

# Evidence-Based Emergency Medicine

## *Clinical Synopsis*

### TAKE-HOME MESSAGE

There is a lack of evidence to support the use of therapeutic hypothermia for closed head injury; specifically, there is no benefit in mortality or neurologic outcome compared with normothermic controls.

## METHODS

### DATA SOURCES

The authors searched the Cochrane Injuries Group Specialized Register, Controlled Trials metaRegister, Zetoc, SCI-EXPANDED, CPCI-S, CENTRAL, MEDLINE, PubMed, and EMBASE. Reference lists from included relevant trials were reviewed and trial authors were contacted for further clarification. Leading investigators in the field were also contacted about unpublished or ongoing trials.

### STUDY SELECTION

Only randomized controlled trials were included that involved closed head injury and featured therapeutic cooling versus normothermic control groups. The target temperature for most studies was 32°C to 33°C (highest 35°C) for a duration of at least 12 hours.

### DATA EXTRACTION AND ANALYSIS

Two authors reviewed search results and independently compared study designs and inclusion criteria. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to compare mortality, unfavorable neurologic outcome, and pneumonia between hypothermia and control groups. Heterogeneity between trials was assessed with  $I^2$  analyses. A priori subgroup analyses were performed according to trial quality, duration of hypothermia, and length of follow-up.

## Is Therapeutic Hypothermia for Closed Head Trauma Beneficial?

### EBEM Commentators

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### Results

Immediate therapeutic hypothermia versus normothermia for closed head injury.

Outcome	Number of Trials (Number of Subjects)	OR (95% CI)
Mortality	21 (1,587)	0.85 (0.68–1.06)
Mortality in trials at low risk of bias	9 (891)	1.11 (0.82–1.51)
Unfavorable neurologic outcome at 3 mo	6 (271)	0.85 (0.52–1.39)
Unfavorable neurologic outcome at 6 mo	9 (839)	0.76 (0.57–1.01)
Unfavorable neurologic outcome at 12 mo	4 (262)	0.52 (0.31–0.87)

Twenty-three randomized controlled trials met the inclusion criteria, for a total of 1,614 randomized patients. Of the 23 trials, 21 specifically reported data on mortality, with moderate heterogeneity between trials ( $I^2=48\%$ ). Of the 23 trials, 9 (n=891)

were considered to have good allocation concealment (low risk for bias). There was little or no heterogeneity among these 9 trials ( $I^2=0\%$  for mortality,  $I^2=18\%$  for neurologic outcome).

### Commentary

Despite precautionary measures to prevent increases in intracranial pressure after head injury, physicians are still in search of definitive therapies that might reduce mortality or permanent neurologic sequelae.<sup>1</sup> Considering the relative success of therapeutic hypothermia after cardiac arrest,<sup>2</sup> research has focused on the possibility that the same treatment intervention would show benefit after traumatic brain injury. However, this review provides unconvincing evidence that hypothermic efforts change outcomes.

Many would argue that in cases of severe brain injury, good neurologic outcome is the patient-centered outcome of greatest interest. Unfortunately, the lack of precision around

the point estimate for favorable neurologic outcome among the 9 higher-quality trials leaves open the possibility of benefit or harm.<sup>3</sup> In addition, 3 of the high-quality trials were pediatric studies; more research in this population is required because the potential exists for a greater benefit in younger patients.

Treatment protocols were standardized in each of the high-quality studies according to evidence-based guidelines for head injury; however, it is difficult to determine how similar the control protocols were between research sites. Regardless, any results extrapolated from these studies are applicable only to centers that use evidence-based protocols for head injury. The majority of the 9 high-quality trials reported no significant difference in baseline characteristics such as age or presenting Glasgow Coma Scale score. Patient comorbidities were consistently unreported in these trials and may be important factors for prognosis.

Some animal and human studies have demonstrated a trend toward better

outcomes if cooling is initiated soon after brain injury.<sup>1,4</sup> In this systematic review, a variety of cooling methods were used, which is a source of clinical heterogeneity among trials. Most of the included studies began cooling once the patient was admitted to the ICU or had already demonstrated evidence of increased intracranial pressure. Because it typically takes hours to achieve target temperature with standard methods of cooling,<sup>5</sup> the efficacy of therapeutic hypothermia may depend on the timing and intensity of the intervention, which lends support to research assessing intravascular cooling devices that achieve target temperature more rapidly after injury. To be effective, these interventions may need to be commenced in the field or emergency department once the patient is stabilized.

1. Polderman K. Application of therapeutic hypothermia in the ICU: opportunities and pitfalls of a promising treatment modality. Part I: indications and evidence. *Intensive Care Med.* 2004;30:556-575.
2. Howes D, Green R, Gray S, et al. Evidence for the use of hypothermia after cardiac arrest. *CJEM.* 2006;8:109-115.
3. Montori V, Kleinbart J, Newman T, et al. Tips for learners of evidence-based

medicine: 2. Measures of precision (confidence intervals). *CMAJ.* 2004;171:611-615.

4. Markgraf C, Clifton G, Moody M, et al. Treatment window for hypothermia in brain injury. *J Neurosurg.* 2001;95:979-983.
5. Marion D, Bullock R. Current and future role of therapeutic hypothermia. *J Neurotrauma.* 2009;26:455-467.

This is a systematic review abstract, a regular feature of the *Annals'* Evidence-Based Emergency Medicine (EBEM) series. Each features an abstract of a systematic review from the Cochrane Database of Systematic Reviews and a commentary by an emergency physician knowledgeable in the subject area. The source for this systematic review abstract is: Sydenham E, Roberts I, Alderson P. Hypothermia for traumatic head injury. *Cochrane Database Syst Rev.* 2009;(2):CD001048. DOI:10.1002/14651858.CD001048.pub4. The *Annals* EBEM editors assisted in the preparation of the abstract of this Cochrane systematic review.

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