Prolonged Therapeutic Hypothermia After Traumatic Brain Injury in Adults
A Systematic Review

Lauralyn A. McIntyre, MD
Dean A. Fergusson, MHA, PhD
Paul C. Hébert, MD, MHSc
David Moher, MSc
James S. Hutchison, MD

Traumatic Brain Injury (TBI) is defined as any brain injury that has been sustained secondary to externally inflicted trauma. This injury can result in death or a lifelong impairment of physical, cognitive, and psychosocial functioning.¹² It is an injury predominantly limited to the younger population. Some of the main causes of TBI include motor vehicle crashes, falls, acts of violence, and sports injuries.³ Although preventive measures have reduced the overall death rate from this devastating injury,¹ no therapy has been shown to reduce mortality and improve neurologic outcome once the injury occurs.

Therapeutic hypothermia has been investigated as a possible neuroprotective strategy for the prevention or reduction of brain injury due to several causes. The exact mechanism by which it reduces the deleterious effects of brain injury is a matter of debate.³ Possible mechanisms include reductions in cerebral metabolic rate, increased intracranial pressure and cerebral edema formation,³⁴ and attenuation in the opening of the blood-brain barrier.⁷ Hypothermia also inhibits the inflammatory re-

Context The benefits of therapeutic hypothermia as a treatment for traumatic brain injury (TBI) remain unclear.

Objective To explore the effects of depth, duration, and rate of rewarming after discontinuation of hypothermia on mortality and neurologic outcome in adults after TBI.

Data Sources An electronic search of MEDLINE (OVID), EMBASE, Current Contents, the Cochrane library and a hand search of key journals were performed. Corresponding authors of identified studies were contacted for additional unpublished or ongoing clinical trials.

Study Selection All randomized controlled trials of therapeutic hypothermia for at least 24 hours vs normothermia in adults with TBI.

Data Extraction Demographic and clinical data, hypothermia interventions and concomitants, mortality and neurologic outcomes, and methodological quality were abstracted by 2 independent reviewers.

Data Synthesis Twelve trials met eligibility criteria and were included in the analysis. We also performed subanalyses by different hypothermia interventions (ie, depth, duration, and rapidity of rewarming after hypothermia) and methodological quality. Therapeutic hypothermia was associated with a 19% reduction in the risk of death (95% confidence interval [CI], 0.69-0.96) and a 22% reduction in the risk of poor neurologic outcome (95% CI, 0.63-0.98) compared with normothermia. Hypothermia longer than 48 hours was associated with a reduction in the risks of death and of poor neurologic outcome (relative risk [RR], 0.70; 95% CI, 0.56-0.87 and RR, 0.65; 95% CI, 0.48-0.89, respectively) compared with normothermia. Hypothermia to a target temperature between 32°C and 33°C, a duration of 24 hours, and rewarming within 24 hours were all associated with reduced risks of poor neurologic outcome compared with normothermia. Assessment of methodological quality did not reveal evidence of bias.

Conclusions Therapeutic hypothermia may reduce the risks of mortality and poor neurologic outcome in adults with TBI. Outcomes were influenced, however, by depth and duration of hypothermia as well as rate of rewarming (≤24 hours) after discontinuation of hypothermia. Nonetheless, the evidence is not yet sufficient to recommend routine use of therapeutic hypothermia for TBI outside of research settings.

JAMA. 2003;289:2992-2999 www.jama.com

©2003 American Medical Association. All rights reserved.
The primary outcome measure was all-cause mortality at the end of the trial.

**METHODS**

**Study Identification**

Published and unpublished RCTs of therapeutic hypothermia in adults with TBI were identified using both electronic and manual search strategies. MEDLINE (OVID) database was searched from January 1, 1966, to week 1 of September 2002, using a combination of the following medical subject heading (MeSH) terms: “induced hypothermia,” “hypothermia,” and “cerebral trauma”; and the following text words with truncation where appropriate: “refrigeration anesthesia,” “cryoanesthesia,” “artificial hybernation,” “hypothermia,” “head trauma,” “head injury,” and “brain concussion.”

An RCT filter and a systematic review filter were applied to the MEDLINE search strategy to identify RCTs and systematic reviews. The electronic search was supplemented by a search of Current Contents from week 27 of 1993 to week 40 of 2002, EMBASE and the Cochrane Library, which contain the CENTRAL Database of Controlled Trials, as well as the Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews Effectiveness. We also conducted a review of the conference proceedings from the Cochrane review. These proceedings included the International Conference on Recent Advances in Neurotraumatology, Rimini, Italy, September 1996; the 2nd International Neurotrauma Symposium, Glasgow, Scotland, 1993; the 3rd International Neurotrauma Symposium, Toronto, Ontario, Canada, July 1995; the 4th International Neurotrauma Symposium, Seoul, South Korea, August 1997; the 27th Meeting of the Society for Critical Care Medicine, San Antonio, Tx, February 1998; and the 10th International Symposium on Intracranial Pressure, Williamsburg, Va, May 1997. The search was not restricted by language or type of publication. The bibliographies of all identified RCTs and review articles were reviewed. Authors of the RCTs were contacted to identify unpublished studies and abstracts, and for their knowledge of any unpublished or ongoing clinical trials.

**Study Selection Criteria**

Each RCT was evaluated on the basis of 4 inclusion criteria: study design (RCT), target population (adults with TBI), therapeutic intervention and comparison (at least 24 hours of therapeutic hypothermia at any time after sustaining TBI vs normothermia), and outcome (all-cause mortality, which was the primary outcome measure). Figure 1 outlines how studies were screened and retrieved for inclusion.

**Data Extraction of Primary Studies**

Two reviewers (L.A.M. and J.S.H.) independently extracted data from the primary studies, and any disagreements were resolved through consensus. Extracted information included demographic data, information on the pattern and extent of injuries, presence of comorbid illnesses, and a detailed description of the hypothermia intervention (ie, depth and duration of cooling and rate of rewarming after discontinuation of hypothermia), as well as other cointerventions and physiologic goals for brain injury management through the cooling period (ie, therapies to control intracranial pressure and cerebral perfusion pressure).
follow-up period. The secondary outcome measure was neurologic outcome at the end of the trial follow-up. Poor neurologic outcome was defined as a Glasgow Outcome Scale score of severe disability, vegetative state, or death. When necessary, authors of the articles were contacted for clarification and for additional information.

Assessment of Methodological Quality of Primary Studies
Two reviewers (L.A.M. and J.S.H.) assessed methodological quality of the individual studies and disagreements were resolved through consensus. Similar to methods used in the Cochrane review, the 2 items used to assess methodological quality were allocation concealment and blinding of the outcome assessment. Both items are potentially associated with bias in estimation of the true treatment effect. We included blinding of neurologic outcome assessment as a measure of quality for these RCTs because unlike mortality, reported neurologic outcome is subjective and thus another potential source of bias. Studies were considered to be of high methodological quality if allocation concealment was present and the outcome assessment was blinded; of moderate methodological quality if allocation concealment was unclear but the outcome assessment was blinded; and of low methodological quality if allocation concealment was unclear and the outcome assessment was not blinded. Studies that reported losses to follow-up and/or missing outcome assessments also were documented.

Prior Hypotheses Regarding Sources of Heterogeneity
Heterogeneity is a major threat to the interpretation and validity of meta-analyses and can be because of differences in methods, study populations, interventions, outcomes, or chance. We deliberately sought to identify significant differences in the hypothermia interventions between trials that may have caused a differential effect on mortality and neurologic outcome. Sources of heterogeneity in these hypothermia interventions included an examination of different depths (32°C-33°C vs 33.5°C-34.5°C); durations (24 hours, 48 hours, and >48 hours) and rates of rewarming (≥24 hours vs >24 hours) after discontinuation of hypothermia. Definitions for mild and moderate hypothermia varied among the individual studies. Therefore, we dichotomized depth of hypothermia as 32°C to 33°C and 33.5°C to 34.5°C.

Sensitivity analyses included an examination for the presence of methodological heterogeneity (high vs moderate vs low quality) between the individual trials for the mortality and the neurologic outcome. We also assessed the effect of the mortality outcome by removing the largest RCT.

Statistical Methods
Data from all 12 studies were combined to estimate the pooled relative risk (RR) and 95% confidence intervals (CIs) with a random-effects model (Meta.Analyst.977, Lau J, Chalmers TC; 1990). An RR less than 1.0 suggests a reduced risk of death or poor neurologic outcome while an RR greater than 1.0 suggests an increased risk of death or poor neurologic outcome, for the hypothermia group compared with the normothermia group. The prespecified analyses for depth, duration, and rate of rewarming following discontinuation of hypothermia and sensitivity analyses were conducted in a similar fashion. Evidence of publication bias was evaluated with an inverted funnel plot. Presence of statistical heterogeneity between studies was evaluated using the Cochran Q test of homogeneity.

RESULTS

Identification of Studies
A total of 867 citations were identified by our search strategy. Of these, 13 RCTs met our initial inclusion criteria. One non–English-language citation was identified as potentially relevant but was not retrievable despite a thorough search by our librarian as well as a search from the Canadian national science library (Canada Institute for Scientific and Technical Information). It is unclear if this study was an RCT. Thus, a total of 12 studies were included in this review. All but 3 citations were identified by the electronic search strategy. These citations were identified through a search of the Cochrane Controlled Trials Register and 1 was a published systematic review. One unpublished study was identified from the Cochrane review.

Study Characteristics
Twelve RCTs comprising a total of 1069 patients were identified: 543 patients in the therapeutic hypothermia group and 526 patients in the control (normothermia) group. Ages of patients ranged from 16 years to 81 years. In the 7 studies that reported the proportion of males to females, males accounted for more than 70% of the sample.

Twelve RCTs comprising a total of 1069 patients were identified: 543 patients in the therapeutic hypothermia group and 526 patients in the control (normothermia) group. Ages of patients ranged from 16 years to 81 years. In the 7 studies that reported the proportion of males to females, males accounted for more than 70% of the sample. Twelve RCTs comprising a total of 1069 patients were identified: 543 patients in the therapeutic hypothermia group and 526 patients in the control (normothermia) group. Ages of patients ranged from 16 years to 81 years. In the 7 studies that reported the proportion of males to females, males accounted for more than 70% of the sample. Twelve RCTs comprising a total of 1069 patients were identified: 543 patients in the therapeutic hypothermia group and 526 patients in the control (normothermia) group. Ages of patients ranged from 16 years to 81 years. In the 7 studies that reported the proportion of males to females, males accounted for more than 70% of the sample.
thermia was 24 hours or less for 6 studies 1,12,32,34,48,51 and more than 24 hours in 4 studies. 33,47,49,50 Two studies did not report the rate of rewarming after discontinuation of hypothermia. 32,53

Nine studies outlined physiologic goals for managing intracranial pressure 1,12,32-34,47-49,51 and 5 outlined physiologic goals for managing both intracranial pressure and cerebral perfusion pressure (Table 2). 31,34,47-49 Cointerventions instituted to achieve these physiologic goals included drainage of ventricular cerebrospinal fluid and hyperventilation, as well as the use of osmotic agents, diuretics, barbiturates, fluid therapy, and vasoactive agents. Four studies described intensity of therapy prescribed for control of intracranial pressure and/or cerebral perfusion pressure. 32,34,47,51 No study described in adequate detail treatment protocols to explain how each cointervention was used in the individual studies, and no study described how often hypothermia goals were achieved during the study period. Baseline characteristics of the study patients also are summarized in Table 2.

Four studies reported mortality and neurologic outcome at 3 months, 1,12,32-34,47,51 4 studies at 6 months, 33,34,49,50 1 at 1 year, 48 and 1 at all these time points. 11 Two studies did not report follow-up times for mortality. 32,53 Mortality in the normothermia group ranged from 0% to 82%, with 2 studies reporting mortality rates between 80% and 90%, 33,32 3 between 40% and 50%, 48,51,53 1 between 30% and 40%, 32 3 between 20% and 30%, 11,34,50 2 between 10% and 20%, 12,47 and 1 with no deaths. 49 Ten of the 12 studies reported neurologic outcomes. 1,12,32-34,47,51

Two studies were graded as high methodological quality, 1,34 3 as moderate quality, 32,48,52 and 5 as low quality (Table 2). 12,33,47,49,51 Three studies reported losses to follow-up or missing information pertaining to the outcome assessment for a total of 5 patients in the hypothermia group and 21 patients in the normothermia group. 1,32,47

Effect of Therapeutic Hypothermia on Mortality
The pooled RR of death was 0.81 (95% CI, 0.69-0.96; Cochran Q=8.12), conferring a significant protective effect of the therapeutic hypothermia relative to normothermia (Figure 2). Although statistical heterogeneity was not detected in the pooled results, we were still concerned about the possibility of heterogeneity in the hypothermia interventions. Indeed, cooling induced for greater than 48 hours was associated with an even greater reduction in the risk of death (RR, 0.70; 95% CI, 0.56-0.87) (Figure 3). This effect remained significant after removal of 1 study 31 that cooled only a subset of patients (30%) for more than 48 hours (RR, 0.72; 95% CI, 0.57-0.91). None of the other subanalyses were statistically significant. Analyses exploring methodological quality did not detect evidence of bias in estimation of the treatment effect for mortality. Reduction in the risk of death remained significant after removal of the largest clinical trial 34 (RR, 0.75; 95% CI, 0.62-0.91). An inverted funnel plot did not suggest evidence of publication bias.

Effect of Therapeutic Hypothermia on Neurologic Outcome
The pooled RR for a poor neurological outcome was 0.78 (95% CI, 0.63-0.98; Cochran Q=16.05) (Figure 4). However, the analysis of heterogeneity did show statistical significance (Figure 5). The benefit also was present when hypothermia was induced for more than 48 hours (RR, 0.65; 95% CI, 0.48-0.89) or for 24 hours (RR, 0.61; 95% CI, 0.39-0.97). Studies that included both induced moderate hypothermia and rewarming within 24 hours

Table 1. Therapeutic Hypothermia Interventions and Assessment of Methodological Quality for All Included Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Source</th>
<th>Target Depth of Hypothermia, °C</th>
<th>Target Duration of Hypothermia</th>
<th>Target Rate of Rewarming</th>
<th>Allocation Concealment</th>
<th>Blinding of Outcome Assessment</th>
<th>Methodological Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shiozaki et al. 1994</td>
<td>33.5-34.5</td>
<td>48 h</td>
<td>1°C/d</td>
<td>Unclear</td>
<td>No</td>
<td>Low</td>
</tr>
<tr>
<td>Clifton et al. 1992</td>
<td>33.5-34.5</td>
<td>48 h</td>
<td>0.5°C/2 h</td>
<td>Present</td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td>Yan and Tang 2001</td>
<td>32-34</td>
<td>3-5 d</td>
<td>NR</td>
<td>Unclear</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Jiang et al. 1997</td>
<td>33-35</td>
<td>3-14 d</td>
<td>1°C/h</td>
<td>Unclear</td>
<td>Yes</td>
<td>Moderate</td>
</tr>
<tr>
<td>Aibiki et al. 2000</td>
<td>32-33</td>
<td>3-4 d</td>
<td>1°C/d</td>
<td>Unclear</td>
<td>Yes</td>
<td>Moderate</td>
</tr>
<tr>
<td>Zhang and Wang 2000</td>
<td>32-33</td>
<td>3-5 d</td>
<td>NR</td>
<td>Unclear</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Shiozaki et al. 1999</td>
<td>33.5-34.5</td>
<td>48 h</td>
<td>1°C/d</td>
<td>Present</td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td>Marion et al. 1999</td>
<td>32-33</td>
<td>24 h</td>
<td>1°C/h</td>
<td>Present</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Hirayama et al. 1999</td>
<td>32-33</td>
<td>48 h</td>
<td>1°C/4 h</td>
<td>Unclear</td>
<td>No</td>
<td>Low</td>
</tr>
<tr>
<td>Clifton et al. 1999</td>
<td>32-33</td>
<td>48 h</td>
<td>1°C/4 h</td>
<td>Unclear</td>
<td>No</td>
<td>Moderate</td>
</tr>
<tr>
<td>Shiozaki et al. 1999</td>
<td>33.5-34.5</td>
<td>48 h</td>
<td>1°C/3 h</td>
<td>Unclear</td>
<td>No</td>
<td>Low</td>
</tr>
<tr>
<td>Clifton et al. 1999</td>
<td>30-32</td>
<td>24 h</td>
<td>1°C/3 h</td>
<td>Unclear</td>
<td>No</td>
<td>Low</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable as study did not assess neurologic outcome; NR, not reported.
*High is allocation concealment present and assessment of neurologic outcome blinded; moderate is allocation concealment unclear and assessment of neurologic outcome blinded; and low is allocation concealment unclear and assessment of neurologic outcome not blinded. Neurologic outcome was measured by the Glasgow Outcome Scale score.
+Rewarmed over a 24-hour period.
after discontinuation of hypothermia also were associated with a reduction in the risk of a poor neurologic outcome (RR, 0.61; 95% CI, 0.45-0.83 and RR, 0.79; 95% CI 0.63-0.98, respectively). No other comparisons between hypothermia interventions were statistically significant. Analyses according to methodological quality did not reveal evidence of bias in estimation of the treatment effect.

**COMMENT**

We observed a significant reduction in the risk of death and poor neurological outcome in favor of therapeutic hypothermia compared with normothermia. However, we hypothesized that heterogeneity related to different hypothermia interventions (ie, depth and duration of cooling and rate of rewarming after discontinuation of hypothermia) could have a differential effect outcome. Indeed, we found that hypothermia induced for 24 hours was associated with a significant reduction in the risk of a poor neurologic outcome, and if induced for more than 48 hours, the reduction in risk was significant both for neurologic outcome and death. The risk of a poor neurologic outcome also was reduced with the induction of hypothermia to a target temperature between 32°C and 33°C, and when rewarming occurred within 24 hours after discontinuation of hypothermia.

Although therapeutic hypothermia appears to show a benefit, it also is important to be aware of its potential complications: the risk of arrhythmias, coagulopathies, and infections.24-26 With hypothermia in the range of 32°C to 34.5°C, infections, and especially pulmonary infections, are the most clinically relevant. Indeed, the Cochrane review found an increased odds of pulmonary infection in the hypothermia group compared with the normothermia group.38 Because no additional studies in our review reported this complication, we did not perform this analysis.

Both laboratory and clinical studies have suggested that time to initiate cooling, as well as duration and depth of cool-

**Table 2.** Baseline Characteristics, Physiologic Goals and Cointerventions to Meet These Goals for All Included Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Source</th>
<th>Total N</th>
<th>Hypothermia Group</th>
<th>Normothermia Group</th>
<th>GCS Score, Mean (SD)</th>
<th>Hypothermia Group</th>
<th>Normothermia Group</th>
<th>Physiologic Goals and Cointerventions to Meet Goals*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shiozaki et al,17 2001</td>
<td>91</td>
<td>35 (20)</td>
<td>42 (17)</td>
<td>5.5 (1.7)</td>
<td>5.1 (1.9)</td>
<td>&lt;25 Hyperventilation, ventricular CSF drainage, osmotic agents, barbiturates</td>
<td>≤60 Albumin, dopamine</td>
</tr>
<tr>
<td>Clifton et al,34 2001</td>
<td>392</td>
<td>31 (12)</td>
<td>32 (13)</td>
<td>5.6 (1.3)</td>
<td>5.8 (1.3)</td>
<td>&lt;20 Hyperventilation, ventricular CSF drainage, mannitol, barbiturates, vecuronium</td>
<td>≥70 ICP control, fluid therapy, vasopressors</td>
</tr>
<tr>
<td>Yan and Tang,10 2001</td>
<td>44</td>
<td>47.0 (18.8)</td>
<td>43.3 (15.8)</td>
<td>4.2 (0.6)</td>
<td>4.0 (0.9)</td>
<td>NR NR</td>
<td>NR NR</td>
</tr>
<tr>
<td>Jiang et al,48 2000</td>
<td>87</td>
<td>42.2 (18.8)</td>
<td>40.6 (15.8)</td>
<td>7.2 (3.7)</td>
<td>7.3 (3.8)</td>
<td>&lt;25 Lasix, mannitol</td>
<td>≥70 MAP 90-120 mm Hg, ICP &lt;25</td>
</tr>
<tr>
<td>Aibiki et al,49 2000</td>
<td>26</td>
<td>38 (8)</td>
<td>34 (6)</td>
<td>5.7 (0.3)</td>
<td>5.7 (0.4)</td>
<td>NR ICP monitors in 12/26 patients</td>
<td>≥70 MAP 90-120 mm Hg*</td>
</tr>
<tr>
<td>Zhang and Wang,33 2000</td>
<td>246</td>
<td>35.9 (10.4)</td>
<td>34.6 (11.6)</td>
<td>5-7†</td>
<td>5-8†</td>
<td>NR NR</td>
<td>NR NR</td>
</tr>
<tr>
<td>Shiozaki et al,50 1999</td>
<td>16</td>
<td>31.4 (12.7)</td>
<td>40.3 (23.1)</td>
<td>5.6 (1.8)</td>
<td>5.4 (2.0)</td>
<td>&lt;20 Hyperventilation, fluid restriction, barbiturates</td>
<td>≥60 Albumin</td>
</tr>
<tr>
<td>Marion et al,11 1997</td>
<td>82</td>
<td>31 (12)</td>
<td>35 (15)</td>
<td>3-7§</td>
<td>3-7§</td>
<td>&lt;20 Hyperventilation, ventricular CSF drainage, mannitol, barbiturates</td>
<td>≥70 MAP 90-100 mm Hg, ICP &lt;20, CVP 6-15; dopamine if ICP high and CPP low</td>
</tr>
<tr>
<td>Hirayama et al,51 1994</td>
<td>22</td>
<td>18-81†</td>
<td>18-81†</td>
<td>≤7§</td>
<td>≤7§</td>
<td>&lt;20† Hyperventilation, mannitol</td>
<td>NR NR</td>
</tr>
<tr>
<td>Clifton et al,52 1993</td>
<td>46</td>
<td>16-60†</td>
<td>16-60†</td>
<td>4-7§</td>
<td>4-7§</td>
<td>&lt;20 Hyperventilation, mannitol, fluids to keep PCWP &gt;8, metocurine</td>
<td>NR NR</td>
</tr>
<tr>
<td>Shiozaki et al,53 1999</td>
<td>33</td>
<td>35.3 (15.3)</td>
<td>35.4 (12.6)</td>
<td>5.5 (1.9)</td>
<td>5.1 (1.8)</td>
<td>&lt;20 Hyperventilation, fluid restriction, barbiturates</td>
<td>NR NR</td>
</tr>
<tr>
<td>Clifton et al,12 1992</td>
<td>10</td>
<td>NR</td>
<td>NR</td>
<td>6.2 (1.3)</td>
<td>5.2 (1.2)</td>
<td>&lt;20 Hyperventilation, ventricular CSF drainage, mannitol</td>
<td>NR NR</td>
</tr>
</tbody>
</table>

Abbreviations: CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; ICP, intracranial pressure; GCS, Glasgow Coma Scale; MAP, mean arterial pressure; NR, not reported; PCWP, pulmonary capillary wedge pressure.

†Cointerventions described (dobutamine, glycerol, positive water balance) but not directed toward specific physiologic goals and only done for hypothermia group.

§Other treatment was "broadly identical" to the protocol by Clifton et al,34 1993.

*Glasgow Coma Scale score required for inclusion into study.

©2003 American Medical Association. All rights reserved.
ing, and rate of rewarming after discontinuation of hypothermia may cause different physiological and biochemical effects, and hence, a potential for varying effects on secondary brain injury and clinical outcome. A randomized controlled experimental study of brain injury in a rat model found that neurologic deficits were reduced to a greater extent when hypothermia was induced within 60 minutes of the injury vs after 90 minutes or more. A secondary analysis of data from a large multicenter RCT of hypothermia and head injury also supported this finding. In a subset of 81 patients who were hypothermic on admission (<35°C) and younger than 45 years, a trend toward a better neurological outcome at 6 months was noted in comparison with patients randomized to the normothermia group (RR, 0.7; 95% CI, 0.5-1.0). However, the studies that we reviewed did not provide sufficient detail to analyze the time from injury to initiation of hypothermia.

Prolonged duration of hypothermia also may reduce the effects of secondary brain injury and thus lead to an improvement in clinical outcome. In an experimental model of brain injury, Markgraf et al reported that cerebral edema remains elevated at 4 days, and possibly as many as 7 days after the injury. These findings suggest that mechanisms of secondary brain injury are mediated for several days after the initial injury and based on the results of this experimental study, we believe it is plausible that cooling for longer than 48 hours may maximize clinical outcome.

Laboratory studies have suggested that depth of hypothermia may have a varying effect on clinical outcomes. Different depths of hypothermia may have varying protective effects due to differing effects on metabolism and on inhibition of molecular mechanisms of secondary brain injury. Our analysis, according to depth of hypothermia, found that the risk of a poor neurologic outcome in the hypothermia group was reduced with induction of hypothermia to target temperatures of 32°C to 33°C as compared with the normothermia group.

Rate of rewarming after discontinuation of hypothermia also has the potential to affect outcome. In a laboratory study, Matsushita et al induced brain injury followed by a hypoxic insult in rats, followed by either hypothermia or normothermia. Rats with hypothermia then were rewarmed over a period of either 15 minutes or 2 hours. In the group that was rewarmed for 2 hours, the volume of contused brain was significantly lower than matched normothermic control brains. However, the hypothermia group rewarmed within 15 minutes showed no benefit, suggesting that rate of rewarming may be important in improving clinical outcome, particularly after sustaining a hypoxic cerebral insult. Our analysis, however, did not detect a protective effect for slower rewarming. Indeed, our results suggest that rewarming within 24 hours may reduce the risk of a poor neurologic outcome. Possible explanations for differences in results between laboratory data and our analysis include different mechanisms of brain injury, different baseline characteristics between the 2 treatment groups, and importantly, possible loss of information because of an arbitrary choice of a time threshold of 24 hours in our analysis.

©2003 American Medical Association. All rights reserved.

(Reprinted) JAMA, June 11, 2003—Vol 289, No. 22 2997
Experience in treating patients with TBI, as well as quality of care,\textsuperscript{55} detailed treatment protocols for hypothermia, and cointerventions for TBI\textsuperscript{56-58} are 4 other important potential sources of heterogeneity in these studies. We did not explore these important aspects of clinical care in any depth given the limitation of information reported in the studies we reviewed.

Two other systematic reviews have evaluated the effect of therapeutic hypothermia on outcomes from TBI\textsuperscript{38-39} We believe that our review adds novel information in our more detailed analysis of hypothermia interventions. We also included 2 more trials than the Cochrane review\textsuperscript{38} and 6 more trials than Harris et al.\textsuperscript{39} Finally, we searched the non–English-language literature and included 1 non–English-language study.\textsuperscript{53}

Our results suggest that the greatest clinical benefit may be derived when patients are cooled to a target temperature of 32°C to 33°C, with a duration of greater than 48 hours, and then rewarmed within 24 hours after discontinuation of hypothermia. However, our results should be interpreted with some caution because our analysis included a small number of high-quality trials, thus perhaps biasing our results in favor of the treatment effect.\textsuperscript{42} In addition, 1 large multicenter trial demonstrated no benefit associated with hypothermia. However, the inclusion or exclusion of this trial did not affect the overall interpretation of the results. Finally, other potential sources of heterogeneity not explored in this review, such as the intensity and quality of care delivered, time from injury to initiation of hypothermia, and achievement and adherence to hypothermia interventions and cointerventions, may have affected the clinical outcome assessments. For these reasons, our results should not influence clinical practice at this time. Instead, we believe this review provides valuable information to assist in the design of future clinical trials.

Additional studies are now underway to examine the role of hypothermia for the treatment of TBI. Clifton is currently conducting an RCT for patients who are between 16 years and 45 years of age and have hypothermia on arrival to hospital (<35°C) (information obtained from the metaRegister of Controlled Trials). Currently in progress are 2 RCTs in children (oral and written communication with J. S. Hutchison, MD, and P. D. Adelson, MD, November 6, 2002). In light of the results of our analysis, it may be important to conduct a clinical trial that induces hypothermia to a target temperature of 32°C to 33°C, with duration greater than 48 hours, and a rewarming period of 24 hours or less, to see if benefit from this therapeutic intervention can be maximized.

**Author Contributions:** Study concept and design: McIntyre, Hébert, Moher, Hutchinson. Acquisition of data: McIntyre, Hutchinson. Analysis and interpretation of data: McIntyre, Fergusson, Hébert, Hutchinson. Drafting of the manuscript: McIntyre, Fergusson, Hébert. Critical revision of the manuscript for important intellectual content: McIntyre, Fergusson, Hébert, Moher, Hutchinson.
Therapeutic Hypothermia After Traumatic Brain Injury


Funding/Support: This work was funded in part by the Ontario Neurotrauma Foundation grant ONTO-0009, the Canadian Neurotrauma Research Partnership through the Canadian Institutes of Health Research grant MCT03098. Dr Ferguson is a recipient of the Canadian Blood Services Doctoral Graduate Fellowship. Dr Ferguson has received a Career Scien-
tist award with the Ontario Ministry of Health.

Acknowledgment: We thank Shi Wu Wen, PhD, for his translation of Chinese studies, Nick Barrowman, PhD, for conducting an analysis for publication bias, and Nancy Cleary and Louise Roy for their adminis-
trative support in preparing the manuscript.

REFERENCES

4. Niu X, Hong X, Saito I. Comparative effects of hyper-
thermia, barbiturate, and osmotherapy for cere-
bral oxygen metabolism, intracranial pressure, and cere-
6. Kawai N, Nakamura T, Okauchi M, Nagao S. Effects of hypothermia on intracranial pressure and brain edema formation: studies in a rat acute subdural he-
7. Smith SL, Hall ED. Mild pre- and posttraumatic hypothermia attenuates blood-brain barrier damage follow-
ing controlled cortical impact injury in the rat. J Neu-
8. Palmer AM, Marion DW, Botscheller ML, Redd EE. Therapeutic hypothermia is cytoprotective without at-
tenuating the traumatic brain injury-induced eleva-
tions in interstitial concentrations of aspartate and glu-
9. Gloeckner DW, Dietrich WD, Busto R, Gins-
berg MD. Glutamate release and free radical produc-
tion following brain injury: effects of posttraumatic hy-
10. Sutcliffe IT, Smith HA, Stanimirovic D, Hutch-
son JS. Effects of moderate hypothermia on L-1-beta-
induced leucocyte rolling and adhesion in pial micro-
11. Marion DW, Penrod LE, Kelsey SF, et al. Treat-
ment of traumatic brain injury with moderate hypo-
14. Stoesser J, Hua J, Garcia-Lastra H, Hayakawa M, Hackett W. Moderate hypothermia in the treatment of pa-
tients with severe middle cerebral artery (MCA) ter-
15. Shaheed MA, Schwartz E, Keller E, Bertram M, Hackett W. Moderate hypothermia in the treatment of pa-
tients with severe middle cerebral artery (MCA) ter-
16. Bernard SA, Gray TW, Buist MD, et al. Treat-
ment of comatose survivors of out-of-hospital car-
18. Rosomoff H, Schulman K, Raynor R. Experimen-
tal brain injury and delayed hypothermia. Surg Gyne-
20. Lazothe G, Campan L. Hypothermia in the treat-
21. Drake CG, Jory TA. Hypothermia in the treat-
24. Rosomoff H, Schulman K, Raynor R. Experimen-
tal brain injury and delayed hypothermia. Surg Gyne-
25. Bohn DJ, Biggar WD, Smith CR, Conn AW, Barker LD. Moderate hypothermia in the treatment of pa-
26. Clifton GL, Jiang JY, Lyeth BG, Jenkins LW, Hamm RR, Hayes RL. Marked protection by moderate hypo-
28. Busto R, Dietrich WD, Globus MYT, Valdes I, Scheinberg P, Ginsberg MD. Small differences in intra-
29. Chopp M, Knight R, Tidwell R, Saper BA. Brown KM. The metabolic effects of mild hypother-
30. Busto R, Dietrich WD, Globus MY, Ginsberg MD. The importance of brain temperature in cerebral is-
31. Clifton GL, Jiang Y, Lyeth BG, Jenkins LW, Hamm RR, Hayes RL. Marked protection by moderate hypo-
33. Shiozaki T, Sugimoto H, Taneda M, et al. Effect of mild hypothermia on uncontrollable intracranial hyper-
34. Shiozaki T, Kato A, Taneda M, et al. Little ben-
efit from mild hypothermia therapy for severely head injured patients with low intracranial pressure. J Neu-
35. Abbioki M, Maekawa S, Yokono S. Moderate hypo-
36. Hirayama T, Katayama Y, Kano T, Hayashi N, Tsukobawa T. Impact of moderate hypothermia on ther-
apies for intracranial pressure control in severe trau-
матic brain injury. In: H. Nagai, S. Ishii, M. Maeda, eds. Intracranial Pressure IX. 9th International Sym-
37. Yan Y, Tang W. Changes of evoked potentials and evaluation of mild hypothermia for treatment of se-
38. Zhang K, Wang JX. Comparative study on mild hypothermia in patients with severe head injury and the most severe head injury. Inner Mongol Med Jour-
39. Shen JH, Shen MW. Application of mild hypo-
43. Patel HC, Menon DK, Tebbs S, Hawker R, Hutchin-

©2003 American Medical Association. All rights reserved.

(Reprinted) JAMA, June 11, 2003—Vol 289, No. 22 2999