

Original Article

Hypothermia for severe traumatic brain injury in adults: Recent lessons from randomized controlled trials

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Abstract

Background: Traumatic brain injury (TBI) is a worldwide health concern associated with significant morbidity and mortality. In the United States, severe TBI is managed according to recommendations set forth in 2007 by the Brain Trauma Foundation (BTF), which were based on relatively low quality clinical trials. These guidelines prescribed the use of hypothermia for the management of TBI. Several randomized controlled trials (RCTs) of hypothermia for TBI have since been conducted. Despite this new literature, there is ongoing controversy surrounding the use of hypothermia for the management of severe TBI.

Methods: We searched the PubMed database for all RCTs of hypothermia for TBI since 2007 with the intent to review the methodology outcomes of these trials. Furthermore, we aimed to develop evidence-based, expert opinions based on these recent studies.

Results: We identified 8 RCTs of therapeutic hypothermia published since 2007 that focused on changes in neurologic outcomes or mortality in patients with severe TBI. The majority of these trials did not identify improvement with the use of hypothermia, though there were subgroups of patients that may have benefited from hypothermia. Differences in methodology prevented direct comparison between studies.

Conclusions: A growing body of literature disfavors the use of hypothermia for the management of severe TBI. In general, empiric hypothermia for severe TBI should be avoided. However, based on the results of recent trials, there may be some patients, such as those in Asian centers or with focal neurologic injury, who may benefit from hypothermia.

Key Words: Critical care, expert opinion, hypothermia, traumatic brain injury, TBI

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INTRODUCTION

Traumatic brain injury (TBI), broadly defined as “an alteration in brain function, or other evidence of brain pathology, caused by an external force,”^[15] is a global health concern which is expected to become the leading international cause of morbidity and mortality by the year 2020.^[10] Worldwide, the majority of TBIs occur

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as a result of motor vehicle collisions, most frequently involving males and people aged 15–24 years old. In the United States, as the population has aged, falls have become the most common cause of TBI. In terms of US healthcare utilization, there are nearly two million annual TBI-related visits to emergency departments, resulting in more than 275,000 hospitalizations.^[25] The long-term implications of TBI often remain unclear, however, patients who recover from the initial cerebral injury are likely at risk of developing chronic, progressive, neurocognitive, and physical impairment.^[19] Regrettably, despite increased awareness of the prevalence of TBI, mortality rates and neurologic outcomes have not measurably improved over the past two decades. Given the significant social and economic costs of TBI, it is imperative that high quality care be delivered in a timely fashion to minimize and mitigate potential sequelae of injury. This is especially true in patients with severe TBI.

Severe TBI is most frequently defined by a score of less than or equal to 8 on the Glasgow Coma Scale,^[8] and is managed according to one of the many different guidelines proposed by international societies. Given the disparate approaches toward severe TBI treatment and recognition of the increasing incidence, TBI societies have been called to revise their protocols toward a standard, simplified approach to be endorsed under the umbrella of World Federation of Neurosurgical Societies.^[7] In general, in the US, severe TBI is managed according to recommendations of the Brain Trauma Foundation (BTF), most recently published in 2007. These guidelines encourage first responders and intensive care providers to provide rapid cardiopulmonary resuscitation and close hemodynamic monitoring to allow adequate pharmacologic intervention to optimize cerebral perfusion, monitor changes in neurologic function, aggressively treat changes in intracranial pressure (ICP). Ultimately, the BTF guidelines are aimed at ensuring that there is adequate oxygen delivery to the brain while ramifications from iatrogenic interventions are limited. Unfortunately, the majority of these recommendations are based on low or only moderate quality evidence.^[3] Furthermore, many commonly used interventions to treat severe TBI (e.g., mannitol, hyperventilation, and barbiturate therapy) have not been shown to be effective at reducing the risk of death.^[28,23,18]

The BTF guidelines do not provide definitive instructions for the use or avoidance of induced hypothermia for patients with severe TBI. Rather, similar to the remainder of the BTF stipulations, the recommendations pertaining to hypothermia are based on relatively low quality data and conflicting results of prior clinical trials. However, hypothermia has remained appealing because it confers several theoretical benefits in severe TBI, including the ability to reduce ICP, increase cerebral perfusion pressure, reduce cerebral oxygen consumption, reduce concentrations of excitatory

neurotransmitters and inflammatory mediators in cerebrospinal fluid, and possibly maintain the integrity of the blood–brain barrier. Early trials in the 1990s showed promising results with employing hypothermia, though these were not always sustained in later studies.^[2,14,27] However, as various other interventional approaches faltered, investigators are returning to the experimental use of hypothermia in an effort to improve outcomes following severe TBI.

Given the discordant findings of available evidence at the time of the creation of the 2007 guidelines, the BTF authors performed a meta-analysis of randomized, controlled trials of moderate quality (there were no good quality trials), in an effort to create meaningful recommendations. Ultimately, their meta-analysis determined that the use of prophylactic hypothermia was not associated with a significant improvement in mortality, and thus cannot be recommended as a routine component of care for severe TBI. However, on secondary analysis, hypothermia maintained for more than 48 hours was associated with lower risk of death, an observation that was independent of the target temperature or the rate of re-warming. Furthermore, prophylactic hypothermia was associated with improved neurologic outcome, particularly when the target temperature was 32–33°C or 33–35°C. For both mortality and neurologic outcome scores, hypothermia was associated with better results when examining studies performed in single institutions rather than multicenter studies. The presence of hypothermia at the time of admission may have confounded the interpretation in analyzed trials, in part due to rather poorly understood physiologic effects of rewarming or continued hypothermia, and the possibility that hypothermia on admission may lead to sedation and therefore a relatively low Glasgow Coma Scale score despite the presence of less serious injuries compared to normothermic patients with the same score.^[3] Two subsequent meta-analyses^[17,24] conducted shortly after the publication of the BTF guidelines, but which included additional trials not included in the BTF analysis, concurred that hypothermia did not significantly reduce mortality or neurologic outcome. However, Peterson's 2008 meta-analysis identified a durable improvement in mortality when hypothermia was continued for at least 48 hours, and this study found that hypothermia led to a statistically significant improvement in trials that combined hypothermia with barbiturate therapy. Furthermore, hypothermia significantly reduced mortality in trials that assessed long-term follow-up (1–2 years). More importantly, both of these analyses seemed to corroborate the conclusion that poor quality trials had created a body of literature that erroneously supported the use of hypothermia, as neither mortality nor neurologic outcome was improved when analyzing “high” quality trials only.^[17,23]

The paucity of high quality studies and the observation that hypothermia may be associated with improved outcomes depending on duration, target temperature, rewarming rate, and time to initiation as well as center of the respective study, led to uncertainty regarding the significance of the 2007 guidelines. Subsequently, several RCTs of hypothermia for TBI have since been conducted, but these have also not been able to provide a basis for consensus.

MATERIALS AND METHODS

This review of recent trials and updated meta-analyses provides insight into the ongoing uncertainty surrounding the use of hypothermia for severe TBI. Expert opinions at the end of this review inform and provide recommendations for clinicians. Publications were selected for inclusion by searching the PubMed database in April 2016 using the following search terms: “(hypothermia) AND (traumatic brain injury),” limited to RCTs, meta-analyses, or systematic reviews conducted on adult (age more than 19 years) patients which were available in English. Studies published prior to 2007 were omitted from further review, as they had been analyzed within the aforementioned BTF guidelines and subsequent systematic reviews. This search strategy yielded 27 publications of interest. After reviewing the abstracts, we excluded feasibility studies, protocol descriptions of ongoing trials, or those performing post-hoc analysis of previously published trials of hypothermia. We also excluded those that involved pediatric populations, did not focus on TBI outcomes, or did not publish mortality or neurologic function outcomes. This approach excluded 20 of the original 27 publications; the remaining 7 manuscripts were included in the study. Review of the respective references of these studies identified one additional trial which was also appropriate for inclusion.^[26] (This trial had not been included in the initial search strategy as it used historical controls to compare contemporary interventions. However, given that this was a single center study with a long history of use of hypothermia for treatment of severe TBI, it was considered appropriate for inclusion). Brief summaries of the findings, merits, and limitations of these 8 studies are included here.

RESULTS AND DISCUSSION

Review of randomized controlled trials of hypothermia for traumatic brain injury

Following the publication of the aforementioned meta-analyses, two trials in 2009 were performed at single center institutions that had previous experience with hypothermia for TBI. Both trials were conducted in an effort to precisely determine the influence of

hypothermia within specific contexts. The first of these trials, conducted at a center in China which had routinely used 48–72 hours of induced hypothermia to 33°C from 1994 to 1999, investigated the impact of more moderate cooling in similar patients enrolled after the year 2000. Hypothermia in the more recent study population was induced for 48–72 hours, though only to 35°C. The authors found that mean ICP did not significantly differ between the groups, though CRP levels were lower in the 35°C group. Complication rates were comparable in both the groups, leading the authors to conclude that more moderate hypothermia was equally effective for ICP control and may be associated with less inflammatory response. Nevertheless, it is hard to interpret outcome data in these patients given the potential for changes in other aspects of critical care treatment (e.g. early goal-directed sepsis treatment) during the time between each group’s enrolment.^[25] Elsewhere, US investigators conducted an RCT of hypothermia versus normothermia with the intent to limit any potential systemic impact of hypothermia by using a specifically designed “cooling cap” for “local cerebral hypothermia” to a goal of 33°C for a duration of 24 hours. Unfortunately, that particular “cooling cap” did not yield a significant difference between cerebral temperature and bladder temperature (taken as a surrogate for systemic temperature), and there were no differences in mortality or neurologic outcome between the groups.^[9]

In 2001, the NABISH I trial identified a possible trend toward improved outcome in patients who were hypothermic at the time of admission when treated with ongoing hypothermia. The fact that a higher rate of hypotension was observed in the hypothermic group in NABISH I was thought to possibly confound the findings, preventing the identification of a durable improvement in outcome.^[4] These results led to the hypothesis that very early initiation of hypothermia may lead to a statistically significant improvement in outcome for patients with severe TBI. Thus, NABISH II, an international, multicenter RCT, was performed in an effort to induce hypothermia in selected patients in close temporal proximity to the time of their injury. Published in 2011, this trial enrolled patients within hours of injury, cooling patients in the hypothermic group to a goal of 33°C for 48 hours. Ultimately, the trial was terminated early for futility after identifying neither significant difference in neurologic outcome between the groups (the primary outcome) nor difference in mortality between the groups. Unique to this study, patients in the hypothermia group displayed higher ICPs than patients in the normothermia group, a finding the authors attributed to aggressive attempts to limit the periods of hypotension. Of particular interest, patients who underwent surgical removal of intracranial hematomas and also received hypothermic treatment had fewer poor outcomes when compared to their normothermic counterparts. On the

other hand, patients with more diffuse injury who were treated with hypothermia had worse outcomes than those in the normothermic group, even though this was not significant. Overall, patients with rather focal hematomas amenable to surgical intervention fared significantly better than patients displaying diffuse injury, suggesting that the pathophysiology associated with each condition may reflect a difference in injury pattern or predispose toward differing responses to hypothermia treatment.^[5]

These findings are in contrast to another Chinese RCT also published in 2011 that determined that hypothermia led to favorable neurologic outcome. In this study, hypothermia was induced within hours of enrolment (though not necessarily within hours of injury) to a goal of 32–33°C for at least 72 hours. However, this was a relatively small cohort study (81 patients) with the primary objective to examine mean glucose and lactate levels between hypothermic and eutermic groups rather than to identify neurologic or mortality benefit from hypothermia. Both laboratory parameters were found to be lower in the hypothermic group – a finding that is more likely to be spurious.^[29] Furthermore, it is hard to generalize outcomes from this single center study to other populations because several Chinese trials have been able to demonstrate improved outcomes with hypothermia, however, these results have not been able to be replicated in subsequent US or multinational multicenter studies. In fact, a 2014 Chinese meta-analysis that analyzed retrospective and cross-sectional studies in addition to prospective trials found an increase in mortality in US patients, however, a decrease in mortality in Asian patients treated with hypothermia. It is worth noting that when all the studies were included no difference in mortality or neurologic outcome between hypothermia or normothermia treatment strategies was found.^[12] Given the wide discrepancies in the methodologies of studies included in this analysis, it remains difficult to find convincing support that reflects a differing outcome by nationality.

More recently, two relevant trials (BHYP0 and EuroTherm3235) were published in 2015 and have added to the emerging concerns surrounding hypothermia for TBI. BHYP0 was a multicenter Japanese trial in which patients were rapidly cooled (32–34°C) or kept eutermic (35.5–37°C) within 6 hours of injury. This trial was notable for a relatively long duration of cooling of at least 72 hours and a slow rewarming speed (<1°C/day). Only 150 of a planned 300 patients were enrolled from 2002 to 2008; the trial was stopped early due to a combination of low enrolment and likely futility. There were no significant differences in neurologic outcome (the primary outcome of interest) or mortality (secondary outcome) between groups, even though the trial was relatively underpowered.^[13] The other trial, EuroTherm3235, was an international multicenter RCT which also failed to identify a benefit

for treatment of severe TBI with hypothermia. In this study, patients were enrolled up to 10 days after TBI who had developed intracranial hypertension and had failed basic, conventional (“Stage 1”) attempts to control ICP. Patients were randomized to either standard care or hypothermia to 32–35°C, and could then receive further treatment termed “Stage 2” (mannitol, hypertonic saline, inotropes) or, if that option failed transition to “Stage 3” treatment (barbiturates or decompressive craniectomy), if necessary. Unfortunately, patients in the hypothermia group had worse neurologic outcomes and a greater risk of death at interim analysis; hence, the trial was stopped early. It is conceivable that the deleterious outcome observed in the hypothermia arm of the study may actually be attributable to the Stage 2 or 3 treatments, which were not controlled for between groups, rather than being the result of the hypothermia itself. Specifically, barbiturate therapy may have added a component of metabolic neuroprotection, which conferred neurologic outcome or survival advantage (and was given to the hypothermic group less frequently).^[1]

Meta-analyses of these results in addition to those of prior well-conducted trials have yet to be performed. As of now, a 2014 systematic review by Crossley found that treatment with hypothermia in TBI patients is associated with a reduced risk of mortality or poor outcome. This finding is in direct contradiction to the results of most of the prior meta-analyses, and thus may be perceived with some skepticism. It must be noted that Crossley’s review contained a relatively low number of well-conducted trials, and hence could not exclude the possibility of bias affecting the results.^[6] Thus, it remains to be seen how the results of BHYP0 and EuroTherm3235 will be reflected in future meta-analyses because they seem in our opinion to add to the weight of well-conducted trials which do not favor hypothermia.

Ultimately, well-designed RCTs with therapeutic hypothermia below 35°C for severe TBI have mostly failed to show a significant improvement in mortality rates. It is important to note that hyperthermia is significantly associated with poor outcomes, and thus temperature control remains a critical component of neurointensive care. Theoretically, modest cooling (i.e., 35–37°C) may provide some of the putative neuroprotective effects of hypothermia while avoiding sequelae with a negative impact on outcome. Unfortunately, as of now there are no RCTs evaluating the effect of modest cooling compared to normothermia.^[20] The PARITY study investigating the effect of intravenous acetaminophen on temperature in TBI has recently been completed and may provide results that are consistent with very modest hypothermia for TBI management.^[21] Finally, there are ongoing trials (POLAR and LTH-1) designed to investigate the impact of sustained hypothermia for at least 3 or 5 days, respectively, which may help to clarify the dilemma surrounding the

proper duration of therapeutic hypothermia for patients with severe TBI.^[16,11]

Expert opinions

As there is a lack of consensus among experts regarding the use of hypothermia for the management of severe TBI, the authors advocate that before considering induction of hypothermia for severe TBI, the following viewpoints should be taken into account:

Dr. Clark Chen, Department of Neurosurgery; University of California San Diego (USA): Hypothermia should be avoided when treating severe TBI.

Hypothermia for severe TBI is an attractive therapy, but has repeatedly failed to meet the expectations of clinicians hoping to improve a patient's chance of death or neurologic outcome. The controversy surrounding the use of hypothermia is driven by the occasional report of clinical benefit of cooling in one trial versus harm in another. However, it is of utmost importance to recognize that there has yet to be a well-designed clinical trial that definitively favors the use of hypothermia. The large, well-conducted trials published within the last 5 years, specifically NABISH II, BHYP0, and EuroTherm3235, have all convincingly proven that moderate hypothermia is associated with deterioration in neurologic outcomes and an increase in mortality. Operating on the basis of these results, therapeutic hypothermia for the empiric treatment of severe TBI should be reserved for experimental use only, pending results from forthcoming studies.

Hypothermia on admission after TBI has been shown to be a predictor of poor outcome. In a retrospective cohort study of 110,000 admissions to 384 ICUs across UK and Australasia with stroke, TBI, or intracranial infection, peak temperature below 37°C within the first 24 hours of admission after TBI was associated with an increased risk of death compared to normothermia.^[22] It should be borne in mind that presenting temperature is a different entity to therapeutic hypothermia, which may be related to multiple extracranial factors such as open body cavities, hemorrhage, circulatory collapse, and prolonged environmental exposure, however, again the data surrounding hypothermia suggests a negative outcome.

Sometimes we do things in medicine not because it works well but because there are frankly no better options. Hypothermia as treatment for severe traumatic brain injury (TBI) patients is a case in point. It is a fact that the four well-designed, albeit admittedly imperfect, RCTs (NABISH I, NABISH II, B-HYPO, Eurotherm3235) summing to >1100 enrolled patients showed that hypothermia is not effective in improving the clinical outcome of severe TBI patients when the trial results were assessed based on the predetermined statistical measures and primary end-points. No amount of post-hoc analysis, meta-analysis, statistical manipulation,

or intellectual rationalization changes this fact. It is also a fact that RCTs are designed to yield evidence when the outcomes are strictly interpreted based on the primary end-points. While it is acceptable to use post-hoc analysis as means of hypothesis generation, it is not acceptable to suggest that these exploratory observations are conclusive. When evaluated in this context, the conclusion from the available RCTs is necessarily that treatment with hypothermia do not significantly alter the clinical outcome of severe TBI patients. That said, nothing modern medicine offers alter the clinical course of severe TBI patients. In this context, hypothermia remains a treatment option. There will always be patients who show remarkable recovery from a severe TBI, hypothermia, or not. The fundamental question in the modern era of health care cost-containment is how many well-designed (and necessarily imperfect) RCTs will it take to divert financial resources from an ineffectual treatment into another societal need? How many prayers must go unanswered before a faith is abandoned?

Dr. Jonathan Hyam, National Hospital for Neurology and Neurosurgery, Queen Square; London (UK): Hypothermia is an acceptable component of care for the patients with severe TBI.

Despite the high morbidity and mortality associated with TBI, the number of therapies available to the neurotraumatologist is limited and their indications for optimal use unclear. As such, therapeutic hypothermia should not be dismissed without strong evidence against its place within the medical armamentarium.

The results of NABISH II, BHYP0, and EuroTherm3235 have all seemingly added to the growing consensus that use of hypothermia for the patient who has suffered severe TBI is harmful. However, each of these trials (and their predecessors) have sought to assess changes in mortality or neurologic outcome using disparate approaches to the management of severe TBI, including the implementation of hypothermia. Specifically, the questions of when to induce hypothermia, how cold to target, and long to cool the patient have never been precisely answered [Table 1]. While NABISH II was stopped early for futility, it did in fact suggest that hypothermia may be helpful for patients with surgically resectable lesions. Certainly, a diffuse injury must confer a different pathophysiological response to hypothermia, corresponding with worse outcomes, and thus it is unfair to include their outcomes with those patients with more focal injuries. Furthermore, NABISH II was adequately powered to examine the empiric use of hypothermia within hours of injury (as opposed to the significantly underpowered BHYP0 trial), whereas EuroTherm3235 enrolled patients up to 10 days after injury. Thus, the results of these three studies together should be interpreted such that hypothermia should not be delayed until after intracranial hypertension has

occurred, but rather implemented early if it is going to be used, especially with patients who are undergoing (or have undergone) surgical intervention. Ultimately, until an adequately powered, well-designed trial demonstrates the risk of moderate early hypothermia, it should be considered a viable option for the management of patients with severe TBI.

Furthermore, there are specific clinical scenarios in which therapeutic hypothermia can tip the balance toward the patient and clinician. An example is in intractably raised ICP. In a patient who has raised ICP despite basic therapy (including removal of any evacuable mass lesions, sedation with targeted pCO₂ control, etc.) the advanced therapeutic options become much narrower.

EuroTherm 3235 concluded that the hypothermia group's neurological outcome was poorer than the control group when patients with an ICP >20 mmHg for more than 5 minutes were entered into the trial and indeed the study was stopped prematurely. Although an excellently executed trial, there are several limitations, many of which the authors acknowledge. First, therapeutic hypothermia was used alone in the intervention group as a second-line of therapy, without "Stage 2" therapy,

i.e., hyperosmolar agents/inotropes, whereas the control group received these as a second-line of therapy. Second, in the hypothermia group there were far fewer first occurrences of raised ICP, suggesting a beneficial effect at least on ICP. As a result of this, fewer hypothermia patients received the benefits of hyperosmolar therapy.

The authors acknowledge that the study did not address patients with intractable raised ICP resistant to stage 2 therapy. Significantly fewer patients in the hypothermia group received barbiturates. The neuroprotective properties of barbiturate therapy may, therefore, have skewed the neurological outcome results away from the hypothermia group.

Therapeutic hypothermia should therefore be considered as part of a multimodal treatment in addition to hyperosmolar agents and inotropes, not as a substitute for them. If control over ICP is not obtained after basic interventions, there is a danger of progression in a vicious cycle of high pressure, vascular and parenchymal compression, ischemia and further increases in ICP/swelling. If this cycle can be interrupted in a timely fashion with a combination of available second-line therapies, this could avoid progression toward the most

Table 1: Major randomized controlled trials in hypothermia for severe traumatic brain injury

Author/Year	Number of Participants	Participants	Interventions	Outcomes/Comments
Clifton ^[4] /2001 (NABISH I)	N=387	16 to 65 years of age with coma after sustaining closed head	hypothermia (body temperature, 33°C), which was initiated within 6 hours after injury and maintained for 48 hours=113	Outcomes were same - disability, a vegetative state, or death of 57% in both the groups. Mortality of 28% in hypothermia group 27% in the normothermia group Hypothermia group: more hospital days with complications, less intracranial hypertension
Clifton ^[5] /2011 (NABISH II)	N=232	Randomized, multicenter clinical trial, non-penetrating brain injury who were aged 16-45. Very early hypothermia induction in patients with severe brain injury	Enrolled within 2-5 h of injury hypothermia, n=119 (33°C for 48 hours), normothermia, n=113	The primary outcome was the Glasgow outcome scale score at 6 months. No utility of hypothermia as a primary neuroprotective strategy stopped early for futility, hypothermia may be helpful for patients with surgically resectable lesions
Maekawa ^[13] /2015 (BHYP0)	N=148	severe TBI (GCS 4-8)	2:1 randomization. Prolonged therapeutic hypothermia (32-34°C, n=98) or fever control (35.5-37°C, n=50). ≥72 h and slowly rewarmed at a rate of <1°C/day	No improvement in neurological outcomes or mortality
Andrews ^[1] /2015 (Eurotherm3235)	N=387	International randomized, multicenter clinical trial. ICP >20 mmHg.	Stepwise methodology: stage 1 (mechanical ventilation and sedation), 2 (osmotherapy), and 3 (barbiturates and decompressive craniectomy)	Recruitment stopped due to safety concerns. Worse outcome in the hypothermia group by E-GOS enrolled patients up to 10 days after injury

aggressive therapies such as decompressive craniectomy and the risk of the significant adverse effects associated with this intervention.

Recommendations

The lack of available high quality evidence is a reflection of the challenges associated with treating severe TBI. Pragmatic study designs have led to discrepancies in approaches to hypothermia implementation and toward goals to be achieved. This applies to the question as to when (e.g., within hours of injury or within 10 days of injury), over what period (e.g., 24, 48, 72, or more hours), or to what target value (ICP) or outcome measure (e.g., improvement in neurologic outcome, or reduction in mortality) hypothermia should be induced.

EXECUTIVE SUMMARY

Well-designed studies which have been rigorously executed are only few in number. However, those that were incorporated in the 2007 BTF guidelines or have been published since generally do not favor use of hypothermia for severe TBI. Specific subgroups of patients, such as those with focal hematomas that can be surgically removed or perhaps patients treated in Asian centers, may benefit from moderate (32–35°C) hypothermia, if such treatment is implemented early and maintained for at least 48 hours. However, this remains speculative at this point. At present, neurointensivists should keep temperature control at their focus with the intent to avoid hyperthermia while limiting hypothermia unless ICP is exceedingly difficult to control.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Andrews PJ, Sinclair HL, Rodriguez A, Harris BA, Battison CG, Rhodes JK, et al. Hypothermia for intracranial hypertension after traumatic brain injury. *N Engl J Med* 2015;373:2403-12.
- Arrich J, Holzer M, Havel C, Mullner M, Herkner H. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. *Cochrane Database Syst Rev* 2012;9:CD004128.
- Bratton SL, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Hartl R, et al. Guidelines for the management of severe traumatic brain injury. *J Neurotrauma* 2007;24:S1-106.
- Clifton GL, Miller ER, Choi SC, Levin HS, McCauley S, Smith KR Jr, et al. Lack of effect of induction of hypothermia after acute brain injury. *N Engl J Med* 2001;344:556-63.
- Clifton GL, Valadka A, Zygun D, Coffey CS, Drever P, Fourwinds S, et al. Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): A randomised trial. *Lancet Neurol* 2011;10:131-9.
- Crossley S, Reid J, McLatchie R, Hayton J, Clark C, MacDougall M, et al. A systematic review of therapeutic hypothermia for adult patients following traumatic brain injury. *Crit Care* 2014;18:R75.
- El-Fiki M. The need for WFNS standard simplified guidelines for the management of severe traumatic brain injuries. *World Neurosurg* 2011;75:458-61.
- Ghajar J. Traumatic brain injury. *Lancet* 2000;356:932-9.
- Harris OA, Muh CR, Surlles MC, Pan Y, Rozycki G, Macleod J, et al. Discrete cerebral hypothermia in the management of traumatic brain injury: A randomized controlled trial. *J Neurosurg* 2009;110:1256-64.
- Hyder AA, Wunderlich CA, Puvanachandra P, Gururaj G, Kobusingye OC. The impact of traumatic brain injuries: A global perspective. *NeuroRehabilitation*. 2008;22:341-53.
- Lei J, Gao G, Mao Q, Feng J, Wang L, You W, et al. Rationale, methodology, and implementation of a nationwide multicenter randomized controlled trial of long-term mild hypothermia for severe traumatic brain injury (the LTH-I trial). *Contemp Clin Trials* 2015;40:9-14.
- Li P, Yang C. Moderate hypothermia treatment in adult patients with severe traumatic brain injury: A meta-analysis. *Brain Inj* 2014;28:1036-41.
- Maekawa T, Yamashita S, Nagao S, Hayashi N, Ohashi Y. Brain-Hypothermia Study Group. Prolonged mild therapeutic hypothermia versus fever control with tight hemodynamic monitoring and slow rewarming in patients with severe traumatic brain injury: A randomized controlled trial. *J Neurotrauma* 2015;32:422-9.
- Marion DW, Penrod LE, Kelsey SF, Obrist WD, Kochanek PM, Palmer AM, et al. Treatment of traumatic brain injury with moderate hypothermia. *N Engl J Med* 1997;336:540-6.
- Menon DK, Schwab K, Wright DW, Maas AI, Demographics and Clinical Assessment Working Group of the International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health. Position statement: Definition of traumatic brain injury. *Arch Phys Med Rehabil* 2010;91:1637-40.
- Nichol A, Gantner D, Presneill J, Murray L, Trapani T, Bernard S, et al. Protocol for a multicentre randomised controlled trial of early and sustained prophylactic hypothermia in the management of traumatic brain injury. *Crit Care Resusc* 2015;17:92-100.
- Peterson K, Carson S, Carney N. Hypothermia treatment for traumatic brain injury: A systematic review and meta-analysis. *J Neurotrauma* 2008;25:62-71.
- Roberts I, Sydenham E. Barbiturates for acute traumatic brain injury. *Cochrane Database Sys Rev* 2012;12:CD000033.
- Roozenbeek B, Maas AI, Menon DK. Changing patterns in the epidemiology of traumatic brain injury. *Nat Rev Neurol* 2013;9:231-6.
- Saxena M, Andrews PJ, Cheng A, Deol K, Hammond N. Modest cooling therapies (35-37.5) for traumatic brain injury. *Cochrane Database Sys Rev* 2014;8:CD006811.
- Saxena MK. The paracetamol after traumatic brain injury study (PARITY). Details available at <https://clinicaltrials.gov/ct2/show/NCT01231139>. [Last accessed on 2014 Oct 26].
- Saxena M, Young P, Pilcher D, Bailey M, Harrison D, Bellomo R, et al. Early temperature and mortality in critically ill patients with acute neurological diseases: Trauma and stroke differ from infection. *Intensive Care Med* 2015;41:823-32.
- Schierhout G, Roberts I. Hyperventilation therapy for acute traumatic brain injury. *Cochrane Database Sys Rev* 2000;2:CD000566.
- Sydenham E, Roberts I, Alderson P. Hypothermia for traumatic head injury. *Cochrane Database Sys Rev* 2009;2:CD001048.
- Taylor CA, Greenspan AI, Xu L, Kresnow M. Comparability of national estimates for traumatic brain injury-related medical encounters. *J Head Trauma Rehabil* 2015;30:150-9.
- Tokutomi T, Miyagi T, Takeuchi Y, Karukaya T, Katsuki H, Shigemori M. Effect of 35 degrees C hypothermia on intracranial pressure and clinical outcome in patients with severe traumatic brain injury. *J Trauma* 2009;66:166-73.
- Wagner AK, Fabio A, Puccio AM, Hirschberg R, Li W, Zafonte RD, et al. Gender associations with cerebrospinal fluid glutamate and lactate/pyruvate levels after severe traumatic brain injury. *Crit Care Med* 2005;33:407-13.
- Wakai A, McCabe A, Roberts I, Schierhout G. Mannitol for acute traumatic brain injury. *Cochrane Database Sys Rev* 2013;8:CD001049.
- Zhao QJ, Zhang XG, Wang LX. Mild hypothermia therapy reduces blood glucose and lactate and improves neurologic outcomes in patients with severe traumatic brain injury. *J Crit Care* 2011;26:311-5.