial hemorrhage: intraparenchymal hemorrhage and intraventricular hemorrhage. As with other types of hemorrhage within the skull, intraparenchymal bleeds are a serious medical emergency because they can increase intracranial pressure (ICP). The mortality rate for intraparenchymal bleeds is >40%.²² Intracerebral hemorrhage (ICH) is classified into different types as described below.

5.1.4. Subarachnoid hemorrhage

Subarachnoid hemorrhages (Figure 3D) occur between the arachnoid and pia mater meningeal layers. Characteristically, blood is seen layering into the brain along the sulci and fissures, or filling cisterns. The classical presentation is the sudden onset of a severe headache (a thunderclap headache).^{23,24} This can be a very dangerous entity and requires emergency neurosurgical evaluation and urgent intervention.

5.1.5. Epidural hemorrhage

In epidural hemorrhage (EDH; Figure 3B), the middle meningeal artery ruptures and blood accumulates between



Figure 2 Closed and open brain injuries. (A) Axial brain computed tomography scan showing a skull fracture of the right orbital roof and soft tissue swelling (white arrow) in a 5-year-old boy who was riding a toy-car and hit a wall. (B) Axial brain computed tomography scan showing an open skull fracture and pneumocephalus over the right frontal region (white arrow) in an 8-year-old boy who fell while riding a bike on a rainy day. Soft tissue lacerations and edematous changes over the right scalp are also noted.

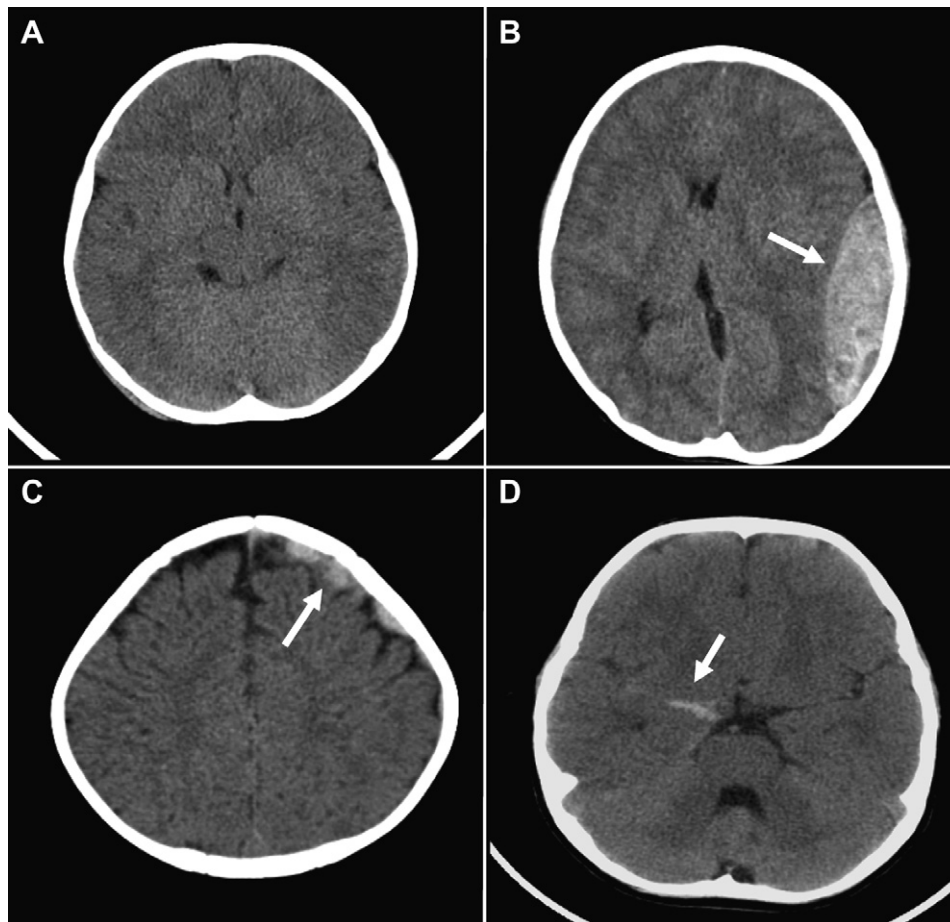


Figure 3 TBI in different locations. (A) Diffuse brain edema in a 5-year-old boy who transiently lost consciousness when involved in a car accident. The patient was not wearing a seat-belt at that time. (B) Axial brain computed tomography (CT) scan showing an epidural hemorrhage over the left frontotemporoparietal lobes in a 9-year-old boy who fell down while roller-skating. (C) Axial brain CT scan showing a left frontal subdural hemorrhage in a 1-year-old boy with a history of head injury due to an accidental fall at home. (D) Axial brain CT scan showing a subarachnoid hemorrhage with a prominent enhancement over the left middle cerebral artery in a 2-year-old boy who presented with a left hemiplegia after a motorcycle accident.

the dura mater and the skull. This is a very dangerous type of injury because the bleed is from a high-pressure system and can lead to rapid and deadly increases in ICP.²⁵ It is estimated that before neurological deterioration, 20–50% of persons with EDH have a 'lucid interval' following a brief loss of consciousness or period of confusion.

5.1.6. Subdural hemorrhage

Subdural hemorrhage (SDH; [Figure 3C](#)) occurs when trauma results in the tearing of bridging veins or dura. The presentation may be acute, subacute, or chronic.²⁶ SDH in more than one location, mixed density, and chronic SDH are more common among children with inflicted injuries, especially with unexplained events and mechanisms.

5.2. Secondary injury

Secondary brain damage in TBI is usually considered to be due to a cascade of molecular injury mechanisms that are triggered at the time of the initial trauma and continues for hours or days. These mechanisms include²⁷ neurotransmitter-mediated excitotoxicity involving glutamate, free-radical injury to cell membranes, electrolyte imbalances, secondary ischemia from vasospasm, focal microvascular occlusion, vascular injury, and others.

6. Acute Evaluation and Management

The primary assessment of a patient with head trauma follows the ABC prioritization scheme: airway, breathing, and circulation.

6.1. Airway and breathing

Children with clear consciousness and normal blood pressure can be managed with supplemental oxygen alone. Advanced airway management may be required to maximize oxygenation and ventilation and to protect against the aspiration of gastric contents in the following situations:²⁸

- decreased level of consciousness (GCS <9);
- marked respiratory distress; and
- hemodynamic instability.

Cervical spine immobilization must be maintained during airway procedures. Nasotracheal intubation should not be performed in patients with midface trauma or basilar skull fracture.

With the exception of cases of severely depressed consciousness, endotracheal intubation is accomplished by using a rapid-sequence technique with the application of cricoid pressure and pre-oxygenation. The following medications should be administered to children with head injuries:²⁹

- Pretreatment – lidocaine may minimize any increase in ICP associated with airway manipulation.
- Sedative agents – etomidate and thiopental have neuroprotective properties and are therefore preferred as sedative agents for children with TBI. Thiopental causes vasodilatation and myocardial depression and

may result in a decrease in systolic blood pressure, therefore it should not be used in patients who are hemodynamically unstable.

- Paralytic agents – although increased ICP has been associated with the use of succinylcholine in patients with brain tumors, there is no definitive evidence that succinylcholine causes a rise in ICP in humans with brain injury.³⁰ However, the risks associated with succinylcholine in children with undiagnosed neuromuscular conditions and a longer duration of paralysis related to rocuronium in patients with airway problems are issues of concern.

Hyperventilation produces hypocapnia, leading to vasoconstriction and decreased cerebral blood flow (CBF). Decreased CBF has been associated with poor outcomes in children with TBI, and severe hypocapnia (PaCO₂ <30 mmHg) has been associated with increased mortality. Patients should only receive temporary hyperventilation (to reduce PaCO₂ to 30–35 mmHg) with signs and symptoms of impending herniation.³¹

6.2. Circulation

The outcomes of children with severe TBI who are hypotensive at initial evaluation are typically poor.³² Isotonic solutions should be used for fluid resuscitation. Blood products should be administered as indicated. In one study of 118 children with moderate to severe TBI and documented hypotension, fluid therapy during early resuscitation was associated with significantly lower mortality (30% vs. 56%) and significantly better functional neurological outcome.³³

The target blood pressure required to maintain the minimum cerebral perfusion pressure is that necessary to meet cerebral metabolic demands. Systolic blood pressures should be maintained above the fifth percentile for age and gender, and improved outcomes have been reported for patients with substantially higher initial blood pressures.³²

6.3. Other initial management considerations

Interventions that are typically used to treat children with severe TBI can improve intermediate outcomes such as ICP, cerebral oxygen consumption, and CBF. Evidence that these treatments improve long-term clinical outcomes is largely indirect.

The head should be kept in a neutral position to avoid jugular venous obstruction. In prospective observational studies, elevating the head to 30° appears to optimize cerebral perfusion pressure and decrease ICP in adult patients, provided that the mean arterial pressure is maintained.³⁴

Adequate sedation and pharmacological paralysis facilitate the safe transportation of intubated children with severe TBI. Oxygenation, ventilation, and blood pressure must be vigilantly monitored in patients who are sedated, with or without paralysis. Limited evidence suggests that cerebral oxygen consumption may be decreased in patients treated by neuromuscular blockade.³⁵

Seizures occurring immediately after severe TBI may increase the brain's metabolic demands and ICP, leading to secondary brain injury. Prophylactic treatment with anti-convulsants reduces the incidence of EPTS among children with severe TBI.³⁶ Experts recommend that children receive anticonvulsant therapy during the first week following severe TBI.³⁷ In our experience, valproic acid is the most commonly-used drug for EPTS, while phenytoin and carbamazepine are both also effective.

Hyperthermia should be aggressively prevented and treated.³⁸ Therapeutic hypothermia has been shown to be beneficial in term neonates after hypoxic-ischemic encephalopathy and in pediatric TBI.³⁹ Hypothermia decreases cerebral metabolism and may reduce CBF and ICP. In addition, it has been suggested to inhibit a myriad of destructive processes that occur after ischemia–reperfusion, including excitotoxicity, neuro-inflammation, apoptosis, free-radical production, seizure activity, blood–brain barrier disruption, and blood vessel leakage.⁴⁰ Although there is no solid evidence supporting hypothermia in pediatric TBI, based on studies in adults therapeutic options include the avoidance of hyperthermia and the consideration of hypothermia for refractory ICP. A target body temperature of 32–33 °C (moderate hypothermia) is recommended according to the current Cool Kids Trial.⁴¹

The effectiveness of mannitol for decreasing ICP in patients with TBI has been demonstrated by extensive clinical experience and in several small series, including adult and pediatric patients.⁴² Evidence from small randomized trials and observational reports suggests that hypertonic saline, administered either as a bolus or as a constant infusion, is effective for reducing ICP.

Hyperglycemia is a marker for the severity of injury, and elevated blood sugar contributes to poor outcome by worsening brain tissue lactic acidosis.⁴³ In an observational study of 101 children <14 years of age who underwent emergent craniotomy for TBI, perioperative hyperglycemia (serum glucose level ≥ 200 mg/dL) was found in 45% of children and was significantly associated with an age of <4 years, GCS ≤ 8 , and the presence of multiple traumatic lesions.⁴⁴ Therefore, maintaining serum glucose levels at ≤ 200 mg/dL is strongly recommended for children with head injury.

Existing research has failed to show that corticosteroids are beneficial for the treatment of patients with head injuries. A large, prospective, multicenter trial has, however, described increased mortality among patients with acute TBI who received corticosteroids.⁴⁵

Immobilization and protection prevent further bleeding events after TBI. Fresh frozen plasma, platelet concentrates, coagulation cofactors (vitamin K) and anti-fibrinolytic agents (tranexamic acid) are used to stop bleeding. Surgical intervention may play a role in stopping life-threatening hemorrhages. Studies have shown that the administration of recombinant coagulation factor VIIa may correct the coagulopathy and stop bleeding.⁴⁶

A patient with an EDH may require emergent drainage through a burr hole.⁴⁷ Decompressive craniectomy for children with severe TBI and refractory intracranial hypertension may be most appropriate in patients meeting some or all of the following criteria:^{48,49}

- diffuse cerebral swelling on cranial CT imaging;
- within 48 hours of injury;
- no episodes of sustained ICP >40 mm Hg before surgery;
- GCS >3 at some point subsequent to injury;
- secondary clinical deterioration; and
- evolving cerebral herniation syndrome.

6.4. Monitoring

Initial monitoring includes the measurement of heart rate, blood pressure, and pulse oximetry. Capnography should be used to monitor end-tidal CO₂ to avoid excessive hyperventilation.⁵⁰

ICP monitoring is recommended for children who have an abnormal initial head CT scan and an initial GCS score between 3 and 8. Children who may need ICP monitoring should be admitted to a pediatric intensive care unit at a trauma center.

6.5. Observation and disposition

Observation is recommended for at least 24 hours after a mild TBI because of the risk of intracranial complications. Hospital admission is recommended for patients at risk for immediate complications from head injury.⁵¹ These include patients with:

- GCS <15 ;
- abnormal CT scan: intracranial bleeding or cerebral edema;
- seizures; and
- underlying bleeding diathesis or oral anticoagulation.

While neurosurgical intervention in the admitting hospital may be preferred, it may not be required if the CT scan is normal. Most patients with an abnormal CT scan should have a follow-up study within 24 hours, regardless of clinical status.^{52,53}

6.6. Outcome and sequelae

Despite physical improvement within the first 6 months after injury, psychosocial complications remain a persistent long-term problem for most individuals with TBI. Morton et al suggested that the psychosocial problems associated with TBI may be the major challenge facing rehabilitation.⁵⁴ EPTS is not rare in childhood TBI and has a particularly high incidence in moderate and severe childhood TBI,⁵⁵ suggesting that anticonvulsant therapy should be used as a protective treatment for childhood EPTS. Prolonged anticonvulsant therapy is still controversial, but may also be beneficial for these patients.⁵⁶ In addition, because of the similarity in the incidence of ocular and vision sequelae between adults and children with brain injuries, children with a history of head trauma should receive a complete optometric evaluation.⁵⁷ Whereas emergency management and critical care of the patient with TBI may improve the outcome, public health measures aimed at

prevention may be more effective in reducing death and disability from TBI than acute management.

6.7. Current preclinical studies of pediatric TBI

Oxidative stress leading to free radical-induced damage, and membrane lipid peroxidation (LP) in particular, are among the most validated secondary injury mechanisms in preclinical TBI models, implying that antioxidants that simultaneously scavenge LP-initiating free radicals may inhibit LP propagation and remove neurotoxic LP byproducts.^{58,59} S-nitrosoglutathione, a nitrosylation-based signaling molecule, was reported to reduce brain levels of peroxynitrite and oxidative metabolites and also improve neurological function in TBI, stroke, and spinal cord injury. Khan et al showed that that S-nitrosoglutathione reduces the levels of oxidative metabolites, protects the neurovascular unit, and promotes neurorepair mechanisms in experimental TBI.⁶⁰ Erythropoietin (EPO) has been demonstrated to have neuroprotective effects after ischemic, hypoxic, metabolic, neurotoxic, and excitotoxic stress, as well as limiting the production of reactive oxygen species in the nervous system.⁶¹ Our recent study also demonstrated that EPO ameliorates multiple sclerosis in an experimental model via the augmentation of endogenous heme oxidase 1 – an important antioxidant.⁶² Furthermore, the neuroprotective effects of EPO have been defined in TBI experimental models, suggesting that EPO is a potential candidate for the treatment of human TBI. Nevertheless, further clinical trials should address the role of complementary antioxidants in pediatric TBI.

7. Concluding Remarks

The rapid identification and stabilization of children with severe TBI is essential for the effective initial management of focal injuries and to prevent conditions that contribute to secondary brain injury. Severe TBI is defined by an initial GCS score of <9 and associated injuries contribute to poor outcomes. Brain injury occurs as a result of the primary insult and secondary events, including the brain's response to the injury and related factors, such as hypoxia and hypotension.

Evaluation of TBI includes a primary assessment to identify life-threatening injuries, followed by a thorough physical examination. The GCS score should be determined and a thorough neurological examination should be performed. The initial imaging of head injuries should be performed by CT scan.

The management of severe TBI includes aggressively maintaining oxygenation, ventilation, and blood pressure. The head should be elevated to 30°, provided that the mean arterial pressure can be maintained. Children with severe TBI should receive anticonvulsants to prevent EPTS.

Immediate management decisions include indications for intubation and emergent neurosurgical consultation. Impending herniation is an emergency situation, and initial treatment with hyperosmolar therapy rather than hyperventilation is recommended in these cases. We prefer mannitol to hypertonic saline for the initial management of these patients. We suggest that patients who do not

respond to hyperosmolar therapy be treated with hyperventilation (PaCO₂ 30–35 mmHg).

Children with moderate or severe TBI who have associated injuries or whose clinical condition is deteriorating should be treated at a trauma center with pediatric capability whenever possible.

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