Traumatic Brain Injury Advances

Deborah M. Stein, MD, MPH[a,*], Cristina B. Feather, MD, MHS[b], Lena M. Napolitano, MD, FCCP, MCCM[c]

KEYWORDS

• Traumatic brain injury • Antiseizure prophylaxis • Hyperosmolar therapy
• Targeted temperature modulation • Intracranial pressure monitoring
• Decompressive craniectomy

KEY POINTS

- Antiseizure prophylaxis is beneficial only in the first 7 days after injury.
- Hyperosmolar therapy, with mannitol or hypertonic saline, can be used to control intracranial hypertension.
- Prevention of hyperthermia can prevent secondary brain injury. However, benefits of hypothermia are unclear.
- Intracranial pressure monitoring can aid in therapy.
- Decompressive craniectomy has not shown long-term benefits.

INTRODUCTION

Traumatic brain injury (TBI) continues to be a significant cause of mortality, morbidity, and economic burden globally.[1] Research on TBI over the last century has shown that a hallmark of treatment of TBI is prevention of secondary insults. Studies have shown that even brief episodes of hypoperfusion and hypoxemia can cause secondary injury and lead to worse short-term and long-term outcomes.[1–3] In order to improve medical care and patient outcomes, it is important to be knowledgeable of current literature regarding treatment of patients with TBI.

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[a] Neurotrauma Critical Care, Section of Trauma Critical Care, R Adams Cowley Shock Trauma Center, University of Maryland Medical Center, 22 South Greene Street, Baltimore, MD 21201, USA; [b] Surgical Critical Care, R Adams Cowley Shock Trauma Center, University of Maryland Medical Center, 22 South Greene Street, Baltimore, MD 21201, USA; [c] Division of Acute Care Surgery [Trauma, Burns, Surgical Critical Care, Emergency Surgery], Department of Surgery, Trauma and Surgical Critical Care, University of Michigan Health System, Room 1C340-UH, 1500 East Medical Center Drive, Ann Arbor, MI 48109-5033, USA
* Corresponding author.
E-mail address: dstein@umm.edu

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PHARMACOLOGIC THERAPY

Posttraumatic Seizures Prophylaxis

Seizures in the acutely injured brain can increase intracranial pressure (ICP) and alter oxygen delivery to the brain.[1,4,5] In an attempt to prevent secondary brain injury, many investigators have studied the benefit of prophylaxis for posttraumatic seizures. A randomized, double-blind, placebo-controlled trial, published by Temkin and colleagues[6] in 1990, studied the role of phenytoin in prevention of early and late posttraumatic seizures. The trial included 404 patients, randomized to phenytoin or placebo treatment arms, for a treatment time of 12 months and a follow-up time of 24 months. The results showed a statistically significant difference in the rate of early posttraumatic seizures in the phenytoin group (3.6%) compared with the placebo group (14.2%).[6] There was no significant difference in the rate of posttraumatic seizures between the two groups from day 8 to end of follow-up. Overall, treatment with phenytoin was shown to be effective in decreasing the rate of posttraumatic seizures in the first 7 days of injury, but had no significant role in prevention of posttraumatic seizures after the first week of injury.[6] Notably, inclusion criteria allowed for a wide range of severity of TBI. Therefore, the difference in the benefit of treatment with phenytoin compared with placebo stratified by severity of TBI remains unclear.

As discussed by Temkin and colleagues,[6] treatment with phenytoin has some disadvantages; including several side effects and the need to monitor serum drug levels.[7] In the past decade, studies that compare the effectiveness of phenytoin with levetiracetam in prevention of early posttraumatic seizure prophylaxis have been conducted in an effort to provide an alternative pharmacologic therapy.[5,8] Zafar and colleagues[8] conducted a meta-analysis to compare the efficacies of phenytoin and levetiracetam in posttraumatic seizure prophylaxis. Eight studies comparing the 2 drugs were included in the meta-analysis: 2 randomized controlled trials (RCTs) and 6 observational studies. The meta-analysis showed no significant difference in the odds of seizures when comparing treatment with phenytoin and levetiracetam.[8]

Since publication of the Zafar and colleagues[8] study, a large multicenter prospective study comparing the efficacy of treatment with phenytoin with that of levetiracetam was completed by Inaba and colleagues.[9] This study, which included 813 patients, found no significant difference in rates of early posttraumatic seizures among patients treated with phenytoin compared with patients treated with levetiracetam.

The current Brain Trauma Foundation Guidelines recommend treatment with anticonvulsants within 7 days of injury.[1,10] Because this recommendation is based on the level II evidence outlined earlier, larger RCTs comparing efficacy of phenytoin with that of levetiracetam are needed to further delineate these recommendations. In addition, the importance of the severity of TBI and the use of anticonvulsants remains unclear, an important aspect to consider, because the long-term disadvantages related to seizure prophylaxis are poorly understood.[7]

Hyperosmolar Therapy

Hyperosmolar therapy is used to decrease high ICP in an effort to maintain cerebral blood flow and prevent secondary brain injury. The 2 most common pharmacologic interventions are mannitol and hypertonic saline. Mannitol increases cerebral blood flow by plasma expansion, decreasing the blood viscosity via deformed erythrocytes, and promotes osmotic diuresis.[1,11] Hypertonic saline promotes mobilization of water across the blood-brain barrier, and improved blood flow via plasma volume expansion.[1] Debate regarding the efficacy of these treatment modalities for increased ICP continues.

Kamel and colleagues[12] conducted a meta-analysis of RCTs comparing mannitol and hypertonic saline in the treatment of increased ICP. Five studies were included, with a total of 112 patients with a diagnosis of TBI, stroke, intracerebral hemorrhage, subarachnoid hemorrhage, or tumor resection. Treatment of increased ICPs with hypertonic saline was more favorable than treatment with mannitol, with a pooled relative risk of successful treatment with hypertonic saline compared with mannitol of 1.16 (95% confidence interval [CI], 1.00–1.33).[12] Importantly, the studies included had small sample sizes and a wide variety of intracranial disorders, limiting the application of the findings.

Mangat and colleagues[13] published a prospective observational study comparing the total ICP burden and cumulative ICP reduction among patients with severe TBI receiving monotherapy. Using propensity score matching, 35 patients treated with mannitol were matched with 35 patients treated with hypertonic saline. Cumulative and daily ICP burdens were calculated as percentages of days or hours with an acute ICP increase during ICP monitoring. Both the cumulative and daily ICP burdens were significantly lower in the patients receiving hypertonic saline compared with those treated with mannitol.[13] Although the patients were matched on factors most predictive of mortality specific to severe TBI, they were not matched on factors predicative of overall trauma mortality. In addition, the small sample size, absence of reporting of adverse effects of treatment, and lack of randomization prevents strong conclusions being made from this study.

Cottenceau and colleagues[14] conducted a RCT comparing equiosmolar doses of mannitol and hypertonic saline in the treatment of increased ICP. Forty-seven patients sustaining severe TBI were included in the study and randomized to mannitol or hypertonic saline treatment in the setting of acute increase of ICP. The difference in average time of increased ICP between the two treatment groups was not statistically significant.[14] The magnitude of ICP decrease from baseline was significantly higher in the subjects treated with hypertonic saline compared with those treated with mannitol.[14] Note that the largest changes in ICP were in patients with diffuse brain injury treated with hypertonic saline.[14] Although no definitive advantage of hypertonic saline versus mannitol in treatment of increased ICP was shown in this study, there was some evidence that injury pattern and severity are important.

A more recent meta-analysis, by Burgess and colleagues,[4] included 7 RCTs and 191 patients. As in the previous meta-analysis, treatment with hypertonic saline was more successful in treatment of increased ICP compared with treatment with mannitol.[4] There was no difference in 6-month mortality, and limited adverse events were reported.

In conclusion, intracranial hypertension can be harmful to the acutely injured brain, leading to decreased perfusion and secondary brain injury. It is important to maintain cerebral perfusion pressure and limit acute increases of ICP. At present, no large randomized controlled trial comparing treatment with mannitol and hypertonic saline in the setting of increased ICP in severe TBI has been completed. In addition, the significance of severity of injury or injury pattern in the treatment of acutely increased ICP is yet to be determined.

OTHER PHARMACOLOGIC THERAPY

Progesterone

Progesterone treatment was associated with robust positive effects in animal TBI models[15] and in 2 phase 2 RCTs.[16,17] However, 2 large phase 3 RCTs (the Study of a Neuroprotective Agent, Progesterone, in Severe Traumatic Brain Injury [SYNAPSE] and the Progesterone for the Treatment of Traumatic Brain Injury [PROTECT III] trial) did not confirm any clinical benefit of progesterone in TBI treatment.[18,19]

Erythropoietin

Erythropoietin (EPO) showed high therapeutic potential as a neuroprotective agent in animal studies, but failed in recently completed clinical trials. However, in an RCT of 200 patients with severe TBI (EPO, n = 102; placebo, n = 98) enrolled within 6 hours of injury, EPO failed to improve favorable outcomes by 20% at 6 months.[20] The EPO-TBI study randomized 606 patients with moderate or severe TBI to EPO or placebo and reported that EPO did not reduce the number of patients with severe neurologic dysfunction (Extended Glasgow Outcome Scale [GOS-E] level 1–4) or increase the incidence of deep venous thrombosis of the lower extremities and had no effect on 6-month mortality (11% EPO vs 16% placebo; RR [risk ratio], 0.68; 95% CI, 0.44–1.03; $P = .07$).[21]

A meta-analysis of 5 RCTs with 915 patients showed that EPO significantly reduced mortality (RR, 0.69; 95% CI, 0.49–0.96; $P = .03$) and shortened hospitalization time ($P<.0001$) for patients with TBI. However, no differences in favorable neurologic outcome and deep vein thrombosis were identified. The investigators suggested that EPO is beneficial for patients with TBI in terms of reducing mortality and shortening hospitalization time without increasing the risk of deep vein thrombosis. However, its effect on improving favorable neurologic outcomes did not reach statistical significance. Therefore, more well-designed RCTs are necessary to ascertain the optimum dosage and time window of EPO treatment of patients with TBI.[22]

Amantadine

Amantadine hydrochloride acts as an *N*-methyl-D-aspartate antagonist and indirect dopamine agonist. Small RCTs have suggested that amantadine was effective in improving functional outcomes after TBI. A placebo-controlled RCT[23] of amantadine for severe TBI randomized 184 patients who were in a vegetative or minimally conscious state 4 to 16 weeks after TBI and who were receiving inpatient rehabilitation to receive amantadine or placebo for 4 weeks. Amantadine accelerated the pace of functional recovery during active treatment as measured by the Disability Rating Scale.

At present, there is no single pharmacologic therapy that unequivocally improves clinical functional outcomes after TBI, but several agents have potential benefit and should be investigated further.[24,25] Potential pharmacologic therapy for TBI matched with pathophysiologic events is shown in **Fig. 1**. Given the recent failures in clinical translation of therapies in TBI, new approaches (such as a rigorous multicenter preclinical drug and circulating biomarker screening consortium, Operation Brain Trauma Therapy [OBTT]) may be helpful in the development of successful pharmacologic strategies for TBI.[26]

NONPHARMACOLOGIC THERAPY

Targeted Temperature Modulation

Hyperthermia can cause secondary brain injury in the setting of TBI by increasing vascular permeability, and promoting edema and inflammation.[27] In the clinical setting, mild hyperthermia has been associated with poorer outcomes and longer intensive care unit stays.[28,29] As a result of these findings, interest in targeted temperature modulation (TTM) to prevent hyperthermia in TBI has grown.[30,31]

The European Study of Therapeutic Hypothermia (32°C–35°C) for ICP Reduction after TBI (Eurotherm3235 Trial) was designed to further define the association of hypothermia and functional outcome in patients with TBI.[32,33] Patients with a sustained ICP of greater than 20 mm Hg despite other therapeutic maneuvers (n = 387) were randomized to hypothermia (32°C–35°C) plus standard care or standard care alone. Guidelines for induction of hypothermia and rewarming were determined a priori.[33] Hypothermia was titrated to ICP, and patients were considered rewarmed after 48 hours of

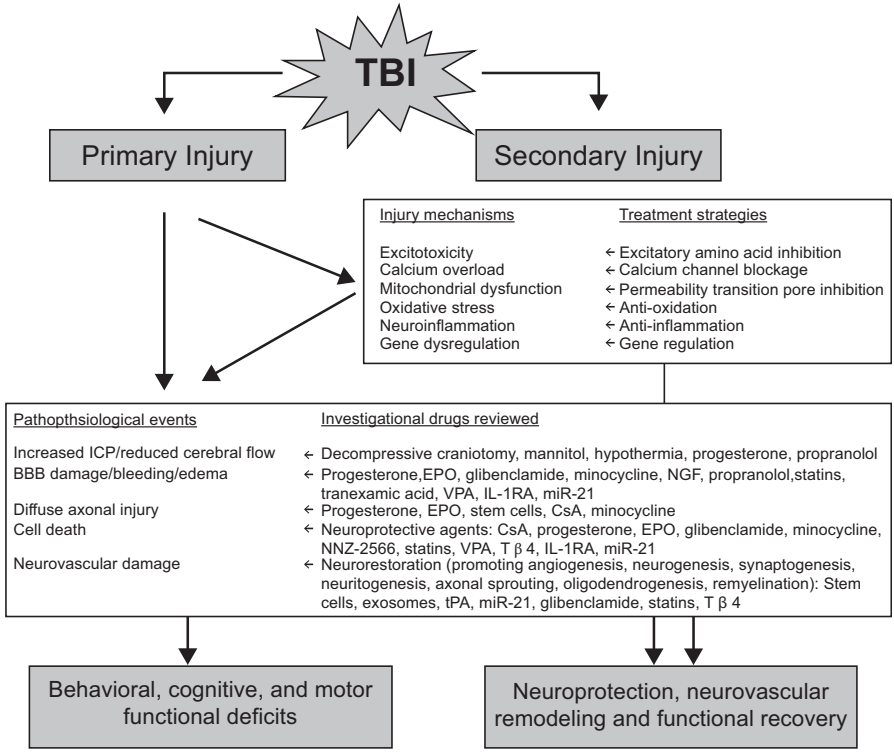

Fig. 1. TBI pathophysiology and recovery phases and potential pharmacologic treatment strategies. BBB, blood-brain barrier; CsA, cyclosporine A; IL-1RA, interleutin-1 receptor antagonist; miR-21, microRNA-21; NNZ-2566, synthetic analogue of the endogenous N-terminus tripeptide glycine-proline-glutamate; NGF, nerve growth factor; Tβ4, thymosin beta 4; tPA, tissue plasminogen activator; VPA, valproic acid. (*From* Xiong Y, Zhang Y, Mahmood A, et al. Investigational agents for treatment of traumatic brain injury. Expert Opin Investig Drugs 2015;24(6):743–60.)

treatment or until ICP was controlled. The trial was terminated early, because signs of harm within the treatment arm were appreciated.[33] Although there were statistically significantly fewer failures of therapy to control acutely increased ICP in the hypothermia group, the treatment group had a lower GOS-E at 6 months compared with the control arm.[33] Two randomized trials in the pediatric population showed similar results of worse outcomes in the hypothermia treatment groups.[30] Of note, the patients treated with the standard-of-care protocol in the Eurotherm3235 Trial received normothermic TTM, confounding the results. In addition, although hypothermia did not improve functional outcome, there was an observed decrease in ICP in the treatment arm.[33,34]

A second RCT is underway (Prophylactic Hypothermia Trial to Lessen Traumatic Brain Injury [POLAR]). Instead of comparing hypothermia with standard of care, prophylactic hypothermia is compared with normothermic TTM.[35] This study may be able to provide improved insights into the benefit of TTM in the clinical setting.

Of note, 1 small retrospective study evaluated the effect of TTM compared with standard of care on clinical complications. O'Phelan and colleagues[36] reported a statistically significant increase in the rate of pulmonary complications in patients treated with TTM compared with standard of care. This difference was explained by the inhibition of fever

to combat infection.[36] However, because of the study design and small sample size, the association of TTM and pulmonary complications warrants further exploration.

SURGICAL TREATMENT OPTIONS

Decompressive Craniectomy

Intracranial hypertension following TBI can result from mass effect from hematoma or contusion. The practice of decompressive craniectomy has been introduced in an effort to control intracranial hypertension and prevent further brain injury.[37,38] The 3 clinical trials for decompressive craniectomy for TBI are reviewed in **Fig. 2**.

Primary decompressive craniectomy refers to the technique of leaving the resected bone flap out after evacuation of a hematoma in order to prevent intracranial hypertension.[39] Presently an RCT is underway that is designed to determine the benefit of primary decompressive craniectomy in the setting of acute subdural hemorrhage (RESCUE-ASDH [Randomized Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intracranial Pressure-Acute Subdural Hematoma]).

Secondary decompressive craniectomy involves resecting a bone flap specifically to decrease intracranial hypertension when there is no other indication for neurosurgical intervention. The DECRA (Decompressive Craniectomy) trial included patients who had refractory increased ICPs between 15 minutes and 1 hour of onset.[40] A total of 155 patients were randomized to decompressive craniectomy and standard of care versus standard of care. Results showed significantly fewer medical interventions to decrease ICP in patients treated with decompressive craniectomy. However, at 6-month follow-up, functional outcome was worse in the decompressive craniectomy group compared with the standard-of-care group.[40]

The RESCUEicp (Randomized Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intracranial Pressure) trial (n=408) compared secondary

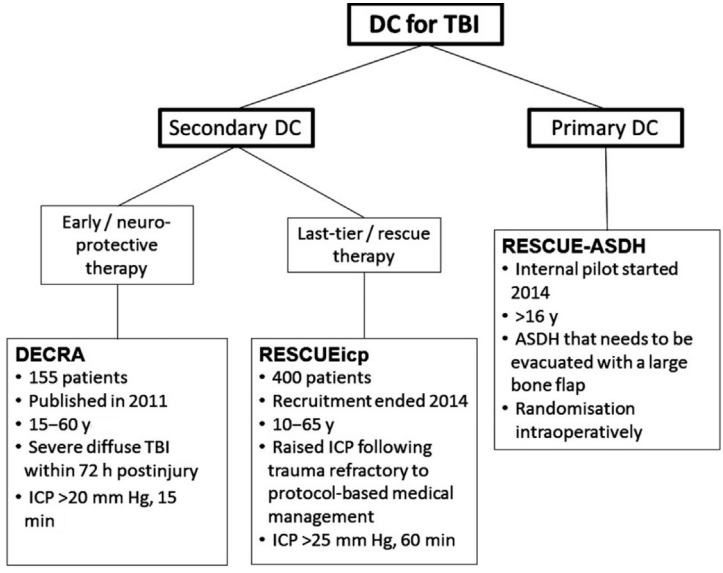

Fig. 2. Randomized trials of decompressive craniectomy (DC) for TBI. (*From* Kolias AG, Adams H, Timofeev I, et al. Decompressive craniectomy following traumatic brain injury: developing the evidence base. Br J Neurosurg 2016;30(2):246–50.)

decompressive craniectomy to optimal medical management.[41,42] In contrast to the DECRA trial, decompressive craniectomy was only performed if ICP remained elevated (ICP > 25 mm Hg for 1-12 hours) despite Stage I [optimal medical management (head elevation, ventilation, sedation, analgesia, neuromuscular blockade)] and Stage 2 (ventriculostomy, inotropes, mannitol, hypertonic saline, loop diuretics, hypothermia) treatment. At 6-months, decompressive craniectomy resulted in lower mortality (26.9% vs. 48.9%) than medical management, but higher rates of vegetative state (8.5% vs. 2.1%), lower severe disability (21.9% vs. 14.4%) and upper severe disability (15.4% vs. 8.0%). Future studies are required to determine which patients will benefit with mortality reduction but minimize risk for vegetative state and poor functional outcomes.[43]

INTRACRANIAL PRESSURE MONITORING

Current guidelines recommend ICP monitoring in patients with severe TBI and a confirmatory radiographic evidence of intracranial disorder, or patients with a normal computed tomography (CT) scan, but more than 40 years of age, with evidence of posturing, or systolic blood pressure less than 90 mm Hg.[1] Guidelines advocate the early treatment of ICP because increased severity and longer duration of increased ICP are associated with poor outcome. Management of increased ICP includes standardized strategies that use a so-called staircase approach with an escalating treatment intensity.[44] The American College of Surgeons TBI Guidelines recommend a 3-tier approach for management of increased ICP (**Boxes 1–3**).[45]

The value of ICP monitoring in medical decision making and patient outcomes was evaluated in the BEST:TRIP (Benchmark Evidence of South American Trials: Treatment of Intracranial Pressure) trial.[46,47] Chesnut and colleagues[46] hypothesized that routine ICP monitoring in severe TBI would decrease mortality and improve neurologic outcome. Patients with severe TBI presenting to 6 trauma centers in South America were included and randomized to ICP monitoring with goal ICP less than 20 mm Hg, or a serial imaging–clinical examination protocol.[47] A total of 324 patients were included, with 92% follow-up rate. There was no mortality or clinical outcome benefit observed when comparing patients in the ICP-monitoring group with patients in the serial imaging–clinical examination protocol group.[46] Pitfalls of this study include limited prehospital care resources, leading

Box 1
Three-tiered management of ICP in TBI: tier 1

Tier 1

- Head of bed elevated at 30° (reverse Trendelenburg) to improve cerebral venous outflow.
- Sedation and analgesia using recommended short-acting agents (eg, propofol, fentanyl, midazolam) in intubated patients.
- Ventricular drainage performed intermittently. Continuous drainage is not recommended unless an additional ICP monitor is placed, because, when the drain is open, it does not accurately reflect the ICP.
- Repeat CT imaging and neurologic examination should be considered to rule out the development of a surgical mass lesion and guide treatment.

If ICP remains greater than or equal 20 to 25 mm Hg, proceed to tier 2.

From American College of Surgeons Trauma Quality Improvement Program. Best practices in the management of traumatic brain injury. Available at: https://www.facs.org/~/media/files/quality%20programs/trauma/tqip/traumatic%20brain%20injury%20guidelines.ashx. Accessed May 1, 2016.

Box 2
Three-tiered management of ICP in TBI: tier 2

Tier 2

- In patients with a parenchymal ICP monitor an EVD should be considered to allow for intermittent cerebrospinal fluid drainage.
- Hyperosmolar therapy should be given intermittently as needed for ICP increase and not on a routine schedule.
  - Mannitol should be administered in intermittent boluses (0.25–1 g/kg body weight). Care should be taken in hypovolemic patients when osmotic diuresis is instituted with mannitol. The serum sodium level and osmolality must be assessed frequently (every 6 hours) and additional doses should be held if serum osmolality exceeds 320 mOsm/L. Mannitol may also be held if there is evidence of hypovolemia.
  - Hypertonic saline may be administered in intermittent boluses of 3% sodium chloride solution (250 mL over 30 minutes) or other concentrations (eg, 30 mL of 23.4%). Serum sodium level and osmolality must be assessed frequently (every 6 hours) and additional doses should be held if serum sodium exceeds 160 mEq/L.
- Cerebral autoregulation should be assessed (see text). If the patient is not autoregulating, the CPP goal should be decreased to reduce ICP (to no less than 50 mm Hg). Additional neuromonitoring (eg, $Pbto_2$, $Sjvo_2$, CBF) may help determine optimal CPP.
- $Paco_2$ goal of 30 to 35 mm Hg should be maintained, as long as brain hypoxia is not encountered. Additional neuromonitoring (eg, $Pbto_2$, $Sjvo_2$, CBF) may help determine optimal $Paco_2$.
- Repeat CT imaging and neurologic examination should be considered to rule out development of a surgical mass lesion and guide treatment.
- Neuromuscular paralysis achieved with a bolus test dose of a neuromuscular blocking agent should be considered if the above measures fail to adequately decrease ICP and restore CPP. If there is a positive response, continuous infusion of a neuromuscular blocking agent should be used (tier 3).

If ICP remains greater than or equal to 20 to 25 mm Hg proceed to tier 3.
Abbreviations: CBF, cerebral blood flow; CPP, cerebral perfusion pressure; EVD, external ventricular drain; $Pbto_2$, perfusion and brain tissue oxygenation; $Sjvo_2$, jugular venous oxygen saturation.

From American College of Surgeons Trauma Quality Improvement Program. Best practices in the management of traumatic brain injury. Available at: https://www.facs.org/~/media/files/quality%20programs/trauma/tqip/traumatic%20brain%20injury%20guidelines.ashx. Accessed May 1, 2016.

to a survival bias. In addition, there was a high mortality after 14 days of injury in both groups, attributable to limited postdischarge resources. In addition, the non-ICP group had a higher incidence of treatment with barbiturates and hypertonic saline, indicating an advantage of ICP monitors to better target other therapeutic measures.[46]

Yuan and colleagues[48] completed a meta-analysis evaluating the association of ICP monitoring and mortality in patients with severe TBI. Fourteen studies were included: 13 observational studies and 1 RCT (Chesnut and colleagues,[46] 2012). There was no measured association between ICP monitoring and mortality benefit in pooled analysis and subgroup analysis.[48] Importantly, there was a large degree of heterogeneity among the included studies with regard to outcome measurements and protocols to control intracranial hypertension.

Noninvasive intracranial monitoring is an emerging technique. Transcranial Doppler ultrasonography (TCD) has been described to estimate ICP. This technique relies on arterial waveform variability, and has a wide range of reported accuracy compared

Box 3
Three-tiered management of ICP in TBI: tier 3

Tier 3 (includes potential salvage therapies)

- Decompressive hemicraniectomy or bilateral craniectomy should only be performed if treatments in tiers 1 and 2 are not sufficient or are limited by development of side effects of medical treatment.
- Neuromuscular paralysis via continuous infusion of a neuromuscular blocking agent can be used if there is a positive response to a bolus dose. The infusion should be titrated to maintain at least 2 twitches (out of a train of 4) using a peripheral nerve stimulator. Adequate sedation must be used.
- Barbiturate or propofol (anesthesia dosage) coma may be induced for patients who have failed to respond to aggressive measures to control malignant intracranial hypertension, but it should only be instituted if a test dose of barbiturate or propofol results in a decrease in ICP, thereby identifying the patient as a responder. Hypotension is a frequent side effect of high-dose therapy with these agents. Meticulous volume resuscitation should be ensured and infusion of vasopressor/inotropes may be required. Prolonged use or high dose of propofol can lead to propofol infusion syndrome. Continuous electroencephalogram may be used to ensure targeting of the infusion to burst suppression.
- Hypothermia (<36°C) is not currently recommended as an initial TBI treatment. Hypothermia should be reserved for rescue or salvage therapy after reasonable attempts at ICP control after the previous tier 3 treatments have failed.

From American College of Surgeons Trauma Quality Improvement Program. Best practices in the management of traumatic brain injury. Available at: https://www.facs.org/~/media/files/quality%20programs/trauma/tqip/traumatic%20brain%20injury%20guidelines.ashx. Accessed May 1, 2016.

with invasive methods ICP monitoring.[49] The reliability of TCD continues to be refined. However, currently it is not standard of care for ICP monitoring.

It is well understood that intracranial hypertension can produce severe effects to the already injured brain. However, there continues to be a lack of evidence to guide management on how best to monitor intracranial hypertension, and with what threshold intervention should be initiated.[50] Furthermore, hospital-level compliance with evidence-based guidelines for ICP monitoring and craniotomy had minimal association with risk-adjusted outcomes in patients with severe TBI.[51]

UPDATED BRAIN TRAUMA FOUNDATION GUIDELINES SEVERE TBI

The updated Guidelines (Fourth Edition)[52] have modified some recommendations based on new evidence, and include the following:

- ***ICP monitoring:*** Management of severe TBI patients using information from ICP monitoring is recommended to reduce in-hospital and 2-week post-injury mortality.
- ***ICP thresholds:*** Treating ICP > 22 mm Hg is recommended because values above this level are associated with increased mortality,.
- ***Cerebral perfusion pressure (CCP) monitoring:*** Management of severe TBI patients using guidelines-based recommendations for CPP monitoring is recommended to decreased 2-week mortality.
- ***CPP thresholds:*** The recommended target CPP value for survival and favorable outcomes is between 60 and 70 mm Hg. Whether 60 or 70 mm Hg is the minimum optimal CPP threshold is unclear and may depend upon the autoregulatory status of the patient.

Table 1
Complications of therapeutic interventions for TBI

Interventions	Complications
Seizure Prophylaxis	
Phenytoin	Adverse drug reactions Must follow serum drug levels
Levetiracetam	Cost Adverse drug reactions
Hyperosmolar Therapy	
Mannitol	Intravascular volume depletion Rebound increased ICP
Hypertonic saline	Hypernatremia Volume expansion
Temperature Modulation	
Hypothermia	Rebound increased ICP during rewarming Altered metabolism
Normothermia	Need for pharmacologic and physiologic intervention Pulmonary complications
ICP Monitoring	
Invasive	Bleeding Infection
Noninvasive	Reliability
Decompressive craniectomy	Poor long-term functional outcome

TREATMENT COMPLICATIONS

Treatment complications are listed in **Table 1**.

EVALUATION OF OUTCOME AND LONG-TERM RECOMMENDATIONS

Most current studies include patients with severe TBIs, and measure long-term functional outcomes at 6 months using The GOS-E. However, the association of severity of injury and current treatment modalities is not well described. In addition, follow-up is limited and complications of therapy are poorly reported.

SUMMARY

There have been many recent advances in the management of TBI. Research regarding established therapies, such as antiseizure prophylaxis, and novel therapies, such as TTM, is ongoing. Future research must not only focus on development of new strategies but determine the long-term benefits or disadvantages of current strategies. In addition, the impact of these advances on varying severities of brain injury must not be ignored. It is hoped that future research strategies in TBI will prioritize large-scale trials using common data elements to develop large registries and databases led by the Federal Interagency Traumatic Brain Injury Research (FITBIR) informatics system as a partnership between the National Institutes of Health (NIH) and Department of Defense (DOD), and leverage international collaborations such as the International Initiative for Traumatic Brain Injury Research (InTBIR).

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