Initial neurocritical care of severe traumatic brain injury: New paradigms and old challenges

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ABSTRACT

Background: Early neurocritical care aims to ameliorate secondary traumatic brain injury (TBI) and improve neural salvage. Increased engagement of neurosurgeons in neurocritical care is warranted as daily briefings between the intensivist and the neurosurgeon are considered a quality indicator for TBI care. Hence, neurosurgeons should be aware of the latest evidence in the neurocritical care of severe TBI (sTBI).

Methods: We conducted a narrative literature review of bibliographic databases (PubMed and Scopus) to examine recent research of sTBI.

Results: This review has several take-away messages. The concept of critical neuroworsening and its possible causes is discussed. Static thresholds of intracranial pressure (ICP) and cerebral perfusion pressure may not be optimal for all patients. The use of dynamic cerebrovascular reactivity indices such as the pressure reactivity index can facilitate individualized treatment decisions. The use of ICP monitoring to tailor treatment of intracranial hypertension (IHT) is not routinely feasible. Different guidelines have been formulated for different scenarios. Accordingly, we propose an integrated algorithm for ICP management in sTBI patients in different resource settings. Although hypervolemic therapy and decompressive craniectomy are standard treatments for IHT, there is a lack high-quality evidence on how to use them. A discussion of the advantages and disadvantages of invasive ICP monitoring is included in the study. Addition of beta-blocker, anti-seizure, and anticoagulant medications to standardized management protocols (SMPs) should be considered with careful patient selection.

Conclusion: Despite consolidated research efforts in the refinement of SMPs, there are still many unanswered questions and novel research opportunities for sTBI care.

Keywords: Intracranial hypertension, Intracranial pressure monitoring, Neurocritical care, Neurotrauma, Thromboembolism prophylaxis, Traumatic brain injury

INTRODUCTION

Every 21 seconds, a traumatic brain injury (TBI) occurs in the USA.[33] Low- and middle-income countries (LMICs) are disproportionately affected; disparities in the delivery of neurosurgical
care in LMICs result in a 2- to 3-fold increase in mortality rates after severe TBI (sTBI). The limitations of the Glasgow Coma Scale (GCS), which has been the standard measure for TBI classification, have driven clinicians to develop more comprehensive classification systems. 

Regardless of the classification used, for many patients, TBI extends beyond being an acute event and evolves into a chronic disability that has long-term consequences. Any TBI initiates a heterogeneous cascade of pathophysiological events that lead to a potentially preventable secondary injury following the irreversible primary injury. 

The central dogma of TBI management is to target the secondary injury affecting susceptible neural tissue.

With the majority of sTBI patients being admitted to trauma, general, and surgical intensive care units (ICUs), standardized management protocols (SMPs) for sTBI may improve clinical outcomes regardless of where patients are admitted. The observed lower mortality and improved neurological outcomes in dedicated neurocritical care units are possibly attributed to greater adherence to SMPs and differences in use and interpretation of neuromonitoring data. Increased engagement of neurosurgeons is warranted as neurocritical care should not be limited to neurointensivists. In fact, a daily briefing between the intensivist and the neurosurgeon is considered a clinical quality indicator for TBI care. Consequently, all neurosurgeons should be minded with the broad lines of TBI neurocritical care and its recent advances.

Neurotrauma is a rapidly evolving field. Knowledge of the latest evidence may not directly change treatment decisions, but it will definitely guide future research initiatives. We are writing this review to highlight some recent advances and ongoing challenges in the early neurocritical care of sTBI since the publication of the 2017 Brain Trauma Foundation’s (BTF) guidelines. These advances and challenges may influence the management decisions of all health-care practitioners involved in the critical care of sTBI patients.

**IDENTIFYING NEUROWORSENING**

Any sTBI patient should be considered a critical patient with the potential risk of further deterioration beyond the initial insult, especially within the first 48 h. Critical neuroworsening is defined as a deterioration in the neurological status of the neurologically debilitated patient necessitating early recognition along with prompt evaluation and management. The criteria and possible etiologies of neuroworsening are shown in Table 1. Repeated clinical examination is the mainstay of prompt detection of neuroworsening. However, severely injured patients are usually sedated in ICUs. To avoid fallacies, evaluation of deeply sedated patients requires a neurological wake-up test (NWT) which poses the risk of inducing a stress response in sTBI patients. For uncertain clinical scenarios when the risk/benefit ratio is unclear, physicians should refer to decision-support matrices designed by the 2019 Seattle International Severe TBI Consensus Conference (SIBICC).

Multimodality neuromonitoring [Table 2] is a less preferable alternative available for unstable patients with contraindications to NWT to detect neurophysiologic worsening. Unfortunately, such a scenario is increasingly being observed in severely brain injured patients who are susceptible to developing multiple organ dysfunction syndrome (MODS). MODS, which has been estimated to occur in more than two-thirds of sTBI patients, can lead to several contraindications to NWT. 

Neuromonitoring can indirectly detect neuroworsening through evaluating the physiologic state of brain tissue in some of these difficult scenarios. In particular, recent evidence has pointed to a survival benefit of using brain tissue oxygen (B\textsubscript{t}O\textsubscript{2}) monitoring. The randomized Phase II BOOST-2 trial (brain oxygen optimization in severe TBI) compared combined B\textsubscript{t}O\textsubscript{2} and intracranial pressure (ICP) monitoring versus ICP monitoring alone. The investigators found a nonsignificant 9% decrease in mortality and 11% increase in favorable outcomes regardless of where patients are admitted.

**Table 1: Definition and etiology of critical neuroworsening.**

| Definition | • Any of the following: |
|-----------|-------------------------|
|           | • Spontaneous decrease in GCS motor score ≥1 point |
|           | • New decrease in pupillary reactivity |
|           | • New pupillary asymmetry ≥2 mm/bilateral mydriasis |
|           | • New focal motor deficit |
|           | • Herniation syndrome (e.g., Cushing’s triad) |
| Etiology  | • Neurological |
|           | • Elevated ICP |
|           | • Expanding intracranial lesion |
|           | • Cerebral edema |
|           | • Seizures or postictal state |
|           | • Stroke |
|           | • CNS infection |
|           | • Systemic |
|           | • Hypotension |
|           | • Hypoxemia |
|           | • Hyper or hypothermia |
|           | • Dehydration |
|           | • Infection or sepsis |
|           | • Impaired renal function |
|           | • Impaired hepatic function |
|           | • Other medical comorbidities |
|           | • Metabolic |
|           | • Electrolyte disturbance |
|           | (e.g., hyponatremia, hypernatremia, etc.) |
|           | • Hypoglycemia |
|           | • Miscellaneous |
|           | • Drug induced |
|           | • Substance withdrawal |

CNS: Central nervous system, GCS: Glasgow Coma Scale, ICP: Intracranial pressure
| Modality                      | Application method                  | Variable monitored | Significance                                                                 | Global or focal measure | Time span | Invasiveness | Derived indices | Values and thresholds | Limitations                                                                 |
|------------------------------|-------------------------------------|--------------------|-------------------------------------------------------------------------------|-------------------------|-----------|--------------|------------------|-----------------------|-----------------------------------------------------------------------------|
| Invasive ICP monitoring      | Intraparenchymal fiber-optic monitor (IPPM) Ventricular catheter (Gold standard ICP monitor for global ICP) Others | ICP                | Recommended to reduce in-hospital and 2-week mortality                         | Focal                   | Continuous | Yes          | Intracranial compliance CPP PRx | ICP threshold < 22 mmHg Normal CPP = 50–70 mmHg PRx > 0.2: Impaired autoregulation |
| Cerebral O₂ monitoring (Indicated for patients with/at risk for cerebral ischemia and/or hypoxia) | Flexible microcatheter placed in white matter of nontraumatized tissue as assessed on CT scan O₂ in the cerebral interstitium is measured using optical luminescence or polarographic techniques depending on the type of microcatheter | Partial pressure of O₂ in brain tissue | Most accurate method Uncertain effect on outcomes Can aid in titrating hyperventilation | Focal                   | Continuous | Yes          | O₂ diffusion Balance between O₂ supply and demand | Normal PbtO₂ = 40 mmHg Threshold: Adults: ≤ 15–20 mmHg Paediatric: ≤ 10 mmHg Variable placement Low sensitivity for detection of cerebral vasospasm after SAH Requires 1 h run in period |

(Contd...)
| Modality                  | Application method                                                   | Variable monitored                      | Significance                                                                 | Global or focal measure | Invasiveness | Derived indices | Values and thresholds             | Limitations                                                                                      |
|--------------------------|-----------------------------------------------------------------------|----------------------------------------|------------------------------------------------------------------------------|-------------------------|--------------|-----------------|-----------------------------------|-----------------------------------------------------------------------------------------------|
| SJVO₂ measurement        | Placement of a catheter/fiber-optic oximeter retrograde into the jugular bulb Catheter tip at the level of the bodies of C1/C2 on lateral neck radiograph suggests correct placement | O₂ saturation of jugular venous blood | Can aid in titrating hyperventilation Desaturation that is sustained (> 10 min) portends poor outcome in TBI | Global                 | Intermittent with fiber-optic catheters | Cerebral AVDO₂                  | SJVO₂ = 55%-69% Ischemic threshold: SJvO₂ < 50% for at least 10 min | Technique is prone to artifact Inherent risks associated with central catheter placement and maintenance, for example, infection, misplacement, pneumothorax, jugular vein thrombosis, etc. May miss critical regional ischemia as it is a global, flow-weighted measure |
| Transcranial cerebral oximetry | Using NIRS to differentiate oxyhemoglobin from reduced hemoglobin Using NIRS to differentiate oxyhemoglobin from reduced hemoglobin | O₂ saturation Relative blood volume | Least reliable When combined with systemic blood pressure and ICP monitors, can potentially assess cerebral autoregulation Screen for intracranial hematomas in prehospital environment | Focal                   | Continuous   | Cerebral blood flow Cerebral autoregulation | Normal value: 60–80% Threshold not clearly defined | Extracranial distortion of signal Inability to distinguish between extracranial and intracranial sources of O₂ Ischemic threshold not defined |
| Electrical activity monitoring | Electrodes affixed to the scalp                                      | Cortical electrical activity           | Detect PTS (majority are nonconvulsive)                                      | Global                  | Continuous   | Seizure activity Abnormal patterns | N/A                               | cEEG is performed for 48 h (as intermittent EEG monitoring has a sensitivity of only 50%) |

(Contd...)
Table 2: (Continued).

| Modality                          | Application method                                                                 | Variable monitored | Significance                                      | Global or focal measure | Time span | Invasiveness | Derived indices                  | Values and thresholds | Limitations                                      |
|----------------------------------|-------------------------------------------------------------------------------------|--------------------|-------------------------------------------------|-------------------------|-----------|--------------|----------------------------------|-----------------------|------------------------------------------------|
| Electrocorticography             | Recording grids and strips are laid on the cortical surface intraoperatively        | Cortical and depth electrical activity | More sensitive than EEG Used for patients with persistent and unexplained alteration of mental status | Focal                   | Continuous | Yes          | Seizure activity Spreading depolarization (CSD) | N/A                   | Requires specific surgical placement            |
| CBF monitoring                   | A probe with 2 thermistors is inserted to measures the tissue's ability to dissipate heat. A microprocessor then converts this into CBF in mL/100 g/min. | CBF                | Quantitative estimate of CBF                     | Focal                   | Continuous | Yes          | Hypoperfusion or hyperperfusion   | Ischemic threshold<18–25 mL/100 g/min Irreversible damage <10 mL/100 g/min Normal CBF in young adults: 50 mL/100 g of brain tissue/min (range 20–70 mL) Mean flow velocity by TCD: ECICA: 30 ± 9 (away) MCA: 55 ± 12 cm/sec (toward) ACA: 50 ± 11 cm/sec (away) PCA segment 1: 39 ± 11 cm/sec (toward) PCA segment 2: 40 ± 10 cm/sec (away) BA: 41 ± 10 cm/sec (away) VA: 38 ± 10 cm/sec (away) | Technical limitations such as measurement drift Normal values in various physiological conditions have not been defined Adverse effects of temperature and hyperthermia Operator dependent Problems of probe fixation to the head and computer interfacing Qualitative estimate due to small sample size (1 mm3) Relative than absolute values Failure in up to 10% of patients due to absent acoustic shadow | |
| Intraparenchymal thermal diffusion flowmetry (TDF)/probe (TDP) | A probe with 2 thermistors is inserted to measures the tissue's ability to dissipate heat. A microprocessor then converts this into CBF in mL/100 g/min. | CBF                | Quantitative estimate of CBF                     | Focal                   | Continuous | Yes          | Hypoperfusion or hyperperfusion   | Ischemic threshold<18–25 mL/100 g/min Irreversible damage <10 mL/100 g/min Normal CBF in young adults: 50 mL/100 g of brain tissue/min (range 20–70 mL) Mean flow velocity by TCD: ECICA: 30 ± 9 (away) MCA: 55 ± 12 cm/sec (toward) ACA: 50 ± 11 cm/sec (away) PCA segment 1: 39 ± 11 cm/sec (toward) PCA segment 2: 40 ± 10 cm/sec (away) BA: 41 ± 10 cm/sec (away) VA: 38 ± 10 cm/sec (away) | Technical limitations such as measurement drift Normal values in various physiological conditions have not been defined Adverse effects of temperature and hyperthermia Operator dependent Problems of probe fixation to the head and computer interfacing Qualitative estimate due to small sample size (1 mm3) Relative than absolute values Failure in up to 10% of patients due to absent acoustic shadow | |
| TCD                             | Transducers placed directly on the patient's skin with a small amount of gel facilitating the ultrasound. The transducer is applied to the patient's temples, base of the skull at the back of the neck area or on closed eyelids. It can also be done through a burr hole in a surgical setting. | Cerebral blood velocity | Qualitative estimate of CBF Detection of vasospasm and DCI in SAH, differentiates hyperemia from vasospasm | Global                   | Intermittent | No           | Critical closing pressure Cerebral arterial impedance | Mean flow velocity by TCD: ECICA: 30 ± 9 (away) MCA: 55 ± 12 cm/sec (toward) ACA: 50 ± 11 cm/sec (away) PCA segment 1: 39 ± 11 cm/sec (toward) PCA segment 2: 40 ± 10 cm/sec (away) BA: 41 ± 10 cm/sec (away) VA: 38 ± 10 cm/sec (away) | Operator dependent Problems of probe fixation to the head and computer interfacing Qualitative estimate due to small sample size (1 mm3) Relative than absolute values Failure in up to 10% of patients due to absent acoustic shadow | |

(Contd...)
| Modality                                      | Application method                                                                 | Variable monitored                          | Significance                                                                 | Global or focal measure | Invasiveness | Derived indices | Values and thresholds | Limitations                                                                 |
|----------------------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------|-------------------------------------------------------------------------------|-------------------------|--------------|------------------|-----------------------|-----------------------------------------------------------------------------|
| Cerebral metabolism monitoring using microdialysis (CMD) | A flexible wire with a 10 mm semi-membrane is inserted into the white matter and a physiologic dialysate is constantly infused | Brain metabolites and biomarkers           | Possible prognostic value for treatment, follow-up, and mortality CMD can distinguish ischemic (strokes) from nonischemic hypoxia. Measurement of drug levels like antibiotics or anticonvulsants. Identify hyperglycolysis and increased glucose utilization post-TBI (may be used to guide insulin therapy while initiating enteral feeds to avoid hypoglycemia). | Focal                   | Intermittent  | Yes              | Cerebral metabolism (LPR+Cerebral glucose level) Cell injury (Glutamate level) Cellular breakdown (Glycerol level) Adenosine, urea, amino acids, nitrate, and nitrite concentrations Other biomarkers of injury severity and neuroinflammation Increased glutamate and lactate are earliest markers of ischemia followed by increased glycerol. | Physiological ranges: Lactate 0.7–3.0 μmol/L Glutamate 2–10 μmol/L Glycerol 10–90 μmol/L Thresholds: Glucose levels < 0.7 mmol/L predict metabolic crisis LPR > 25–40 predicts poorer outcome Trend is more useful than absolute values | Focal biochemical changes occurring elsewhere or away from the catheter may be different from those occurring adjacent to the catheter. Labor intensive. Requires at least 1 h for equilibration of cerebral interstitial molecular markers and their measurement. |
| Temperature monitoring                        | Intraparenchymal probe                                                              | Brain temperature                          | The difference between brain temperature and core body temperature may be associated with changes in cerebral perfusion. | Focal                   | Continuous   | Yes              | N/A                   | N/A                                                                          |
| Noninvasive ICP monitoring                   | Optic nerve sheath ultrasonography                                                  | ONSD                                        | Novel noninvasive method to detect ICP                                        | Global                  | Intermittent  | No               | ICP                   | Operator dependent. Less accurate compared to invasive monitoring           |

ACA: Anterior cerebral artery, AVDO2: Cerebral arteriovenous oxygen content difference, BA: Basilar artery, cEEG: Continuous electroencephalography, CBF: Cerebral blood flow, CPP: Cerebral perfusion pressure, CSD: Cortical spreading depression, DCI: Delayed cerebral ischemia, ECICA: Extracranial internal carotid artery, ICP: Intracranial pressure, LPR: Lactate-to-pyruvate ratio, MCA: Middle cerebral artery, N/A: Not applicable, NIRS: Near-infrared spectroscopy, O2: Oxygen, ONSD: Optic nerve sheath diameter, PbtO2: Partial pressure of oxygen in brain tissue, PCA: Posterior cerebral artery, PRx: Pressure reactivity index, PTS: Posttraumatic seizures, SAH: Subarachnoid hemorrhage, SJVO2: Jugular bulb venous oxygen saturation, TCD: Transcranial Doppler, VA: Vertebral artery
6-month neurologic outcomes.\textsuperscript{[73]} Although promising results have also been demonstrated in large observational studies, routine adoption of \textsubscript{H}O2 monitoring will likely be influenced by the anticipated BOOST-3 trial (NCT03754114).\textsuperscript{[42,49]}

**DEFINING THRESHOLDS**

Most TBI patients are susceptible to altered cerebral autoregulation and detrimental increases in ICP with resultant fluctuations in cerebral blood flow (CBF).\textsuperscript{[77]} The latest BTF guidelines recommend, based on Class II evidence, an ICP cutoff of 22 mmHg, and a cerebral perfusion pressure (CPP) threshold of 60–70 mmHg. The minimum value of CPP should be determined on a case-by-case basis with some authors suggesting different thresholds for different age groups.\textsuperscript{[8,103]} However, it has been suggested that aggressive treatments to maintain a high CPP increase the risk of acute respiratory distress syndrome in adults.\textsuperscript{[17]} It is now well-known that the most important determinant of CPP is ICP and not mean arterial pressure (MAP). Therefore, treatment is usually tailored according to the ICP. However, one number does not fit all. Sorrentino et al. analyzed 459 patients and found a lower ICP cutoff (18 mmHg) for favorable neurological outcomes in patients above 55 years ($\chi^2 = 5.14; P = 0.023$) and females ($\chi^2 = 8.23; P = 0.004$).\textsuperscript{[88]} Interestingly, the cutoff for mortality was 22 mmHg across all subgroups. Other investigators suggested utilizing "patient-specific" thresholds.\textsuperscript{[3,54,56]}

The variability in defining optimum thresholds has ignited interest in pursuing patient-specific measurements based on the physiology of cerebral vascular reactivity instead of targeting static ICP and CPP thresholds.\textsuperscript{[38]} The most basic yet most common continuous method for assessment is the pressure reactivity index (PRx) which is a correlation coefficient between MAP and ICP.\textsuperscript{[108]} A negative correlation between both indicates intact autoregulation. A PRx >0.20–0.25 is significantly associated with increased mortality and worse neurological outcome. Therefore, the PRx can be used to guide treatment by targeting the optimal CPP and ICP with the lowest PRx.\textsuperscript{[48,50,34,56,71,81,107,110]} Alternative cerebrovascular reactivity indices have shown superior predictive abilities than PRx. These include the pulse amplitude index, which is a correlation coefficient between MAP and pulse amplitude of ICP, and the regression coefficient between CPP and pulse amplitude of ICP (RAC).\textsuperscript{[109]} However, international experts could not reach a consensus on how to implement these indices, and a research agenda was accordingly proposed.\textsuperscript{[25]} Other researchers have pursued noninvasive methods altogether for real-time assessment of CPP such as the transcranial Doppler. Varsos et al. estimated the CPP using the critical closing pressure in a cohort of 280 patients; they found their model to be significantly predictive of low CPP values (90% diagnostic accuracy).\textsuperscript{[98]}

**MANAGING INTRACRANIAL HYPERTENSION (IHT)**

The initiation of ICP reducing measures is triggered when patients meet certain criteria and exceed prespecified thresholds. Maintaining these thresholds is a challenging task complicated by the lack of sufficient high-quality evidence as previously mentioned. The SIBICCC adopted a consensus-based tier system to categorize the interventions commonly employed to prevent and control secondary IHT in patients with ICP monitors. Treatments within the same tier are employed without a specific order and are based on individual cases. Tier-zero, ideally initiated in the ICU, represents the primary management of patients to stabilize the condition and achieve neuroprotection regardless of the eventual ICP reading. Beyond tier-zero, the tiers target lowering the ICP according to the recommended thresholds by the BTF guidelines.\textsuperscript{[17,40]}

For patients who do not undergo ICP monitoring, especially in under-resourced LMICs, the Consensus Revised Imaging and Clinical Examination (CREVICE) Protocol employs a similar tier-based algorithm that is initiated based on major and minor criteria [Table 3].\textsuperscript{[2,66]} The original ICE protocol

| Table 3: CREVICE protocol criteria for initiating therapy for intracranial hypertension. |
| --- |
| **CREVICE** protocol criteria |
| **Major criteria** |
| 1. CT Marshall Class III |
| 2. CT Marshall Class IV |
| 3. CT Marshall Class VI |
| **Minor criteria** |
| 1. GCS motor score ≤4 |
| 2. Pupillary asymmetry |
| 3. Abnormal pupillary reactivity |
| 4. CT Marshall Class II |
| **Marshall CT classification** |
| A. DI I |
| a. No visible intracranial pathology |
| B. DI II |
| a. Midline shift 0–5 mm |
| b. Basal cisterns visible |
| c. No high or mixed density lesions > 25 cm$^3$ |
| C. DI III |
| a. Midline shift 0–5 mm |
| b. Basal cisterns compressed or completely effaced |
| c. No high or mixed density lesions > 25 cm$^3$ |
| D. DI IV |
| a. Midline shift > 5 mm |
| b. No high or mixed density lesions > 25 cm$^3$ |
| E. EML V |
| a. Any lesion evacuated surgically |
| F. Non-EML VI |
| a. High or mixed density lesions > 25 cm$^3$ |
| b. Not surgically evacuated |

CT: Computed tomography; DI: Diffuse injury, EML: Evacuated mass lesion, GCS: Glasgow Coma Scale
followed a “tranquillity” approach that avoids potential neurotoxic ICP surges by keeping ICP levels at a presumed minimum using fixed scheduled usage of ICP reducing measures.[20] It is prudent to understand that despite showing comparable outcomes to an ICP monitoring protocol, the CREVICE protocol should not replace monitoring when it is available. ICP monitoring allows a more personalized approach to patient care. Moreover, the patients in the ICE protocol were directly monitored by trained intensivists and neurosurgeons not nursing staff making their protocol potentially hard to replicate.[20,40] An integrated algorithm for the management of suspected IHT in different resource settings is illustrated in Figure 1.

Hyperosmolar therapy still has many controverses with no recommendations regarding the type of agent (hypertonic saline [HTS] vs. mannitol) or concentrations to be used.[18] HTS-induced volume expansion may reduce ICP through raising the CPP and causing cerebral vasoconstriction if static pressure autoregulation is intact.[74,77] A MAP challenge can be performed to test autoregulation.[40,86] A meta-

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**Figure 1:** Algorithmic approach to the management of raised intracranial pressure. BP: Blood pressure, CPP: Cerebral perfusion pressure, CT: Computed tomography, EEG: Electroencephalogram, EVD: External ventricular drain, GCS: Glasgow Coma Scale, ICP: Intracranial pressure, MAP: Mean arterial pressure, OR: Operating room. *A postoperative CT scan is obtained, and patients are reclassified using the Marshall classification using a dual system. **Escalating treatment is defined as using another measure from the same tier of therapy or upgrading to a higher tier. ^Refers to the dosing frequency of hyperosmolar therapy.
A more recent meta-analysis of 18 studies with decompressive craniectomy (DC) for pediatric sTBI patients is still preliminary, and the results of an ongoing RCT are anticipated (NCT03766087).

SHOULD ICP BE INVASIVELY MONITORED?

Elevated ICP is detrimental to cerebral physiology through reduction of CBF and compression or herniation of cerebral structures. Invasive cerebral monitoring in general and ICP monitoring in specific allow real-time assessment of cerebral physiology and dynamic titration of treatment modalities to optimize cerebral tissue conditions. Although ICP monitoring should logically be used for critical patients when available, the previous indications for ICP monitoring are no longer supported by the 2017 BTF guidelines, especially since prior guideline compliance was poor, and neither survival nor functional outcomes were significantly improved as evidenced in the landmark BEST: TRIP RCT (Benchmark Evidence from South American Trials: Treatment of ICP).

Cohort studies that had found better mortality rates at centers that utilize ICP monitoring found that ICP monitoring could only explain 10–15% of the variability between institutions. A systematic review by Yuan et al. found no evidence that ICP monitoring reduces mortality rates (OR, 0.93; 95% CI, 0.77–1.11). However, a separate analysis of seven studies published after 2012, which included 12,944 patients, revealed a statistically significant decrease in mortality (OR, 0.56; 95% CI, 0.41–0.78).

These results imply that temporal changes in management strategies and technological advances in monitoring devices may have a substantial impact on patient outcomes. A more recent meta-analysis of 18 studies with 25,229 patients found a significantly lower mortality rate with ICP monitoring (RR, 0.85; 95% CI, 0.73–0.98). Once again, a

Table 4: Complication rates of intracranial pressure monitoring devices.

| Complication                      | EVD          | ICPM         |
|-----------------------------------|--------------|--------------|
| Access site infections            | 7.3–10.4%    | 0.0–7.4%     |
| Without antibiotic prophylaxis    |              |              |
| AI-EVDs                           | 0.0–2.3%     | N/A          |
| Postprocedural hemorrhage         | 0.7–41.0%    | 0.025–0.900% |
|                                    | 0.8–14.6%    | clinically   |
| Misplacement                      |              | significant  |
| Freeway technique                 | 8.0–45.0%    | N/A          |
| Bolt-connected placement          | 6.5–30.9%    |              |
| Stereotactic image-guided placement | 5.3–5.9%  |              |
| CT guided                         | 0.0%         |              |
| Venous thromboembolism            | 9.2%         |              |

AI: Antibiotic impregnated, CI: Confidence interval, CT: Computed tomography, EVD: External ventricular drain, ICPM: Intracranial pressure monitor, N/A: Not available, OR: Odds ratio
temporal change in trends was observed in a subanalysis of studies published after 2007 that showed an even larger effect size for ICP monitoring (RR, 0.72; 95% CI, 0.63–0.83). The findings of these meta-analyses are limited by the largely observational nature of included studies and by significant heterogeneity of included studies.

Several recent large cohort studies have shown significantly lower mortality rates with ICP monitoring. The recent international prospective cohort study by Robba et al. analyzed 1287 TBI patients. They showed a significantly lower 6-month mortality (hazard ratio [HR], 0.31; 95% CI, 0.20–0.47) and 6-month unfavorable neurological outcome (HR, 0.53; 95% CI, 0.30–0.93) in TBI patients undergoing ICP monitoring with at least one unreactive pupil but not patients with bilaterally reactive pupils. The largest retrospective study to date included the data of 36,929 sTBI patients of which 6025 had an ICP monitor placed. When controlling for confounding factors (age, GCS, injury severity score, and craniotomy), ICP monitoring was found to decrease in-hospital mortality by 25%. However, this was at the expense of increased ICU LOS (13.1 ± 11.6 days vs. 6.0 ± 10.8 days; P < 0.0001). However, a recent cohort study analyzing trends of ICP monitoring in Level I trauma centers in the USA has cast doubt over the benefits that ICP monitoring offers. The authors analyzed 4880 patients with sTBI while controlling for various confounders. The analysis revealed higher in-hospital mortality (OR, 1.63; 95% CI, 1.28–2.07) and decreased functional independence at discharge (OR, 1.71; 95% CI, 1.29–2.26). In the pediatric age group, ICP monitoring remains underutilized and has an uncertain effect on pediatric TBI with some patients having worse outcomes. Further studies are still needed to adequately define the pediatric population that stands to benefit from ICP monitoring. It must be noted that cohort studies, although including large sample sizes, are susceptible to inherent selection bias. Patients who did not receive ICP monitoring could have been deemed, by either unreported objective measures or subjective measures, too unstable by clinical assessment or neuroimaging. In addition, geographic trends and hospital characteristics may influence the selection of patients eligible for ICP monitoring. To this day, there have been no new RCTs of ICP monitoring.

**PLACING THE ICP MONITOR**

In the event that the neurocritical care team elects to place an ICP monitor, they will still be faced with several decisional dilemmas. The optimal ICP monitoring modality is still unknown. Historically, the superiority of the external ventricular drain (EVD) as an ICP monitoring modality was related to its accuracy, ability to recalibrate, cost-effectiveness, and the fact that it could be used as a therapeutic modality to lower ICP through cerebrospinal fluid drainage. However, recent evidence has challenged this concept, and intraparenchymal monitors (IPMs) have emerged as a promising monitoring tool that is less invasive than EVDs with comparable outcomes. In fact, Bales et al. found that the in-hospital mortality (OR, 2.46; 95% CI, 1.20–5.05), Glasgow outcome scale-extended (GOS-E) at day 180 (weighted difference, −0.97; 95% CI, −1.58–−0.37), and neuropsychological performance at day 180 were all worse with EVDs placed within 6 h compared to IPMs. A recent meta-analysis of six studies with 3968 patients compared the outcomes of EVDs and IPMs. They concluded that there is no difference in mortality (RR, 0.90; 95% CI, 0.60–1.36) or functional outcomes (MD, 0.23; 95% CI, 0.67–1.13), but there is a higher rate of complications (RR, 2.56; 95% CI, 1.17–5.61), especially infections, associated with EVDs.

The risks of ICP monitoring recorded in the literature are shown in Table 4. The future research interests will revolve around noninvasive modalities of ICP monitoring that is considerably safer such as transcranial acoustic signal transmission, ultrasonographic assessment of optic nerve sheath diameter, and others. The timing of ICP monitor placement is a matter of debate. Early ICP monitor placement, defined as within 6 h of admission, was not found to be associated with better mortality rates in neither adult nor pediatric patients.

This could be explained by the early coagulopathy that usually associates sTBI and may result in hemorrhagic complications during placement of invasive monitors. Another potential confounder is the severity of patients’ injuries that necessitate early ICP monitoring and could be the underlying cause of poor outcomes. However, other outcomes as LOS and days ventilated were significantly better in the early group; this is possibly the result of earlier detection and faster treatment of IHT. Robba et al. found that 80% of TBI patients had the ICP monitor placed on day 1 (ICU admission), and 60% of patients had it placed in an operating room.

**ANTI-SEIZURE PROPHYLAXIS AND NEUROPROTECTION**

Posttraumatic seizures (PTSs) can potentially worsen the secondary brain injury by increasing cerebral metabolism and inducing neural excitotoxicity. They are subdivided into early PTS and late PTS. The incidence reaches 16.9% and 30.0%, respectively. The BTF guidelines recommend the use of phenytoin prophylaxis in the setting of TBI to decrease the rate of early PTS with no role in late PTS. However, a recent systematic review displayed contradictory results with regard to sTBI. The subgroup analysis of observational studies showed a protective effect of antiepileptic drugs (AEDs) (mostly phenytoin) on early PTS (RR, 0.50; 95% CI, 0.28–0.87). On the other hand, results from the subgroup analysis of RCTs demonstrated high heterogeneity and showed that...
the effect of AEDs was not statistically significant (RR, 0.58; 95% CI, 0.20–1.72). These results demonstrate the lack of definitive high-quality evidence on the prophylactic use of AEDs, and therefore, the utmost need for adequately designed future RCTs. The side effect profile of phenytoin has prompted clinicians to explore the use of alternative AEDs. Fang et al. conducted a systematic review of AEDs in neurocritical care and identified 10 studies comparing levetiracetam to phenytoin in the prevention of PTS. They found no significant difference between both AEDs (OR, 1.02; 95% CI, 0.72–1.45). However, levetiracetam is still a popular AED because of a more favorable side effect profile.

Paroxysmal sympathetic hyperactivity (PSH), an important differential of PTS, is an undiagnosed syndrome of adrenergic surge with characteristic symptoms of tachycardia, tachypnea, hypertension, hyperthermia, sweating, and posturing during paroxysmal episodes. Up to 80% of cases of PSH are due to TBI and around 10% of patients with TBI suffer from PSH. PSH portends an unfavorable prognosis up to death due to long ICU stays, longer mechanical ventilation time, increased infectious episodes, and worse GOS scores. Adrenergic blockers can potentially counteract this systemic dysregulation. Recent research, including a systematic review published in 2021, strongly favors the routine administration of beta-blockers (especially propranolol) as part of SMPs to ameliorate the potential dysregulation.

延迟

A consolidated research effort is being put into the development of effective neuroprotective agents that can improve long-term outcomes after TBI. The discussion of the potential neuroprotective role of beta-blockers merits a short discussion of another promising neuroprotective agent: amantadine. Amantadine is an indirect dopamine agonist and N-methyl-D-aspartate antagonist. It is believed to improve posttraumatic cognitive function and accelerate functional recovery by replenishing depleted dopamine in neural circuits responsible for attentional and arousal functions (frontostriatal, nigrostriatal, and mesolimbic circuits). A recent meta-analysis of 20 studies found that amantadine significantly improved cognitive function (standardized MD (SMD), 0.50; 95% CI, 0.33–0.66), especially if administered in the 1st week (SMD, 0.97; 95% CI, 0.45–1.49) for <1 month (SMD, 0.83; 95% CI, 0.56–1.11). The effect in sTBI specifically was still statistically significant (SMD, 0.45; 95% CI, 0.11–0.78).

### Table 5: Modified Berne-Norwood criteria.

| Risk category | Criteria | Proposed management |
|---------------|----------|---------------------|
| Low risk      | No moderate- or high-risk criteria | Anticoagulant prophylaxis if CT stable at 24 h |
| Moderate risk | Subdural or epidural hematoma > 8 mm; Contusion or intraventricular hemorrhage > 2 cm; Multiple contusions per lobe; Subarachnoid hemorrhage with abnormal CT angiogram | Anticoagulant prophylaxis if CT stable at 72 h |
| High risk     | Evidence of progression on imaging at 24 h; Craniotomy; ICP monitor placement | Consider IVC filter placement |

CT: Computed tomography, ICP: Intracranial pressure, IVC: Inferior vena cava

### THROMBOEMBOLISM PROPHYLAXIS

In general, trauma is a hypercoagulable state, and TBI specifically leads to a systemic coagulopathy due to the release of procoagulant molecules and platelet-activating molecules in addition to prolonged immobilization. The current recommendations for venous thromboembolism (VTE) prophylaxis are to use anticoagulants in addition to pneumatic compression stockings if the TBI is stable and after considering the risk-benefit ratio to avoid resorting to therapeutic anticoagulation dosing. Most centers use low-molecular-weight heparin as the primary thromboprophylaxis agent for both adult and pediatric patients.

Several systematic reviews have highlighted the safety of early initiation of anticoagulants provided that repeat head CT scans do not show progressive hemorrhagic injury (PHI) within the first 24 h. Recently, Spano et al. systematically reviewed 17 studies and found the rates of PHI to vary between 0% and 47%, but their recommendations are that anticoagulants reduce VTE without a corresponding increase in PHI. The majority of providers initiated anticoagulation within 24–72 h and a minority also initiated them within the first 24 h without demonstrating PHI. Delaying...
anticoagulation initiation beyond 72 h may put patients at a higher risk of VTE. The exception to these trends is sTBI patients who require neurosurgical intervention. A cohort study of 4951 patients undergoing neurosurgical interventions by Byrne et al. found that although each day of prophylaxis delay after the first 24 h increased the odds of VTE (OR, 1.08 per day; 95% CI, 1.04–1.12), it also decreased the odds of repeat neurosurgical intervention during the first 3 days (OR, 0.72 per day; 95% CI, 0.59–0.88). Prophylaxis delay also decreased odds of mortality in patients who initially underwent intracranial monitor/drain insertion (OR, 0.94 per day; 95% CI, 0.89–0.99).[16]

The successful protocol by Tignanelli et al. stratified patients according to their risk of TBI progression using the modified Berne-Norwood criteria and accordingly used prophylactic anticoagulation for low- and medium-risk patients.[78,95] The criteria are illustrated in Table 5. Their median time to VTE prophylaxis initiation decreased from 140 to 59 h, and their VTE rates decreased from 5.2% to 2.2%; both these results were statistically significant. Patients considered at high risk of brain injury progression and with concomitant high-risk injuries are eligible for inferior vena cava filter placement.[78]

LIMITATIONS OF THIS REVIEW

This is a narrative review intended to provide a qualitative overview of the literature. Based on their subjective evaluations, the authors reviewed the literature and cited relevant articles. Despite the fact that this method is comprehensive, its nonsystematic nature is prone to bias. Robust deductions are limited due to a lack of quantitative synthesis of data from included studies. High-quality RCTs and systematic reviews of sTBI neurocritical care are limited in the literature. Due to the methodological limitations of narrative reviews, readers should cautiously interpret the conclusions brought forward by the authors of this study. Finally, although this review tackled several research questions that were proposed by the 2022 National Trauma Research Action Plan Neurotrauma Research Panel Delphi Survey,[90] many controversial topics in sTBI care were not sufficiently covered including the use of biomarkers, neuroprognostication, and geriatric TBI.

CONCLUSION

Severe TBI is a multifaceted disease process that requires diligent critical care to improve outcomes. SMPs are integral to achieve this. Repeated clinical examination should be used to detect critical neuroworsening, but multimodality neuromonitoring may be needed in select cases. Individualized ICP management may lead to better outcomes. The use of dynamic cerebrovascular reactivity indices such as the PRx may help achieve this. Hypertonic saline has theoretical advantages over mannitol as an ICP-lowering measure for IHT but supporting evidence is sparse. Although DC can be used to lower mortality for refractory IHT, poor functional outcomes limit its universal application for all patients. ICP monitoring continues to be a standard of care that likely improves outcomes. However, high-quality evidence should still be sought to define patients that stand to benefit most especially in pediatric age groups. The choice of device and timing of monitor placement are a matter of debate. Prophylaxis against seizures and VTE should be considered in SMPs but careful consideration is needed in patient selection for anti-seizure and anticoagulant prophylaxis. Beta-blockers can be added to SMPs to improve outcomes through prevention of PSH and posttraumatic hyperthermia. Amantadine is another promising neuroprotective agent that may improve cognitive recovery of sTBI patients. In spite of the consolidated research efforts in the refinement of SMPs, there are still many unanswered questions and novel research opportunities. We encourage future well-designed trials with clearly defined endpoints relevant to optimal patient care.

Authors’ contributions

STE conceived the idea and contributed to designing the review. MK participated in data extraction from the literature and drafting the manuscript. SHA participated in data extraction from the literature and drafting the manuscript. BB participated in data extraction from the literature and drafting the manuscript. MAR participated in data extraction from the literature and critical review. AA participated in data extraction from the literature and critical review. AEMA participated in data extraction from the literature and critical review. AKB designed the review and performed critical revision of the manuscript. STE, MK, and AKB designed the algorithm.

Declaration of patient consent

Patient’s consent not required as there are no patients in this study.

Financial support and sponsorship

Publication of this article was made possible by the James I. and Carolyn R. Ausman Educational Foundation

Conflicts of interest

There are no conflicts of interest.

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