Current Concepts in Prognostication and Critical Care for Traumatic Brain Injury

AC Sallie

Moderator: C Nurse

School of Clinical Medicine
Discipline of Anaesthesiology and Critical Care
Table of Contents

PROGNOSTICATION .................................................................................................................. 3
  Glasgow Coma Scale ................................................................................................................ 3
  GCS-Pupil Score ....................................................................................................................... 4
  Abbreviated Injury Scale ......................................................................................................... 4
  Computed Tomography Based Classification ......................................................................... 5
  Glasgow Outcome Scale and Extended Glasgow Outcome Scale ......................................... 5
RISK FACTORS FOR POOR PROGNOSIS .................................................................................. 6
  Demographics .......................................................................................................................... 6
  Cause of Injury ......................................................................................................................... 6
  High- or Low-Middle Income Countries ................................................................................ 7
  Chronic Medications .............................................................................................................. 7
CEREBRAL NEUROPROTECTION .............................................................................................. 7
  Physiological .......................................................................................................................... 9
    Control of hypoxaemia .......................................................................................................... 9
    Blood pressure control .......................................................................................................... 9
    Hypercapnia and hypocapnia ............................................................................................... 10
    Haemoglobin ....................................................................................................................... 10
    Temperature control and hypothermia ............................................................................... 10
    Glycaemic control and nutrition ......................................................................................... 11
    Seizures ............................................................................................................................... 11
  Pharmacological .................................................................................................................... 12
    Tranexamic acid ................................................................................................................... 12
    Deep vein thrombosis prophylaxis ..................................................................................... 13
    Sepsis ................................................................................................................................... 14
    Sedation ............................................................................................................................... 14
    Steroids ................................................................................................................................ 15
    Hyperosmolar agents .......................................................................................................... 15
  Surgical ................................................................................................................................... 16
    Decompressive craniectomy ................................................................................................. 16
    External Ventricular Drain ................................................................................................. 16
    Target thresholds for invasive cranial monitors ................................................................. 17
CONCLUSION ............................................................................................................................. 18
REFERENCES ............................................................................................................................. 19
INTRODUCTION

Trauma is a major burden of disease in low-middle income countries (LMICs) and trauma constitutes about 25% of the emergency workload at most of the government hospitals in KwaZulu-Natal Province (KZN). (2) Extrapolation of the figures from a 2015 study, done in the Pietermaritzburg area, speculates that KZN has almost 35 000 trauma admissions/year. (3) The World Health Organisation (WHO) predict that in the near future, the global injury mortality rate will exceed that of HIV/ AIDS, tuberculosis, malaria and obstetric causes combined. For every trauma mortality that occurs there are between 10 – 50 injured survivors, 50% of these survivors will have a permanent disability. (2) Traumatic brain injury (TBI) is the leading cause of severe disability and death in the survivors of severe blunt trauma. (4) Up to 50% of those with severe TBI will have long-term complications, with up to 30% developing long-term neurological deficits. (2, 5)

The public hospitals of KZN have limited capacity and accessibility to rehabilitation post-injury (common in most LMIC’s), this leads to severe loss of disability adjusted life-years (DALYs). The availability of intensive care facilities beds are also a scarce resource in LMIC’s. (2) The incidence of TBI in Latin America and sub-Saharan Africa is higher at 150 – 170 /100 000, than the global rate of 106/100 000. (4)

Inkosi Albert Luthuli Central Hospital (IALCH), constitutes the sole neurosurgical unit (NSU) referral centre in public health for KZN. The province of KZN has the second largest population, it is estimated to be nearly 11.5 million people, as of July 2020 (20% of South Africa total population 59.6 million). (6) Comparatively, the Western Cape Province has a population 6.8 million, as of July 2019, and it has four public health NSU’s – 3 of which are in Cape Town and include a paediatric NSU at Red Cross Hospital. (7)

PROGNOSTICATION

Estimates of prognosis are best made using mathematical models that combine information about multiple aspects of the patient’s condition. However, these have not found widespread acceptance in clinical practice. Instead, simple bedside clinical scoring systems for stratifying injury severity, appeals to all clinicians. (8) The availability of applications on our mobile phones and web-based calculators may change this way of thinking.

Glasgow Coma Scale

The widely used Glasgow Coma Scale (GCS) is the simplest measure of brain injury severity, it describes the level of consciousness in patients with head injuries. This scale measures a TBI patient’s best eye, motor, and verbal responses and facilitates the assessment and grading of brain dysfunction severity. (9-11) There are several confounding factors following severe trauma that can alter the reliability of the GCS. These include pre-existing comorbidities, analgesia and sedation (to facilitate intubation, ventilation and computed tomography (CT) imaging), hypoxaemia, being under the influence of alcohol/ illicit drugs and poor cerebral perfusion secondary to hypovolaemic shock. (11, 12)

The injury severity is classified as mild (GCS 13–15), moderate (GCS 9–12), or severe (GCS ≤ 8). (8) In resource poor hospitals, GCS is relied to accurately prognosticate outcome of mortality or disability, and therefore, to determine resource allocation after TBI. (9) Inadequate neurological monitoring of the TBI patient in hospital is a common occurrence in
high- and LMIC’s. Staff are inadequately trained in neurological assessment and are unable to detect early signs of patient deterioration. (13) Serial GCS monitoring provides a dynamic tool that allows early clinical warning of neurological deterioration in patients with TBI. (9, 10)

**IMPACT** (International Mission for Prognosis and Analysis of Clinical Trials in TBI) project database includes 11,989 patients from 11 different studies between 1984 – 1997 [8 Randomized Control Trial’s (RCT’s) and 3 epidemiological], with moderate and severe TBI (GCS < 12) in high-income countries. (14) Penetrating injuries such as gunshot wounds (GSW) were excluded. (14)

**CRASH-1** (Corticosteroid Randomisation After Significant Head Injury) trial was a double-blinded placebo-controlled RCT, they recruited 10,008 patients, 75% of these patients were from low income countries, with GCS < 14 within 8h of injury. Primary outcomes were death at two weeks and severe disability or death at 6 months follow up. (15, 16)

A 2018 review of this pooled data from IMPACT and CRASH-1 trials demonstrated that the mortality rate was 51% at GCS score of 3 and improved progressively to only 3% at GCS score 15. Similarly, there was a significant decline in the rate of unfavourable outcome at 6 months post-injury from 70% at GCS score of 3 to 12% at GCS score of 15. (8)

**GCS-Pupil Score**

The same 2018 review, mentioned above, published the GCS-Pupil (GCS-P) score, which is the GCS score minus the number of non-reacting pupils (0, 1, or 2). (8) The GCS-P increases the information obtained to an extent comparable to that calculated using more complex methods. Combining these features yields more informative data than using either alone. The relationship between decreases in the GCS-P and worsened outcome was noted across the full range of possible scores. (8)

The additional 2 lowest points offered by the GCS-Pups scale (GCS-P 1 and 2) extended the prognostic information. The GCS score of 3 mortality rate of 51% and an unfavourable outcome rate of 70%, increased to a mortality rate of 74% and an unfavourable outcome rate of 90% at GCS-P 1. Abnormal pupil response is more common in patients with severe brain injury and a low GCS score, therefore the pupil response provides additional information at low GCS scores. (8)

If patients’ loss of pupil reactivity is used in the pooled data (inclusive of higher GCS scores), there is a deteriorating outcome with overall mortality rising from 16% when both pupils reacted, to 38% when only one reacted, and to 59% when neither pupil reacted. (8)

**Abbreviated Injury Scale**

Isolated traumatic brain injury can be defined as head abbreviated injury scale (AIS) ≥ 3, with other injuries <3, according to a 2014 systematic review and meta-analysis. AIS dictionary used commonly in studies doing retrospective reviews of data from clinical registries. AIS should probably be limited to clinical registries and another limitation of AIS that the injuries are based on their anatomical features rather than physiology. Anatomical features can be documented as an ordinal scale, but it does not always correspond to prognosis. For example:
smaller haematoma of the posterior fossa may have a poorer prognosis than a similar sized frontal haematoma. However, AIS coding is performed at discharge or death and therefore, it will incorporate unexpected progression of pathophysiology. (11)

**Computed Tomography Based Classification**

Intracranial haemorrhage (ICH) size is strongly linked with patient morbidity and mortality outcome. Those with a larger ICH, wherever the location, have a significantly higher mortality than patients with a smaller haemorrhage. (17)

Marshall Computed Tomography (CT) classifications of structural brain damage are based on head CT findings of TBI patients. Imaging based classifications help identify TBI patients at risk of developing intracranial hypertension (HPT). (11) They disregard brain stem and cerebellar injuries that are present in the AIS dictionary. (11) The CT based scoring systems are focused on closed TBI’s only. (11)

![Table illustrating Marshall score (Maas et al 2005: p.1174). (1)](table)

**Glasgow Outcome Scale and Extended Glasgow Outcome Scale**

Prognostic models that use admission data are beneficial to support early clinical decision-making, as that information is readily available. (18) Many prognostic models have been described in the literature, but no single prognostic model is practised broadly. These were mostly developed using small patient samples in high-income countries and few were validated in external populations. (15, 19)

The 6-month Glasgow Outcome Scale (GOS), also known as extended GOS (GOSE), was formulated from the prognostic analyses of the data the IMPACT and CRASH-1 trials. (5, 18) The intricacy of these models differs, and their analysis make use of clinical features, imaging and laboratorial measurements that are available shortly after admission. These recent predictive scores have overcome limitations of previous scores, in terms of their lack of validation and are more practical for use during early resuscitation. (5) The GOS has five categories: 1 = dead; 2 = vegetative state; 3 = severe disability; 4 = moderate disability; and lastly, 5 = good recovery. (18, 19) The scale predicts mortality (GOS 1) versus survival (GOS 2–5) and of unfavourable (GOS 1–3) versus favourable outcome (GOS 4–5). (18, 19)

There are three prognostic models. The core model included age, the GCS motor score, and the reactivity of the pupils. (14, 18) The extended model included the three predictors from the core model plus information on secondary insults (hypoxia, hypotension), Marshall CT
Classification of head CT, traumatic subarachnoid haemorrhage (SAH), and epidural hematoma. (14, 18) The laboratory model included the characteristics from the extended model and additional information on glucose and haemoglobin (Hb). (14, 18)

IMPACT identified most powerful independent prognostic variables were the patient’s age, GCS motor score, reactivity of the pupils and the CT characteristics. (14) These CT characteristics include the Marshall CT classification and presence of traumatic subarachnoid haemorrhage. (14) There is a web-based prognostic calculator available at http://www.tbi-impact.org

The fact that the CRASH-1 trial is a double-blinded RCT, with a sample size of more than 10 000 patients, facilitates accurate and valid predictions. The high recruitment of patients from LMICs means that models developed with this data are relevant to the South African setting. (15, 16) However, two models were developed, one for LMICs and another for high-income countries. (15, 16) There is an interactive prognostic calculator mobile phone application, based on CRASH-1, called “TBI prognosis”, developed by Hyperexsis.

**RISK FACTORS FOR POOR PROGNOSIS**

**Demographics**

Violence and transport contribute significantly to trauma that occurs in LMICs. They occur mostly among young men influenced by alcohol and drug misuse. (2, 15, 20) A recent study in Pietermaritzburg which demonstrated an almost 4:1 male/female ratio in terms of incidence. (3) There is no suggestion of any link between gender and patient GOS. (14, 21)

Age has been identified as one of the most powerful independent prognostic variables. This predictive power expands across each of the core, extended and lab prognostic models. (14, 18) The higher the patient’s age at time of injury is strongly associated with worse outcomes (10, 15, 21), this association was apparent only in patients over the of age 40. (15)

**Cause of Injury**

As stated above, violence and transport, lead to majority of the trauma injuries in LMICs. (2, 15, 20) This is mirrored in South African data, which emulates the same trauma cause of injury pattern. (2) Several studies have been published recently reporting this same pattern from the Western Cape (20), KwaZulu Natal (22-24) and Eastern Cape (25, 26) provinces. In LMICs: motorcyclists, cyclists and pedestrians at extremes of ages (children and elderly patients) are most at risk of transport related TBIs. (27) In the developing world intentional trauma (violence) has a higher incidence than unintentional trauma as a cause of TBI and this is in keeping with most reported forms of trauma in South Africa. (13)

After adjustment for age, the cause of injury effectively loses its independent predictive power. (14, 28) Falls are associated with increasing age and a more frequent incidence of mass lesions, therefore these have poorer outcomes compared to other causes of injury. (28)

Assaults, suicides and accidents are the three causes of cerebral GSWs, which are highly lethal TBI’s. Most of these patients do not make it to hospital. (29, 30) There is limited
literature from the developing world, with only three studies to date all done in South Africa. The study done in Pietermaritzburg Metropolitan Trauma Service (public institution) reported an overall mortality of 38% (29), Baragwanath Hospital (public institution in Johannesburg) reported 27% (30), and from Milpark Hospital (private institution in Johannesburg) reported 58% (31).

**High- or Low-Middle Income Countries**

Although patients from LMICs experienced higher mortality, there wasn’t a noteworthy difference in unfavourable outcome at six months follow up. (15) It is possible that many patients with a severe TBI die before reaching hospital, considering the long delays in transfer from the scene and between hospitals which is inherent in developing countries. (13, 32)

**Chronic Medications**

Patients with bleeding disorders or those that have co-morbidities that require anticoagulants or antiplatelet agents, have an increased risk of immediate and delayed intra-cranial injury in patients with TBI. (10)

**CEREBRAL NEUROPROTECTION**

Cerebral perfusion pressure (CPP) is the difference between the mean arterial blood pressure (MAP) and intracranial pressure (ICP). (33) The ability of the brain to maintain a constant cerebral blood flow (CBF) through a range of CPP is known as cerebrovascular autoregulation. (33, 34)

The primary brain injury, which occurs at the moment of impact, triggers a cascade of events that lead to cerebral cell death. Reduction of cerebral perfusion can lead to an extension of the primary injury due to ischaemic insult, creating a secondary brain injury. Secondary brain injury leads to oedema formation with brain swelling, cellular ischaemia, and disruption of the blood brain barrier. This then results in an increased ICP, which further reduces CPP setting up a vicious cycle of ischaemic insult. Minimising the associated morbidity requires prevention of secondary brain injury, which is usually caused by hypoxia, hypovolaemia/hypotension, hypoglycaemia and raised ICP. (12, 13, 33-36) As ICP increases, there can be a shift of the brain tissue which can lead to cerebral herniation, this can result in disability or death. (33)

The cranial compartment normally has three components: blood, brain and cerebrospinal fluid (CSF). If one of these component volumes increase – for e.g. brain oedema – then compensation must occur to maintain ICP within normal range of 0-10 mm Hg. These measures include displacement of CSF and venous blood downward into the spinal spaces, with a decrease in blood volume. (33)

The oedema pathophysiology of secondary brain injury is that the tissue ischaemia leads to anaerobic glycolysis with an accumulation of lactic acid. (36) The ATP stores deplete due to the inefficient energy production due to anaerobic metabolism. (36) The cellular membrane
ion pumps are energy-dependent and therefore fail as the ATP is depleted, once these pumps fail there is an increased membrane permeability with cellular and tissue oedema. (36)

**Box 1 Causes of secondary brain damage** (36)

The treatment focus is on minimizing and preventing secondary injury following severe TBI. This is achieved by optimizing oxygenation, a reduction of ICP and supporting systemic perfusion, thereby ensuring adequate CPP. (12, 13, 34, 35)

Management principles will include the majority of recommendations from the 2016 Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition, from the Brain Trauma Foundation (BTF). These guidelines only include one surgical topic. (33) These guidelines are what is followed at Neurosurgical department at IALCH.
Physiological

Control of hypoxaemia

Hypoxaemia, which is defined as PaO2 < 60 mmHg (8 kPa), is associated with a significant increase in the mortality rate in severe TBI patients. (34, 36) Decreased brain tissue oxygen tension often demonstrates ongoing cerebral ischaemia and rapid correction of hypoxaemia is required. (36)

Early tracheal intubation and mechanical ventilation may facilitate correction of hypoxaemia in the most severe of cases. Guidelines suggest that we should target a PaO2 > 100 mmHg (13 kPa). (36) Severe TBI patients require definitive airway, because they are at risk of pulmonary aspiration and a decompensated respiratory function. (33) The harmful effects of hypoxaemia (<60 mmHg) and arterial hypotension (systolic BP < 90 mmHg) in the early stages after TBI have been demonstrated in literature and they are independently associated with significant increases in morbidity and mortality. (14, 34) Rapid correction of arterial hypotension and hypoxia is therefore necessary. (34)

Note: Hypoxaemia and hypoxia are commonly used interchangeably. Hypoxaemia is defined as a condition where PaO2 is below the normal range of 80–100 mmHg. (37) Hypoxia is defined as the failure of oxygenation at the tissue level, which is linked to an increased arterial lactate level. (37) Hypoxemia can occur without hypoxia, if the patient compensates for a low Pao2 by increasing oxygen delivery. (37)

Blood pressure control

A decrease in systolic blood pressure (SBP) triggers vasodilation in an attempt to maintain adequate brain perfusion, if autoregulation remains intact. (33) This results in increased CBF, which in turn elevates ICP. (33)

When autoregulation is disrupted, there is dependency on SBP to maintain cerebral perfusion and prevent cerebral ischemia. (33, 36) Current guidelines do not recommend a specific target SBP to aim for, it suggests avoiding moderate hypotension (SBP < 90 mmHg), which is
associated with increase in mortality. (33, 36) Hypotension should be managed with adequate fluid resuscitation and vasoressor agents. (36) BTF guidelines suggests aiming for SBP at ≥100 mm Hg for patients 50 to 69 years old or at ≥110 mm Hg or above for patients 15 to 49 or over 70 years old to decrease mortality rate and improve outcomes. (33) This suggestion is based on level III evidence, which is obtained from well-designed controlled trials without randomization. (33)

**Hypercapnia and hypocapnia**

Within normal physiological conditions, PaCO2 is the most significant determinant of CBF. (33) The CBF is linearly responsive to PaCO2 within a range of 20 – 80 mm Hg. (33) CBF is essential in meeting the brain’s metabolic demands. (33)

Severe TBI patients receive invasive ventilation which allows manipulation of PaCO2 with strict control, through minute ventilation adjustments. (33, 35) Hypoventilation with high PaCO2 levels can result in increased CBF (cerebral hyperaemia) with raised ICP. (33, 35) Older evidence suggested that cerebral hyperaemia occurred more commonly, than cerebral ischaemia, and that’s why hyperventilation to achieve significant hypocapnia in patients used to be popular. (33, 35) Hypocapnia due to excessive hyperventilation may worsen perfusion to some ischaemic areas of the brain following a TBI, due to decrease in CBF. (33, 36) Recent evidence reveals that after severe TBI, cerebral ischaemia is more prevalent than previously thought. (33)

With the recognition of a higher prevalence of cerebral ischaemia in this patient population, the guidelines suggest aiming for normocapnia with PaCO2 35 – 45 mmHg, (4.6 – 6 kPA); this practice will avoid further cerebral ischaemia and infarction. (33) With acutely raised ICP in cases of severe TBI, hyperventilation can be considered to temporarily reduce ICP while other medical therapies are administered or neurosurgery is considered; close monitoring of the blood flow and oxygen delivery to the brain must be done during this intervention. (33, 36)

**Haemoglobin**

Low haemoglobin (Hb) level is frequent amongst trauma patients with severe TBI and is associated to poor outcomes. A low transfusion trigger (Hb of 7 g/dL) is suggested in critically ill patients, in the absence of significant cardiac disease. Compromised brain tissue oxygenation may occur at higher Hb levels in severe TBI patients, than in other critically ill ICU patients. The benefits of blood transfusion in improving brain tissue oxygenation or decreasing brain metabolic distress, must exceed the possible risks. (34)

This physiological parameter recommendation not covered in BTF guidelines.

**Temperature control and hypothermia**

The brain temperature has been shown to be 1 – 2°C higher than the core body temperature in various types of brain injury. Fever, irrespective of the cause, is linked to adverse outcome in patients with acute brain injury. (34)

Hypothermia is known to preserve tissue and cells in view of metabolic challenge. (33) In experimental models, there is a 7% reduction of the cerebral metabolic rate per degree Celsius fall in temperature. (36) Animal studies have demonstrated that therapeutic
hypothermia may mitigate ischaemia-reperfusion injury and reduce the complication of brain oedema (therefore reducing ICP). (33, 34)

Prevention of ischaemia-reperfusion injury would theoretically require rapid treatment, ideally established in the early stages of injury and lasting up to 72 hours. Brain oedema would require treatment for as long as it lasts, the treatment periods would differ vastly and could be very prolonged. (34)

The risks of hypothermia include coagulopathy and immunosuppression, and profound hypothermia has the additional serious risks of cardiac dysrhythmia and death. (33, 36) Human studies evidence has not revealed a decrease in mortality rate and the guidelines do not recommend prophylactic hypothermia. (33)

Glycaemic control and nutrition

There is an increased energy expenditure after severe TBI, the belief is that the TBI itself intrinsically increases the metabolism, with an increased requirement for caloric support. Hyperglycaemia is a common response observed after severe stress in the critically ill, and this includes severe TBI patients. (33) This hyperglycaemic response can be controlled with the use of insulin. Normoglycaemia improves the outcomes of critically ill TBI patients (33, 36), as there is direct association between elevated serum glucose and poor outcomes after TBI. (33) Hypoglycaemia is also linked to poor outcomes after TBI, so the other extreme of insulin-induced hypoglycaemia must be avoided. (33) Neuroprotection protocols suggest that there should be reasonable control of blood glucose levels (<10 mmol/L), while avoiding hypoglycaemia. (33, 36)

Nutrition is an important aspect of critical care and assisting patients to receive basal caloric replacement at day 5 – 7 post-injury is recommended to decrease mortality. Feeding should be commenced, when not-contra-indicated, via a nasojejunal tube if possible, to decrease risk of ventilator associated pneumonia (VAP). A nasogastric tube will also suffice. (33)

Seizures

Post-traumatic seizures (PTS) may occur as a result a complication of severe TBI. If the PTS occur within 7 days of the injury they are classified as early; they are late PTS when they occur for the first time more than 7 days following injury. The incidence of clinical PTS may be as high as 12%. (33) They are difficult to detect in sedated and/or paralysed patients. Early recognition through clinical examination and investigation such as an electroencephalogram (EEG), will help detect the subclinical seizures. (33, 36) The incidence of subclinical seizures detected on EEG ranges from 20% to 25%, in severe TBI patients. (33) Seizures compromise the supply and demand of the brain for oxygen and substrate, by increasing its metabolic demands, therefore early treatment is important. (36)

Routine seizure prophylaxis is recommended due to high rate of PTS in severe TBI patients, and there are potential benefits to preventing its complications (e.g. increased cerebral metabolic demands, post-traumatic chronic epilepsy, herniation, and death). Phenytoin is recommended to decrease the incidence of early onset PTS, not late PTS. As with all treatments, it should be used only when the overall benefit is felt to outweigh the risks/complications associated with its administration. (33)
Pharmacological

Tranexamic acid
Coagulopathy occurs in about one third of TBI patients. The patients with coagulopathy have a greater risk of an increase in size of ICH, a higher mortality rate and poorer outcomes. (11, 38) The cause of the coagulopathy in the trauma setting can be attributed to two causes: acute traumatic coagulopathy (ATC) and delayed coagulopathy secondary to haemodilution (due to fluid resuscitation). Massive transfusion of red cells also can result in thrombocytopenia due to a dilutional effect; this can easily be mistaken for true platelet dysfunction. The mechanism of ATC stems from an imbalance in the intricate dynamic equilibrium which exists between anti and procoagulant factors, platelets, endothelium function and fibrinolysis. (11) Hypoperfusion and tissue damage (including endothelium damage) triggers this imbalance by stimulating the release of various proteins. (11, 39)

Thrombomodulin, a protein, is released and combines with thrombin to form a complex which leads to the over-activation of protein C. This activation leads to inhibition of co-factors Va and VIIa is thought to play key role in the development of ATC. The utilization of thrombin to make up this complex also leaves less available to cleave fibrinogen to fibrin. This decreased conversion of fibrinogen to fibrin causes an overall disruption in coagulation. It is accepted that there is also increased fibrinolysis, due to the high levels of fibrinogen degradation products, which is a common feature of the coagulopathy in TBI. (11, 39)

Tranexamic acid (TXA), as an antifibrinolytic, has demonstrated how beneficial it is in the management of traumatic haemorrhage. (38, 39) This drug is a synthetic derivative of the amino acid lysine that inhibits fibrinolysis by blocking the lysine binding sites on plasminogen. (38, 39) TXA has been found to reduce mortality of any cause in trauma patients with significant haemorrhage, with no increase in vascular occlusive events. (38, 39) These are the findings from the CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) Trial (>20,000 trauma patients), which included patients TBIs and a GCS score of ≤14. (38, 39)

The Intracranial Bleeding Study (CRASH-2 IBS) was conducted nested within the CRASH-2 trial, the TBI sub-group consisted of 270 patients, with significant protocol deviations including 11% of patients with a GCS of 15 at baseline. The nested trial was done to quantify the effect of TXA on mortality, ICH extension and new focal cerebral ischaemic lesions in patients with TBI. Analysis of this showed a trend toward less mortality with TXA. The adjusted analysis showed a greater reduction in total ICH extension in the TXA group compared to the placebo group. The CRASH-2 IBS was done in TBI patients with significant (extracranial) haemorrhage (SBP <90 mm Hg or heart rate >110, or both) and the effect of TXA might differ in patients with isolated TBI. (38, 39)

The possibility that TXA might reduce intracranial bleeding has been evaluated in spontaneous subarachnoid haemorrhage (SAH). A systematic review of randomised controlled trials of TXA administration in these patients found that TXA reduced the rate of rebleeding by approximately 40%. However, because of an increase in cerebral ischaemia there was no overall clinical benefit. The effect of TXA from the spontaneous SAH trials might not be directly generalisable to TBI patients as the patient characteristics and risk of ischaemia are different. The duration of TXA treatment in the spontaneous SAH trials was up to 6 weeks and this may account for the increase in cerebral ischaemia reported. (38, 40)
Shock, with haemodynamic instability, increases the risk of developing ATC by three-fold. It contributes to acidaemia caused by tissue hypoperfusion and hypoxaemia leading to anaerobic build-up of lactic acid. This acidaemia alters protease function and further increases risk of developing ATC. Hypothermia inhibits coagulation, and hampers platelet function. The combination of acidaemia, hypothermia and coagulopathy, known as the triad of death – will lead to significantly increased morbidity and mortality. (11)

In CRASH-2 and CRASH-3 loading dose of 1 g of TXA is given over 10 min, followed by an intravenous infusion of 1 g given over 8 h. (38, 39, 41) In CRASH-2 it was administered within 8h of injury. (38, 39) In CRASH-3, more than 12 700 TBI patients were recruited, those with GCS ≤ 12 or any ICH on CT scan, and no major extracranial bleeding were eligible; and GCS score of 3 or bilateral unreactive pupils were excluded. Patients received TXA within 3 h of injury, this change in timing was done in response to external evidence suggesting that later treatment is unlikely to be beneficial. The mortality risk of TBI’s were decreased with TXA in mild-to-moderate TBI, but not in patients with severe TBI. Earlier treatment was more effective than delayed treatment in patients with mild-to-moderate TBI, but the timing of the administration of the drug had no obvious effect in patients with severe TBI. (41) In summary it is suggested that early TXA administration might be more effective. Also, the statistic that most deaths caused by haemorrhage occur in the first few hours after injury, there is the implication that every patient should be treated as soon as possible after their injury. (38, 39, 41)

Progressive tissue damage and oedema develops in the neighbouring regions surrounding the ICH lesions, and is associated with a worse outcome (42). Tissue plasminogen activator (tPA) has been shown to play an essential role in this process of peri-ICH oedema in two animal studies. (43, 44) By blocking the conversion from plasminogen to plasmin, TXA counteracts the effect of tPA and could possibly also be beneficial in traumatic ICH by decreasing peri-ICH oedema through a specific neuroprotective effect. (45)

**Deep vein thrombosis prophylaxis**

The incidence rate of deep venous thrombosis (DVT) without prophylactic treatment in TBI’s is 50%, with a reduction to a 25% incidence in patients with isolated TBI treated with sequential compression devices. Venous thromboembolism (VTE) risk increases with increasing TBI severity. This is due to due to hypercoagulability resulting from the primary brain injury, prolonged periods of immobilization, and focal motor deficits. Pharmacological VTE prophylaxis, which, in conjunction with mechanical compression devices, has increased effectiveness over mechanical prophylaxis alone. Obviously, even with low dose anticoagulation, it has the potential to result in clinically significant intracranial haemorrhage expansion. (33)

Low molecular weight heparin (LMWH) or low-dose unfractionated heparin may be considered if the brain injury is stable and the benefit is considered to outweigh the risk of increased intracranial haemorrhage. Evidence from studies, that were not sufficiently powered, suggest that 72h post injury might be the right time to start prophylactic anti-coagulation. (33)
Sepsis
Some studies have shown lower CBF in septic patients than in healthy volunteers, but other factors, such as sedative agents or hypocapnia associated with hyperventilation, may also explain the CBF reduction in such patients. Sepsis is also associated with impaired CBF autoregulation, however, especially when shock is present. (34)

Severe TBI can increase a patient’s susceptibility to infection because of ventilation to prevent airway obstruction, aspiration, and consequential hypoxia, in addition to invasive monitoring. Infection risks such as VAP and central line associated bacteraemia (central venous catheter for inotrope and total parenteral nutrition administration), are increased in all critically ill patients. Patients undergoing invasive ICP monitoring are reported to have related infection rates as high as 27%. For external ventricular drains (EVDs), the historic focus of routine catheter exchanges has been replaced by attention to proper care during insertion and cerebrospinal fluid (CSF) sampling techniques. Antimicrobial-impregnated catheters may be considered to prevent catheter-related infections during EVD insertion. There is the question of whether prophylactic intravenous (IV) antibiotics reduces infection rates or increases the risk for emergence of drug-resistant organisms. (33) Although, elective EVD changes seem to still be practiced at IALCH.

According to the Centres for Disease Control and Prevention (CDC) definition, VAP requires a positive culture, purulent respiratory secretions, or positive results on one of several tests. Prior to the revision of definitions in 2011, data showed that VAP in patients with TBI may be as high as 40%, and it is strongly associated with longer exposure to mechanical ventilation. The occurrence of VAP is associated with factors such as hypoxia, fevers, hypotension, and increased ICP, known to increase worsen the TBI patient’s morbidity. Similarly, the risk of infection associated with EVDs is of particular concern for TBI patients. (33)

Early tracheostomy is recommended to reduce mechanical ventilation days when the overall benefit outweighs the complications associated with such a procedure. There is no evidence that early tracheostomy reduces mortality or the rate of nosocomial pneumonia. (33)

Sedation
Anaesthetics, analgesics, and sedatives are often used acute TBI for prophylaxis or control of intracranial HPT and for seizures. Sedation drugs may optimize supply of regional blood flow to metabolic demands, resulting in higher brain oxygenation with lower cerebral blood flow, and decreased ICP. (33)

Side effects of sedation drugs include hypotension and decreased cardiac output, as well as increased intrapulmonary shunting, which may lead to hypoxia. This hypoxia will cause a decrease in CPP, which may negate the benefits of decreased ICP. The administration of these medications may preclude the physical examination in following a patient’s progress and may therefore necessitate more advanced therapeutic modalities such as continuous electroencephalographic (EEG) monitoring. (33)
Barbiturates have a long history of being used to control ICP with suppression of metabolism and oxygen consumption with an alteration of cerebral vascular tone, this can be neuroprotective in some patients. High-dose barbiturate administration is recommended to control elevated ICP refractory to maximum standard medical and surgical treatment. Patients need to be haemodynamically stable as it can cause hypotension at high dose. (33)

Propofol offers neuroprotection as both cerebral metabolic rate and CBF are reduced in a dose-dependent manner with use of this agent. Propofol has a shorter half-life than barbiturates and is therefore a favoured sedative agent. (36) Propofol Infusion Syndrome can occur in patients treated with long-term high-dose infusions of this agent (more than 48 hours and at doses greater than 5 mg/kg/h) and these patients should be monitored closely. (33, 36)

Volatile agents suppress cerebral metabolism and at lower concentrations they offer neuroprotection by suppressing energy requirements. (34, 36) However, at higher levels they increase the CBF due to vasodilatation. Sevoflurane has the least effect on CBF. (36)

Steroids
According to the findings of CRASH-1, those in the treatment arm (receiving high dose Methylprednisone of 2g and a 48h infusion) had a higher risk of death before 6 months: 25.7% vs 22.3%. The risk of death or severe disability at six months was also higher in the group allocated corticosteroids 38.1% dead or severely disabled, versus 36.3%. These results provide clear evidence that treatment with corticosteroids following TBI affords no material benefit. (46) Steroids are immunosuppressive and can lead to hyperglycaemia. (36) Therefore, use of steroids is not recommended for improving outcome or reducing ICP. (33)

Hyperosmolar agents
Intravenous administration of hyperosmolar agents has become routine in the management of intracranial hypertension and herniation syndromes. However, insufficient evidence exists to recommend the optimal agent, dose or means of administration (bolus vs. continuous infusion), and their precise mechanisms of action continue to be investigated. (33)

Mannitol and hypertonic saline are routinely employed hyperosmolar agents, commonly used for their effects on cerebral oedema and raised ICP. (33, 36) Hypertonic saline administration may be deleterious for a hyponatremic patient. Mannitol’s diuretic effect is undesirable in hypotensive patients and patient’s intravascular volume loss should be replaced. In the presence of an intact blood brain barrier, mannitol draws out water from brain tissue into the plasma via osmosis. (36) Previously it was believed that mannitol worked exclusively by dehydrating the brain. (33) Both mannitol and hypertonic saline work to reduce ICP, by reducing blood viscosity, which in turn results in increased blood flow leading to vasoconstriction secondary to an increased oxygen delivery. This results in decreased cerebral blood volume and ICP. (33, 36) Additionally, mannitol has been shown to decrease the rate of CSF production. (36) Hypertonic saline acts as an osmotic agent like mannitol, but it also causes endothelial cell dehydration thereby increasing the lumen of blood vessels and increasing cerebral perfusion. (36)
The third edition guidelines recommended mannitol is effective for control of raised intracranial pressure (ICP) at doses of 0.25 g/kg to 1 g/kg body weight. The literature does not currently support recommendations that meet the strict criteria for contemporary evidenced-based medicine approaches for guideline development. (33)

Surgical

Decompressive craniectomy

Cerebral oedema can result from a combination of several pathological mechanisms associated with TBI. (33) As ICP increases, brain tissue displacement can lead to cerebral herniation, resulting in disability or death. (33)

Surgical removal of a portion of the skull, known as decompressive craniectomy (DC), can be used in TBI patients with raised ICP not responding to first-tier intensive care and neurosurgical therapies. Removing part of the skull bone, thus giving brain tissue space to expand and therefore decreasing the ICP and improving cerebral perfusion. The opinions on the benefits of this procedure are divided. (33, 34, 36)

The BTF recommends that if a DC is required a larger DC should be done in the fronto-temporo-parietal area – at least 12 x 15 cm or 15 cm diameter. This reduces mortality and leads improved neurologic outcomes in patients with severe TBI. (33)

This procedure improves survival in many patients who would otherwise die of a raised ICP that has failed to respond to other measures. (34, 36) However, it has been noted that many of these patients actually survive to have more unfavourable outcomes with a poor quality of life after surgery and with persistent vegetative state. (34, 36) A 2016 study published after the most recent BTF guidelines looked at 408 patients, 10 to 65 years of age, with TBI with refractory elevated intracranial pressure (>25 mm Hg) to undergo decompressive craniectomy or receive ongoing medical care. The primary outcome was the rating on the GOSE. At 6 months the mortality was 26.9% amongst the surgical group versus 48.9% in the medical group. The surgical group had higher rates of: vegetative state, lower severe disability and upper severe disability than the medical group. The rates of moderate disability and good recovery were similar in the two groups. (47)

External Ventricular Drain

The external ventricular drainage systems in severe TBI patients can be used in a closed position, which allows for monitoring of ICP, and in an open position, drainage of CSF can occur. Paediatric patient management usually has continuous CSF drainage with improvements in ICP management. Adult patient management is more variable with some departments preferring to continuously monitor ICP with intermittent CSF drainage for raised ICP. Other departments employ continuous drainage of CSF with intermittent ICP readings. (33)

It is recommended that an EVD, zeroed at the midbrain, with persistent drainage of CSF may be considered to lower ICP burden more effectively than intermittent use. It can also be used to decrease ICP in patients with baseline GCS < 6, this should only be considered during the first 12h post-injury. (33)
Target thresholds for invasive cranial monitors

ICP should be monitored in severe TBI patients and with an abnormal CT scan revealing bleeding, contusions, oedema, herniation, midline shift or compressed basal cisterns. ICP monitoring can be considered in a normal CT scan severe TBI patient two or more of these factors are present at baseline: age > 40 years, unilateral or bilateral motor posturing, or SBP <90 mm Hg. Management of severe TBI patients using information from ICP monitoring is recommended to reduce in-hospital and 2-week post-injury mortality. Treating ICP above 22 mm Hg is recommended because values above this level are associated with increased mortality. (33)

CPP can only be calculated when the ICP is known, CPP is equal to MAP minus ICP, and this should be considered into decision about placement of an ICP monitor. CPP is a valuable measurement in the optimization of the TBI patient. It is thought to be a surrogate marker for the delivery of nutrients to the brain. Patients with intact autoregulation are best served by higher CPP values, while those with non-intact autoregulation do better with lower CPP values. Patients who had no time periods with CPP below 60 mm Hg had higher survival rates than patients who did. The recommended range to target is between 60 – 70 mm Hg. Avoiding aiming for a target CPP > 70 mmHg because of the risk of respiratory complications. Guidelines recommend that CPP monitoring is recommended in severe TBI to decrease 2-week mortality. (33)
CONCLUSION

As with all evidence-based medicine, you need to be aware of the latest literature and consider the strength of the evidence. These big sample size trials, that are pertinent to this booklet, have significant critiques in the medical community, despite their reported results being so substantial.

We play an important role in our ability to possibly reduce poor long-term outcomes in these patients who are neuroprotected in our ICU’s and who come to our theatre for varying procedures. Trauma and its associated injuries will always be relevant in our South African context.
REFERENCES


