Trauma Surgery & Acute Care Open

Controversies and evidence gaps in the early management of severe traumatic brain injury: back to the ABCs

Seif Tarek El-Swaify ,[1] Mazen A Refaat ,[1] Sara H Ali,[1] Abdelrahman E Mostafa Abdelrazek,[1] Pavly Wagih Beshay,[1] Menna Kamel,[1] Bassem Bahaa,[1] Abdelrahman Amir,[1] Ahmed Kamel Basha[2]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/tsaco-2021-000859).

[1]Department of surgery, Ain Shams University Hospital, Cairo, Egypt
[2]Department of neurosurgery, Ain Shams University Faculty of Medicine, Cairo, Egypt

Correspondence to
Dr Ahmed Kamel Basha; ahmedbasha@med.asu.edu.eg

Received 6 November 2021
Accepted 10 December 2021

To cite: El-Swaify ST, Refaat MA, Ali SH, *et al*. *Trauma Surg Acute Care Open* 2022;**7**:e000859.

SUMMARY

Traumatic brain injury (TBI) accounts for around 30% of all trauma-related deaths. Over the past 40 years, TBI has remained a major cause of mortality after trauma. The primary injury caused by the injurious mechanical force leads to irreversible damage to brain tissue. The potentially preventable secondary injury can be accentuated by addressing systemic insults. Early recognition and prompt intervention are integral to achieve better outcomes. Consequently, surgeons still need to be aware of the basic yet integral emergency management strategies for severe TBI (sTBI). In this narrative review, we outlined some of the controversies in the early care of sTBI that have not been settled by the publication of the Brain Trauma Foundation's 4th edition guidelines in 2017. The topics covered included the following: mode of prehospital transport, maintaining airway patency while securing the cervical spine, achieving adequate ventilation, and optimizing circulatory physiology. We discuss fluid resuscitation and blood product transfusion as components of improving circulatory mechanics and oxygen delivery to injured brain tissue. An outline of evidence-based antiplatelet and anticoagulant reversal strategies is discussed in the review. In addition, the current evidence as well as the evidence gaps for using tranexamic acid in sTBI are briefly reviewed. A brief note on the controversial emergency surgical interventions for sTBI is included. Clinicians should be aware of the latest evidence for sTBI. Periods between different editions of guidelines can have an abundance of new literature that can influence patient care. The recent advances included in this review should be considered both for formulating future guidelines for the management of sTBI and for designing future clinical studies in domains with clinical equipoise.

INTRODUCTION

Traumatic brain injury (TBI) accounts for around 30% of all trauma-related deaths. In the USA, seven TBI-related deaths occur every hour.[1] There is an alarming increase in these numbers, and hence a constant need for improving preventive and therapeutic strategies. The initial trimodal distribution of death has changed over the past 40 years to a single early peak of immediate deaths. However, TBI remains a major cause of mortality after trauma across all time periods.[2] The change in patterns can be attributed to a widespread adoption of the concepts of the 'Golden Hour' and 'Platinum 10 Minutes' which reflect early resuscitation and prompt emergency medical services (EMS) stabilization and transport (Scoop and Run method), respectively. The aforementioned concepts are not arbitrary, and early intervention should always be sought even if minutes-to-hours have passed since the injury.[3] Consequently, surgeons still need to be aware of the basic yet integral emergency management strategies, which are often defined in the literature as within the first 24 hours, for severe TBI (sTBI).

TBI is an index term that comprises many grades and classifications. It is prudent to adequately define the type of injury that has occurred to guide management decisions and assign a prognosis. Classically, sTBI has been defined as a Glasgow Coma Scale (GCS) ≤8 after resuscitation. However, the limitations of the GCS, which include difficulty in assessing intoxicated, intubated, or paralyzed patients, have driven clinicians to develop more comprehensive classification systems. The most popular classification is that developed by the United States Department of Defense (DoD) and Department of Veteran Affairs (VA) (VA/DoD classification).[4] A thorough understanding of the pathophysiology of sTBI has led to better management protocols for these patients. The primary injury caused by the injurious mechanical force leads to irreversible damage to brain tissue. This triggers ongoing alterations in cerebral cellular metabolism and cerebral blood flow (CBF) regulation. These alterations lead to an insidious secondary injury of neural tissue that leads to further neurological deterioration. In the context of polytrauma, systemic physiological derangements can accentuate the secondary injury.[5] Evidence supports the notion that early assessment and adequate resuscitation are of paramount importance to prevent this secondary injury and improve outcomes.[6]

We are writing this review to discuss controversies in the resuscitation and emergency management of sTBI that have not been settled by the publication of the Brain Trauma Foundation's (BTF) guidelines in early 2017.[7] These evidence gaps require further research as they may influence the management

decisions of all healthcare practitioners involved in the care of patients with sTBI.

PREHOSPITAL TRANSPORT

An effective and rapid triage by EMS is critical to achieve better TBI outcomes. The mode of transport is an important variable to consider as evidenced by the findings of Bekelis *et al*. They analyzed outcomes of 209 529 patients and showed that helicopter transport (H-EMS) was associated with improved survival after TBI when compared with ground services (G-EMS) (OR 1.88; 95% CI 1.74 to 2.03). This difference persisted after using regression models and propensity score matching. The elapsed time from dispatch to delivery was not reported but the authors claim to have included it in their models.[8] These results were replicated in 51 400 pediatric patients where the median total prehospital time was 13 min longer for H-EMS (OR 1.81; 95% CI 1.24 to 2.65).[9] However, the true benefit of H-EMS for TBI could not be established in a systematic review that included six studies of which none was randomized controlled trials (RCTs). The authors attributed the very low quality of evidence to significant heterogeneity and methodological weakness.[10] Chen *et al* recently performed a case-control study of 8307 matched pairs transported by H-EMS or G-EMS to identify patients who would benefit from hospital transport regardless of transport time. Although the median transport time was 13 min longer with H-EMS, three patient groups were found to have significantly better survival: abnormal respiratory rate (OR 2.39), GCS ≤8 (OR 1.61) and hemothorax/pneumothorax (OR 2.25).[11]

Although faster transport times may account for the better outcomes seen with H-EMS, other confounders may account for the observed differences such as the presence of physicians on board, advanced crew capabilities (eg, advanced airway techniques, prehospital blood product services), differences in designated trauma centers and protocols, and other unmeasured confounders. In areas with equivalent crew capabilities between H-EMS and G-EMS, crew expertise has been proposed as a possible reason for the difference in outcomes. Consequently, there is a growing call to improve and standardize evidence-based EMS protocols.[12] It should be noted that in many lower-middle-income countries, EMS systems are not yet adequately developed, therefore, a hospital emergency department may be the primary point of care for delivering essential life-saving interventions.[13]

THE AIRWAY AND CERVICAL SPINE

Hypoxia is a predictor of poor outcome for patients with sTBI because reduced brain tissue oxygen augments reduced cerebral oxidative metabolism.[14 15] Consequently, endotracheal intubation should be considered to secure the airway and assist ventilation in patients with sTBI.[16] One would think that early intubation in the field would therefore consistently lead to better outcomes.[17 18] Bernard *et al* demonstrated in an RCT of 312 patients that paramedic intubation led to better neurological outcome at 6 months (risk ratio (RR) 1.28; 95% CI 1.00 to 1.64), but there was no improvement in survival.[17] Interestingly, recent studies have shown the opposite to be true. A large cohort-matched study of 16 278 patients demonstrated that prehospital intubation led to longer transport times (median 26 vs 19 min, p<0.001) and higher in-hospital mortality (OR 1.40; 95% CI 1.21 to 1.62).[19] A recent systematic review of 6 studies including 4772 patients found a twofold increase in mortality when intubation was performed by healthcare providers with less experience.[20] This observation could be explained by either difficulty in prehospital intubation with longer hypoxia during attempts or inadvertent manual hyperventilation leading to hypocapnic cerebral vasospasm and reduced CBF. The overall variability between different centers in reported outcomes could be explained by the variation in EMS training, intubation protocols, and drug regimens used.[21] Consequently, prehospital use of facemask oxygenation or supraglottic airway devices may be preferred for patients with isolated sTBI. Although evidence supports faster transport times as part of the 'Scoop and Run' transport method, some authors argue that significant extracranial injury may warrant prehospital intubation. Choffat *et al* showed in a multicenter study from Switzerland that prehospital intubation trended toward worse outcomes (HR 2.83; 95% CI 0.93 to 8.56). However, patients with Injury Severity Scores >25 had significantly better 14-day mortality rates when prehospital intubation was used (HR 0.25; 95% CI 0.08 to 0.74).[22] A registry analysis of 3736 patients from 59 European centers showed that prehospital intubation was only associated with better Glasgow Outcome Scale- Extended (GOS-E) scores at 6 months after injury when patients had increasing severity of thoracic (p=0.009) and abdominal injuries (p=0.02).[23]

Endotracheal intubation is usually indicated in trauma patients with either airway compromise, hemodynamic instability, respiratory failure, or altered mental status (GCS ≤8). The use of a GCS cut-off has long been challenged.[24] Several authors have demonstrated that depending mainly on the GCS to guide the decision of intubation leads to an increase in mortality.[25 26] In fact, Jakob *et al* have suggested using a policy of intubating patients with isolated TBI ≤45–65 years with head Abbreviated Injury Scale score of 5 and GCS score of 7 with a high specificity but low sensitivity.[26] Providers must always remember the potential risks of intubation in sTBI, which include increased intracranial pressure (ICP) due to sympathetic autonomic activation, dependent head position during laryngoscopy, and positive pressure ventilation. Most patients are intubated orally using rapid sequence intubation to blunt the autonomic responses, therefore, a thorough knowledge of the physiological alterations from using these drugs is essential.[27] Patients can be intubated in the reverse Trendelenburg position or have their heads elevated after intubation to limit increases in ICP.[28]

Cervical spine (C-spine) injuries can occur with blunt trauma, and they are particularly more likely with sTBI. All patients with suspected C-spine injury routinely have a rigid cervical collar placed to avoid excessive movement and prevent spinal cord injury. Unfortunately, cervical collars compromise ICP by increasing jugular venous pressure, although semi-rigid collars may be less harmful.[29] However, the effect of measured increases in ICP on clinical outcomes is not well-established. Another important drawback of cervical collars is the need to remove the anterior portion and use manual in-line stabilization (MILS) while intubating patients. MILS reduces mouth opening and therefore narrows the laryngoscopic view. The use of alternative intubation devices such as video laryngoscopes (eg, AirTraq) and modified laryngoscope blades (eg, McCoy hinged blade, Miller straight blade, etc) permits better and faster intubation rates with less C-spine extension.[30 31] Patients with head and neck injuries that limit intubation or those who have failed intubation and ventilation should have a surgical airway established promptly.

BREATHING AND VENTILATION

The priority that follows is to ensure adequate ventilation through the secure airway. The current recommendations are

to maintain normoxia (PaO_2 60–100 mm Hg) and normocapnia ($PaCO^2$ 35–45 mm Hg) while avoiding hyperventilation and major hyperoxia during the first 24 hours after injury.[32] The use of mild hyperoxia (100–250 mm Hg) is controversial and evidence is still lacking as to the true benefit of it.[33–37] When hyperventilation is needed for ICP management, jugular bulb oxygen saturation (S_jO_2) or brain tissue oxygen ($B_{tp}O_2$) measurements should be used to monitor oxygenation while mild hypocapnia (30–35 mm Hg) is briefly achieved (15–30 min) to avoid cerebral ischemia.[7 38–40]

A unique problem arises in the pulmonary physiology of patients with TBI; these patients are susceptible to develop acute lung injury that could be exacerbated by mechanical ventilation leading to ventilator-induced lung injury.[41] A challenge arises when trying to maintain a 'brain-lung balance'; Kim *et al* comprehensively review the evidence and demonstrate several cases where there was an obvious brain-lung conflict and how they were managed.[42] Providers can use high tidal volumes to maintain normoxia and mild hypocapnia with low levels of positive end-expiratory pressure (PEEP) to preserve CBF and reduce impedance to cerebral venous return via increases in intrathoracic pressure. On the other hand, many of these patients are prone to develop post-traumatic acute respiratory distress syndrome (ARDS) that requires a lung-protective ventilation strategy.[43] Clinicians must assess both the degree of ICP elevation and the effect of PEEP on ICP to implement the best ventilatory strategy.[44] The intracranial-to-central venous pressure gap can be used to guide decision-making in these situations. A lower gap was found to strongly predict ICP responsiveness to PEEP using receiver operating characteristic analysis (area under curve (AUC)=0.957; 95% CI 0.918 to 0.996).[45] In patients with moderate-to-severe ARDS (PaO_2/FiO_2 ratio <150), prone positioning can be considered provided that there is no significant ICP elevation and with diligent cerebral monitoring. An additional consideration during prone positioning is to avoid abdominal compression on the bed and the subsequent detrimental increase in intra-abdominal pressure. Specialized rotatory beds can avoid this dilemma altogether.[46]

CIRCULATION: OPTIMIZING CARDIOVASCULAR PHYSIOLOGY

Optimizing the cerebral perfusion pressure and CBF begins with the adjustment of the mean arterial pressure to prevent poor neurological outcome after TBI.[47] A single episode of hypotension (defined as systolic blood pressure (SBP) <100 mm Hg) has been found to double the odds of death with an increment up to six times if it reaches <70 mm Hg.[48] The study analysis showed that the odds of death were 19.9 (95% CI 12.7 to 31.2) times higher with SBP <70 mm Hg when compared with SBP of 130–139 mm Hg. The current BTF guidelines recommend different SBP thresholds for different age groups: ≥100 mm Hg for patients aged 50–69 years and ≥110 mm Hg for patients aged 15–59 or above 70 years.[7] Currently, there is a growing initiative to consider higher SBP thresholds than those stated by the BTF because of the potential for better outcomes. A recent database review studied 154 725 patients and concluded that both early (at 1 day, 0.8% vs 1.4%; p=0.004) and late in-hospital mortality rates (at 30 days, 3.1% vs 4.7%; p<0.001) of patients with SBP of 110–129 mm Hg were significantly lower than patients with SBP of 90–109 mm Hg. Their findings, as well as others', showed that the optimal blood pressure to maintain for patients with isolated TBI of all ages and genders was >110 mm Hg.[49 50] Other authors have even advocated for a higher threshold of 120 mm Hg.[51–53]

Damage control resuscitation is currently recommended in several guidelines to improve patient outcomes in the setting of polytrauma. Essentially, it revolves around two concepts: hypotensive resuscitation (maintaining an SBP <90 mm Hg to prevent clot disruption and re-bleeding) while rapidly diagnosing and obtaining surgical damage control, and hemostatic resuscitation (limiting crystalloids and using whole blood (WB) or blood products in fixed ratios combined with early tranexamic acid (TXA) use to restore normal physiology). Although the evidence is more favorable in the setting of penetrating trauma, existing guidelines do not make a clear distinction between blunt and penetrating trauma. Until more evidence is available, many centers will employ a permissive hypotension strategy for some blunt trauma patients as well. However, the presence of a concomitant TBI complicates the management strategy for both blunt and penetrating trauma because a low SBP target compromises the CBF. A panel of experts including trauma surgeons, neurosurgeons, and intensive care unit physicians recommended that the optimal SBP for a patient suffering from polytrauma associated with TBI should be an SBP maintained at >100 mm Hg.[32] These recommendations align with the findings of the large cohort study of around 4000 patients by Spaite *et al*.[51]

CIRCULATION: THE OPTIMAL RESUSCITATION FLUID

Fluid therapy is integral in achieving volume expansion and reaching the SBP targets mentioned previously. However, this must be balanced with maintaining a neutral fluid balance and avoiding hyponatremia and worsening cerebral edema.[54] There has been an ongoing debate over the optimal crystalloid due to insufficient evidence concerning different aspects: how much volume should be given, does using a bolus versus infusion affect mortality rates, and whether the solution used should be hypertonic or isotonic. The initiative to compare crystalloid with colloid resuscitation for TBI has lost momentum since the publication of the Saline versus Albumin Fluid Evaluation (SAFE) trial in 2007. The trial showed that albumin resuscitation caused a twofold increase in mortality compared with saline resuscitation. However, the comparison of crystalloids is still a subject of ongoing research.

Rowell *et al* compared the use of normal saline and lactated Ringer's (LR) administration in prehospitalized patients and found a higher 30-day mortality rate with LR (HR 1.78; 95% CI 1.04 to 3.04) despite no difference in admission biochemical or physiological parameters, 6-hour RBC, or crystalloid requirement in either group.[55] A possible explanation could be that balanced salt solutions closely resemble human plasma and thus have a lower sodium and chloride content than 0.9% saline with the addition of a buffer such as acetate or lactate. These fluids (eg, Ringer's lactate, Hartmann's solution) have minimal effects on pH but are relatively hypotonic which can exacerbate edema particularly cerebral edema in the injured brain.[56]

The potential utility of hypertonic crystalloids in TBI is twofold; they are potent vascular compartment expanders, and they can reduce cerebral edema. A recent RCT compared the effect of continuous hypertonic saline (20%) for 48 hours with standard hospital care on 359 patients. The study showed that there was no significant difference in neurological outcome (GOS-E) at 6 months (OR 1.02; 95% CI 0.71 to 1.47). There was no significant difference in the secondary outcomes of 6-month mortality (HR 0.79; 95% CI 0.48 to 1.28) or development of intracranial hypertension (IHT) (absolute difference −2.6%; 95% CI −12.3% to 7.2%).[57] These findings are in line

Table 1 Risk factors for coagulopathy after traumatic brain injury

Category	Risk factors
I. Patient characteristics	► Age ≥75 years ► Preinjury anticoagulant and/or antiplatelet therapy ► ICU admission ► Intravenous fluids resuscitation ≥2–3 L ► Hemoglobin <12.4 mg/dL ► Hypothermia (temperature <35°C) ► Hypotension (SBP ≤90 mm Hg) ► SI ≥1 ► Base excess ≤−6
II. Injury characteristics	► GCS ≤8 before intubation ► Abnormal pupils (unilateral or bilateral unreactive) ► Penetrating head trauma ► AIS_{head} ≥5 ► ISS ≥16 ► Midline shift on head CT ► Cerebral edema on head CT ► SAH on head CT

AIS, Abbreviated Injury Scale; GCS, Glasgow Coma Scale; ICU, intensive care unit; ISS, Injury Severity Score; SAH, subarachnoid hemorrhage; SBP, systolic blood pressure; SI, shock index (heart rate/systolic blood pressure).

Table 2 Predictors of progressive hemorrhagic injury after traumatic brain injury

Category	Predictors
I. Clinical	► Older age ► Lower admission GCS ► Higher AIS_{head} ► Higher blood product requirement ► Intraparenchymal brain contusions
II. Initial conventional coagulation parameters	► Lower platelet count (especially <100×10⁹/L) ► Lower functional fibrinogen (especially <356 mg/dL) ► High INR (especially >1.2) ► Lower factor VII activity (especially <77.5%) ► Higher admission D-dimer levels ► Higher fibrin monomers (especially ≥131.7 µg/mL)
III. Initial viscoelastic measurements	► Narrower median alpha angle (especially ≤65°) ► Prolonged κ-time (especially ≥1.65 min) ► Prolonged R-time (especially ≥5.65 min)

AIS, Abbreviated Injury Scale; GCS, Glasgow Coma Scale; INR, international normalized ratio; ISS, Injury Severity Score; R-time, reaction time; κ-time, kinetic time.

with a recent meta-analysis of six RCTs comparing prehospital hypertonic fluids with isotonic fluids in terms of survival.[58]

CIRCULATION: UTILITY OF BLOOD PRODUCTS

Packed red blood cells (pRBCs) are used for replacement in traumatic bleeding theoretically leading to better outcomes after sTBI. However, higher thresholds may be associated with increased thromboembolic events and progressive hemorrhagic injury (PHI).[59 60] The World Society of Emergency Surgery guidelines recommend pRBCs transfusion for hemoglobin level <70 g/L during interventions for life-threatening hemorrhage or emergency neurosurgery; higher thresholds may be considered for 'at-risk' patients.[32] More evidence is still needed to consolidate this recommendation. Two RCTs, The HEMOTION (Hemoglobin Transfusion Threshold in Traumatic Brain Injury Optimization) trial and TRAIN (Transfusion Strategies in Acute Brain Injured Patients) trial, would hopefully offer valuable insights (NCT03260478 and NCT02968654, respectively). Due to the associated risks of pRBC transfusion, recent research has focused on the use of erythropoietin as a less hazardous alternative. A meta-analysis using data from 1181 patients demonstrated significant reduction in mortality (OR 0.64; 95% CI 0.45 to 0.92; p=0.02) and no difference in the rate of deep vein thrombosis (risk difference (RD) −0.02; 95% CI −0.06 to 0.02) or neurological outcomes (OR 1.58; 95% CI 0.84 to 2.99), but, erythropoietin cannot be recommended for routine use in TBI because trials were insufficiently powered.[61] An important limitation to consider in this meta-analysis is that the follow-up duration of the different studies varied from 1 to 26 weeks.

TBI-induced coagulopathy, often considered a systemic sequela of localized trauma to the brain, can lead to PHI. The risk factors and predictors for both conditions are detailed in tables 1 and 2, respectively.[62–72] Both platelet functions and coagulation pathways are affected.[73] In a retrospective review of 35 patients with TBI presenting with platelet dysfunction, Furay *et al* reported that platelet transfusion, guided by thromboelastography, was independently associated with decreased mortality (OR 0.23; 95% CI 0.06 to 0.92; p=0.038).[74] This goal-directed transfusion strategy shows a stark difference when compared with other studies that showed worse outcomes such as the one conducted by Anglin *et al*, which used conventional assays to guide platelet transfusion.[75] A novel alternative under investigation directed at treating TBI-induced coagulopathy is desmopressin. In a study of 57 patients with sTBI and platelet dysfunction, a similar correction of ADP inhibition was seen in both platelet transfusion and desmopressin groups (p=0.28).[76]

The utility of fresh frozen plasma in targeting coagulation abnormalities and therefore potentially improving outcomes is the subject of intense research.[62] In a secondary analysis of 166 patients with TBI in the PreHospital Air Medical Plasma (PAMPer) trial, receipt of prehospital plasma improved 30-day survival among patients with GCS <8 (HR 0.56; 95% CI 0.35 to 0.91) and those with polytrauma (HR 0.50; 95% CI 0.28 to 0.89).[77] In a retrospective study of 633 patients with isolated TBI, Chang *et al* compared early (within 4 hours) plasma transfusion versus no plasma transfusion. Early transfusion was not associated with improved survival (OR 1.18; 95% CI 0.71 to 1.96); however, on subgroup logistic regression analysis patients with multifocal intracranial hemorrhage (ICH) (n=61) who received early plasma transfusion were found to have improved survival (OR 3.34; 95% CI 1.20 to 9.35).[78] This suggests that although plasma transfusion might not be associated with in-hospital survival of all patients with TBI, it might play a role in improving survival in specific groups as those with multifocal ICH. In an observational study of 101 pediatric patients with TBI, Leeper *et al* found in a regression model (controlled for sTBI, admission INR, polytrauma, and clinical bleeding) that only plasma remained an independent predictor of sustained fibrinolysis shutdown (OR 1.17; p=0.031).[79] Patients with sTBI and plasma transfusion had 100% sustained fibrinolysis shutdown, 75% mortality, and 100% disability in survivors. They noted that INR did not correlate with bleeding/clinical coagulopathy nor with rapid thromboelastography results. Despite this important finding, provider discomfort with elevated INR still prompted the use of plasma transfusion. The implications of these results are that plasma transfusion may be less promising in pediatric patients perhaps due to still unknown pathophysiological mechanisms, and the use of real-time viscoelastic assays gives a more reliable idea of patients' hematological physiology.[80] Cryoprecipitate is another promising blood product that has shown

favorable results, both in isolated and polytrauma TBI, in two small studies based out of Japan.[81 82] There is a growing initiative, initially inspired by the military medicine philosophy of 'walking blood banks', to use fresh WB. It is believed to achieve hemostatic resuscitation with less requirement for blood transfusion while avoiding the anticoagulant additives of balanced blood component therapy. Outcomes have been comparable between WB and component therapy in trauma.[83] The use of WB for concomitant TBI and hemorrhagic shock resuscitation has the potential to optimize oxygen delivery while minimizing fluid overload and cerebral edema. Although animal models have shown excellent results with the use of WB, there is no clinical data on the use of WB in the setting of sTBI.[84] Perhaps the results of the ongoing Shock, Whole Blood, and Assessment of TBI trial (S.W.A.T) (NCT03402035) will better inform clinicians of the true utility of WB.

CIRCULATION: PREINJURY ANTITHROMBOTICS AND THEIR REVERSAL

An increasing number of brain-injured patients are injured while on antiplatelets or anticoagulants. These patients are susceptible to PHI from the inherent coagulopathy of TBI, and they have iatrogenic derangement of hemostatic mechanisms.[62] Although knowledge of antithrombotics and their reversal strategies is essential, the true benefit of these strategies is unclear (see online supplemental table 3).[85–87] For patients taking antiplatelets, platelet transfusion may be associated with higher mortality (OR 1.29; 95% CI 0.76 to 2.18), and it has no significant effect on PHI (OR 0.88; 95% CI 0.34 to 2.28) or need for neurosurgical intervention (OR 1.00; 95% CI 0.53 to 1.90). The effect on PHI was similar even when guided by platelet function assays.[87]

CIRCULATION: IS TRANEXAMIC ACID THE SOLUTION WE NEED?

The evidence is clear when it comes to TXA: TXA should be used within 3 hours of injury in unstable (SBP <90 mm Hg) polytrauma patients with extracranial bleeding. The evidence is not as clear when it comes to isolated TBI, specifically sTBI. The publication of the Clinical Randomisation of an Antifibrinolytic in Significant Head Injury (CRASH-3) trial was the primary driver of interest in using TXA in TBI. Despite excluding the most patients with sTBI, investigators could only find a significant difference in early deaths (within 24 hours) in patients with sTBI who received TXA.[88 89] A recent meta-analysis of 14 747 patients demonstrated no significant difference in mortality outcomes between TXA and placebo (RR 0.95; 95% CI 0.88 to 1.02). Mirroring the findings in terms of mortality, TXA was not found to have any significant effect on neurological outcome assessed by Disability Rating Scale (mean difference −0.18 points; 95% CI −0.43 to 0.08).[90] Although the purported mechanistic effect of TXA correlates with current understanding of TBI-induced coagulopathy, TXA had a non-significant effect on hematoma expansion (RD 3.6% reduction; 95% CI 6.6% reduction to 0.5% increase). The most commonly used regimen is 1 g bolus followed by 1 g over 8 hours. Lawati *et al* could not perform subgroup analyses based on TBI severity or timing of TXA administration because of a lack of reporting of separate data.[90]

One of the included studies in the meta-analysis was a multicenter RCT that analyzed 966 patients with moderate-or-severe TBI randomized to different regimens of prehospital TXA or placebo. There was no significant difference between TXA or placebo groups in terms of the primary outcome of GOS-E score >4 at 6 months (absolute difference −3.5%; 90% one-sided confidence limit for benefit −0.9%; p=0.16). There were also no significant differences between both groups in 28-day mortality (adjusted difference −2.9%; 95% CI −7.9% to 2.1%), 6-month Disability Rating Scale score, or progression of ICH. Among patients with documented ICH, exploratory subgroup analyses revealed that the bolus-only group (2 g intravenous TXA bolus in the out-of-hospital setting) had significantly lower mortality rates (18%) than the bolus maintenance (1 g intravenous TXA bolus in the out-of-hospital setting followed by a 1 g intravenous TXA infusion initiated on hospital arrival and infused over 8 hours) (26%) and placebo groups (27%). However, the 15% loss to follow-up and imputation of several variables make the study inadequately powered to answer several of these questions.[91] In a recent observational study of 1827 patients with sTBI by Bossers *et al*, a significant trend toward increased 30-day mortality in the isolated sTBI TXA subgroup (OR 2.05; 95% CI 1.22 to 3.45) was found. There was no significant difference in 30-day mortality for the entire cohort of isolated and combined sTBI (OR 1.19; 95% CI 0.92 to 1.53). It should be noted, however, that an argument can be made for confounding by indication; TXA was administered based on prehospital GCS without documentation of TBI progression (GCS following resuscitation and CT imaging data). In addition, most of the intervention arm (>90%) received a dose of 1 g or less.[92]

The safety of TXA is a major factor considered by physicians when making treatment decisions. Data from 216 trials have shown that the drug does not significantly increase thromboembolic events (RR 1.02; 95% CI 0.94 to 1.11) even in patients with a history of thromboembolism.[93] In conclusion, TXA appears to be a safe drug that does not confer a significant additional risk of thromboembolism. Clinicians can consider its use for concomitant TBI in the setting of polytrauma given its proven mortality benefits on extracranial bleeding and possible benefit on TBI until further high-quality research is published. For isolated sTBI further well-designed RCTs are needed to definitively determine the utility of TXA, especially in patients with documented ICH.

DIFFICULT NEUROSURGICAL DECISIONS

The presence of a trained neurosurgeon facilitates more comprehensive care of sTBI through thorough knowledge of cerebral physiology and surgical expertise in several emergency procedures. However, two of the most essential procedures have generated controversy over the past decade: invasive cerebral monitoring and decompressive craniectomy (DC). The recent publication of several trials has dramatically changed surgeons' perceptions of both procedures.

Invasive cerebral monitoring is considered the window by which a surgeon can assess cerebral physiology. ICP monitoring specifically allows the detection of deleterious IHT and subsequent titration of ICP reducing measures using evidence-based tiers.[94] The 2017 BTF guidelines downgraded their recommendations for ICP monitoring based on the paradigm-changing Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure (BEST:TRIP) RCT of 324 patients with sTBI where ICP monitoring did not lead to better survival or functional outcomes over clinical assessment.[7] In fact, the groundbreaking results of the trial have been revised and analyzed to develop the Consensus Revised Imaging and Clinical Examination Protocol for use in resource-limited settings.[95] On the other hand, a meta-analysis of 18 studies with 25 229 patients with sTBI found a significantly lower overall mortality for ICP-monitored patients (RR 0.85; 95% CI 0.73 to 0.98).

The effect size was larger when only analyzing studies published after 2007 (RR 0.72; 95% CI 0.63 to 0.83).[96] The findings of the meta-analysis are limited by both the significant heterogeneity of included studies and by the overwhelming weight of observational studies on the effect size. To date, no new RCTs of ICP monitoring have been published.

Brain tissue oxygen ($B_{tp}O_2$) monitoring is often considered the second integral component of multimodality invasive cerebral monitoring for its potential to inform clinical decisions related to cerebral hypoxia. Although the BTF guidelines do not support a specific recommendation, evidence is growing to support routine $B_{tp}O_2$ monitoring. The recently published phase II Brain Oxygen Optimization in Severe TBI (BOOST-2) trial randomized 119 patients to $B_{tp}O_2$ and ICP-based treatment or ICP-based treatment alone. The dual-data arm had significantly lower cerebral hypoxia time (66% lower) and a non-significant trend toward lower mortality (9% lower) and better 6-month GOS-E (11% more had favorable outcomes).[97] Similar trends have been observed with large observational studies, but the results of the BOOST-3 trial (NCT03754114) are eagerly anticipated.[98]

DC, which is non-permanent removal of a skull bone flap, can be used as a primary procedure when performed for evacuation of a mass lesion to control postoperative ICP. This is particularly attractive for acute subdural hematomas (ASDHs) due to the high incidence of cerebral edema and IHT. Although observational studies have shown conflicting results due to possible selection bias, an international consensus of neurosurgeons recommends primary DC for ASDHs with intraoperative cerebral bulging.[99] Alternatively, secondary DC is performed as part of tiered therapy for refractory IHT after sTBI. The BTF recently updated their guidelines to reflect the findings from two recently published RCTs. The DECRA (Decompressive Craniectomy in Patients with Severe Traumatic Brain Injury) and RESCUEicp (Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intracranial Pressure) studies randomized patients with sTBI with refractory IHT to either secondary DC or medical management. DECRA investigated early (within the first 72 hours of admission) refractory ICP >20 mm Hg, whereas RESCUEicp investigated late (within 10 days of admission) refractory ICP >25 mm Hg. Although both studies showed successful reduction of ICP with DC, only RESCUEicp showed significantly lower 12-month mortality with DC (30.4% vs 52.0%). In fact, the DECRA study showed fewer good neurological outcomes with DC at 12 months (OR 0.33; 95% CI 0.12 to 0.91). Accordingly, the current recommendations to improve mortality and functional outcomes (level IIA) are to perform secondary DC for late refractory ICP elevation but not for early refractory ICP elevation.[100] Several ongoing trials are anticipated on the role of primary DC for epidural hematomas (NCT04261673) and ASDHs (ISRCTN87370545), secondary DC for children (NCT03766087), and secondary DC versus decompressive laparotomy for IHT (NCT05115929).

LIMITATIONS OF THIS REVIEW

This is a narrative review intended to provide a qualitative overview of the literature. The authors reviewed the literature and cited articles based on their subjective assessments. Although this review method is comprehensive, it is susceptible to bias. Lack of quantitative synthesis of evidence from included studies limits robust deductions. High-quality RCTs and systematic reviews of sTBI resuscitation are limited in the literature. Therefore, readers should interpret the conclusions of this review cautiously.

CONCLUSION

Optimal resuscitation strategies that attenuate the secondary injury after sTBI can lead to better outcomes. Helicopter prehospital transport leads to better outcomes, but the impact of possible confounders is still poorly understood. Prehospital intubation was found to have regional variation in outcomes; possible contributors should be further explored. The optimal oxygenation levels for sTBI require further analysis to determine. Evidence-based protocols for the management of sTBI with concomitant ARDS are lacking. The ideal resuscitation fluid and the indications for blood component therapy should be evaluated in future prospective studies. Although several antithrombotic strategies are described, their impact on clinical outcomes in sTBI is still uncertain. TXA is a promising drug that still requires further research to better define the patient population that will benefit most from its administration. The controversies surrounding the adjunctive role of invasive cerebral monitoring and DC will require further well-designed and adequately powered RCTs. Overall, future higher-quality trials and larger analyses with well-defined end points are needed to guide optimal patient care (see online supplemental file 2). Clinicians should always remember that guidelines are made to be refined and improved.

Contributors STE-S conceived the idea and contributed to designing the review. MAR participated in data extraction from the literature and drafted the manuscript. SHA participated in data extraction from the literature and drafted the manuscript. AEMA participated in data extraction from the literature and drafted the manuscript. PWB participated in data extraction from the literature and critical review. MK participated in data extraction from the literature and critical review. BB participated in data extraction from the literature and critical review. AA participated in data extraction from the literature and critical review. AKB designed the review and performed critical revision of the manuscript. STE-S, SHA, PWB, and AKB designed the tables.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study does not involve human participants.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Seif Tarek El-Swaify http://orcid.org/0000-0001-9472-9596
Mazen A Refaat http://orcid.org/0000-0001-6935-5860

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