Initial treatment priorities for the physiological optimization of patients with severe traumatic brain injury

J Sappenfield1*, S Galvagno2, J Blenko2

Abstract
Introduction
Severe brain injury is the most common cause of death in trauma. Although surgical intervention is important, prompt, directed medical management is imperative to ensure favourable outcomes. Optimization of perfusion and ventilation are paramount, but other therapies, including glycemic control, prophylaxis against deep-vein thrombosis and, perhaps, the use of tranexamic acid, are used to maximize survival. The aim of this review is to describe the initial treatment priorities for the physiological optimization of the patient with severe traumatic brain injury.

Conclusion
The key to successful resuscitation of patients with a traumatic brain injury is a rapid and systematic assessment, optimization of patient physiology and the prevention of secondary injury.

Introduction
Severe brain injury is the most common cause of death in trauma. Severe brain injury is defined as a Glasgow coma scale (GCS) ≤8 or abbreviated injury score ≥3. About 56% of all severe brain injuries are caused by motor vehicle crashes, and another 31% are due to falls. Of the patients who die from severe brain injury, 60% will die before they reach the hospital and about another quarter will die in the first 24 h. Risk factors associated with an increase in mortality include older age, higher injury severity scores, loss of consciousness, the consumption of anticoagulants and/or antiplatelet medications and hypothermia. Although the consumption of an antiplatelet medication increases the risk of mortality, each additional antiplatelet medication does not confer a larger increase in risk. The association between trauma and the administration of anticoagulant medications is difficult to assess because patients may have one or more medical comorbidities that could influence outcome. Trauma patients who are hypothermic at admission also have an increased risk of mortality even in the setting of isolated severe brain injury.

A large portion of the care of the patient with a traumatic brain injury (TBI) is nonsurgical. This article provides a review of the current recommendations for initial patient assessment, the strategies for optimization of perfusion, the management of ventilation and the use of adjunctive medical therapies.

Discussion
The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964), and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Initial assessment and support
The patient who arrives in the trauma bay or emergency department should undergo a primary survey, with maintenance of the cervical spine in a neutral, immobilized position until spinal cord trauma is ruled out. The airway should be rapidly assessed and breath sounds confirmed on both sides of the chest. An airway examination in a TBI patient also consists of assessment for tracheal deviation, jugular venous distension or palpation of crepitus. Blood pressure, presence of central and peripheral pulses and capillary refill should be documented. Adequate intravenous access should be obtained. A focused neurological assessment is indicated, starting with determination of level of consciousness and an examination of the eyes for pupil size. A GCS score should be calculated (see Table 1). Muscular strength can be quickly assessed by testing bilateral finger grip and dorsi/plantar flexion. There is a high incidence of concomitant spinal injury, which must be taken into account when formulating management plans.

Because the patient with severe TBI is unable to protect his/her airway, rapid securing of the airway should follow. In addition to controlling ventilation, another benefit of intubation is the prevention of aspiration, which can lead to further decompensation of the patient’s respiratory status. The patient’s body should then be exposed to see if there are additional injuries. In large trauma centres, much of the primary survey occurs simultaneously by members of the trauma team.

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Table 1  Glasgow Coma Scale for adults

<table>
<thead>
<tr>
<th>Eye response</th>
<th>Verbal response</th>
<th>Motor response</th>
</tr>
</thead>
<tbody>
<tr>
<td>4: Spontaneous</td>
<td>5: Oriented</td>
<td>6: Obey commands</td>
</tr>
<tr>
<td>3: Opens to verbal command</td>
<td>4: Confused</td>
<td>5: Purposeful movement to pain</td>
</tr>
<tr>
<td>2: Opens to pain</td>
<td>3: Inappropriate</td>
<td>4: Withdraws from pain</td>
</tr>
<tr>
<td>1: None</td>
<td>2: Incomprehensible</td>
<td>3: Flexion/decorticate posturing</td>
</tr>
<tr>
<td></td>
<td>1: None</td>
<td>2: Extension/decerebrate posturing</td>
</tr>
</tbody>
</table>

The best response is recorded. The minimum score is 3.

Secondary injury is the degeneration of neurons and glial cells caused by the biomolecular and physiological changes after a primary insult. With TBI, the primary insult has already occurred. After the primary survey and any urgent interventions have been completed, patient management goals include treating common sequelae and preventing secondary injury to the brain, because the injured tissue in the brain is more susceptible to additional ischemia due to inadequate cerebral perfusion. To prevent further compromise, blood pressure should be maintained or increased to maintain oxygen supply to tissues where normal autoregulation is absent. Systolic blood pressure should be kept >90 mmHg. When intracranial pressure (ICP) is monitored, a cerebral perfusion pressure (CPP) of >70 should be maintained (CPP is mean arterial pressure minus central venous pressure or ICP, whichever is greater). The patient should be resuscitated to a normovolemic state using a combination of the static and dynamic indices shown in Table 2. Although it is important to maintain euvolemia, albumin should not be used in patients with TBI because of an association with higher mortality. After the patient is euvolemic, if hypotension is still present, vasopressors may be given to maintain an adequate perfusing pressure to the brain. Hypocapnea and respiratory alkalosis have a direct vasococonstrictive effect on cerebral vasculature, and these two states should be prevented as they may cause ischemia through tenuous perfusion to the penumbra. Alkalosis also causes a decrease in ionized calcium, causing cell membrane instability, and shifting of the oxygen–haemoglobin dissociation curve to the left, causing less oxygen unloading.

Assessment of the extent of brain injury requires a CT scan, which helps determine whether surgical management is necessary. Neurologic changes should be evaluated with repeat CT imaging. The anticoagulant effects of warfarin should be reversed with fresh-frozen plasma if a patient has intracranial bleeding. Alternatively, plasma concentrates may also be considered. Tranexamic acid is a compound that prevents fibrinolysis by inhibiting the proteolytic activity of plasmin. Tranexamic acid does not have Food and Drug Administration approval for use in the setting of trauma, thus the use of this agent in the setting of TBI remains controversial. Evidence does not show a strong benefit of tranexamic acid in patients with subarachnoid haemorrhage after aneurysmal rupture, or in the setting of TBI. No study

Table 2  Dynamic and static indices used to ensure normovolemia

<table>
<thead>
<tr>
<th>Dynamic indices</th>
<th>Static indices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>Serum lactate</td>
</tr>
<tr>
<td>Mean arterial blood pressure (&gt;65)</td>
<td>Serum base excess</td>
</tr>
<tr>
<td>Urine output (&gt;0.5 mL/kg/h)</td>
<td>Haematocrit (i.e., when elevated, may indicate hypovolemia and haemoconcentration)</td>
</tr>
<tr>
<td>Pulse pressure variation (&lt;10%)</td>
<td>Serum blood urea nitrogen</td>
</tr>
<tr>
<td>Stroke volume variation (&lt;13%)</td>
<td>Serum creatinine</td>
</tr>
<tr>
<td>Stroke volume index (&gt;35)</td>
<td>Urine electrolytes (including fractional excretion of sodium: FENa)</td>
</tr>
<tr>
<td>Inferior vena cava diameter (ultrasound; &lt;3 cm but &gt;1 cm)</td>
<td>Vascular pedicle width on a P-A upright chest radiograph (rarely available in trauma patients)</td>
</tr>
<tr>
<td>Respiratory variability of the inferior vena cava (ultrasound)</td>
<td>Central venous pressure (8–12 mmHg)</td>
</tr>
<tr>
<td>Response to passive leg raising (decreased pulse pressure variation or increased central venous pressure)</td>
<td>Pulmonary artery occlusion pressure (&lt;12 mmHg)</td>
</tr>
<tr>
<td>End-expiratory occlusion pressure (when mechanically ventilated; decreased pulse pressure variation at end-expiratory occlusion)</td>
<td></td>
</tr>
</tbody>
</table>
has administered tranexamic acid to patients with isolated TBI. However; an almost significant reduction in mortality was seen in the CRASH-2 intracranial bleed study, with no increase in the incidence of focal cerebral ischemic lesions.

**Optimization of cerebral perfusion**

Patients with multiple traumatic injuries make up one-third to one-half of patients with moderate-to-severe brain injuries while the rest have isolated brain injuries. In patients with multiple traumatic injuries, controlling haemorrhage is crucial. The patient with ongoing haemorrhage may not only die from blood loss, but may also have difficulty maintaining adequate perfusion to injured brain tissue.

According to the most current Brain Trauma Foundation guidelines, a systemic blood pressure ≥90 mmHg should be maintained, because hypotension is a significant predictor of adverse outcomes before the patient reaches the hospital and during the early resuscitation in a patient with TBI. Hypotension is even a significant predictor of mortality even after controlling for the presence of multiple severe injuries. Three-quarters of the patients that arrive both hypotensive and hypoxic to the hospital will die. Each additional episode of hypotension is associated with an increased risk of mortality.

The current standard of care is to monitor ICP in trauma patients who have a GCS ≤ 8 and an abnormal CT scan. Monitoring ICP is also indicated in patients who have a GCS ≤ 8 and a normal CT scan if at least two or more of the following are present at the time of admission: age > 40, systolic blood pressure < 90 and/or unilateral or bilateral motor posturing. It is important to correlate and compare elevated ICPs with the neurologic exam. It is recommended to treat an ICP ≥ 20 mmHg. However, pupillary changes have been reported with an ICP of 18 mmHg. Methods for acutely reducing ICP are listed in Table 3. The clinician should also be careful to not impede venous flow from the head, which may increase ICP. For example, cervical collars have been associated with an increase in ICP.

Hypotension should be avoided when sedation is given to patients with increased ICP. Cranial decompression may be considered after neurological consultation.

Monitoring of ICP is supported by a large, nonrandomized prospective study that showed a relative risk reduction in mortality of 41% in patients with ICP monitors compared to patients followed by clinical exam and imaging alone. There were many differences between the two treatment groups in the study, and intraventricular catheters, a standard modality for ICP management in many regions, were not used. Because of the limitations and results from this study, it is unclear whether the standard will change in countries where ICP monitoring is routine. The current standard is to monitor ICP when indicated, as described above.

Improvement in patient outcomes has been reported when CPP is continuously monitored. An increased duration of CPP <60 mmHg is associated with a worse disposition at time of discharge and a greater mortality. However, a clinician must balance augmentation of CPP in a patient without intact autoregulation against potential systemic adverse effects. Increasing systemic blood pressure to increase cerebral blood flow may not improve neurologic outcomes, but may increase the patient’s risk of developing acute respiratory distress syndrome. Because no benefit has been demonstrated by increasing the CPP above 70 mmHg, this practice is currently not recommended.

The choice of hyperosmolar agent to use for the acute lowering of ICP remains controversial. Hyperosmolar agents use an osmotic gradient between blood and brain to force water out of the vasculature. Hyperosmotic agents decrease intracranial volume, improve elastance of the intracranial compartment, and decrease intracranial pressure. However, these effects are transient, and agents must be repeated to maintain efficacy. The choice of hyperosmolar agent should be based on the presence of increased ICP and the ability to maintain CPP above 70 mmHg.

### Table 3: Critical actions to be implemented for reduction of acutely elevated ICP

<table>
<thead>
<tr>
<th>Action/Drug</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevation of the head of bed to at least 30 degrees</td>
<td></td>
</tr>
<tr>
<td>Adjust ventilation to target a PaCO₂ of 35–38 mmHg</td>
<td>(while therapies below are prepared)</td>
</tr>
<tr>
<td>Titrate sedatives or analgesics if the patient is agitated or in pain</td>
<td></td>
</tr>
<tr>
<td>Ensure normothermia</td>
<td></td>
</tr>
<tr>
<td>Prevent or stop seizures (consider dose of lorazepam 0.1 mg/kg IV/IM or midazolam 10 mg IV)</td>
<td></td>
</tr>
<tr>
<td>Initiate hyperosmolar therapy:</td>
<td></td>
</tr>
<tr>
<td>Mannitol 20–25%, 0.25–1.5 g/kg</td>
<td></td>
</tr>
<tr>
<td>Hypertonic saline 2–3%, 4–6 mL/kg</td>
<td></td>
</tr>
<tr>
<td>Hypertonic saline 23.4%, 30 mL (the “saline bullet”)</td>
<td></td>
</tr>
<tr>
<td>Drainage of cerebral spinal fluid (if ICP monitor is an intraventricular catheter)</td>
<td></td>
</tr>
<tr>
<td>Initiation of barbiturate coma*</td>
<td></td>
</tr>
<tr>
<td>Therapeutic hypothermia*</td>
<td></td>
</tr>
<tr>
<td>Surgical consultation for emergent decompression*</td>
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</tbody>
</table>

*Usually reserved for refractory cases.
nial vault, and may cause a small, but significant and lifesaving, reduction in brain water content in patients with life-threatening ICP elevation. While current Brain Injury Foundation Guidelines only endorse mannitol, hypertonic saline is increasingly used at many trauma centres. Mannitol, an osmotic diuretic, can cause depletion of intravascular volume and hypovolemia. Metabolic acidosis, hyperkalaemia, and renal failure are additional complications associated with this agent. Hypertonic saline augments and does not deplete intravascular volume. Hypertonic saline has also been shown to have additional extraosmotic properties that may be beneficial22,23. To date, no large, controlled trials have compared hypertonic saline to mannitol. More rigorous studies are indicated to determine the comparative effectiveness of mannitol versus hypertonic saline for patients with severe TBI.

Optimization of gas exchange

Preventing hypoxia, defined as a PaO2 < 60 mmHg or O2 saturation <90%, is the standard of care in patients with TBI9,10. The presence of an oxygen saturation <90% is an independent risk factor for increased mortality9,10. Whether the patient sustains multiple injuries or isolated TBI, a decrease in blood pressure or oxygen saturation is detrimental to the overall outcome of the patient7.

Just as important as the PaO2 is the PaCO2. Patients who have a sudden change in mental status or an acute neurologic finding that is suspected to be caused by elevated ICP, can be rapidly hyperventilated to decrease ICP. Prophylactic hyperventilation in a patient with TBI is contraindicated9,10 because hypcapneic-induced vasoconstriction can cause exacerbation of cerebral ischaemia9. Thus, hyperventilation should only be used to lower ICP acutely and routine use in the first 24 h after injury should be avoided9,10. When using mechanical ventilation, the tidal volumes should be limited to <10 mL/kg of ideal body weight because acute respiratory distress syndrome is more likely to occur in patients with TBI who are ventilated with higher tidal volumes24.

Adjunctive Therapies

After TBI, patients are at risk for electrolyte abnormalities. Patients may develop diabetes insipidus, which can result in severe hypovolemia.3 After severe TBI, patients have a greater than 60% risk for developing coagulopathy, which is most likely caused by a release of tissue factor, activation of protein C, and platelet dysfunction25. Coagulopathy may present within 12 h after trauma and has been reported up to 5 days afterwards25,26. Episodes of hyper- or hypoglycaemia should be prevented because these worsen outcomes in patients with brain injury9.

Patients with severe TBI should receive phenytoin or levetiracetam for post-traumatic seizures27-29. Other risk factors for seizures are listed in Table 4. Valproate is not used routinely because of an observed trend toward increased risk of death in the study, which proved its efficacy30. Mechanical deep-vein thrombosis prophylaxis, including graduated compression or intermittent pneumatic compression stockings, is indicated in patients who sustain a TBI because they are at increased risk of developing deep-vein thrombosis and pulmonary embol31,32. Although antithrombotic medications are more effective than mechanical measures for prevention, they may cause enlargement of hematomas and increase intracranial bleeding9,10.

Patients with TBI become hypermetabolic, and full caloric replacement should be instituted within 7 days to reduce mortality10. Enteral feeding can help prevent gastric stress ulcers3. Patients should also receive medications to prevent stress ulcers3. Prophylactic antibiotic administration while a ventricular catheter is in place and the routine exchange of ventricular catheters do not improve outcomes3,10. To assess for infection, CSF can be examined via Gram stain, by measuring glucose, protein and by assessing the cell count6. Although the mechanism is unclear, mortality is increased when steroids are given in the setting of TBI and are not indicated for this condition10,31.

Conclusion

The key to successful resuscitation of patients with a TBI is a rapid and systematic assessment, optimization of patient physiology, and the prevention of secondary injury. These patients should be kept euvoletic and normotensive. Oxygenation and ventilation should be maintained. Adjuncts should be administered as indicated. The cornerstone for improving patient outcomes in TBI remains robust medical support combined with prompt surgical interventions when indicated.

Abbreviations list

CPP, cerebral perfusion pressure; GCS, Glasgow coma scale; ICP, intracranial pressure; TBI, traumatic brain injury

References

Table 5  Summary of Grade I, II, and III recommendations from the Brain Trauma Foundation Guidelines for the Management of Severe TBI10

Grade I recommendations:

- Steroids should not be used for improving ICP in patients with moderate to severe TBI

Grade II recommendations:

- Avoid hypotension (systolic blood pressure <90 mmHg)
- Consider mannitol (0.25–1 g/kg body weight) to control elevated ICP
- ICP monitoring is indicated for patients with a GCS of 3 to 8 and with abnormal head CT findings
- Treatment should be initiated with ICP is >20 mmHg
- Cerebral perfusion pressure (CPP) should be maintained above 70 mmHg
- Ancillary monitoring of cerebral perfusion (blood flow, oxygenation, and metabolism) may be considered if used to facilitate CPP management
- Propofol, not high-dose barbiturates, is recommended for control of ICP; high-dose propofol can produce significant morbidity
- Patients should be fed to attain full caloric replacement by day 7 post-injury
- Prophylactic use of phenytoin or valproate is not recommended beyond 7 days to prevent post-traumatic seizures
- Prophylactic hyperventilation (PaCO₂ < 25 mmHg) is not recommended; if hyperventilation is used, SjO₂ or PbrO₂ measurements are recommended to monitor oxygen delivery

Grade III recommendations:

- Avoid hypoxemia (PaO₂ < 60 mmHg or SpO₂ <90%)
- ICP monitoring is indicated in patients with a severe TBI with a normal CT scan if two or more of the following are present at the time of admission: age <40 years, unilateral or bilateral motor posturing, systolic blood pressure < 90 mmHg
- CPP < 50 mmHg should be avoided
- Jugular venous saturation <50% or brain tissue oxygen tension <15 mmHg are treatment thresholds
- Grade I recommendations are derived from good quality, randomized, controlled trials. Grade II recommendations are derived from moderate quality, randomized trials or good quality, case-control, or cohort studies. Grade III recommendations are derived from poor quality, randomized trials and moderate/poor quality cohort, case control, case series, or other types of trials.

Review

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