Published in final edited form as:

Anesthesiol Clin. 2012 June ; 30(2): 333–346. doi:10.1016/j.anclin.2012.04.003.

Perioperative Management of Adult Traumatic Brain Injury

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Synopsis

This article presents an overview of the management of traumatic brain injury (TBI) as relevant to the practicing anesthesiologist. Key concepts surrounding the pathophysiology, anesthetic principles are used to describe potential ways to reduce secondary insults and improve outcomes after TBI.

Keywords

perioperative management; cerebral resuscitation

Introduction

Traumatic brain injury (TBI) is a major public health problem and a leading cause of death and disability.¹ Approximately 1.7 million people sustain TBI annually in the United States, accounting for 275,000 hospitalizations and 52,000 deaths.¹ Traumatic brain injury is a contributing factor in about one-third of all trauma deaths and affects primarily children aged 0–4 years, adolescents aged 15–19 years and elderly aged ≥ 65 years with males being more affected.¹ Falls and motor vehicle-traffic injury are the leading causes of TBI in the United States.¹ Multidisciplinary research efforts have led to the development of evidence-based guidelines for pre-hospital and intensive care management of TBI.^{2–13} However, evidence-based guidelines specific for intraoperative and anesthetic management do not exist and intraoperative recommendations are frequently based on extrapolation from these other guidelines, physiological and pharmacological data and limited direct evidence.

Pathophysiology of Traumatic Brain Injury

Following TBI, the primary injury to the brain is caused by the initial mechanical impact resulting in skull fracture, brain contusion, vascular and parenchymal injury causing intracranial bleed and increased intracranial pressure (ICP).¹⁴ This is followed by an inflammatory process, edema formation and excitotoxicity, resulting in further increase in

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ICP and reduced cerebral perfusion pressure (CPP).^{14,15} While the severity of primary injury is the major factor determining the outcome of TBI patients, secondary damage to the brain tissue caused by physiological perturbations (*secondary insults*) contribute further to the worsening of outcomes.^{14,15} The most important secondary insults are hypotension [systolic blood pressure (SBP) < 90 mmHg in adult patients] and hypoxemia (PaO₂ < 60 mmHg)¹⁶ which are independently associated with increased morbidity and mortality from severe TBI.¹⁷⁻¹⁹ Other common secondary insults include hypoglycemia, hyperglycemia, hypercarbia, hypocarbia, and raised ICP.²⁰⁻²⁵ All these can manifest both early and late in the course of TBI (Table 1). Moreover, the consequences of TBI may be evident in other organ and systems besides the brain and may require prompt attention (Table 2). **Sections ▼**

Importance of Perioperative Period

Current TBI management focuses on prevention of primary injury and avoidance of secondary injuries. The key elements of TBI management are early resuscitation and hemodynamic optimization, emergent surgical evacuation of mass lesions, control of ICP, support of CPP and optimization of physiological milieu. The immediate perioperative period may be particularly important in the course of TBI management because despite the aggressive interventions to rapidly correct hypoxemia, hypotension, hypo and hypercarbia, hypoglycemia and hyperglycemia in the emergency department, one or more of these complicating factors may persist or remain undetected as the patient is transported to the operating room. Hence, the perioperative period provides an opportunity to continue and refine ongoing resuscitation, and to correct pre-existing secondary insults. Moreover, surgery and anesthesia may predispose to new onset secondary insults, which may contribute adversely to outcomes.

Since secondary injury is potentially preventable and treatable, the perioperative period may be a window to initiate interventions that may improve the outcome of TBI. Perioperative management involves rapid evaluation, continuation of resuscitation (cerebral and systemic), early surgical intervention, intensive monitoring and anesthetic planning.

Initial Assessment and Ongoing Resuscitation

The initial assessment and stabilization is usually achieved as soon as the patient arrives in the emergency department. Nevertheless, another rapid but relevant assessment should be performed as the patient is received in the operating room. This should involve evaluation of airway, breathing and circulation, a rapid assessment of neurological status and associated extracranial injuries as well as evaluation of anemia, coagulopathy, glycemia and the presence of adequate vascular access. Information about time and mechanism of injury can be valuable. Brief neurological assessment is performed using Glasgow Coma Scale (GCS)²⁶ score and pupillary responses. Associated thoracic, abdominal, spinal and long bone injuries may be stable or evolve during the perioperative period and must be considered in differential diagnosis of new onset hypotension, anemia, hemodynamic instability or hypoxemia during anesthesia and surgery.

Airway Management

While many patients arrive in the operating room already intubated, some, particularly those with extradural hematoma, may be conscious and breathing spontaneously. Airway management in TBI is complicated by a number of factors, including urgency of situation (because of pre-existing or worsening hypoxia), uncertainty of cervical spine status, uncertainty of airway (due to presence of blood, vomitus, debris in the oral cavity or due to laryngo-pharyngeal injury or skull base fracture), full stomach, intracranial hypertension and uncertain volume status. All TBI patients requiring urgent surgery must be considered to

have full stomach and airway management must account for possible underlying cervical spine injury.^{27,28}

Technique - best practices

The choice of technique for tracheal intubation is determined by urgency, individual expertise and available resources and generally incorporates rapid sequence intubation with cricoid pressure and manual in-line stabilization.²⁹ The anterior portion of the cervical collar may be removed when manual in-line stabilization is established to allow greater mouth opening and facilitate laryngoscopy. Newer airway devices, particularly videolaryngoscopes, have gained popularity in recent years for use in trauma victims and may be useful in difficult airway scenarios.³⁰ Nasal intubation should be avoided in patients with base of skull fracture, severe facial fractures or bleeding diathesis. In any case, it is advisable to have a back-up plan ready in case of difficult intubation, given the significant risk of intracranial hypertension resulting from increased cerebral blood volume (CBV) because of hypoxemia and hypercarbia.

Appropriate pharmacological selection is important for uncomplicated airway management. Sodium thiopental, etomidate and propofol decrease cerebral metabolic rate for oxygen (CMRO₂) and attenuate increases in ICP with intubation. However, propofol and thiopental may cause cardiovascular depression leading to hypotension. Etomidate offers the advantage of hemodynamic stability during induction but may cause adrenal insufficiency leading to delayed hypotension.³¹ Ketamine, which causes limited cardiovascular compromise, has been associated with increased cerebral blood flow (CBF) and increased ICP, and may be relatively contraindicated for intubating patients with pre-existing intracranial hypertension.³² The choice of muscle relaxant for rapid sequence induction is between succinylcholine and rocuronium.³³ Succinylcholine may contribute to increased ICP,^{34,35} the clinical significance of which is questionable.^{36,37} More importantly, hypoxia and hypercarbia during airway interventions are more likely to cause clinically significant increases in ICP. Hence, in patients with TBI, succinylcholine may not be avoided if difficult airway is anticipated.³⁷

Anesthetic Management

The major goals of anesthetic management of TBI are to facilitate early decompression, provide adequate analgesia and amnesia, treat intracranial hypertension and maintain adequate cerebral perfusion, provide optimal surgical conditions, and avoid secondary insults such as hypoxemia, hyper and hypocarbia, hypo and hyperglycemia.

Anesthetic technique

Intravenous anesthetic agents including thiopental, propofol and etomidate cause cerebral vasoconstriction and reduce CBF, cerebral blood volume, CMRO₂ and ICP.³⁸ Opioids have no direct effects on cerebral hemodynamics when the ventilation is controlled.³⁹ All volatile anesthetic agents (isoflurane, sevoflurane, desflurane) decrease CMRO₂ but may cause cerebral vasodilation, resulting in raised ICP. However, at less than 1 minimum alveolar concentration (MAC) concentration, the cerebral vasodilatory effects are minimal and hence inhaled anesthetics may be used in low concentrations in patients with TBI.⁴⁰ Nitrous oxide should be avoided since it increases CMRO₂ and causes cerebral vasodilation and increased ICP.⁴¹ Importantly, the effects of anesthetic agents on outcome of TBI have not been demonstrated and inhaled as well as intravenous anesthetic agents may be used judiciously. More importantly, the principles of anesthetic management should adhere to the guidelines for the management of severe TBI (Table 3).²⁻¹³

Ventilation

Ventilation should be adjusted to ensure adequate oxygenation ($\text{PaO}_2 > 60$ mmHg) and normocarbica (PaCO_2 35-45 mmHg). Monitoring arterial PaCO_2 is recommended and hypercarbia ($\text{PaCO}_2 > 45$ mmHg) induced increases in CBF resulting in further increased ICP should be avoided.¹² Hyperventilation should be used judiciously for short-term control of ICP and to facilitate surgical exposure during craniotomy. Excessive and prolonged hyperventilation may cause cerebral vasoconstriction leading to ischemia. Normocarbica should be restored before dural closure. It is ideal to monitor cerebral oxygenation and CBF during prolonged hyperventilation. In the intraoperative period, this may be accomplished by jugular venous oximetry^{9,42} and in the postoperative period by brain tissue oxygenation (PbtO_2) or CBF monitoring (e.g. using Transcranial Doppler ultrasonography).⁹

Monitoring

In addition to standard American Society of Anesthesiology (ASA) monitors, arterial catheterization is recommended for continuous blood pressure monitoring, blood gas analysis and glucose sampling in patients who require surgical intervention. Central venous catheterization may be useful for resuscitation but it is advisable not to delay surgical evacuation of expanding intracranial hematoma for the institution of invasive monitoring. According to the current guidelines, ICP monitoring is recommended in all salvageable patients with a severe TBI (GCS < 9) and an abnormal CT scan (hematomas, contusions, swelling, herniation or compressed basal cistern), and in patients with severe TBI with a normal CT scan if two or more of the following features are present: age > 40 years, unilateral/bilateral motor posturing, or SBP < 90 mmHg.⁵ The use of multimodal monitoring for postoperative and intensive care of patients with TBI is increasing and monitoring cerebral oxygenation (global or focal) or CBF and metabolism parameters may be helpful in making important treatment decisions.⁹ Jugular venous oximetry is often useful for assessment of adequacy of global cerebral oxygenation.⁴³ The indications are generally the same as those for ICP monitoring and jugular venous oxygen saturation values < 50% may indicate the need to optimize ventilation, systemic hemodynamics or institute ICP lowering measures.⁴³ Brain tissue oxygen monitors have the advantage of identifying focal areas of ischemia which may not be picked up by jugular venous oximetry.⁴³ Brain tissue $\text{PO}_2 < 15$ mmHg indicates ischemia.⁴³ Near Infrared Spectroscopy (NIRS) offers the capacity to conveniently and non-invasively monitor cerebral oxygen in the intensive care unit.⁴³ Transcranial Doppler (TCD) ultrasonography is a non-invasive, nonradioactive, bedside monitor, which can provide useful instantaneous cerebrovascular information including changes in cerebral blood flow velocity, cerebral vasospasm and autoregulation.⁴⁴

Intravenous Fluids, Blood Pressure Management and Vasopressor Use

Hypotension following TBI is well known to adversely affect outcomes. Therefore, blood pressure management, including choice of fluids and vasopressors, is of paramount importance. Brain Trauma Foundation guidelines for the management of TBI recommend avoiding hypotension (SBP < 90 mmHg) and maintaining CPP between 50 and 70 mmHg.^{2,8} Hypotension during craniotomy also contributes to adverse outcomes and is frequently encountered at the time of dural opening.⁴⁵ This “decompression hypotension” may be predicted by low GCS score, absence of mesencephalic cisterns on computed tomographic (CT) scan and bilateral dilated pupils.⁴⁵ Moreover, the presence of multiple CT lesions, subdural hematoma, maximum thickness of CT lesion and longer duration of anesthesia increase the risk for intraoperative hypotension, and anesthesiologists can use the presence of these factors to anticipate and expediently address these complications.⁴⁶ Perioperative hypotension should be treated promptly. Warm, non-glucose containing

isotonic crystalloid solution is preferable for intravenous administration in TBI patients. The role of colloid, however, is controversial. A *post-hoc* analysis of the Saline versus Albumin Fluid Evaluation (SAFE) study demonstrated that resuscitation with albumin was associated with higher mortality and unfavorable neurological outcome at 24 months.⁴⁷ Hypertonic saline may be beneficial resuscitation fluid for TBI patients because it increases intravascular fluid and decreases ICP. However, a double-blind randomized controlled trial comparing prehospital resuscitation of hypotensive TBI patients with hypertonic saline with standard fluid resuscitation protocols found no difference in neurological outcome at 6 months.⁴⁸ Data comparing the effectiveness of commonly used vasopressors in TBI are limited and indicate that the effects of norepinephrine and dopamine on cerebral blood flow velocity^{49,50} and cerebral oxygenation or metabolism⁵¹ are comparable but the former produces more predictable and consistent effect⁵⁰ while the later may lead to higher ICP.⁴⁹ A recent single-center retrospective study of patients with severe TBI who received phenylephrine, norepinephrine or dopamine reported maximum increase in MAP and CPP from baseline with phenylephrine use with no difference in ICP.⁵² Current evidence does not support preference of one vasopressor over the other to support cerebral perfusion and the choice may have to be individualized to patient characteristics.

Blood Transfusion

Anemia is associated with increased in-hospital mortality⁵³ and poor outcome in TBI.^{54,55} Yet, there is little evidence to support red blood cell transfusion to correct anemia in TBI. Anemia may cause cerebral injury via various possible mechanisms including tissue hypoxia, reactive oxygen species induced damage, inflammation, disruption of blood-brain barrier (BBB) function, vascular thrombosis and anemic cerebral hyperemia.⁵⁶ It may also impair cerebral autoregulation.⁵⁷ However, a number of cerebroprotective physiological mechanisms become effective with anemia which include aortic chemoreceptor activation, increased sympathetic activity leading to increased heart rate, stroke volume and cardiac index, reduced systemic vascular resistance, and enhanced oxygen extraction. Moreover, a number of cellular mechanisms of cerebral protection become effective. These include increased Hypoxia Inducible Factor (HIF), nitric oxide synthase and nitric oxide in the brain (nNOS/NO), erythropoietin and vascular endothelial growth factor (VEGF) mediated angiogenesis and vascular repair.⁵⁶ Besides increasing the oxygen-carrier capacity of blood, red blood cell transfusion increases the circulating volume and can increase CBF in patients with impaired cerebral autoregulation secondary to the TBI. However, most studies have failed to demonstrate a consistent improvement in brain tissue oxygenation (PbtO₂) with blood transfusion.^{58,59} In fact, the increased hematocrit after red cell transfusion may potentially decrease CBF and increase the risk of cerebral ischemia.⁶⁰ The overall effects of anemia on the brain may depend on the relative balance between the competing protective and harmful factors of anemia and blood transfusion, and it is unclear whether transfusion trigger in patients with TBI should be any different from other critically ill patients. Although the optimal hemoglobin level in TBI patients is unclear, there is no benefit of a liberal transfusion strategy (transfusion when Hb <10 g/dl) in moderate to severe TBI patients and it is not recommended.⁵⁵

Coagulopathy and Factor VII

Coagulation disorders may be present in approximately one-third TBI patients and is associated with an increased mortality and poor outcome.⁶¹ Brain injury leads to the release of tissue factor. Later, pro-coagulant factors are activated resulting in thrombin formation and conversion of fibrinogen to fibrin. Disseminated intravascular coagulation (DIC) inhibits the antithrombotic mechanism, causing imbalance of coagulation and fibrinolysis. Patients with GCS 8, Injury Severity Score (ISS) 16, associated cerebral edema,

subarachnoid hemorrhage and midline shift are likely to have coagulopathy.⁶² Currently, there are no guidelines for management of coagulopathy in TBI although hemostatic agents including antifibrinolytic agents such as tranexamic acid and pro-coagulant drugs such as recombinant activated factor VII (rFVIIa) are sometimes used. A Cochrane review found two randomized controlled trials that evaluated the effects of rFVIIa, but both the trials were too small to draw a conclusion regarding the effectiveness of rFVIIa for TBI patients.⁶³ The Clinical Randomization of Antifibrinolytics in Significant Hemorrhage (CRASH-2) trial, a large international placebo-controlled trial evaluating the effect of tranexamic acid on death, vascular occlusion events and blood transfusion in adult trauma patients, demonstrated that tranexamic acid was associated with a reduction of mortality.⁶⁴

Hyperosmolar Therapy

Mannitol is commonly used for hyperosmolar therapy and there is no level-1 evidence supporting the use of one agent over another. The recommended dose of mannitol is 0.25-1 g/kg body weight. Due to osmotic diuresis, which can result in hypovolemia and hypotension, it is recommended only in presence of signs of transtentorial herniation or progressive neurological deterioration not attributable to extracranial causes.³ In patients with severe TBI and elevated ICP refractory to mannitol treatment, 7.5% hypertonic saline administered as second tier therapy can increase cerebral oxygenation and improve cerebral and systemic hemodynamics.⁶⁵

Glycemic Control

Hyperglycemia after TBI is associated with increased morbidity and mortality.⁶⁶⁻⁶⁸ It is unclear to what extent it reflects the injury severity,⁶⁹ or contributes to worse outcomes by itself.^{69,70} Nevertheless, hyperglycemia can cause secondary brain injury, leading to increased glycolytic rates evidenced by increased lactate/pyruvate ratio, resulting in metabolic acidosis within brain parenchyma, overproduction of reactive oxygen species, and ultimately neuronal cell death.⁶⁹⁻⁷² Some early studies reported lower mortality with that intensive insulin therapy (target blood glucose 80-110 mg/dl) in critically ill patients.⁷³ However, more recent studies not only failed to demonstrate the mortality benefit of intensive insulin therapy but also found an increased risk of hypoglycemia.^{74,75} Hence, tight glucose control with intensive insulin therapy remains controversial. While a number of studies have investigated hyperglycemia in adult TBI in different contexts (admission vs. ICU, transient vs. persistent, early vs. late, etc.), the intraoperative data are scarce. Nonetheless, intraoperative hyperglycemia is common in adults undergoing urgent/emergent craniotomy for TBI with up to 15% patients experiencing new onset hyperglycemia which may be predicted by severe TBI, the presence of subdural hematoma, preoperative hyperglycemia, and age $\geq$ 65 years. Similarly, perioperative hyperglycemia during craniotomy for TBI is common in children, hypoglycemia in the absence of insulin treatment is not rare, and TBI severity and the presence of subdural hematoma predict intraoperative hyperglycemia.⁶⁸ Given the current evidence for glucose control for TBI in perioperative period, a target glucose range of 80-180 mg/dl seems reasonable.

Therapeutic Hypothermia and Steroids

Hypothermia reduces cerebral metabolism during stress, reduces excitatory neurotransmitters release, attenuates BBB permeability, and has been used for brain protection in TBI patients for decades. Yet, clinical evidence in terms of mortality and functional outcomes is still inconclusive. A recent meta-analysis reported statistically insignificant reduction in mortality and increased favorable neurological outcome with hypothermia in TBI.⁷⁶ The benefits of hypothermia were greater when cooling was maintained for more than 48 hours, but the potential benefits of hypothermia may likely be

offset by a significant increase in the risk of pneumonia.⁷⁶ These observations support previous findings that hypothermic therapy constitutes a beneficial treatment of TBI in specific circumstances. Accordingly, the BTF/AANS guidelines task force has issued a Level III recommendation for optional and cautious use of hypothermia for adults with TBI.⁴ Steroids have not been shown to improve outcomes or lower ICP in TBI.¹³ In fact, findings from a randomized multicenter study on the effect of corticosteroids (MRC CRASH trial) showed that administration of methylprednisolone within 8 hours of TBI was associated with higher risk of death, and the risk of death or severe disability was more compared to placebo.⁷⁷ Therefore, the use of high-dose methylprednisolone is contraindicated in patients with moderate or severe TBI.¹³

Summary

The Perioperative period is a critical period for TBI management and TBI outcomes. While it may predispose the patient to new onset secondary injuries which may contribute adversely to outcomes, it is also an opportunity to detect and correct undiagnosed pre-existing secondary insults. It may also be a potential window to initiate interventions that may improve the outcome of TBI. While more research focused specifically on the intraoperative and perioperative TBI management is awaited, clinical management should continue to be based on physiological optimization.

Acknowledgments

Funding Support: 5R01NS072308-02

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Key Points

1. Traumatic brain injury is a major public health concern.
2. Secondary insults are common after TBI and include physiological derangements such as hypotension, hypocarbia, hyperglycemia and hypoxemia.
3. The perioperative period is window of opportunity for anesthesiologists to prevent and reduce the burden of secondary insults after TBI.
4. The choice of anesthetic agent must consider the pathophysiological processes after TBI as well as the effects of the anesthetic agents.

Table 1
Time Course and Mechanisms of Secondary Insults in Traumatic Brain Injury

Secondary Insult	Early Causes	Delayed Causes
Hypoxemia	Aspiration Apnea Pneumothorax Pulmonary Contusion Endobronchial Intubation Neurogenic Pulmonary Edema	Adult Respiratory Distress Syndrome Ventilator Acquired Pneumonia Transfusion Related Acute Lung Injury Pulmonary Embolism
Hypotension	Associated High Spinal Cord Injury Long Bone Fracture Thoracic/Abdominal bleeding	Shock Sepsis
Hypercarbia	Apnea Brainstem Injury Inadequate Ventilation	Iatrogenic (opioids) Pneumonia
Hypocarbia	Unwanted Hyperventilation	Unwanted hyperventilation
Hyperglycemia	Stress	Persistent/New onset
Seizures	Electrolyte Abnormalities Hypoglycemia	Syndrome of Inappropriate Antidiuretic Hormone
Vasospasm	-	In patients with traumatic subarachnoid hemorrhage
Intracranial Hypertension	Mass effect of hematoma Herniation	Cerebral edema

Table 2
Multisystem Effects of Traumatic Brain Injury

Cardiopulmonary
<ul style="list-style-type: none"> • Abnormal breathing patterns/apnea/hypoventilation • Neurogenic pulmonary edema • Pulmonary embolism • Adult Respiratory Distress Syndrome (ARDS) • Neurogenic stunned myocardium/myocardial ischemia <ul style="list-style-type: none"> ○ Abnormal electrocardiographic patterns ○ Elevated cardiac isoenzymes (CK MB and creatinine kinase) ○ Left ventricular dysfunction
Metabolic
<ul style="list-style-type: none"> • Hyperglycemia and insulin resistance • Increased catecholamine levels • Increased caloric demand and nitrogen loss
Autonomic Dysfunction Syndrome
<ul style="list-style-type: none"> • Hypertension, tachycardia • Fever, tachypnea • Pupillary dilatation • Extensor posturing
Endocrine
<ul style="list-style-type: none"> • Anterior pituitary insufficiency • Posterior pituitary insufficiency • Diabetes insipidus (DI) • Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Hematologic
<ul style="list-style-type: none"> • Coagulopathy (↓ platelet count and/or ↑ International Normalized Ratio and/or activated partial thromboplastin time) • Disseminated Intravascular Coagulation (DIC)
Gastrointestinal
<ul style="list-style-type: none"> • Cushing's ulcers (stress ulcers) • Gastrointestinal dysfunction and increased mucosal permeability

Table 3
Recommendations from the 2007 guidelines for management of severe traumatic brain injury[2-13]

Parameters	Recommendations
Blood pressure	<ul style="list-style-type: none"> Monitor and avoid hypotension (Systolic Blood Pressure < 90 mmHg). (level II)
Oxygenation	<ul style="list-style-type: none"> Monitor and avoid hypoxia (PaO₂ < 60 mmHg or oxygen saturation < 90%) (level III)
Hyperventilation	<ul style="list-style-type: none"> Prophylactic hyperventilation (PaCO₂ 25 mmHg) is not recommended. (level II) Hyperventilation is recommended as a temporizing measure for the reduction of elevated intracranial pressure. (level III)
Hyperosmolar therapy	<ul style="list-style-type: none"> Mannitol (0.25 - 1.0 g/kg) is effective for control of raised intracranial pressure. Hypotension should be avoided. (level II) Restrict mannitol use prior to intracranial pressure monitoring to patients with signs of transtentorial herniation or progressive neurological deterioration not attributable to extracranial causes. (level III)
ICP	<ul style="list-style-type: none"> ICP should be monitored in patients with severe TBI and abnormal CT scan (level II) and in patients with normal CT scan if two or more of following are present: age > 40 years, motor posturing, systolic blood pressure < 90 mmHg (level III). Treatment should be initiated if intracranial pressure is > 20 mmHg (level II)
Temperature	<ul style="list-style-type: none"> Prophylactic hypothermia is not significantly associated with decreased mortality. (level III) Hypothermia may have higher chances of reducing mortality when cooling is maintained for more than 48 hours. (level III)
CPP	<ul style="list-style-type: none"> Maintain cerebral perfusion pressure between 50-70 mmHg. Avoid aggressive treatment with fluid and pressors to maintain CPP > 70 mmHg. (level II) Avoid CPP < 50 mmHg. (level III)
Brain Oxygenation	<ul style="list-style-type: none"> Treat when SjvO₂ < 50% or brain tissue oxygen tension < 15 mmHg. (level III)
Steroids	<ul style="list-style-type: none"> In patients with moderate or severe TBI, high-dose methylprednisolone is associated with increased mortality and is contraindicated. (level I)