Early induction of hypothermia for evacuated intracranial hematomas: a post hoc analysis of two clinical trials

Clinical article

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Object. The authors hypothesized that cooling before evacuation of traumatic intracranial hematomas protects the brain from reperfusion injury and, if so, further hypothesized that hypothermia induction before or soon after craniotomy would be associated with improved outcomes.

Methods. The National Acute Brain Injury Study: Hypothermia I (NABIS:H I) was a randomized multicenter clinical trial of 392 patients with severe brain injury treated using normothermia or hypothermia for 48 hours with patients reaching 33°C at 8.4 ± 3 hours after injury. The National Acute Brain Injury Study: Hypothermia II (NABIS:H II) was a randomized, multicenter clinical trial of 97 patients with severe brain injury treated with normothermia or hypothermia for 48 hours with patients reaching 35°C within 2.6 ± 1.2 hours and 33°C within 4.4 ± 1.5 hours of injury. Entry and exclusion criteria, management, and outcome measures in the 2 trials were similar.

Results. In NABIS:H II among the patients with evacuated intracranial hematomas, outcome was poor (severe disability, vegetative state, or death) in 5 of 15 patients in the hypothermia group and in 9 of 13 patients in the normothermia group (relative risk 0.44, 95% CI 0.22–0.88; p = 0.02). All patients randomized to hypothermia reached 35°C or lower within 1.5 hours of surgery start and the remaining 23 patients reached 35°C at later time points. Outcome was poor in 14 (45%) of 31 patients reaching 35°C within 1.5 hours of surgery, in 14 (61%) of 23 patients reaching 35°C more than 1.5 hours of surgery, and in 35°C at later time points. Outcome was poor in 9 of 13 patients treated with normothermia who did not reach 35°C within 1.5 hours of surgery start showed a significantly reduced rate of poor outcomes (41%) compared with 94 patients treated with hypothermia who did not reach 35°C within that time and patients treated at normothermia (62%, p = 0.009).

Conclusions. Induction of hypothermia to 35°C before or soon after craniotomy with maintenance at 33°C for 48 hours thereafter may improve outcome of patients with hematomas and severe traumatic brain injury. Clinical trial registration no.: NCT00178711. (http://thejns.org/doi/abs/10.3171/2012.6.JNS111690)

Key words • severe traumatic brain injury • evacuated hematoma • hypothermia

We performed 2 randomized, multicenter trials of hypothermia induction in patients with severe TBI (NABIS:H I and NABIS:H II; clinical trial registration no.: NCT00178711). The second trial differed from the first primarily in that hypothermia was induced much earlier after injury and a unified protocol led to a reduced rate of hypothermia-induced hypotension. In both trials, we performed a set of subgroup analyses that were specified before unblinded data were examined. In these subgroup analyses, we analyzed the differences between treatment effects in patients with intracranial hematomas that were surgically evacuated within the first 24 hours and in those who did not have evacuated hematomas (diffuse brain injuries). In our first clinical trial (NABIS:H I), a total of 392

ABBREVIATIONS USED IN THIS PAPER: CPP = cerebral perfusion pressure; GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; ICP = intracranial pressure; MABP = mean arterial blood pressure; NABIS:H I = National Acute Brain Injury Study: Hypothermia I; NABIS:H II = NABIS: Hypothermia II; TBI = traumatic brain injury.
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patients were enrolled. Of these, 191 patients were treated with hypothermia. In this trial, there was no difference in the rate of poor outcomes between treatment groups (hypothermia and normothermia) in patients with hematomas evacuated in the first 24 hours.

By contrast, in our most recent clinical trial (NABIS:H II), 97 patients were randomized; 52 patients were treated with hypothermia, reaching 35°C a mean of 2.6 ± 1.2 hours and 33°C a mean of 4.4 ± 1.5 hours after injury. In this trial, patients with hematomas evacuated in the first 24 hours had fewer poor outcomes (hypothermia, 5 of 15 patients [33% poor outcomes]; normothermia, 9 of 13 patients [69% poor outcomes; p = 0.02]), whereas patients who did not have evacuated hematomas had weak evidence of poorer outcomes (hypothermia, 26 of 37 patients [70% poor outcomes]; normothermia, 16 of 32 patients [50% poor outcomes; p = 0.09]). The difference in the direction of treatment effect of hypothermia on those with evacuated hematomas and those without evacuated hematomas was highly significant (p = 0.001).

In NABIS:H II, all patients treated with hypothermia reached 35°C and 33°C within 1.5 and 5.55 hours, respectively, after surgery start. We hypothesized that this early cooling in the second study was associated with improved outcome by protecting from reperfusion injury after hematoma evacuation, similar to its presumed mechanism in cardiac arrest and neonatal hypoxia/ischemia. Therefore, we applied the cooling times of NABIS:H II as a benchmark for NABIS:H I and examined post hoc the relationship between time of hypothermia induction relative to time of surgery and neurological outcome. Patients from both studies were further grouped for a meta-analysis.

We also examined differences in GCS scores, age, and pupillary reactivity, as well as percentages of patients with increased ICP, decreased MABP, and decreased CPP that could confound any differences in outcome between patients with evacuated intracranial hematomas who underwent early cooling compared with those who underwent cooling later or those treated at normothermia.

Methods

The NABIS:H I was a prospective, multicenter, randomized trial of cooling to 33°C for 48 hours versus treatment at normothermia in patients with severe brain injury (392 patients). The criteria for inclusion were an age of 16–65 years, nonpenetrating brain injury, and a GCS score of 3–8 after resuscitation. Exclusion criteria were a GCS score of 4 or higher, 1 systolic blood pressure less than 90 mm Hg or oxygen saturation less than 94% after resuscitation, pregnancy, active bleeding, known preexisting medical conditions, and inability to be randomized within 6 hours of injury.

The NABIS:H II was a prospective, multicenter, randomized trial of very early cooling to 33°C maintained for 48 hours in patients with severe brain injury with a planned sample size of 240 patients. However, randomization was halted following futility analysis; therefore, only 97 patients were included. The trial used a modified intent-to-treat design in which patients unable to follow commands after a nonpenetrating brain injury were randomized unless they were hemodynamically unstable, out of the study age range, or outside the study’s time window (2.5 hours after injury). Patients randomized to the hypothermia arm were cooled to 35°C with intravenously administered chilled crystalloid. After trauma evaluation, patients continued in the protocol in the same assignment to which they were randomized if they had none of a second set of exclusion criteria. The second set of exclusion criteria differed from NABIS:H I only in excluding patients older than 45 years of age and in setting higher blood pressure limits for exclusion (systolic blood pressure less than 110 mm Hg and diastolic blood pressure less than 60 mm Hg in NABIS:H II; systolic blood pressure less than 90 mm Hg in NABIS:H I). Surgery start times in both studies were recorded as either the time when anesthesia was induced or the time when the skin was cut. Patients designated as having operatively evacuated hematomas were those who underwent surgery within 24 hours of injury; therefore, all patients had 24–48 hours of hypothermia after surgery. Patients in both studies were randomized with a waiver of consent if legally authorized representatives could not be contacted at the time of study inclusion.

Patient Care

The management protocols in the 2 studies have been reported and differ primarily in the mean dosage of morphine and mean fluid balance.6,7 Because of differences in regulations regarding the use of waivers of consent, limits in cooling technology, and differences in trial design, hypothermia induction occurred later after injury in NABIS:H I than in NABIS:H II. In NABIS:H I, hypothermia was induced by ice applied to the skin, gastric lavage of cold water, and use of room temperature ventilated air. Hypothermia was maintained by a specially equipped bed that is only useable in the ICU. In NABIS:H II, hypothermia was induced and maintained by rapid intravenous infusion of cold crystalloid, gastric lavage of cold water, use of room temperature ventilated air, and by a portable surface-induced temperature control device (Arctic Sun Temperature Management System). The rate of rewarming was the same in both studies, that is, 0.5°C per 2-hour period (about 17 hours).

The primary outcome measure in both studies was the 5-category GOS score at 6 months after injury, dichotomized into 2 outcomes. “Good recovery” and “moderate disability” were designated as good outcomes and “severe disability,” “vegetative state,” and “death” as poor outcomes.

Statistical Analysis

In NABIS:H II, the temperatures of 11 patients were lower than 35°C before the start of surgery, and 3 reached 35°C within 1.5 hours of surgery. One patient reached 35°C 6 hours before surgery and had no further temperature data collected until 3 hours after surgery, at which time the patient’s temperature was 33°C. We inferred that
this patient reached 35°C within 1.5 hours of surgery. All patients in NABIS:H II reached 33°C within 5.55 hours of the start of surgery. In NABIS:H I, the hypothermia group was subdivided according to whether the patient reached 35°C within 1.5 hours of surgery start or later in one analysis and whether the patient reached 33°C or lower within 5.55 hours or later in another analysis. The same logistic regression models were fit to the data from both studies. However, for the NABIS:H I study, the p values represent comparisons of the group that reached a temperature of 35°C or lower within 1.5 hours of surgery or 33°C within 5.55 hours of surgery versus a combination of the hypothermia treatment groups that did not reach those temperatures by those times and the normothermia group.

The main outcome of interest involved a 2-sided test to assess the effect of induction of hypothermia on the percentage of poor outcomes at 6 months after injury. Percentages in each group were compared using a logistic regression model, with a log link to determine relative risks, using admission age and baseline GCS score as co-variates. The times to 35°C, 33°C, and surgery and mean age and mean GCS score were compared within each group of patients using a t-test. Comparisons of pupillary reactivity and physiological thresholds between the groups were performed using a chi-square or Fisher exact test, as appropriate.

A meta-analysis combining the data on all patients with hematomas from the NABIS:H I and NABIS:H II studies examined the consistency of the findings of efficacy outcome among patients with surgically removed hematomas who reached 35°C within 1.5 hours of surgery start and the combined group of those who reached 35°C at later times plus patients who were treated at normothermia. A second meta-analysis examined the consistency of efficacy outcome among those who reached 33°C within 5.55 hours of surgery and the combined group of patients who reached 33°C later plus those who were treated at normothermia. Because individual patient data were available from both studies, the meta-analysis involved fitting a generalized linear model using generalized estimating equations. The corresponding model included a study-specific random effect as well as fixed effects for treatment group, baseline age, and baseline GCS score. Mean values are presented as the mean ± SD.

Results

Outcome and Time to Hypothermia

In NABIS:H II, patients underwent surgery 4.9 ± 4.4 hours after injury. Hypothermia-treated patients with an operatively evacuated intracranial hematoma reached a temperature of 35°C or lower 1.5 hours after surgery start time at the latest, with patients reaching 35°C or lower 0.4 ± 0.9 hours on average after surgery started. All patients reached 33°C within 5.55 hours of surgery, with patients reaching 33°C 2.2 ± 2.0 hours on average after surgery started. As previously discussed, patients treated with hypothermia whose hematomas were evacuated in the first 24 hours had significantly fewer poor outcomes than those treated with normothermia (hypothermia, 5 [33%] of 15 patients; normothermia, 9 [69%] of 13 patients [p = 0.02]).

In NABIS:H I, 392 patients were randomized, but only 371 patients were included in the primary analysis due to missing age and/or baseline GCS scores for 19 patients. Of those, 112 patients had operatively evacuated hematomas within the first 24 hours after injury and had requisite injury, physiological, and temperature data; therefore, they were included in this analysis. For all 112 patients, the GOS score was measured at 6 months after injury (109 patients), or the score obtained at 3 months after injury was used to impute the 6-month score (3 patients) using previously described methodology.3 Patients underwent surgery 4.4 ± 3.6 hours after injury, and 31 of 54 hypothermia-treated patients reached a temperature of 35°C or lower within 1.5 hours after surgery start time. The remaining 23 patients reached 35°C at later times, usually much later (Table 1). There was weak evidence for better outcome in patients in NABIS:H I who reached 35°C within 1.5 hours of surgery start compared with patients who reached 35°C more than 1.5 hours after surgery start and patients treated at normothermia (p = 0.16).

A meta-analysis of 46 patients with hematomas who reached 35°C within 1.5 hours of surgery start time in NABIS:H I and II showed a significantly reduced rate of poor outcomes (41%) compared with 94 patients treated with hypothermia who failed to reach 35°C within that time and patients treated at normothermia (62%, p = 0.009) (Fig. 1).

Of the 54 patients in NABIS:H I who were treated with hypothermia, 37 reached a temperature of 33°C or less within 5.55 hours of surgery and 17 reached this temperature later; in 2 of these 17 patients, 33°C was never reached (Table 2). The rate of poor outcomes in those who reached 33°C within 5.55 hours of surgery was 49%. The rate of poor outcomes in those reaching 33°C later or not at all was 59% and that for those treated at normothermia was 60% (p = 0.33).

We examined factors other than time to 35°C and time to 33°C that could influence our findings. Table 3 shows mean age, mean GCS score, and the percentage of patients with bilaterally dilated and unreactive pupils by treatment assignment and time to 35°C. There were no significant differences among groups. In NABISH I but not in NABISH II, patients older than 45 years were randomized and 4 were included in this analysis. There also were no significant differences in these prognostic factors in patients reaching 33°C early versus late (data not shown). There was no discernable pattern of differences relative to the types of hematomas (epidural vs subdural, intraparenchymal, or multiple) among cohorts of patients. Fifteen percent of patients (7 of 46) reaching 35°C or lower within 1.5 hours of surgery in NABIS:H I and II had epidural hematomas, whereas 13% (12 of 94) of patients in the 2 studies who were treated at normothermia or who did not reach 35°C within 1.5 hours of surgery had epidural hematomas (p = 0.53). The pattern of hematoma types was similarly nonsignificant in patients reaching 33°C within 5.55 hours of surgery and later and patients treated at normothermia (data not shown).

Table 4 shows the percentage of patients in each cohort of time to 35°C who had reduced MABP, increased
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<table>
<thead>
<tr>
<th>TABLE 1: Relationship of outcome to hypothermia and normothermia treatment assignment and to the time of reaching 35°C relative to surgery start time</th>
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<tbody>
<tr>
<td>Trial</td>
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<tr>
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<tr>
<td>NABIS:H I†</td>
</tr>
<tr>
<td>≤35°C w/in 1.5 hrs</td>
</tr>
<tr>
<td>&gt;35°C w/in 1.5 hrs</td>
</tr>
<tr>
<td>normothermia</td>
</tr>
<tr>
<td>NABIS:H II††</td>
</tr>
<tr>
<td>hypothermia</td>
</tr>
<tr>
<td>normothermia</td>
</tr>
</tbody>
</table>

* In NABIS:H I, 392 patients were randomized and 371 had both a randomizing GCS score and a GOS score measured at 6 months after injury (368 patients), or a GOS score measured at 3 months after injury was used to impute the 6-month score (3 patients). Of these, 113 patients had operatively evacuated hematomas during the first 24 hours. One patient did not have a temperature at the time of surgery or a postoperative temperature taken within 1.5 hours of surgery and was excluded from this analysis. The p values for this trial represent comparisons of the group that reached a temperature of 35°C or less within 1.5 hours of surgery versus a combination of the group that did not reach a temperature of 35°C or less within 1.5 hours and the normothermia group.
† In NABIS:H II, the time to 35°C was recorded for all patients. Of 97 randomized patients, all had a randomizing GCS score and a GOS score at 6 months that was either directly measured or imputed from the 3-month GOS score. Of these, 28 patients had operatively evacuated hematomas during the first 24 hours and were included in this analysis. Eleven patients reached 35°C before surgery start and 3 reached 35°C within 1.5 hours of surgery. One patient reached 35°C at 6 hours before surgery with the next recorded temperature being 33°C at 3 hours after surgery.

ICP, and decreased CPP, all factors that affect outcome.2–4 In NABIS:H I, patients who reached 35°C within 1.5 hours of surgery had a lower incidence of severely elevated ICP, with weak evidence that fewer patients had decreased CPP and decreased MABP than patients who did not reach 35°C early and patients treated at normothermia. In NABIS:H II there was little difference in the rate of occurrence of severely elevated ICP or decreased CPP between patients treated at normothermia and hypothermia, although there was weak evidence that more hypothermia-treated patients had hypotension.

Table 2 shows rates of occurrences of severely elevated ICP, hypotension, and decreased perfusion pressure in patients reaching 33°C within 5.55 hours of surgery and later and patients treated at normothermia. There is a marginally significant decrease in the percentage of patients with elevated ICP in NABIS:H I and a marginally significant increased percentage of patients with low MABP in NABIS:H II. Leaving the bone flap out at craniotomy tends to lower ICP. In NABIS:H II, bone flaps were left out at craniotomy in 33% of patients in the hypothermia group and in 46% of patients treated at normothermia (p = 0.49).

A risk of hypothermia treatment in patients with hematomas is rehemorrhaging. However, the combined rate of intracranial rehemorrhaging in patients with hematomas in NABIS:H I and NABIS:H II was not significantly increased in patients treated at hypothermia (10 [14%] of 69) versus patients treated at normothermia (8 [11%] of 71, p = 0.16). Similarly, the risk of rehemorrhage in patients with hematomas in NABIS:H I and NABIS:H II was not significantly increased in patients who reached 35°C within 1.5 hours of surgery compared with those who did not and patients treated at normothermia (p = 0.40).

**Discussion**

In a combined analysis of 2 randomized clinical trials, early induction of hypothermia in patients with TBI requiring craniotomy for hematoma evacuation was associated with improved 6-month neurological outcome. In a meta-analysis we found that patients who reached 35°C before or during craniotomy showed a significantly reduced rate of poor outcomes compared with patients treated with hypothermia who did not reach 35°C early and patients treated at normothermia (41% vs 62% poor outcomes, p = 0.009). Since it takes some time after an-
esthesia induction to evacuate a hematoma, usually 30
minutes to 1 hour, it can be inferred that patients reached
35°C before or immediately after hematoma evacuation.
These findings suggest that in future trials the critical
variable is to reach 35°C or lower before hematoma evac-
uation but not necessarily 33°C.
This analysis suffers from the weakness of being
post hoc. While the subgroup analyses of patients with
and without hematomas was specified before unblinded
data were examined in both studies in accordance with
accepted policies,13 the designations of patients as having
reached 35°C within 1.5 hours after surgery start time
and 33°C within 5.55 hours of surgery were post hoc.
The time frames to 35°C and 33°C were extrapolated to
NABIS:H I from the observed findings in NABIS:H II.
Cooling was neither as rapid nor as effectively maintained
in NABIS:H I as in NABIS:H II because cooling technol-
ogy was inferior. The weaker effect of early cooling to
35°C in NABIS:H I as compared to NABIS:H II could be
the result of less effective maintenance of hypothermia.

We examined factors that could have influenced our
findings other than induction of hypothermia to 35°C
or 33°C. There were no imbalances in baseline factors
that most strongly predict outcome: age, GCS score, and

| TABLE 2: Percentage of patients assigned to hypothermia and normothermia treatment with at least 1 occurrence (single or multiple) of
critical ICP, MABP, and CPP within the first 96 hours after injury |
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<tbody>
<tr>
<td>Trial</td>
<td>No. of Patients</td>
<td>% Poor Outcomes</td>
<td>RR (95% CI)</td>
<td>% w/ MABP&lt; 70 mm Hg*</td>
</tr>
<tr>
<td>NABIS:H I§</td>
<td>112</td>
<td>0.33</td>
<td>0.83 (0.57–1.21)</td>
<td>0.94</td>
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<tr>
<td>≤33°C w/in 5.55 hrs</td>
<td>37</td>
<td>49</td>
<td>54</td>
<td>46</td>
</tr>
<tr>
<td>&gt;33°C w/in 5.55 hrs</td>
<td>17</td>
<td>59</td>
<td>41</td>
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<tr>
<td>normothermia</td>
<td>58</td>
<td>60</td>
<td>57</td>
<td>70</td>
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<td>NABIS:H II‡</td>
<td>0.02</td>
<td>0.44 (0.22–0.88)</td>
<td>0.12</td>
<td>0.99</td>
</tr>
<tr>
<td>hypothermia¶</td>
<td>15</td>
<td>33</td>
<td>60</td>
<td>27</td>
</tr>
<tr>
<td>normothermia</td>
<td>13</td>
<td>69</td>
<td>31</td>
<td>23</td>
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</table>

* The occurrence of an MABP less than 70 mm Hg is associated with a worsened outcome from severe brain injury.4
† The occurrence of an ICP greater than 20 mm Hg is the usual threshold for treatment because values above this level are associated with worse
outcomes. We used a level of 30 mm Hg, which is severely elevated, because in NABIS:H I hypothermia treatment reduced the occurrence of severely
elevated ICP during the period of hypothermia treatment but had no effect on elevations in the range of 20–30 mm Hg.1,4 The ICP data are missing for
1 NABIS:H I normothermia patient.
‡ Cerebral perfusion pressure is the difference between MABP and ICP. The occurrence of CPP less than 60 mm Hg is associated with worsened
outcome from severe brain injury.4 The CPP data are missing for 1 NABIS:H I normothermia patient.
§ The p values for NABIS:H I represent comparisons of the group that reached a temperature of 33°C or less within 5.55 hours of surgery versus a
combination of the group that did not reach a temperature of 35°C or less within 5.55 hours and the normothermia group. The ICP and CPP data are
missing for 1 NABIS:H I patient.
¶ All reached 33°C or less within 5.55 hours of surgery.

| TABLE 3: Age, GCS score, and pupillary reactivity in patients assigned to hypothermia and normothermia treatment and by time of
reaching 35°C relative to surgery start time |
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<tbody>
<tr>
<td>Trial</td>
<td>No. of Patients</td>
<td>Mean Age (yrs)</td>
<td>p Value</td>
<td>Mean GCS Score</td>
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<td>0.23</td>
<td>0.91</td>
<td>0.85</td>
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<tr>
<td>≤35°C w/ in 1.5 hrs</td>
<td>31</td>
<td>33 ± 11</td>
<td>5.9 ± 1.2</td>
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<td>&gt;35°C w/ in 1.5 hrs</td>
<td>23</td>
<td>33 ± 11</td>
<td>6.0 ± 1.4</td>
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<td>29 ± 11</td>
<td>5.8 ± 1.3</td>
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<td>NABIS:H II‡</td>
<td>28</td>
<td>0.18</td>
<td>0.51</td>
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<td>15</td>
<td>28 ± 10</td>
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<td>13</td>
<td>34 ± 14</td>
<td>4.6 ± 1.6</td>
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* Pupillary reactivity could not be determined in two NABIS:H I patients (1 normothermia and 1 hypothermia patient who did not reach 35°C or less
within 1.5 hours) and 1 normothermia patient in NABIS:H II.
† The p values for NABIS:H I represent comparisons of the group that reached a temperature of 35°C or less within 1.5 hours of surgery versus a
combination of the group that did not reach a temperature of 35°C or less within 1.5 hours and the normothermia group.
‡ Eleven patients were at or below 35°C by the time of surgery and 3 reached 35°C within 1.5 hours after surgery start. One patient reached 35°C at 6
hours before surgery with the next recorded temperature being 33°C at 3 hours after surgery.
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TABLE 4: Percentage of patients assigned to hypothermia and normothermia treatment with at least one occurrence (single or multiple) of critical ICP, MABP, and CPP within the first 96 hours after injury

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<thead>
<tr>
<th>Trial</th>
<th>No. of Patients</th>
<th>% w/ MABP &lt; 70 mm Hg†</th>
<th>p Value</th>
<th>% w/ ICP &gt; 30 mm Hg†</th>
<th>p Value</th>
<th>% w/ CPP &lt; 60 mm Hg‡</th>
<th>p Value</th>
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<td>≤35°C w/ in 1.5 hrs</td>
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<td>28</td>
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<td>hypothermia†</td>
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* The occurrence of an MABP less than 70 mm Hg is associated with a worsened outcome from severe brain injury.5
† The occurrence of an ICP higher than 20 mm Hg is the usual threshold for treatment because values above this level are associated with worsened outcome. We used a level of 30 mm Hg, which is severely elevated, because in NABIS:H I hypothermia treatment reduced the occurrence of severely elevated ICP during the period of hypothermia treatment, but it had no effect on elevations in the range of 20–30 mm Hg.14 The ICP data are missing for 1 NABIS:H I normothermia patient.
‡ The CPP data are missing for 1 NABIS:H I normothermia patient.
§ The p values for NABIS:H I represent comparisons of the group that reached a temperature of 35°C or less within 1.5 hours of surgery versus a combination of the group that failed to reach a temperature of 35°C or less within 1.5 hours and the normothermia group. The ICP and CPP data are missing for 1 NABIS:H I patient.
¶ Eleven patients were at or below 35°C by the time of surgery, and 3 reached 35°C within 1.5 hours after the start of surgery. One patient reached 35°C at 6 hours before surgery with the next recorded temperature being 33°C at 3 hours after surgery.

Pupillary reactivity. Among the physiological factors evaluated, the only significant finding among groups in NABIS:H I was a decrease in the percentage of patients with severely elevated ICP who reached 35°C within 1.5 hours of surgery, compared with patients who reached 35°C later and patients treated at normothermia.

We induced hypothermia early after injury in all patients with severe TBI in both studies; however, it is not necessary to do so to induce hypothermia before surgery in patients with hematomas necessitating evacuation. In NABIS:H I, surgery commenced at 3.1 ± 3.6 hours after admission and in NABIS:H II, 3.9 ± 4.3 hours after admission. With use of chilled crystalloid infusion, gastric lavage of cold water, and use of a portable surface cooling device after CT scanning, or with use of intravascular cooling devices, there should be little difficulty in reducing core temperature from 37°C to 35°C within an hour in this patient population.

There is a plausible explanation for why early hypothermia induction may improve the outcome of patients undergoing surgery for hematomas but does not improve the outcome of patients with diffuse brain injury. Early hypothermia induction has been established as an effective treatment after cardiac arrest and neonatal hypoxia. Both conditions are characterized by brain energy failure during the insult and then delayed energy failure with the attendant damaging biochemical changes during or after reperfusion, a biochemical cascade that hypothermia appears to abort.9,10 However, widespread ischemia occurs in only a minority of patients with severe brain injury without mass lesions.12,14 Experimentally, mechanical axonal injury is the most prominent feature of diffuse brain injury, not ischemia.8

However, in animal models, intracranial hematomas produce severe ischemia in the surrounding brain after hematoma evacuation by reperfusion.11 Intraischemic hypothermia after experimental hematoma removal is associated with improved outcome.5

An explanation for the mechanism of our findings is that hypothermia rendered before hematoma removal could protect the brain from the damaging biochemical processes that accompany energy failure during the reperfusion that occurs after hematoma evacuation. While we speculate about a mechanism of hypothermic protection in patients with evacuated hematomas, we conclude that clinical trials are warranted to determine whether cooling before hematoma removal improves outcome. We do not suggest that achieving 35°C within 1.5 hours of surgery start or 33°C within 5.5 hours of surgery start is a parameter that should be the objective of future clinical trials. Rather, our findings indicate that trial design should be targeted to reaching 35°C or lower before hematoma evacuation with maintenance at 33°C for at least 48 hours thereafter.

Conclusions

In a post hoc analysis of 2 randomized clinical trials, early induction of hypothermia in patients with TBI requiring craniotomy for hematoma was associated with a 50% reduction in poor outcome. Induction of hypothermia to 35°C before or soon after craniotomy with maintenance at 33°C for 48 hours thereafter may improve outcomes of patients with severe TBI with surgically treated hematomas.

Disclosure

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