“Brain Cooling: Head, Whole Body, Both or Neither?"

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Disclosure

• I have the following financial relationships with the manufacturer(s) of commercial product(s) and/or provider(s) of commercial services discussed in this CME activity:
  – In the past 12 months I have been a consultant for BrainZ Instruments, and the University of Michigan received grant support from BrainZ Instruments for an unrelated project on which I was an investigator. Both projects relate to amplitude-EEG but neither relates to cooling.
  – At various times over 12 months ago I served as a speaker for Olympic Medical on 2 occasions, performed FDA-mandated validation testing of the prototype commercial Cool-Cap® device, appeared at the FDA advisory panel hearing and was reimbursed for related travel expenses.
• However, I acknowledge that today’s activity is certified for CME credit and thus cannot be promotional. I will give a balanced presentation using the best available evidence to support my conclusions and recommendations.
• I intend to discuss an unapproved use of commercial products:
  – To the best of my knowledge, use of the Blanketrol II® or Blanketrol III® for hypothermic treatment of neonatal encephalopathy constitutes an off-label use of those devices.

Overview: Cooling for HIE

• Results of major published trials
  – Eicher trial
  – Cool Cap trial
  – NICHD trial
• Differences among trials
• Meta-analyses
• Pending trials
• “Is that your final answer?”
HYPOXIC-ISCHEMIC ENCEPHALOPATHY (HIE)

- Estimated 1-4/1000 term births
- ~4,000-16,000 babies/year (US)
- Frequently associated with chronically disabling conditions including CP, MR, and Sz
- Abnormal neurologic behavior in neonatal period (Sz, EEG abnormalities) best predictors of neurologic disability and death

Summary of Immature Animal Data:

- The longer the hypothermia duration, the better the protection, both %damage reduction and “durability”
- Window of opportunity may be several hours (up to 6-8), but earlier is better
- Optimal “protective” temperature may vary by brain region
- Mechanism likely “multi-pronged”
- Hyperthermia increases HI injury

Does Neonatal Hypothermia Work?

- 3 medium-large randomized controlled trials (RCTs) published: 507 infants
  - 1 SHC, 2 WBC
- multiple pilot and/or small randomized studies
- 1 RCT (China, SHC) presented (Shao, Hot Topics, 2006), not published
“South Carolina Body Cooling Trial” (I)

- N=65, ≥ 35 wks GA, ≥ 2000 gm BW; Evidence of perinatal or postnatal hypoxic-ischemic event, + neonatal encephalopathy (77% Sarnat III)
- Primary outcome death or severe motor disability at 12 mo.
- Cooling by 6h, ice bags to head and body ~2h, then cooling blanket, T, 33 ±0.5°C for 48 h (controls - radiant warmer, T, 37 ±0.5°C)
- Cooling initiated during transport
- Time to entry 3.1 - 4.6 h; median time to target temp. 80 min. outborn, 142 min. inborn
- Eicher et al, Pediatr Neurol 32:11 & 32:18, 2005

“South Carolina Body Cooling Trial” (II)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Normothermic (n=33)</th>
<th>Hypothermic (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or severe disability</td>
<td>84%</td>
<td>52% (p=0.019)</td>
</tr>
<tr>
<td>Death</td>
<td>14 (42%)</td>
<td>10 (31%) (p=0.35)</td>
</tr>
<tr>
<td>Severe motor disability</td>
<td>7/11 (64%)</td>
<td>4/17 (24%) (p=0.053)</td>
</tr>
<tr>
<td>Severe cognitive abnormality</td>
<td>5/12 (42%)</td>
<td>4/17 (24%) (p=0.4)</td>
</tr>
<tr>
<td>Lost/incomplete</td>
<td>8</td>
<td>5</td>
</tr>
</tbody>
</table>

The Cool-Cap Trial

- ≥36 weeks GA, start within 6 h of birth
- Staged selection
  - Evidence of birth depression (10 min Apgar<6 or resuscitation @ 10 min or pH<7 or BD≥16)
  - Moderate to severe clinical encephalopathy
  - Moderate to severe EEG amplitude reduction (lower margin < 5 μV) or seizures on aEEG
- Randomization, stratified by center, to selective head cooling plus mild central hypothermia with T_{rectal} 34.5±0.5 °C for 72 h, then controlled warming @ 0.5 °C/h vs. “routine care” (T_{rectal} 37.0 ±0.2 °C for 72 h)
  - Mean age at entry 4.7-4.8h
  - Median time to cool within 2 hrs.
- Primary Outcome: death or severe disability at 18 mo.
  - Bayley II MDI<70, Neurologic exam (GMF 3-5 = severe)

Gluckman et al., Lancet 365:663, 2005
CoolCap Primary Outcome

- # Enrolled: 235
- Final Count: 234
- Cancelled: 1
- Lost to Follow-up: 16

18-Month Primary Outcome

- Cooled: 108 Favorable 49 (45%), Unfavorable 59 (55%)
- Control: 110 Favorable 37 (34%), Unfavorable 73 (66%)

OR: Uncorrected

Uncorrected

Logistic Regression

A priori defined group excluding infants with severely abnormal aEEG w/seizures

n=172

- Cooled: 84 Favorable 44 (52%), Unfavorable 40 (48%)
- Control: 88 Favorable 30 (34%), Unfavorable 58 (66%)

Fisher’s exact p=0.02: logistic regression, OR: 0.42 (0.22, 0.80), p=0.009

Cooling improved intact survival in the group excluding the most abnormal baseline EEG changes

- Mortality 39% (control) vs 29% (cooled), p=0.2
- Severe neuromotor disability, defined as Gross Motor Function level 3-5 in survivors
  - 27.8% of control infants, 11.7% of cooled infants (p=0.035)
- BSID II MDI and PDI (treated as continuous variable) p<0.05
- Note: p<0.025 required for significance
NICHD Body Cooling Trial (I)

- Eligibility and exclusions similar to Cool Cap, except no uEEG selection step (next slides)
- N=208 (NT=106, HT=102)
- HT: 72h at target $T_{esoph}$ 33.5 °C (servo cooling mattress, readily available device)
  - Mean age at randomization 4.3±1.3
  - Time to target temp. <90 min.
- Primary outcome death or moderate-severe disability at 18 mo. (BSID II, Neuro exam)
  - Severe: MDI<70, GMF 3-5, hearing, blind
  - Mod: MDI 70-85, GMF 2, ↓ hearing, Sz disorder
- S. Shankaran et al. NEJM 353:1574-84, 2005

NICHD Body Cooling Criteria (A)

- Infants (36 wks or greater) will be evaluated in two steps; evaluation by clinical and acid-base criteria (A), followed by neurological exam (B).
- (A) Criteria:
  1. History of an acute perinatal event (abruptio placenta, cord prolapse, severe FHR abnormality: variable or late decelerations).
  2. An Apgar score <5 at 10 minutes.
  3. Cord pH or any postnatal blood gas pH at <1 hour <7.0.
  4. Base deficit on cord gas or any postnatal blood gas at <1 hour >16 mEq/L.
  5. Need for ventilation initiated at birth and continued for at least 10 minutes.

Body Cooling Criteria (A cont’d)

<table>
<thead>
<tr>
<th>A1: IF BLOOD GAS IS AVAILABLE:</th>
<th>A2: IF BLOOD GAS IS NOT AVAILABLE, OR pH 7.01 to 7.15, OR BASE DEFICIT 10 to 15.9mEq/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cord pH or any postnatal blood gas pH &lt;7.0 OR</td>
<td>Acute perinatal event AND</td>
</tr>
<tr>
<td>Base deficit on cord pH or any postnatal blood gas at &gt;16 mEq/L</td>
<td>An Apgar score &lt;5 at 10 minutes OR Continued need for ventilation initiated at birth and continued for at least 10 minutes</td>
</tr>
</tbody>
</table>
Body Cooling Criteria (B)

- If infant meets either A1 or A2 criteria, proceed to neurologic examination (B).
- Eligible if: moderate/severe encephalopathy defined as seizures OR presence of one or more signs in three of the following six categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Moderate Encephalopathy</th>
<th>Severe Encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Level of consciousness</td>
<td>Lethargic</td>
<td>Stupor/coma</td>
</tr>
<tr>
<td>2. Spontaneous activity</td>
<td>Decreased</td>
<td>No activity</td>
</tr>
<tr>
<td>3. Posture</td>
<td>Dorsal flexion, full extension</td>
<td>Decerebrate</td>
</tr>
<tr>
<td>4. Tone</td>
<td>Hypotonia (neck, general)</td>
<td>Flaccid</td>
</tr>
<tr>
<td>5. Primitive reflexes</td>
<td>Suck</td>
<td>Moro</td>
</tr>
<tr>
<td>6. Autonomic system</td>
<td>Constricted</td>
<td>Skull deviation/dilated/ non-reactive to light</td>
</tr>
<tr>
<td>Pupils</td>
<td>Bradycardia</td>
<td>Heart rate</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Respirations</td>
<td>Periodic breathing</td>
</tr>
<tr>
<td>Respiration</td>
<td>Constricted</td>
<td>Skull deviation/dilated/ non-reactive to light</td>
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<tr>
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<td>Constricted</td>
<td>Skull deviation/dilated/ non-reactive to light</td>
</tr>
</tbody>
</table>

The infant lies supine on the infant-size blanket


The NICHD Body Cooling Trial (II)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NT</th>
<th>HT</th>
<th>OR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or mod/sev dis.</td>
<td>62%</td>
<td>44%</td>
<td>.72 (.54-.95)</td>
</tr>
<tr>
<td>Disabling CP</td>
<td>30%</td>
<td>19%</td>
<td>.68 (.38-.122)</td>
</tr>
<tr>
<td>MDI &gt;85</td>
<td>40%</td>
<td>52%</td>
<td></td>
</tr>
<tr>
<td>MDI 70-84</td>
<td>21%</td>
<td>23%</td>
<td>NS</td>
</tr>
<tr>
<td>MDI &lt; 70</td>
<td>39%</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Death by 18 mo.</td>
<td>37%</td>
<td>24%</td>
<td>.68 (.44-.1.05)</td>
</tr>
<tr>
<td>Death/dis after Mod HIE</td>
<td>48%</td>
<td>32%</td>
<td>.69 (.44-.1.07)</td>
</tr>
<tr>
<td>Death/dis after Sev HIE</td>
<td>85%</td>
<td>72%</td>
<td>.95 (.64-.1.41)</td>
</tr>
</tbody>
</table>
Reconciling “different” results

• SHC (CoolCap) vs. WBC (NICHD):
• Apparent differences in outcome are minor and explainable by…
• Differences in trial designs
  – Primary Outcome measures
  – Thermoregulation in controls
  – Patient selection criteria

Differences between NICHD and Cool-Cap trials (I): 1° Outcome measures

• NICHD trial: Death or moderate or severe disability at 18 mo.
• CoolCap trial: Death or severe disability at 18 mo.
• Broader definition of “bad outcome” in NICHD trial makes it statistically easier to detect a between-group difference

Differences between NICHD and Cool-Cap trials (II): Thermoregulation in Controls

• In CoolCap trial core temperature was actively managed to 37.0 ±0.2 °C in the control group (actual 37.0 ±0.5 °C); NICHD “usual thermoregulation”
• In NICHD WBC trial, with usual abdominal skin thermoregulation in control group, 39% had core hyperthermia (Tm >38.0 °C) at some time
• NICHD controls: Range of median Tm 36.3-38.9 °C
• NICHD: 1°C increase in peak Tm -> 3.6-4-fold increase in death or disability (Laptook, PAS, 2006)
• CoolCap: 31% of controls >38°C at some time, pyrexia increased risk of bad outcome [OR 3.2 (1.2-8.4)]
NICHD vs Cool Cap: Thermoregulation in Controls

- The active temperature management in the CoolCap trial, resulting in less hyperthermia in controls, might have decreased the apparent difference between cooling and controls
- Temp. management in NICHD trial controls might have accentuated apparent benefit of cooling

Differences between NRN and Cool-Cap trials (III): Different populations

- CoolCap aEEG step excluded 94 infants with HIE who would have qualified for NRN trial
- Higher incidence of seizures at enrollment in CoolCap [61%] vs. NICHD trial [46%]
  - p=0.0016 Fisher's Exact test
  - Suggests cool cap population more severely affected, but CoolCap defined seizures electrically, NICHD clinically

Differences between NRN and Cool-Cap trials (III): Different populations

- Worse outcome in CoolCap trial control group vs. NICHD trial control group
  - death or severe disability
    - 66% Cool Cap vs. 56% NICHD
      - (p<0.125 Fisher's Exact test)
    - 62% death or moderate or severe disability
  - Suggests CoolCap trial had a larger representation of infants expected a priori not to respond to cooling
Summary of Three Trials

- Hypothermia had a modest beneficial effect on combined outcome in term infants with moderate-to-severe HIE
  - NNT = 6-9
- Each had insufficient power to address death and disability separately
- Babies with HIE have multiple organ system complications, which are not worse with cooling as used in trials

Summary of Three Trials

Preliminary meta-analysis:
Reduced [Death + disability]

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>Hypothermia (n)</th>
<th>Control (n)</th>
<th>RR (95% CI)</th>
<th>Weight</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooling</td>
<td>39/106</td>
<td>37/107</td>
<td></td>
<td>0.79 (0.62-1.01)</td>
<td>0.79 (0.62-1.01)</td>
</tr>
<tr>
<td>Edwards &amp; Azzopardi</td>
<td>17/72</td>
<td>18/75</td>
<td></td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>HD (N=4)</td>
<td>53/109</td>
<td>51/110</td>
<td></td>
<td>0.75 (0.62-0.91)</td>
<td>0.75 (0.62-0.91)</td>
</tr>
<tr>
<td>Total (50%)</td>
<td>132</td>
<td>131</td>
<td></td>
<td>0.79 (0.62-0.99)</td>
<td>0.79 (0.62-0.99)</td>
</tr>
</tbody>
</table>


Updated Meta-analysis Oct. 2007

- Cochrane review: 638 infants
  - DOI: 10.1002/14651858.CD003311.pub2
- Cooling decreases death, disability or combination in term or near-term infant
  - Combined: RR 0.76 (0.65-.89), NNT 7 (4-14)
  - Death: RR 0.74 (0.58-.94), NNT 11 (6-50)
  - Disability: RR 0.68 (0.51-.92), NNT 8 (4-33)
- Thrombocytopenia with cooling

Also:
Limitations of published trials

- Cool Cap and NICHD w/ mean trial entry about 4.5 hrs, and cooled to target even later (60-90 min)
  - Time = brain cells !!!
- Differences in study design likely account for apparent differences in results (Cool Cap and NICHD)
- Cool Cap and NICHD did not cool on transport; Eicher did (and showed efficacy with smaller numbers and more severe babies)

Updates

- 300 babies received non-randomized selective head cooling with CoolCap trial device
- NICHD trial sites use WBC; other NICUs too
- Selective head cooling system FDA approved Dec. 2006; dozens cooled
- Chinese head cooling trial reported “successful” but no peer-reviewed paper yet
- TOBY trial closed 11/30/06
- NeoNeuroNetwork closed 4/30/2006
- ICE trial closed late 7/27/2007

SHC vs. WBC or Both?

- In UM NICU: First Choice = SHC
  - Greatest familiarity (>35 cases), from Cool Cap trial
- Timely communication is key (time = brain cells)
- Consider initiation of cooling during transport
- Use whole body cooling in selected cases, e.g.
  - Baby that meets clinical but not aEEG criteria would have qualified for NICHD trial, therefore offer body cooling
  - Baby that can be cooled on transport before 6 hrs but can’t get to UMHS by 6 hrs
- Back-transfer after cooling, when safe
Who should not be cooled

- Patients who do not meet criteria for any of the 3 published RCTs
- Infants < 35 wks: safety, efficacy unknown
- Infants with traumatic, hemorrhagic brain and/or spinal cord injury
- Infants “in extremis”, i.e. a reasonable neonatologist would not continue resuscitation or intensive care
- Infants with evidence of serious congenital CNS problem, e.g. microcephaly, Trisomy 13 or 18, syndrome with known poor prognosis (mortality, disability)

Is Cooling “standard of care?”

- Distinct thresholds: loss of equipoise for investigators vs. standard of care for wider community
- Why not “Standard of Care?”
  - Limitations of published trials
  - No statement to that effect from official bodies
  - Can we currently ensure universal access?
  - Statistical arguments re how many patients are needed to be reasonably certain cooling works
- If you are convinced: Use a protocol with established safety and efficacy (there are 3)