Background and Overview

Article Title/Citation:

Study objectives/purpose: (and research hypothesis if applicable)
Does early hypothermia result in reduction of poor neurological outcomes or mortality in patients with traumatic brain injury.

Brief Background: (why issue is important, summary of previous literature)
Hypothermia has shown improved outcome in other forms of neurologic injury (cardiac arrest). A previous trial (NABISH I) did not show a benefit for early hypothermia but there was a trend towards improved outcome in patients who were already hypothermic on admission.

Methods

Study design and Methodology: (type of trial, Randomization, blinding, Controls, study groups, Length of study, etc.)
Randomized control trial of patients with traumatic injury.
- Randomly assigned (1:1), stratified by centre, to hypothermia or normothermia
- Random number generator with assignments in numbered opaque envelopes
- Investigators who assessed the outcome measures were masked to treatment allocation
- Others were unmasked to treatment allocation

Patient selection and Enrollment: (inclusion/Exclusion criteria, sample size etc.)
Inclusion:
- Non-penetrating brain injury with post-resuscitation GCS < 8
- Age > 16 and < 45 years old
- Time of injury within 2.5hrs of arrival at hospital

Two sets of Exclusion Criteria:
- Initial set measured in the field or upon arrival at the emergency department but before resuscitation
- Second set measured after complete assessment and resuscitation

First Set (on arrival or with EMS):
- suspected pregnancy
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- SBP < 110 mm Hg
- DBP < 60 mm Hg
- HR > 120 beats per minute
- could not be reached by study-affiliated personnel within 2.5 h of injury

Second Set (after assessment):
- GCS = 3 AND bilaterally non-reactive pupils
- GCS = 7–8 with normal brain CT scan or mild SAH or skull fracture
- GCS > 9 post-randomization
- inability to measure an accurate GCS
- Abbreviated Injury Score (AIS) > 4 for any body area except head
- Positive abdominal ultrasound or CT scan
- Persistent hypotension (SBP < 110mmHg or DBP < 60 mmHg)
- Persistent hypoxia (O2 Sat < 94%)
- Positive pregnancy test

Sample size:
- 240 patients
  - To detect a 17% difference in the percentage of patients with poor outcomes with 80% power

Interventions: (if applicable)

Hypothermia Group
- maintained at 35°C by up to 2 L of cold crystalloid and wet sheets or gel packs
- Those not excluded were cooled to 33°C by the Arctic Sun, use of room temperature ventilated air, continuation of chilled intra-venous crystalloid, and gastric lavage with cold water
- maintained at 33°C for 48 h and then rewarmed by 0.5°C every 2 h

Normothermia Group
- maintained at 37°C

Outcome measures/Endpoints:
- Primary outcome
  - Glasgow outcome scale score 6 months after injury, adjusted for age at enrolment and baseline GCS
- Secondary outcomes
  - 58 complications categorized as critical and non-critical

Statistical analysis:
- Comparisons between groups were done with two-tailed t test, χ2 test, or Fisher’s exact test as appropriate
- “Modified intention-to-treat analysis”
  - included all randomised patients who met the second set of inclusion criteria
Results

Enrollment & Baseline Characteristics:

<table>
<thead>
<tr>
<th></th>
<th>Hypothermia (n=52)</th>
<th>Normothermia (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>26 (9)</td>
<td>31 (11)</td>
</tr>
<tr>
<td>GCS score 5–8</td>
<td>33 (63%)</td>
<td>22 (49%)</td>
</tr>
<tr>
<td>GCS score 3–4</td>
<td>19 (37%)</td>
<td>23 (51%)</td>
</tr>
<tr>
<td>Non-reactive pupils*</td>
<td>6 (12%)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>Surgical lesion removed in first 24 h after injury</td>
<td>15 (29%)</td>
<td>15 (33%)</td>
</tr>
<tr>
<td>Prehospital hypotension†</td>
<td>7 (13%)</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>Prehospital hypoxia‡</td>
<td>11 (23%)</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Injury severity score</td>
<td>30 (6)</td>
<td>30 (9)</td>
</tr>
<tr>
<td>Abbreviated injury severity score for head</td>
<td>4 (8-6)</td>
<td>4 (6-3)</td>
</tr>
<tr>
<td>Positive blood alcohol§</td>
<td>17 (59%)</td>
<td>17 (59%)</td>
</tr>
<tr>
<td>First temperature (°C)</td>
<td>36.1 (0.8)</td>
<td>36.0 (0.9)</td>
</tr>
</tbody>
</table>

Data are mean (SD) or number (%). GCS=Glasgow coma scale. *Data missing for three patients in the hypothermia group and one in the normothermia group. †Data missing for four patients in the hypothermia group and two in the normothermia group. ‡Data missing for two patients in the hypothermia group and one in the normothermia group. §Data missing for one patient in the hypothermia group.

Table 1: Demographics and baseline characteristics

Summary of primary & secondary outcomes: (including subgroup analysis etc. include both efficacy and safety parameters)

<table>
<thead>
<tr>
<th></th>
<th>Poor outcome</th>
<th>Died</th>
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<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Primary analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients (n=97)</td>
<td>56 (58%)</td>
<td>--</td>
</tr>
<tr>
<td>Hypothermia (n=52)</td>
<td>31 (60%)</td>
<td>1.08 (0.76-1.52)</td>
</tr>
<tr>
<td>Normothermia (n=45)</td>
<td>25 (56%)</td>
<td>--</td>
</tr>
<tr>
<td>Subgroup analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse brain injury (n=60)</td>
<td>42 (61%)</td>
<td>--</td>
</tr>
<tr>
<td>Hypothermia (n=37)</td>
<td>26 (70%)</td>
<td>1.44 (0.95-2.17)</td>
</tr>
<tr>
<td>Normothermia (n=22)</td>
<td>16 (50%)</td>
<td>--</td>
</tr>
<tr>
<td>Surgically removed haematoma (n=28)</td>
<td>14 (50%)</td>
<td>--</td>
</tr>
<tr>
<td>Hypothermia (n=15)</td>
<td>5 (33%)</td>
<td>0.44 (0.22-0.88)</td>
</tr>
<tr>
<td>Normothermia (n=13)</td>
<td>9 (69%)</td>
<td>--</td>
</tr>
</tbody>
</table>

Data are number (%). RR=relative risk.

Table 2: Outcome and mortality rates
Your Discussion and Conclusions

- No difference in mortality or likelihood of poor outcome with hypothermia
  - Trial was stopped early
    - Interim analysis was done early
    - Funding agency involvement in decision to stop?
    - Trial stopped for futility not harm
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– Did we really expect hypothermia to work?

• **Increased episodes of ICP in the hypothermia group**
  – Why?
    • “more rigorous measures to reduce hypotension in this trial resulted in higher levels of critically raised intracranial pressure”
    • Reflex intracranial hypertension?
    • Are the groups really similar?
    • Does GCS predict potential for raised ICP?

• **Trend towards better outcome in subgroup with surgical evacuated hematomas**
  – “differing pathophysiology of patients with haematomas and those with diffuse brain injury”
  – “In experimental models, ischaemia occurs during haematoma expansion followed by reperfusion after removal this is similar in pathophysiology to that of patients with cardiac arrest”
  – “Experimentally, intra-ischaemic hypothermia after haematoma removal is associated with improved outcomes

Conclusion: This paper is unlikely to change our current practice pattern. Our use of hypothermia is for rescue ICP treatment and not for prophylactic neuroprotection and while this paper may not conclusively prove hypothermia is not useful certainly there is currently no evidence to start using it for that purpose.