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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 in the military healthcare system, which includes active-duty service members and some beneficiaries. Although severe TBIs constitute less than 1% of all TBIs in the military health system, (*DoD Numbers for Traumatic Brain Injury Worldwide: 2000-2014*, February 2015) 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 have 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, which can lead to significant morbidity and mortality. (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 between-site differences in clinical practice both lead to differences in outcomes that can obscure risks and benefits of interventions. 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

Therapeutic hypothermia

Therapeutic hypothermia is considered here as a mechanism for managing intracranial hypertension in severe TBI patients. We do not address fever suppression here. Pre-clinical studies suggest that therapeutic hypothermia 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.; Tang & Yenari) The approach typically involves cooling the body to 32-35 °C as quickly as possible after the injury by external cooling or with the use of intravascular closed-circuit cooling catheter systems, and maintaining the lowered temperature for more than 24 hrs. (Crossley et al., 2014) In severe TBI patients, brain temperatures are generally higher than core body temperatures. (Henker et al., 1998; Kirk et al., 2009; Rossi et al., 2001; Rumana et al., 1998) Under therapeutic hypothermia treatment, brain temperatures decline, but remain higher than body temperatures. (Henker et al.)

Table 1. Recommendations regarding therapeutic hypothermia

Guideline	Recommendations
BTF, 2007 (Brian Trauma Foundation et al., 2007)	Regarding prophylactic hypothermia, Class III evidence suggests decreased mortality risk when target temperature is maintained more than 48 h. No recommendations regarding therapeutic hypothermia.
American College of Surgeons, 2015 (Cryer et al., 2015)	Salvage therapy option, for use only after all other recommended options have failed
Tactical Combat Casualty Care Guidelines, 2014 (U.S. Army Institute of Surgical Research, 2014b)	Not included in recommendations.
JTS CPG, 2014 (U.S. Army Institute of Surgical Research, 2014a)	Not included in recommendations.
BTF Field Management Guidelines, 2005 (Knuth et al., 2005)	Not included in recommendations.

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

Controlled trials have provided inconsistent results regarding the efficacy of this intervention 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. (U.S. Army Institute of Surgical Research, 2014b) The Brain Trauma Foundation (BTF) guidelines published in 2007 state that Class III evidence (i.e., observational or retrospective studies, or flawed randomized controlled trials) suggests prophylactic hypothermia (used regardless of ICP for preventing fever) may decrease mortality risk. (Brian Trauma Foundation et al., 2007) 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)

A multi-site, randomized, controlled trial with 232 non-responsive patients tested the effect of hypothermia induction within 2.6 hrs of TBI in addition to standard care, as compared to standard care alone. Outcome favorability (e.g., morbidity or mortality) was not significantly different between the two groups, although critics have noted a potential weakness in the protocol. As patients were warmed back to normal temperature after a period of therapeutic hypothermia, when instances of elevated ICP occurred, the warming was continued, and critics have argued that warming should have been stopped in those cases. (Clifton et al., 2011) Complications including increased ICP episodes were higher in the hypothermia group.

Two multi-center randomized studies published in 2015 found similar results. Maekawa, et al. assessed 148 severe TBI patients at 6 months post-injury using the Glasgow Outcome Scale (GOS). The primary outcome was a dichotomized GOS in which good recovery or moderate disability were classified as favorable outcomes and severe disability, vegetative state, and death were classified as unfavorable outcomes. There was no significant difference in rates of favorable outcome between the hypothermia plus standard care and standard care only groups. (Maekawa et al., 2015) Subanalyses of data from the 2015 study by Maekawa, et al. showed that patients under 50 years with an evacuated mass lesion were found to benefit from hypothermia therapy, but among those with grade III diffuse injury, this intervention increased mortality. (Suehiro et al., 2015) Based in part on these findings, a prospective randomized multi-center trial of therapeutic moderate hypothermia for severe TBI patients undergoing craniotomy for evacuation of subdural hematomas has been initiated by the University of Texas, Houston. (ClinicalTrials.gov, 2015c)

Andrews et al. randomized 387 patients with elevated ICP to standard care or standard care plus hypothermia. A target temperature of 32 to 35°C was maintained at least 48 hours. The trial was halted early due to results suggesting the hypothermia treatment led to worse outcomes. Subanalyses did not show a significant effect due to age or other variables. (Andrews et al., 2015)

Single-center studies have shown more promising results. A randomized controlled trial by Zhao et al. compared normothermia with mild hypothermia (32.7 °C, N = 81). Results showed that more patients in the hypothermia group had a favorable recovery (good recovery or moderate disability on GOS). (Zhao et al., 2011) A randomized study of hypothermia in combination with ICP and cerebral perfusion pressure (ICP/CPP) or brain tissue oxygenation monitoring included 45 patients with severe TBI (GCS 4 to 8). Patients were divided into three arms: one, hypothermia with ICP/CPP monitoring; two, hypothermia with brain tissue oxygenation monitoring; and three, ICP/CPP monitoring only. Outcomes were time in ICU and a dichotomized GOS (as used in Maekawa et al., (2015) see above). The two hypothermia groups spent significantly more time in the ICU than the one non-hypothermia group, which had only ICP/CPP monitoring. Despite that, the hypothermia and brain tissue oxygenation monitoring group had a significantly higher rate of favorable outcome than either the hypothermia plus ICP/CPP monitoring group or the non-hypothermia group. (Lee et al., 2010) The differences

between the single-center and multi-center trial findings may be related to inconsistent management of blood pressure or fluid balance. (Marion & Regasa, 2014)

A meta-analysis by Crossley, et al. (Crossley et al., 2014) found that the positive results in these small trials outweighs the negative results in the larger trials, although this was published before the recent Andrews, et al. study. (Andrews et al., 2015) In 18 randomized controlled trials including 1,839 patients, mortality data showed a significantly reduced risk of death in hypothermia groups as compared to control groups. In 20 trials that included data on the incidence of poor outcome (defined as long-term disability, vegetative state, or death) the risk of poor outcome was significantly higher in control groups as compared to hypothermia groups. (Crossley et al., 2014) A non-significant increase in the risk of pneumonia was observed in the hypothermia groups. An older systematic review including 12 studies and 1,069 patients also found benefits for varied hypothermia protocols as compared to normothermia. (McIntyre et al.)

Overall, data from single-center studies are promising, but results from multi-site trials have failed to show improved outcomes with therapeutic hypothermia. Many factors contribute to results in severe TBI trials; more sophisticated cooling technology, longer hypothermia exposure, different target temperatures, or more close protocol monitoring may provide more conclusive results. (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 2007 BTF guidelines stated that there was insufficient evidence to recommend HTS for reducing elevated ICP in TBI. (Brian Trauma Foundation et al., 2007) The 2005 BTF Field Management Guidelines list HTS as an option for ICP management, indicating that the supporting data was of low or moderate quality. (Knuth et al., 2005) The 2014 Joint Trauma System Clinical Practice Guideline (CPG) for Management of Patients with Severe Head Trauma recommends using a bolus of (3%) HTS. (U.S. Army Institute of Surgical Research, 2014a) The American College of Surgeons recommends mannitol as an osmotic agent, and presents HTS as an option. (Cryer et al., 2015)

Two recent meta-analyses compared hypertonic saline to mannitol solutions for traumatic brain injury. Li et al. included six randomized controlled trials and one retrospective study with 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, with a pooled difference in means at 120 min of 4 mmHg ($p = .004$). Serum osmolarity data was available from three studies, and showed no differences between the HTS and mannitol arms. Rickard et al. included six randomized trials, five of which were also included by Li et al., with 171 patients and 599 episodes of raised ICP. No significant differences between HTS and mannitol were observed in ICP-lowering effectiveness, but a non-significant trend showed hypertonic saline lowering ICP more effectively (relative risk for ICP control 1.05, 95% confidence interval, 0.94 to 1.19). (Rickard et al., 2014) In Rickard et al., two studies used a saline/starch solution for the HTS arm, and one used sodium dextran. In Li et al., only one study used saline/dextran, all other HTS treatments used sodium chloride solutions. In the eight studies considered by the two meta-analyses, HTS concentrations ranged from 7.45% to 15%, volumes and sodium equivalents

varied in both fixed-dose protocols and by-weight protocols, and infusion times ranged from 5 min boluses to continuous infusions. Neither analysis subdivided the studies based on variations in HTS treatments, or performed other analysis to account for those variations. Variations in criteria for hyperosmolar interventions were not discussed in detail. 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.

An earlier meta-analysis examined the use of 23.4% HTS for various neuropathologies. The analysis identified four small retrospective TBI studies including a total of 78 patients. While HTS showed efficacy in reducing ICP, the studies were limited by their design and sample size. (Lazaridis et al., 2013)

Table 2. Recommendations regarding hypertonic saline (HTS)

Guideline	Recommendations
BTF, 2007 (Brian Trauma Foundation et al., 2007)	When hyperosmolar therapy is indicated, mannitol is recommended (this even though there is no Class I evidence to support the therapeutic efficacy of mannitol).
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.
Tactical Combat Casualty Care Guidelines, 2014 (U.S. Army Institute of Surgical Research, 2014b)	If unilateral pupillary dilation accompanied by a decreased level of consciousness, then deliver 250 cc of 3% or 5% HTS bolus.
JTS CPG, 2014 (U.S. Army Institute of Surgical Research, 2014a)	If elevated ICP and GCS <9, asymmetric motor posturing, unilateral or bilateral fixed, dilated pupil, or deteriorating level of consciousness, then initiate following protocol: 3% HTS delivered as a bolus of 250 cc over 10-15 min, followed by 3% HTS at 50 cc/hr. While awaiting transport, monitor serum sodium hourly. If sodium < 150 mEq/L, bolus 150 cc 3% HTS over 1 hr, then resume 50 cc/hr infusion. If sodium 150-154 mEq/L, increase infusion of 3% HTS to 10 cc/hr. If sodium 155-160 mEq/L, continue 3% HTS at 50 cc/hr. If sodium > 160 mEq/L, pause infusion and re-check in 1 hr.
BTF Field Management Guidelines, 2005 (Knuth et al., 2005)	Option for ICP management, HTS bolus, no concentration or volume specified. Guideline for fluid resuscitation states that HTS is safe in doses < 500 cc.

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; GCS, Glasgow coma scale.

Two prospective studies have investigated osmotic agents by randomizing by elevated ICP episode rather than by patient. The first study by Sakellaridis, et al. compared 20% mannitol to 15% HTS in 29 patients with 199 elevated ICP episodes. No significant differences were observed in treatment effect or duration on ICP. (Sakellaridis et al., 2011) The second study compared 8.4% sodium bicarbonate to 5% HTS. In 11 patients who underwent 20 elevated ICP episodes, no difference was observed in treatment effect 60 min after infusion, but at 150 min the bicarbonate group had lower ICP. (Bourdeaux & Brown, 2011)

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 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, but may not be superior to mannitol, sodium lactate (Ichai et al., 2013), or other osmotic agents. (Bourdeaux & Brown, 2011) 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. Risks include hypernatremia. (Kolmodin et al., 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 and the Tactical Combat Casualty Care Guidelines, recommend 3% HTS, (U.S. Army Institute of Surgical Research, 2014a, 2014b) 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 et al., 2015) 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) Neither the 2007 BTF guidelines nor the 2014 Joint Trauma System CPG include recommendations regarding DC.

Two randomized controlled trials comparing DC to non-surgical interventions have been published and only one included an adult population. (Cooper et al., 2011; Taylor et al., 2001) The Decompressive Craniectomy (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 Extended Glasgow Outcomes Scale (GOS-E) as compared to the medical management group patients. However, 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.

Table 3. Recommendations regarding decompressive crainiectomy

Guideline	Recommendations
BTF, 2007 (Brian Trauma Foundation et al., 2007)	Not included in recommendations.
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.
Tactical Combat Casualty Care Guidelines, 2014 (U.S. Army Institute of Surgical Research, 2014b)	Not included in recommendations.
JTS CPG, 2014 (U.S. Army Institute of Surgical Research, 2014a)	Not included in recommendations.
BTF Field Management Guidelines, 2005 (Knuth et al., 2005)	Not included in recommendations.

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

An ongoing international randomized controlled trial, Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intracranial Pressure (RESCUEicp), had a recruitment goal of 400 patients, but results have not yet been published. (Hutchinson et al., 2006) A 2012 meta-analysis that included retrospective and observational studies showed that DC is effective at reducing ICP for 48 hrs following surgery, but longer-term outcomes were not reported. (Bor-Seng-Shu et al., 2012)

A recent retrospective cohort study by Kramer et al. included 644 consecutive critical care patients with severe TBI at a Canadian university hospital, of whom 51 (8%) underwent DC. (Kramer et al., 2016) Most of those patients had radiographic or clinical evidence of uncal herniation or midline shift. In the majority of cases (34; 67%) the DC was a part of surgery done to evacuate a post-traumatic hematoma or contusion. For 8 patients (16%) neurological or radiographic deterioration led to the DC, and for 9 patients (18%) there was intracranial hypertension refractory to medical management, usually associated with worsening midline shift or signs of uncal herniation. Of the 51 individuals who had DC, 10% and 16% would have met inclusion criteria for the DECRA and RESCUEicp trials. The results of Kramer et al. call into question whether the results from these two clinical trials can be generalized to the typical population in which DC is performed.

An earlier retrospective analysis of 164 severe TBI patients treated with DC showed frequent post-surgical complications including subdural effusion and seizures, which were present in 49% and 22% of patients, respectively. (Honeybul & Ho, 2011)

Recommendations regarding DC are based on only one or two Class I studies (i.e., well-designed randomized controlled trials (Brian Trauma Foundation et al., 2007)), and additional trials will help establish the risks and benefits of these interventions for different patient groups. Clinical judgment remains the mainstay for determining whether individual patients with refractory ICP should undergo DC.

DISCUSSION

Therapeutic hypothermia

Data on therapeutic hypothermia are not consistent, but a recent meta-analysis of randomized controlled trials suggests that it is a safe and effective way to reduce ICP and improves outcomes in severe traumatic brain injury as compared to normothermia. (Crossley et al., 2014)

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) HTS has demonstrated superiority over mannitol for ICP control in some randomized controlled trials and in a recent meta-analysis. (Li & Yang, 2014; Rickard et al., 2014)

Decompressive craniectomy

Decompressive craniectomy is a highly invasive procedure and associated with significant risks. (Honeybul & Ho, 2011) With only two high-quality studies available, limited evidence demonstrates that decompressive craniectomy is not superior to non-surgical management of ICP in closed-head severe TBI. (Cooper et al., 2011)

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