Southern African Journal of Anaesthesia and Analgesia 2018; 24(3)(Supplement 1)

South Afr J Anaesth Analg
ISSN 2220-1181 EISSN 2220-1173

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Severe traumatic brain injury

K K Purbhoo

Department of Anaesthesia, Helen Joseph Hospital, University of the Witwatersrand
Correspondence to: kashmirapurbhoo@gmail.com

Traumatic brain injury (TBI) is a nondegenerative, noncongenital insult to the brain from an external mechanical force, possibly leading to permanent or temporary impairment of cognitive, physical and psychosocial factors with an associated diminished or altered state of consciousness.[1]

TBI is a heterogeneous disease. There are many different ways to categorise patients in terms of clinical severity, mechanism of injury, and pathophysiology, each of which may impact prognosis and treatment.[2]

TBI has traditionally been classified using injury severity scores. The Glasgow Coma Scale (GCS) is the most commonly used.[3] The GCS is universally accepted because it is simple, reproducible and has predictive value for overall prognosis. A GCS score of 13–15 is considered mild TBI, 9–12 is considered moderate TBI, and 8 or less is considered severe TBI. It is, however, limited by confounding factors such as medical sedation and paralysis, endotracheal intubation, and intoxication. All these factors are often prominent in patients with a low GCS score.[4,5]

Pathophysiology

The pathophysiology of TBI-related brain injury is divided into primary brain injury and secondary brain injury.

Primary brain injury occurs at the time of trauma. The mechanisms include direct impact, rapid acceleration/deceleration, penetrating injury, and blast waves. They all result from external mechanical forces transferred to intracranial contents. The damage that results includes a combination of focal contusions and haematomas, as well as shearing of white matter tracts (diffuse axonal injury) along with cerebral oedema and swelling.[2]

Secondary brain Injury in TBI is usually considered as a cascade of molecular injury mechanisms that are initiated at the time of initial trauma and continue for hours or days. These mechanisms include neurotransmitter-mediated excitotoxicity causing free-radical injury to cell membranes, electrolyte imbalances, mitochondrial dysfunction, inflammatory responses, apoptosis and secondary ischaemia from vasospasm, focal microvascular occlusion and vascular injury.[6-11]

These lead in turn to neuronal cell death as well as to cerebral oedema and increased intracranial pressure that can further exacerbate the brain injury. A critical aspect of preventing secondary brain injury after TBI is the avoidance of secondary brain insults, which would otherwise be well-tolerated but can exacerbate neuronal injury in cells made vulnerable by the initial TBI. Examples include hypotension and hypoxia (which decrease substrate delivery of oxygen and glucose to injured brain), fever and seizures (which may further increase metabolic demand), and hyperglycaemia (which may exacerbate on-going injury mechanisms).[2]

Traumatic brain injury guidelines

One of the major advances over the past 2 decades in the management of patients with severe TBI has been the development of standardised approaches that follow international guidelines.[12,13] The guidelines use existing evidence to provide recommendations for current care in order to lessen heterogeneity and improve patient outcomes. The lack of randomised clinical trials addressing many aspects of care in the severe TBI patient does unfortunately mean that the strength of supporting data for most treatment concepts is relatively weak.[14] Despite this there is evidence that in centres with neurosurgical support, where protocol-driven neurointensive care units operate on these guidelines, the patient outcomes are better.[15,16]

Patients with severe TBI may frequently have other traumatic injuries with management being complex and requiring a multidisciplinary approach. The management lends itself to protocol-based treatment and standardised hospital order sets derived from these guidelines.[14]

Brain Trauma Foundation Guidelines for the Management of Severe Traumatic Brain Injury (4th Edition)[12]

The Brain Trauma Foundation is a service organisation dedicated to improving outcomes from TBI. The aim is to produce evidence-based guidelines, not comprehensive protocols. Development

of rigorous and comprehensive evidence-based protocols is essential to the appropriate utilisation of these guidelines.

The scope of the guidelines was not to cover all topics relevant to the care of patients with severe TBI. The guidelines address treatments, monitoring and treatment thresholds specific to TBI.

In this 4th Edition, there are 189 publications used for evidence – 5 Class 1, 46 Class 2, 136 Class 3 studies, and 2 meta-analyses, to support 28 recommendations covering 18 topics. Ninety-four new studies were added to the evidence between the 3rd and 4th Editions. The guidelines include changes in the evaluation of previous work, an increase in the quality of the included studies, and essential improvements in the precision of the recommendations. Despite these improvements, the recommendations are limited in many areas reflecting persisting gaps in the evidence base for severe TBI management.

The 4th Edition was developed as 'Living Guidelines', meaning that it is transitional. There is no intention to produce a 5th Edition; instead the Brain Trauma Foundation is moving to a model of continuous monitoring of the literature, rapid updates to the evidence review, and revisions to the recommendations as the evidence warrants.

The development of the guidelines involved two major activities: firstly, a systematic review and synthesis of the evidence, and secondly, the derivation of recommendations. Class 1, 2, or 3 studies constitute the evidence on which recommendations are based. Class 1 is the highest class and is limited to good-quality randomised controlled trials (RCTs). Class 2 includes moderate-quality RCTs and good-quality cohort or case-control studies. Class 3 is the lowest class and is given to low-quality RCTs, moderate- to low-quality cohort or case-control studies, and case series and other non-comparative designs.

The level of recommendation is determined by the assessment of the quality of the body of evidence, rather than the class of the included studies. Level I recommendations were based on a high-quality body of evidence. Level IIA recommendations were based on a moderate-quality body of evidence. Level IIB and III recommendations were based on a low-quality body of evidence. The class of studies in the body of evidence was the basis for making the distinction between a Level IIB or a Level III recommendation. Level IIB recommendations were based on a body of evidence with Class 2 studies that provided direct evidence but were overall low quality. Level III recommendations were based on Class 3 studies or on Class 2 studies providing only indirect evidence. If the evidence was insufficient, no recommendation was made.

Topics included in this edition are organised in three categories that are specific to severe TBI in adults.

Part 1: Treatments

1. Decompressive craniectomy (DC)

Several pathological mechanisms associated with primary and secondary injury patterns in TBI can result in cerebral oedema.[17] As the pressure within the skull increases, cerebral herniation can occur resulting in disability or death.[18,19] DC (surgical removal of a portion of the skull) has been performed for relieving increased intracranial pressure with improvement in some TBI patients.[20,21] However, with data now available from the DECRA trial (Decompressive Craniectomy In Diffuse Traumatic Brain Injury, 2011) and the RESCUEicp trial (Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of intracranial pressure, 2016) there is likely to be concern that lifesaving surgery may not predictably result in sufficiently good functional survival as more survivors in the surgical group than in the medical group were dependent on others.[20-22]

Recommendations

Level I

- Insufficient evidence to support a Level I recommendation.

Level IIA

- Bifrontal DC is not recommended to improve outcomes as measured by the Glasgow Outcome Scale–Extended (GOS-E) score at six months post-injury in severe TBI patients with diffuse injury (without mass lesions), and with intracranial pressure (ICP) elevation to values > 20 mm Hg for more than 15 minutes within a 1-hour period that are refractory to first-tier therapies. However, this procedure has been demonstrated to reduce ICP and to minimise days in the intensive care unit (ICU).
- A large frontotemporoparietal DC (not less than 12 x 15 cm or 15 cm diameter) is recommended over a small frontotemporoparietal DC for reduced mortality and improved neurologic outcomes in patients with severe TBI.[20-22]

2. Prophylactic hypothermia

Hypothermia is well recognised to preserve cells and tissue in the face of metabolic challenges. Evidence supports the administration of hypothermia as standard of care for neuroprotection after cardiac arrest from acute coronary syndromes.[23,24] In addition to suggested neuroprotective effects, hypothermia is well known for its ability to reduce ICP. There has been long-standing interest in applying hypothermia post central nervous system trauma; however, benefit cannot be presumed. Hypothermia is also associated with many complications, including coagulopathy and immunosuppression, and profound hypothermia bears the additional risk of cardiac dysrhythmia and death.[25] Hypothermia can be administered as either "prophylactic" (early after injury and prior to ICP elevation) or "therapeutic" (treatment for refractory ICP elevation). The quality of the body of evidence for the comparison of hypothermia with normothermia is low because the findings were inconsistent.

Recommendations

Level I and IIA

- Insufficient evidence to support a Level I or IIA recommendation.

Level IIB

- Early (within 2.5 hours), short-term (48 hours post-injury) prophylactic hypothermia is not recommended to improve outcomes in patients with diffuse injury.[26]

3. Hyperosmolar therapy

Mannitol and hypertonic saline are both hyperosmolar agents routinely employed in North America. Hypertonic saline administration may be hazardous for a hyponatraemic patient.[27] Although mannitol can be used as a resuscitation fluid, its eventual diuretic effect is undesirable in hypotensive patients and attention needs to be paid to replacing intravascular volume loss.[28] While mannitol was previously thought to reduce ICP through simple brain dehydration, both mannitol and hypertonic saline work to reduce ICP, at least in part, through reducing blood viscosity, leading to improved microcirculatory flow of blood constituents and consequent constriction of the pial arterioles, resulting in decreased cerebral blood volume and ICP.[27-29]

Recommendations

Level I, II, and III

- Although hyperosmolar therapy may lower ICP, there was insufficient evidence about effects on clinical outcomes to support a specific recommendation, or to support use of any specific hyperosmolar agent, for patients with severe TBI.

4. Cerebrospinal fluid drainage

External ventricular drainage (EVD) systems in patients with severe TBI are a controversial topic. An EVD in a closed position allows for monitoring of ICP, while in an open position drainage of cerebrospinal fluid (CSF) can occur. Practice patterns regarding whether the EVD should be maintained in a closed or open position vary widely based on a number of variables, including patient age, institutional resources, and physician preferences.

Recommendations

Level I and II

- Insufficient evidence to support a Level I or II recommendation.

Level III

- An EVD system zeroed at the midbrain with continuous drainage of CSF may be considered to lower ICP burden more effectively than intermittent use.
- Use of CSF drainage to lower ICP in patients with an initial GCS < 6 during the first 12 hours after injury may be considered.[30]

5. Ventilation therapies

Patients with severe TBI require definitive airway protection because they may have a compromised respiratory drive and may be at risk of pulmonary aspiration. Under normal conditions, $PaCO_2$ (partial pressure of carbon dioxide in arterial blood) is the most powerful determinant of cerebral blood flow (CBF) and, between a range of 20 mmHg and 80 mmHg, CBF is linearly responsive to $PaCO_2$. Cerebral blood flow is important in meeting the brain's metabolic demands. Low $PaCO_2$ results in low CBF and may result in cerebral ischaemia while high $PaCO_2$ levels can result in cerebral hyperaemia and high intracranial pressure (ICP).[12] Older studies suggested that cerebral hyperaemia was more common than cerebral ischaemia, and hyperventilation was recommended in the care of patients with TBI.[31,32] Cerebral ischaemia has, however, been documented in a number of studies after severe TBI, changing longstanding recommendations concerning ventilation therapy.[33-35] The Brain Trauma Foundation does however recognise the potential need for hyperventilation as a temporising measure.

Recommendations

Level I and IIA

- Insufficient evidence to support a Level I or IIA recommendation.

Level IIB

- Prolonged prophylactic hyperventilation with $PaCO_2$ of 25 mmHg or less is not recommended.

6. Anaesthetics, analgesics and sedatives

Anaesthetics, analgesics and sedatives are important in TBI for a variety of reasons, including prophylaxis or control of intracranial hypertension and seizures.[36,37] Anaesthetics and sedatives work presumably by preventing unnecessary movement, coughing, and straining against tubes as well as suppression of metabolism and alteration of cerebral vascular tone. Depressed cerebral metabolism and oxygen consumption is said to be neuro-protective in some patients.[37,38] Another brain protective mechanism includes inhibition of oxygen radical mediated lipid peroxidation.[37,39,40] The side-effects of these drugs, such as hypotension and decreased cardiac output, may, however, give rise to a paradoxical decrease in cerebral perfusion pressure which may negate the benefits of decreased ICP.[37,39] Sedation will also preclude the physical examination in following a patient's progress.

Recommendations

Level I and IIA

- Insufficient evidence to support a Level I or Level IIA recommendation.

Level IIB

- Administration of barbiturates to induce burst suppression measured by EEG as prophylaxis against the development of intracranial hypertension is not recommended.
- High-dose barbiturate administration is recommended to control elevated ICP refractory to maximum standard medical and surgical treatment. Haemodynamic stability is essential before and during barbiturate therapy.[41]
- Although propofol is recommended for the control of ICP, it is not recommended for improvement in mortality or six-month outcomes. Caution is required as high-dose propofol can produce significant morbidity.[42,43]

7. Steroids

Recommendations

Level I

- The use of steroids is not recommended for improving outcome or reducing ICP. In patients with severe TBI, high-dose methylprednisolone was associated with increased mortality and is contraindicated.[44-46]

8. Nutrition

Severe TBI is associated with increased energy expenditure early after injury.[47] More recent evidence suggests that contemporary neurocritical care may blunt this response.[48,49] There is an increase in serum glucose observed after severe stress, including severe TBI.[50] Despite studies showing an improved outcome in critically ill patients in whom insulin was used to control this response, "tight glucose control" in patients with severe TBI could have a deleterious effect.[51,52] For glycaemic control, the available evidence was inconsistent and insufficient to support a recommendation.

Recommendations

Level I

- Insufficient evidence to support a Level I recommendation.

Level IIA

- Feeding patients to attain basal caloric replacement at least by the fifth day and, at most, by the seventh day post-injury is recommended to decrease mortality.[53,54]

Level IIB

- Transgastric jejunal feeding is recommended to reduce the incidence of ventilator-associated pneumonia.[55,56]

9. Infection prophylaxis

Infection risks such as ventilator-associated pneumonias (VAP) and central line-associated bacteraemia are increased in all critically ill patients.[12] Patients undergoing ICP monitoring are reported to have related infection rates as high as 27%.[57] There is a strong movement to reduce hospital-acquired infections and minimise their potentially devastating effects on hospital morbidity, mortality, and length of stay.

Recommendations

Level I

- Insufficient evidence to support a Level I recommendation.

Level IIA

- Early tracheostomy is recommended to reduce mechanical ventilation days when the overall benefit is felt to outweigh the complications associated with such a procedure. However, there is no evidence that early tracheostomy reduces mortality or the rate of nosocomial pneumonia.[58,59]
- The use of povidone-iodine (PI) oral care is not recommended to reduce ventilator-associated pneumonia and may cause an increased risk of acute respiratory distress syndrome.[60]

Level III

- Antimicrobial-impregnated catheters may be considered to prevent catheter-related infections during EVD.[61-64]

10. Deep vein thrombosis (DVT) prophylaxis

Severe TBI patients are high risk for venous thromboembolism (VTE) due to a number of reasons including, hypercoagulability resulting from the primary brain injury, prolonged periods of immobilisation, and focal motor deficits.[65-68] If untreated, DVT can result in potentially debilitating or fatal pulmonary embolism. Problematically, drugs used have the potential to result in clinically significant intracranial haemorrhage expansion.

Recommendations

Level I and II

- Insufficient evidence to support a Level I or II recommendation.

Level III

- Low molecular weight heparin (LMWH) or low-dose unfractioned heparin may be used in combination with mechanical prophylaxis. However, there is an increased risk for expansion of intracranial haemorrhage.

  In addition to compression stockings, pharmacologic prophylaxis may be considered if the brain injury is stable and the benefit is considered to outweigh the risk of increased intracranial haemorrhage. There is insufficient evidence to support recommendations regarding the preferred agent, dose, or timing of pharmacologic prophylaxis for deep vein thrombosis.[69]

11. Seizure prophylaxis

Seizures may occur secondary to TBI and are classified as early post-traumatic seizures (PTS) if they occur within seven days of the injury, or late when they occur after seven days following the injury.[12] The risk factors for early PTS include: GCS of ≤ 10; immediate seizures; post-traumatic amnesia lasting longer than 30 minutes; linear or depressed skull fracture; penetrating head injury; subdural, epidural, or intracerebral haematoma; cortical contusion; age ≤ 65 years; or chronic alcoholism.[70] Post-traumatic epilepsy (PTE) is defined as recurrent seizures more than seven days following injury.[12] Those most at risk for PTE are individuals who have suffered the following: severe TBI and early PTS prior to discharge; acute intracerebral haematoma or cortical contusion; posttraumatic amnesia lasting longer than 24 hours; age > 65 years; or premorbid history of depression.[70] Seizure prophylaxis for PTS refers to the practice of administering anticonvulsants to patients following TBI in order to prevent the occurrence of seizures.

Recommendations

Level I

- Insufficient evidence to support a Level I recommendation.

Level IIA

- Prophylactic use of phenytoin or valproate is not recommended for preventing late PTS.
- Phenytoin is recommended to decrease the incidence of early PTS (within seven days of injury), when the overall benefit is felt to outweigh the complications associated with such treatment. However, early PTS have not been associated with worse outcomes.[71]

  At the present time there is insufficient evidence to recommend levetiracetam over phenytoin regarding efficacy in preventing early PTS and toxicity.[72]

Part Ii: Monitoring

It is not monitoring that affects outcomes but rather using the information from the monitoring to direct treatment that will. It is important to acknowledge that clinical practice in most high-income countries incorporates multiple monitoring approaches whereas limited resources in low- and middle-income countries often do not allow for monitoring. Therefore, the application of these guidelines will vary depending upon the medical environment in which they are used.

12. Intracranial pressure monitoring

Cerebral swelling after TBI can lead to brain herniation which leads first to death of those areas of the brain and ultimately of the brain itself. Intracranial hypertension is an important secondary insult after severe TBI, and its alleviation plays a pivotal role in providing good patient care to achieve optimal outcomes.

Recommendations

Level I and IIA

- Insufficient evidence to support a Level I or IIA recommendation.

Level IIB

- • Management of severe TBI patients using information from ICP monitoring is recommended to reduce in-hospital and 2-week post-injury mortality.[73-76]

13. Cerebral perfusion pressure (CPP) monitoring

CPP = MAP-ICP/JVP (whichever is greater)

MAP = Mean arterial pressure

ICP = Intracranial pressure

JVP = Jugular venous pressure

The question remains as to whether CPP can, itself, influence outcome, separate from MAP and ICP monitoring.

Recommendations

Level I

- Insufficient evidence to support a Level I recommendation.

Level IIB

- Management of severe TBI patients using guidelines-based recommendations for CPP monitoring is recommended to decrease two-week mortality.[75]

14. Advanced cerebral monitoring

When oxygen or glucose delivery to tissue is limited to the point that tissue needs are not met, metabolism fails and cells die. Advanced cerebral monitoring techniques for blood flow and oxygen include: transcranial Doppler (TCD)/duplex sonography, differences between arterial and arterio-jugular venous oxygen ($AVDO_2$) (measuring cerebral O_2 extraction), and measurements of local tissue oxygen. Additional monitoring methods include microdialysis to measure brain metabolism (glucose, lactate, pyruvate, and glutamate) and electrocorticography to determine cortical spreading depression; however, use of these last two monitoring techniques is not common outside of research settings. The relationship between brain tissue oxygen, oxygen delivery, and diffusion of dissolved oxygen across the blood brain barrier is not simple. Theoretically, use of advanced monitoring in tandem with ICP and CPP monitoring adds to the assessment of brain metabolic needs and the effects of therapies to meet them. However, all techniques have limitations and potential risks.

Recommendations

Level I and II

- Insufficient evidence to support a Level I or II recommendation.

  (Although patients with desaturations identified with advanced cerebral monitoring have poorer outcomes, Level II evidence showed no improvement in outcomes for monitored patients.)

Level III

- Jugular bulb monitoring of arteriovenous oxygen content difference ($AVDO_2$), as a source of information for management decisions, may be considered to reduce mortality and improve outcomes at three and six months post-injury.[77,78]

Part Iii: Thresholds

The threshold can be a value to avoid in order to decrease the probability of negative outcomes or a value to aim for in order to increase the probability of positive outcomes, and it can be a value that triggers a change in treatment.

15. Blood pressure thresholds

If autoregulation remains intact, a drop in systolic blood p[ressure (SBP) triggers an auto regulatory vasodilation in an attempt to maintain adequate brain perfusion. This results in increased cerebral blood volume, which in turn elevates intracranial pressure. If autoregulation is not intact, there is dependency on SBP to prevent cerebral ischaemia, which has been ascribed to be the single most important secondary insult.

Recommendations

Level I and II

- Insufficient evidence to support a Level I or II recommendation.

Level III

- Maintaining SBP at ≥ 100 mmHg for patients 50 to 69 years old or at ≥ 110 mmHg or above for patients 15 to 49 or over 70 years old may be considered to decrease mortality and improve outcomes.[79-81]

16. Intracranial pressure thresholds

The Monro-Kellie hypothesis states that under normal conditions, the intracranial compartment space, cerebral blood volume, and volume inside the cranium are fixed volumes. If any of these component volumes increase, then compensation must occur to maintain ICP within normal range. It is important to remember that ICP must be considered in the context of its inverse relationship with cerebral perfusion pressure.

Recommendations

Level I and IIA

- Insufficient evidence to support a Level I or IIA recommendation.

Level IIB

- Treating ICP above 22 mm Hg is recommended because values above this level are associated with increased mortality.[82]

Level III

- A combination of ICP values and clinical and brain CT findings may be used to make management decisions.[83]

17. Cerebral perfusion pressure thresholds

CPP, at least to some degree, is a surrogate measure for the delivery of nutrients to the brain. Patients with intact autoregulation are best served by higher CPP values while pressure-passive patients with dysfunctional pressure autoregulation do better with lower CPP values.

Recommendations

Level I and IIA

- Insufficient evidence to support a Level I or IIA recommendation.

Level IIB

- The recommended target CPP value for survival and favourable outcomes is between 60 and 70 mmHg. Whether 60 or 70 mmHg is the minimum optimal CPP threshold is unclear and may depend upon the patient's auto regulatory status.[82,84]

Level III

- Avoiding aggressive attempts to maintain CPP above 70 mmHg with fluids and pressors may be considered because of the risk of adult respiratory failure.[85]

18. Advanced cerebral monitoring thresholds

The goal of medical management for severe TBI patients is to ensure that oxygen and nutrient delivery to the brain is optimised. The only way to be assured that this is being achieved to the greatest extent possible is to measure brain metabolites which provide reassurance that the needs of oxidative metabolism are being met. Substantial gaps in our knowledge currently exist regarding how the data provided by advanced cerebral monitors should be used. Uncertainty remains as to the precise thresholds that should be employed.

Recommendations

Level I and II

- Insufficient evidence to support Level I or II recommendation.

Level III

- Jugular venous saturation of < 50% may be a threshold to avoid in order to reduce mortality and improve outcomes.[86,87]

Conclusion

Although there have been some major developments in severe TBI management, for some topics it was not possible to make new evidence-based recommendations. The Brain Trauma Foundation vision is a recursive structure for the reviews and guidelines to contribute to the development and execution of a research agenda that can provide the evidence base for better guidelines.[12]

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