Chapter 9. Temperature control

I. RECOMMENDATIONS

Strength of Recommendations: Weak.

Quality of Evidence: Moderate, from class II and III studies with some contradictory findings.

A. Level I

There are insufficient data to support a level I recommendation for this topic.

B. Level II

Moderate hypothermia (32–33°C) beginning early after severe traumatic brain injury (TBI) for only 24 hrs' duration should be avoided.

Moderate hypothermia (32–33°C) beginning within 8 hrs after severe TBI for up to 48 hrs' duration should be considered to reduce intracranial hypertension.

If hypothermia is induced for any indication, rewarming at a rate of >0.5°C/hr should be avoided.

C. Level III*

Moderate hypothermia (32–33°C) beginning early after severe TBI for 48 hrs, duration may be considered.

*After completion of these guidelines, the committee became aware that the *Cool Kids* trial of hypothermia in pediatric TBI was stopped because of futility. The implications of this development on the recommendations in this section may need to be considered by the treating physician when details of the study are published.

II. EVIDENCE TABLE (see Table 1)

III. OVERVIEW

The definitions of hypothermia and hyperthermia are controversial. Posttraumatic hypothermia is often classified as a core body temperature <35°C, whereas a temperature >38.0–38.5°C represents fever/pyrexia if it results from an altered thermoregulatory set point and represents hyperthermia if it is imposed on a normal set point. For simplicity, the term *hyperthermia* is used to reflect an elevated core body temperature throughout this chapter. At present, the data in the basic science literature on adult animal models indicate that hyperthermia contributes to greater posttraumatic damage by increasing the acute pathophysiological response after injury through a multitude of mechanisms.

The rationale for use of therapeutic hypothermia is a reduction in mechanisms of secondary injury resulting from decreased cerebral metabolic demands, inflammation, lipid peroxidation, excitotoxicity, cell death, and acute seizures. Clinical studies reviewed on temperature regulation have focused, by definition for these guidelines, on global functional outcome but also the effect on intracranial hypertension. The impact of reduction of intracranial pressure (ICP) after severe TBI in children on outcome remains to be determined. As discussed in previous chapters, the lowering of severely elevated ICP with respect to the treatment threshold may be a desirable outcome.

Lastly, based on experimental studies in animal models and clinical studies in adults, in which hyperthermia was correlated with poor outcome, it has been recommended that hyperthermia after TBI in children should be prevented. However, no study of the impact of hyperthermia on outcome after TBI met the inclusion criteria for this guideline. There also may be a role for therapeutic hypothermia in reducing intracranial hypertension in severe pediatric TBI.

IV. PROCESS

For this update, MEDLINE was searched from 1996 through 2010 (Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 17 potentially relevant studies, two were added to the existing table for this topic.

V. SCIENTIFIC FOUNDATION

Two moderate-quality class II studies and one poor-quality class III study met the inclusion criteria for this topic and provide evidence to support the recommendations (1–3).

Level II Recommendations

Outcome. This review provides a level II recommendation for the avoidance of moderate hypothermia (32–33°C) initiated early after severe TBI and applied for only 24 hrs' duration followed by rapid rewarming at a rate of >0.5°C/hr. This was based on the Hutchison et al (3) study that reported a phase III multicentered randomized trial (225 children with severe TBI; Glasgow Coma Scale Score 3–8) of moderate hypothermia (32–33°C) for 24 hrs followed by rewarming at a rate of 0.5–1.0°C every hour. In this study, hypothermia was used in a prophylactic manner as a neuroprotective strategy whether or not raised ICP was present. The findings from this study trended toward worse outcomes at 6 months after injury in children treated with hypothermia vs. normothermia using the Pediatric Cerebral Performance Category score (30% vs. 22%; $p = .08$) and increased mortality (21% vs. 14%; $p = .06$). In this study, the investigators screened the patients within 8 hrs, and the mean time to initiation of cooling was 6.3 hrs with a range of 1.6–19.7 hrs. As well, the protocol included a rapid rewarming rate as described previously so that the patients were normothermic by a mean of 19 hrs or within 48 hrs of injury. They found that hypothermia reduced intracranial hypertension with ICP significantly lower in the hypothermia vs. normothermia group during the cooling period, but this was followed by a significantly higher ICP in the hypothermia vs. normothermic groups during rewarming. A potentially confounding factor in this study was that marked hyperventilation ($Paco_2$ <30 mm Hg) was used as part of standard management in >40% of the patients in the study and hypertonic (3%) saline use was significantly reduced in the hypothermia vs. normothermia group.

Intracranial Hypertension. In contrast, a level II recommendation was made supporting the use of moderate hypothermia (32–33°C) in severe pediatric

DOI: 10.1097/PCC.0b013e31823f664b

Table 1. Evidence table

Reference	Description of Study	Data Class, Quality, and Reasons	Results and Conclusion
Studies from previous guidelines			
Hendrick et al, 1959 (1)	Design: uncontrolled case series N = 18 Protocol: patients who presented with decerebrate posturing were cooled to 32– 33°C; adjunctive therapies included promethazine and chlorpromazine	Class III Poor quality: no control for confounders	8 deaths Among 10 survivors, 4 no disability, 1 minimal hearing loss, 2 minimal hemiparesis and aphasia, 1 hemiparesis, 1 diplopia and mild personality changes, 1 gross intellectual impairment
New studies			
Adelson et al, 2005 (2)	Design: randomized controlled trial N = 75 Protocol: cooled to 32–33°C within 8 hrs of injury for 48 hrs as compared with normothermia Outcome: mortality, 3- and 6-month Glasgow Outcome Scale	Class II Moderate quality: unclear reporting of randomization methods, allocation concealment methods, and attrition	No difference between groups in mortality or 3- and 6-month Glasgow Outcome Scale ICP: overall, there was no statistical difference in mean ICP between the groups during the 5-day period ($p = .37$) except within the first 24 hrs, when the ICP was reduced in the hypothermia group ($p = .024$) No difference between groups in complication rates
Hutchison et al, 2008 (3)	Design: randomized controlled trial N = 225 Protocol: Randomized to cooling to 32–33°C within 8 hrs of injury for 24 hrs vs. normothermia; patients rewarmed at 0.5°C per hour	Class II Moderate quality: some differences between groups on baseline prognostic factors	No difference between groups on functional outcomes at 6 months Trend toward increased mortality and morbidity in the hypothermia group ICP was lower during cooling in the hypothermia group at 16 hrs and 24 hrs ($p < .02$ and $p < .01$, respectively) Significant increase in hypotension and pressor requirements in the hypothermia group

ICP, intracranial pressure.

TBI in the setting of refractory intracranial hypertension for 48 hrs' duration followed by slow rewarming at a rate of 0.5–1.0°C per 12–24 hrs if the injury occurred within 8 hrs. The recommendation was based on two class II studies with benefit of hypothermia on ICP (2, 3).

As mentioned, Hutchison et al (3) showed that hypothermia reduced intracranial hypertension with ICP significantly lower in the hypothermia vs. normothermia groups during the cooling period, although this rebounded to higher ICP during rewarming. However, hypothermia in that study was used only for up to 24 hrs. A study by Adelson et al (2) was a phase II multicentered randomized trial in 75 children with severe TBI (Glasgow Coma Scale score 3–8) of moderate hypothermia (32–33°C) for 48 hrs followed by rewarming at a rate of 0.5–1.0°C every 3–4 hrs. Additional details of this study as it relates to outcome are provided subsequently. Although there was no overall effect of hypothermia vs. normothermia on ICP, ICP was significantly decreased in the initial 24 hrs after TBI in the hypothermia vs. normothermia groups.

Level III Recommendation

Outcome. Supporting the level III recommendation for early administration of therapeutic hypothermia for 48 hrs' duration with slow rewarming, Adelson et al (2) carried out a phase II multicentered randomized trial in 75 children with severe TBI (Glasgow Coma Scale score 3–8) of moderate hypothermia (32–33°C) for 48 hrs followed by rewarming at a rate of 0.5–1.0°C every 3–4 hrs. They reported that hypothermia was safe, associated with a decreased mortality rate (8% vs. 16%), and did not increase complications. Once again, in this study, hypothermia was used in a prophylactic manner as a neuroprotective strategy whether or not raised ICP was present. Similar to the report of Hutchison et al (3), they also noted rebound intracranial hypertension in the previously cooled patients during rewarming.

In support of this recommendation is Hendrick (1), a case series of 19 children with severe TBI who presented with decerebrate posturing that, although before actual classification of severity of injury, would translate to a present-day Glasgow Coma Scale score of 4. These children were treated with moderate hypothermia (32–33°C). There were ten long-term survivors with only one severely impaired. It was concluded that systemic cooling after injury was effective as a "useful adjunct" that could improve outcome in children after TBI.

VI. INFORMATION FROM OTHER SOURCES

A. Indications From the Adult Guidelines

In the third edition of the adult guidelines (4), there was a chapter entitled "Prophylactic Hypothermia" based on a sufficient number of studies assessing the efficacy of therapeutic hypothermia after severe TBI in adults. Much of the previous edition of the pediatric guidelines was based on a scarcity of pediatric spe-

cific information with the use of hypothermia to treat patients with severe TBI originally reported >50 yrs ago (1). However, its use did not become established because early studies lacked modern scientific methods and adequate outcome measures to definitively prove or refute efficacy, and there were concerns over side effects. Renewed interest in moderate hypothermia after severe TBI did not occur until the past 15–20 yrs, when preliminary data from single-center clinical trials were published in adults. Studies by Shiozaki et al (5), Marion et al (6), Clifton et al (7), and Marion et al (8) all demonstrated that moderate hypothermia reduced ICP and tended to improve overall outcomes. In the first randomized controlled trial that followed these single-center studies, Clifton et al (9) reported lack of effectiveness in adults in a multicentered clinical trial of moderate hypothermia after severe TBI. Despite failure to replicate the earlier single-center findings in the larger multicentered trial, there was a suggestion of improved outcome in those patients who presented as hypothermic and were then kept cool and in the younger age groups within the study (<40 yrs of age). Children (≤16 yrs) were not included in the Clifton study or in subsequent studies. In the recent adult guidelines (4), it was noted that although hypothermia is often induced prophylactically on admission and used for ICP elevation in the intensive care unit in many trauma centers, the scientific literature has failed to consistently support its positive influence on mortality and morbidity. Four meta-analyses of hypothermia in adult patients with TBI have been published (10–13). All analyses concluded that the evidence was insufficient to support routine use of hypothermia and recommended further study to determine factors that might explain variation in results. As a result, the authors of the adult guidelines undertook another meta-analysis of the six trials that were assessed to be of moderate quality (7–9, 14–16). The overall risk reduction for mortality from this large data set was not significantly different between hypothermia and normothermia treatment groups, but hypothermia was associated with a 46% increased chance of good neurologic outcome (relative risk, 1.46; 95% confidence interval, 1.12–1.92). This led to a level III recommendation based on this pooled data. Additionally, preliminary findings suggested that a greater decrease in mortality risk is observed when target temperatures are maintained for >48 hrs (4). The results of these clinical trials of hypothermia in adult patients with TBI and even the resultant meta-analyses cannot be extrapolated directly to the management of severe TBI in children because children were not included in the samples analyzed.

B. Information Not Included as Evidence

A study by Li et al (17) reported on the use of local hypothermia (head cooling) rather than systemic cooling to an intracranial temperature of 34.5 ± 0.5°C within 8 hrs of injury vs. normothermia (37.5–38.5°C) for a period of 72 hrs. Although the study showed a positive effect of cooling on intracranial hypertension and biomarkers, neuron-specific enolase, S-100B, and CK-BB at 8, 24, and 48 hrs after injury, suggesting neuronal protection, neurologic outcomes could only be determined for eight patients (three of whom had died), because almost two-thirds were lost to clinical follow-up. A study by Biswas et al (18) reported on 21 children with severe TBI (Glasgow Coma Scale score 3–8), ten of whom were cooled to moderate hypothermia (32–34°C) within 6 hrs of injury for 48 hrs followed by rewarming to normothermia within 12 hrs. Although the study showed a positive effect of cooling on intracranial hypertension, there was no significant difference between hypothermic and normothermic groups in other outcome measures including Glasgow Outcome Scale, Pediatric Cerebral Performance Category, or Pediatric Overall Performance Category. Despite the small sample size overall, of the 21 children treated, 11 of 11 and six of six in the normothermia group had a good outcome at 3 and 12 months postinjury, respectively, whereas six of ten and five of eight in the hypothermia group had a good outcome at 3 and 12 months postinjury. Both of these studies supported the level II recommendation despite being poor-quality studies for the end points defined.

A study by Aibiki et al (14) evaluated ventilated adults and children with severe TBI (Glasgow Coma Scale score 3–8) treated with moderate hypothermia (32–33°C) for 3–4 days as compared with normothermia for prostanoid production. Although not the focus on the article, data as to age and outcome (Glasgow Outcome Scale at 6 months) could be abstracted. There were 11 children treated and two of four in the normothermia vs. six of seven in the hypothermia groups had a good outcome. Similar to the study by Gruszkiewicz et al (19), confounding this study was the cotreatment with dexamethasone. The study by Grinkeviciute and Kevalas (20) reported on a prospective cohort to determine the safety of mild hypothermia after TBI. There were eight patients included in the study, with a mean age of 10.7 yrs, who had severe TBI (Glasgow Coma Scale score 4–8), and who were treated with mild hypothermia (33–34°C) with a rapid induction of 2–3 hrs and maintained for 48 hrs with passive rewarming at 1°C per 4 hrs. Using the Glasgow Outcome Scale, all patients had a good outcome. Average Glasgow Outcome Scale score was 4.13 at 6 months after injury.

Finally, a study by Gruszhiewicz et al (19) reported on a prospective, randomized study of 20 children <16 yrs of age who had severe TBI presenting with a clinical examination of decerebrate rigidity (Glasgow Coma Scale score = 4). The children were randomized to hypothermia vs. hypothermia combined with dexamethasone (2 mg twice a day). There was no normothermic group. Sixteen of these 20 patients were hyperthermic at presentation and sustained various mechanisms of injury. Outcome was determined by duration of coma and time until "recovery," although the length of follow-up was <7 months in all instances. Although no statistical analysis was performed, the authors described a similar duration of coma and neurologic recovery for the two groups, although the depth and duration of the hypothermia differed. Some patients were cooled to 30–32°C, whereas others to 35–36°C. There was also variability of application from 18 hrs to 17 days. There were 19 survivors. Adjunctive therapies included promethazine, chlorpromazine, mannitol, and lumbar puncture to reduce ICP.

Although no study on the effect of hyperthermia after TBI in children met the inclusion criteria for these guidelines, a study by Heindl and Laub (21) reported that posttraumatic hyperthermia (defined as a temperature >38.2°C, lasting for at least 1 wk) was associated with a poor outcome vs. normothermia in an extremely severe cohort of 82 patients who remained in a persistent vegetative state at least 30 days postinjury. In this purely observational study, patients with hyperthermia had a poorer outcome

vs. those that did not (81% vs. 19%; $p < .01$). The time window that hyperthermia may contribute to secondary injury after severe TBI and the best approach to preventing or treating it were not addressed, although this study suggests that it may be important to prevent or treat hyperthermia after pediatric TBI.

VII. SUMMARY

Considerable uncertainty exists regarding the specifics of the use of targeted temperature management in pediatric TBI. A number of studies, including two new studies with class II evidence, show that mild or moderate hypothermia, vs. normothermia, can attenuate intracranial hypertension. However, the efficacy of this therapy vs. others as either a first-line agent or to treat refractory intracranial hypertension remains unclear. Similarly, conflicting results have been obtained regarding the effect of hypothermia on mortality and/or neurologic outcomes. It appears that details of the protocols used both to induce and maintain hypothermia and rewarm may be extremely important with short (24-hr) periods of cooling and rapid rewarming exhibiting the most complications. Finally, no study of the effect of hyperthermia on outcome after TBI in children met the inclusion criteria to allow a recommendation on this aspect of management.

VIII. KEY ISSUES FOR FUTURE INVESTIGATION

- The effect of temperature control, including prevention of hyperthermia, on outcome after pediatric TBI needs to be further studied.
- Issues such as the duration of vulnerability to hyperthermia and the optimal way to prevent or treat it should be addressed.
- The role of therapeutic hypothermia, both as a neuroprotective measure and for refractory intracranial hypertension, deserves investigation in pediatric TBI. Direct comparisons to other therapies should be conducted.
- Evaluations of therapeutic hypothermia should be age-stratified. Additional documentation of the effect of hypothermia and temperature regulation in studies restricted to infants and children are needed.
- Studies of the effect of hypothermia on specific TBI pathologies such as contusion, diffuse injury, and abusive head trauma are needed.
- Studies addressing both the therapeutic window and optimal duration are needed.
- Studies of the optimal timing and rate of rewarming are also needed.
- Studies are needed to better understand the effect of temperature regulation on key physiological and pharmacologic parameters (e.g., ICP, cerebral perfusion pressure, cardiac output, immune status, drug metabolism and drug dosing, etc.) and how these effects might influence long-term outcome.

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