

**RESEARCH REVIEW
ON
ACUTE MANAGEMENT OF INTRACRANIAL PRESSURE IN SEVERE
TRAUMATIC BRAIN INJURY**

OVERVIEW

The purpose of this research review is to provide an update on recent scientific literature regarding the acute treatment of severe closed-head traumatic brain injuries in adults. The three topics discussed here relate to the management of intracranial pressure (ICP): therapeutic hypothermia, hypertonic saline (HTS), and decompressive craniectomy. Specifically, the research questions considered are: whether therapeutic hypothermia improves patient outcomes; whether HTS is effective at reducing ICP or improving outcomes, and whether it is superior or equivalent to mannitol; and whether decompressive craniectomy improves patient outcomes. While there have been important findings on a number of therapies for acute severe TBI, these three areas were chosen based on their position at the forefront of research inquiry in the past 5 to 10 years.

BACKGROUND

Severe traumatic brain injuries (TBIs) are characterized by: a loss of consciousness lasting more than 24 hours, memory loss lasting more than 7 days, or a Glasgow Coma Scale (GCS) score of 3 to 8 (Department of Defense & Department of Veterans Affairs, 2009). In the last 15 years, over 3,000 severe traumatic brain injuries (TBIs) have occurred among active-duty service members. Although severe TBIs constitute only 1% of all TBIs in the military health system, (*DoD Numbers for Traumatic Brain Injury Worldwide: 2000-2016*, February 2017) they have high rates of mortality and morbidity, and are a significant public health concern. Severe TBI can and often does result in long-term or permanent disability and has a serious financial impact on patients and their families due to lost income and care needs that can last for decades.

Management of severe TBI patients in acute care facilities focuses on preventing secondary injury (Haddad & Arabi, 2012). Secondary injury can result from increased intracranial pressure, hypotension, hyperthermia, or hypoxemia. Providers have a number of tools available to avoid these risks, including fluid resuscitation, fever suppression, and mechanical ventilation (Haddad & Arabi, 2012). This review will focus on three acute care interventions aimed at reducing elevated intracranial pressure: therapeutic hypothermia, HTS, and decompressive craniectomy.

This research review includes data on clinical outcomes where available. Researchers face significant challenges conducting randomized controlled trials in severe traumatic brain injury for multiple reasons. The heterogeneity of injury mechanism, injury pathology, and regional differences in clinical practice all lead to differences in outcomes that can obscure risks and benefits of interventions. In some cases, ethical concerns limit experimental design choices, and informed consent cannot be obtained from a comatose patient. Despite this, a number of high-quality studies have influenced the development of treatment guidelines.

INFORMATION

Targeted temperature management

The most recent recommendations that directly address hypothermia for severe TBI were published by six French medical organizations including the French Intensive Care Society and the French Society of Anesthesia and Intensive Care Medicine (Cariou et al., 2017). These guidelines state that “targeted temperature management” is the appropriate phrase to describe efforts to prevent hyperthermia and maintain a temperature at or slightly below normal (35-37 °C). Previous literature and recommendations have discussed “therapeutic hypothermia,” an approach that calls for lower temperatures (32-35 °C) and has not been supported by multi-center clinical trials (Clifton et al., 2011; Maekawa et al., 2015; Suehiro et al., 2015). However, it is well known that hyperthermia is associated with poorer outcomes (Bohman & Levine, 2014; Madden & DeVon, 2015) and that brain temperatures often rise in severe TBI patients (Childs & Lunn, 2013; Henker, Brown, & Marion, 1998). For this reason, targeted temperature management is thought to be beneficial.

Targeted temperature management is considered here as a mechanism for managing intracranial hypertension in severe TBI patients. Pre-clinical studies suggest that low body temperature has multiple beneficial effects, including reducing metabolism and oxidative stress, inhibiting inflammation and apoptosis, and reducing production of glutamate, which can be excitotoxic in TBI (Antonic et al., 2014; Tang & Yenari, 2010). In patients, the body is typically cooled externally or with the use of intravascular closed-circuit cooling catheter systems (Crossley et al., 2014). In severe TBI patients, brain temperatures are generally higher than core body temperatures (Henker et al., 1998; Kirk, Rainey, Vail, & Childs, 2009; Rossi, Zanier, Mauri, Columbo, & Stocchetti, 2001; Rumana, Gopinath, Uzura, Valadka, & Robertson, 1998). With temperature management, brain temperatures decline, but remain higher than body temperatures (Henker et al., 1998).

Table 1. Recommendations regarding targeted temperature management or therapeutic hypothermia

Guideline	Recommendations
BTF, 2017 (Carney et al., 2017)	Regarding prophylactic hypothermia, Level IIB evidence (based on a low-quality body of evidence) suggests “early (within 2.5 h), short-term (48 h post-injury), prophylactic hypothermia is not recommended to improve outcomes in patients with diffuse injury.” No recommendations regarding therapeutic hypothermia.
American College of Surgeons, 2015 (Cryer et al., 2015)	Therapeutic hypothermia is listed as a salvage therapy option, for use only after all other recommended options have failed.
JTS CPG, 2017 (McCafferty et al., 2017)	“Avoid and treat hyperthermia.”
French Intensive Care Society & French Society of Anesthesia and	Recommends targeted temperature management at 35-37 °C to reduce ICP and improve outcomes. For

Intensive Care Medicine (Cariou et al., 2017)	refractory ICP, recommends considering 34-35 °C. For pediatric patients, normothermia is recommended.
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Abbreviations: BTF, Brain Trauma Foundation; JTS CPG, clinical practice guideline, Joint Trauma System Clinical Practice Guideline for Management of Patients with Severe Head Trauma; ICP, intracranial pressure

Controlled trials provided inconsistent results regarding the efficacy of therapeutic hypothermia in improving outcomes. The Tactical Combat Casualty Care Guidelines, developed by the Joint Trauma System of the US Army Institute of Surgical Research, do not recommend pre-hospital treatment of casualties with therapeutic hypothermia (McCafferty et al., 2017). The Brain Trauma Foundation (BTF) guidelines updated in 2017 state that a low-quality body of evidence discourages prophylactic hypothermia (Carney et al., 2017). The BTF guidelines did not address therapeutic hypothermia, which is applied in cases where less invasive management fails to adequately manage ICP. The American College of Surgeons recommends hypothermia for ICP management only as a “rescue” therapy when other methods including, for example, sedation, ventricular drainage, hyperosmolar therapy, neuromuscular paralysis, decompressive craniectomy, and induced coma have failed (Cryer et al., 2015).

Three multi-center randomized studies of therapeutic hypothermia did not show benefit with interventions targeting 32 to 35 °C for more than 48 hrs (Andrews et al., 2015; Clifton et al., 2011; Maekawa et al., 2015). These results contrasted with earlier single-center trials that had more promising results (Lee et al., 2010; Zhao, Zhang, & Wang, 2011). Many factors contribute to results in severe TBI trials; more sophisticated cooling technology, varied exposure times, different target temperatures, or more close protocol monitoring may provide more information on ideal target temperatures and cooling durations (ClinicalTrials.gov, 2014, 2015a, 2015b, 2015c, 2016).

Hypertonic saline

Hypertonic saline (HTS) is an osmotic agent used to increase the osmotic pressure gradient between blood and tissues in order to draw water out of the brain and reduce intracranial pressure. Standard HTS solutions include 3%, 7%, and 23.4% (weight/volume). The 2017 BTF guidelines did not specifically address HTS, and recommended mannitol solution for reducing elevated ICP in TBI (Carney et al., 2017). The 2017 Joint Trauma System Clinical Practice Guideline (CPG) for Neurosurgery and Severe Head Injury includes a protocol for administering (3%) HTS (McCafferty et al., 2017). The American College of Surgeons recommends mannitol as an osmotic agent, and presents HTS as an option (Cryer et al., 2015). The 2005 BTF Field Management Guidelines state that HTS for ICP management is supported by low or moderate quality data, but these have not been updated since 2005 (Knuth et al., 2005).

Evidence consistently shows that HTS is effective at reducing ICP and does not pose additional risks for patients. Reviewers do not agree on whether HTS is more effective at managing elevated ICP than other interventions. A recent meta-analysis evaluated randomized controlled trials of HTS as compared to mannitol, normal saline, or sodium bicarbonate. The analysis included 11 studies and 1,820 patients. Six of the studies were not blinded, and only two studies were deemed to have a low risk of bias (Berger-Pelleiter, Emond, Lauzier, Shields, &

Turgeon, 2016). The authors concluded that HTS did not provide better ICP management or better patient outcomes as compared to other interventions. Rickard et al. included six randomized trials with 171 patients and 599 episodes of raised ICP. No significant differences between HTS and mannitol were observed in ICP-lowering effectiveness (Rickard et al., 2014).

These conclusions contrast with those of two other reviews. Li et al. conducted a meta-analysis with 6 randomized controlled trials and a total of 169 patients (Li & Yang, 2014). The authors found that hypertonic saline is more effective than mannitol at lowering ICP 60 min or 120 min after intervention. In both the Li et al. and Rickard et al. analyses, studies varied on HTS concentrations, dosages, infusion times, and the inclusion of starch or dextran in the HTS solution. The authors of both meta-analyses noted that most of the randomized controlled trials had inadequate blinding of participants and personnel, and several lacked outcomes blinding as well. Both meta-analyses included three studies that accepted both TBI and stroke patients. A recent, more qualitative systematic literature review considered 48 studies on pharmacologic agents for reducing ICP. The authors discussed osmotic agents (HTS, mannitol, and sodium lactate), barbiturates, sedatives (propofol, benzodiazepines), and analgesics (including fentanyl). They concluded that HTS is associated with faster reduction of elevated ICP as compared to other interventions (Alnemari, Krafcik, Mansour, & Gaudin, 2017).

Table 2. Recommendations regarding hypertonic saline (HTS)

Guideline	Recommendations
BTF, 2017 (Carney et al., 2017)	Regarding hyperosmolar therapy: mannitol is “effective for control of raised ICP at doses of 0.25 to 1 g/kg body weight. Arterial hypotension (systolic blood pressure <90 mm Hg) should be avoided. Restrict mannitol use prior to ICP monitoring to patients with signs of transtentorial herniation or progressive neurologic deterioration not attributable to extracranial causes.”
American College of Surgeons, 2015 (Cryer et al., 2015)	As a tier 2 therapy when head elevation, sedation, and ventricular drainage have failed, use hyperosmolar therapy with intermittent boluses when needed. Mannitol is recommended, HTS is presented as an option. Boluses should be held if serum sodium > 160 mEq/L.
JTS CPG, 2017 (McCafferty et al., 2017)	For intracranial hypertension, consider 3% HTS delivered as a bolus of 250 cc, followed by 50-100 cc/hr infusion for resuscitation during transport. Mannitol is presented as an alternative or second option.

Abbreviations: BTF, Brain Trauma Foundation; JTS CPG, clinical practice guideline, Joint Trauma System Clinical Practice Guideline for Management of Patients with Severe Head Trauma; cc, cubic centimeter; mEq/L, milliequivalents per liter; ICP, intracranial pressure.

One of the largest studies of HTS was a randomized controlled trial testing HTS as compared to HTS with dextran or normal saline. A single 250-ml bolus of one of these three solutions was administered to severe TBI patients (GCS < 8) prior to hospital admission. The study was terminated for futility after data from 1087 patients showed no superior 6-month

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neurological outcome seen in the HTS or HTS with dextran groups as compared with the normal saline group (Bulger et al., 2010).

Abundant data shows that HTS is safe and effective, (Tan et al., 2016; Wang, Cao, Zhang, Ge, & Bie, 2017) but may not be superior to mannitol, sodium lactate (Ichai et al., 2013), or other osmotic agents (Bourdeaux & Brown, 2011). It is also unclear whether any advantage in ICP management that HTS may offer translates into improved long-term outcomes like decreased mortality or disability (Jagannatha, Sriganesh, Devi, & Rao, 2016). HTS offers the advantage of expanding of intravascular volume, which is useful in cases where low volume resuscitation is required, and does not carry the risk of hypotension and volume depletion via diuresis associated with mannitol (Haddad & Arabi, 2012). In addition, HTS has pragmatic advantages including lower cost, easier storage, and lower volume dosages. Hypernatremia is a possible adverse effect of HTS administration (Kolmodin, Sekhon, Henderson, Turgeon, & Griesdale, 2013). Valid comparisons of the multiple clinical HTS trials, and determination of efficacy of HTS for reducing ICP or improving neurologic outcomes after severe TBI, is difficult because of at least three key variables: the concentration of saline solutions used (from 3% to 23.4%), the volume of the solution used both in terms of the individual bolus and frequency of boluses, and the comparator solutions (normal saline vs colloids of various kinds). While many, including the Joint Trauma System Clinical Practice Guideline, recommend 3% HTS, (McCafferty et al., 2017) others recommend 7% at lower doses.

Decompressive craniectomy

Decompressive craniectomy (DC) is a neurosurgical intervention used to reduce intracranial pressure. This review focuses on DC used as a last-tier treatment for refractory intracranial pressure. DC is a procedure that involves removing part of the skull to provide space for the swollen brain to expand. Typically within 6 to 12 weeks, the original stored bone flap may be replaced, or a synthetic cranioplasty may be performed. The timing of the follow-up surgery is influenced by several factors. The risk of infection is reduced if the surgery is delayed until the original surgical incision has healed, and other possible sources of infection have been treated. However, if the follow-up surgery is delayed too long, the risk of syndrome of the trephined increases (Kurland et al., 2015; Sedney, Dillen, & Julien, 2015). This syndrome involves severe headache, tinnitus, dizziness, fatigue, behavioral or emotional symptoms, sensorimotor or autonomic deficits, and cognitive impairments, which resolve upon replacement of the bone flap (Vasung et al., 2016).

The American College of Surgeons recommends DC when most other treatments such as osmotic agents and neuromuscular paralysis have failed or are limited by side effects (Cryer et al., 2015). The 2017 BTF guidelines do not recommend DC (Carney et al., 2017). The 2017 Joint Trauma System CPG recommends considering DC for penetrating TBI only (McCafferty et al., 2017).

A recently published international randomized controlled trial, Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intracranial Pressure (RESCUEicp) included 408 patients with severe TBI and refractory elevated intracranial pressure (>25 mm Hg; Hutchinson et al., 2016). Although 6-month mortality was lower in the DC group, the risk of vegetative state or severe disability was higher as compared to the medical management group. The proportion of patients with a favorable outcome (dichotomized Extended Glasgow

Outcomes Scale; GOS-E) was higher in the DC group at 6 months, but there was no difference between the groups at 12 months. An editorial noted that these results bring attention to the importance of selecting appropriate patients for DC, and engaging with patient surrogates regarding questions of quality of life (Shutter & Timmons, 2016).

The results of the RESCUEicp trial are more positive than those of the previous DECRA (Decompressive Craniectomy) trial. The DECRA trial was conducted in Australia, New Zealand, and Saudi Arabia and included 155 adults randomized to medical management or medical management plus DC (Cooper et al., 2011). After 6 months, the craniectomy group patients had worse outcomes as determined by the GOS-E as compared to the medical management group patients. Baseline group differences in pupil reactivity motivated a post-hoc adjustment and reanalysis of the data, which still did not find that DC was beneficial (Cooper et al., 2011). In this study, those patients who required neurosurgery to evacuate a mass lesion were excluded.

A retrospective study showed that DC has been performed on patients that would not meet inclusion criteria for the DECRA and RESCUEicp trials (Kramer et al., 2016). This calls into question whether the results from these two highly-cited clinical trials can be generalized to the typical population in which DC is performed. These criticisms, as well as findings of poor outcomes with DC in some studies (Tapper, Skrifvars, Kivisaari, Siironen, & Raj, 2017), contribute to the controversy around this invasive procedure.

Table 3. Recommendations regarding decompressive craniectomy

Guideline	Recommendations
BTF, 2017 (Carney et al., 2017)	A moderate-quality body of evidence suggests: “Bifrontal DC is not recommended to improve [6 month] outcomes... in severe TBI patients with diffuse injury (without mass lesions), and with ICP elevation to values >20 mm Hg for more than 15 min within a 1-h period that are refractory to first-tier therapies. However, this procedure has been demonstrated to reduce ICP and to minimize days in the ICU.”
American College of Surgeons, 2015 (Cryer et al., 2015)	Recommended as a tier 3 treatment, when, for example, sedation, ventricular drainage, hyperosmolar therapy, and neuromuscular paralysis have failed or are limited by development of side effects.
JTS CPG, 2017 (McCafferty et al., 2017)	“Surgical decompression, or craniectomy, should be strongly considered following penetrating combat brain trauma.”

Abbreviations: BTF, Brain Trauma Foundation; JTS CPG, clinical practice guideline, Joint Trauma System Clinical Practice Guideline for Management of Patients with Severe Head Trauma; ICP, intracranial pressure.

A recent systematic review and meta-analysis included DECRA, RESCUEicp, two additional randomized trials, (Qiu et al., 2009; Taylor et al., 2001) and several retrospective and observational studies, for a total of 10 studies (Zhang et al., 2017). The authors concluded that

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mortality was reduced with DC as compared to medical management, but that no significant difference between groups was found for functional outcomes (dichotomized Glasgow Outcome Scale or GOS-E). Among those who had DC within 36 hrs of injury, DC did improve functional outcomes as compared to medical management. The authors noted that complications occurred twice as often in the DC group, which is consistent with previous findings of frequent complications (Honeybul & Ho, 2011; Zhang et al., 2017). Vedantam et al. recently found that DC patients with interhemispheric hygroma or younger age had an increased risk of shunt-dependent hydrocephalus (Vedantam, Yamal, Hwang, Robertson, & Gopinath, 2017).

Recommendations regarding DC are based on a small number of well-designed randomized controlled trials (Carney et al., 2017), and additional studies will help establish the risks and benefits of these interventions for different patient groups. Even for patients requiring surgical intervention to evacuate an intracranial hemorrhage or acute subdural hematoma, DC is not clearly superior to craniectomy (Jehan et al., 2017; Phan et al., 2017). Determination of whether an individual patient should undergo DC rests on clinical judgment and surrogate engagement.

SUMMARY**Targeted temperature management**

After several multi-center trials failed to show benefit for therapeutic hypothermia, (Andrews et al., 2015; Clifton et al., 2011; Maekawa et al., 2015), some current guidelines recommend managing temperatures of acute severe TBI patients at or slightly below normal (35-37 °C). (Cariou et al., 2017)

Hypertonic saline

Randomized controlled trials, meta-analyses, and retrospective studies show HTS is a safe and effective method of reducing ICP, (Sakellaridis et al., 2011) although mid-term and long-term outcome data is limited (Bulger et al., 2010). Some studies and meta-analyses show that HTS is superior to mannitol for ICP control, (Li & Yang, 2014; Rickard et al., 2014) but some show no difference between HTS and other hyperosmotic interventions (Berger-Pelleiter et al., 2016).

Decompressive craniectomy

Decompressive craniectomy is a highly invasive procedure and associated with significant risks (Honeybul & Ho, 2011). With few high-quality studies available, limited evidence demonstrates that decompressive craniectomy may not provide improved long-term outcomes in closed-head severe TBI (Shutter & Timmons, 2016).

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