Randomized Trial of Targeted Temperature Management with Whole Body Hypothermia for Moderate and Severe Encephalopathy in Premature Infants 33-35 Wks Gestation – A Bayesian Study

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Therapeutic Hypothermia for Infants < 36 weeks Gestation

• Randomized Trials
  • Gestational age ≥ 35 weeks
    • Eicher et al (Pediatr Neurol 2005;32:11) – personal communication
      • Total enrollment: 65
      • Enrollment at 350-356 weeks: 2 (1 control, 1 cooled)
      • Outcome: control died, cooled survived with CP
Therapeutic Hypothermia for Infants < 36 weeks Gestation

• Randomized Trials (continued)
  • Jacobs et al, ICE (Arch Pediatr Adolesc Med, 2011;165:692) – personal communication
    • Total enrollment: 221
    • Enrollment at 350-356 weeks: 5 (1 control, 4 cooled)
    • Control: survived (normal)
    • Cooled: Deaths (n=2), survived (n=2, moderate motor/cognitive delay, n=1, normal, n=1)
Therapeutic Hypothermia for Infants < 36 weeks Gestation

• Registry data
  • Toby registry 2006-2011 (PLOS One, 2012; e38504)
    • Forms for 1384 of 2069 infants
    • TH provided for 38 infants (2.8%) < 36 wks
    • Born at 34 wks, n=4, at 35 wks, n=34
    • Outcomes not available
  • VON registry 2006-2011 (PAS, 2013, abstract 1400.1)
    • Data for 2116 of 2457 infants
    • TH provided for 123 (5.8%) < 36 wks
    • Outcomes not available
Therapeutic Hypothermia for Infants < 36 weeks Gestation

- Other published data
  - “Cooling neonates who do not fulfill the standard cooling criteria”
  - 36 129 infants cooled outside of the TOBY/CoolCap criteria
  - 6 of 36 had gestational age 340 to 354 weeks
    - 0 deaths
    - 25% had an MDI/PDI < 70
  - Conclusion: Cooling should be considered for preemies 34-35 weeks
Incidence of Encephalopathy in Infants 33-35 wks GA

- Unknown
- Multiple retrospective cohorts:
  - Salhab et al (Ped Neurol 2005)
  - Chalak et al (J Pediat 2012)
  - Schmidt et al (J Peri Nenat Med 2010)
  - Estimated rate of NE: 1-8/1000 live births
- 2009 survey of NRN centers
  - Admissions/yr of 33-35wks: 292 infants/center
  - Extrapolated to 18 centers: 5256/yr
  - Potentially 5-40 study candidates/yr
- Schmidt/Walsh: 2 center feasibility trial for infants 32-36 wks (NCT00620711): enrolled 5 infants in 3yrs
COFN: Hypothermia and Neonatal Encephalopathy (Pediatrics 2014; 133:1146-1150)

• Knowledge from large trials
  • Hypothermia is safe and modestly effective for infants born > 35 weeks gestation

• Areas of uncertainty
  • Efficacy of cooling encephalopathic infants < 35 weeks is lacking

• Conclusions
  • Cooling infants < 35 weeks … be performed in a research setting

NRN perspective: infants < 36 weeks are under-studied
Equipoise exists for a RCT including infants 350-356 weeks
Adverse Events Associated with Therapeutic Hypothermia

Well tolerated therapy for infants ≥ 36 wks

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of studies / number of participants</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmia</td>
<td>5 / 806</td>
<td>4.08 (1.55, 10.74)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>8 / 1108</td>
<td>1.03 (0.93, 1.13)</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>7 / 1114</td>
<td>0.96 (0.80, 1.15)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4 / 638</td>
<td>1.28 (1.07, 1.52)</td>
</tr>
<tr>
<td>Seizure after enrolment</td>
<td>8 / 1102</td>
<td>0.96 (0.86, 1.06)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>5 / 310</td>
<td>0.95 (0.53, 1.70)</td>
</tr>
<tr>
<td>Hepatic side effects</td>
<td>5 / 678</td>
<td>0.85 (0.69, 1.04)</td>
</tr>
<tr>
<td>Infection</td>
<td>7 / 544</td>
<td>0.86 (0.40, 1.88)</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>5 / 636</td>
<td>1.36 (0.95, 1.96)</td>
</tr>
</tbody>
</table>

Risk Profile of Therapeutic Hypothermia in Infants 33-35 wks

• Minimal human data available
• Case reports: no adverse events reported
• Walsh et al, (PAS, 2011, abstract 3675.4)
  • Is survival of infants < 36 wks treated with TH similar to infants treated with TH ≥ 36 wks?
  • Pediatrix database and TOBY registry 12/06-11/10
  • 1337 infants received TH
    • 48 infants (3.6%) were 32-35 wks
• Mortality
  • < 36 wks: 29%
  • ≥36 wks : 20.1% (p=.14)
Challenges for the Proposed Trial

- Are there enough affected infants?
- Can affected infants be identified as encephalopathic?
  - Neurological assessment of preterm infants is challenging
- Is the safety profile of TH similar to its use in infants ≥ 36 weeks
Hypothesis

The risk of death or moderate/severe disability at 18-22 months corrected age will be decreased in infants 330 – 356 wks GA and ≥ 1500 gms BW with moderate or severe encephalopathy at < 6hrs of age who undergo therapeutic hypothermia to 33.5oC (Tes) for 72 hrs compared to infants maintained at 37oC.
Inclusion Criteria

- Gestational age: 330 – 356 weeks (Ob estimate)
- BW: ≥ 1500 grams
- < 6 hours of age
- Biochemical and/or clinical criteria for an exam:
  - Cord blood gas or Blood gas < 1hr of age available
    - pH ≤ 7.0 OR Base def ≥ 16mEq/L
    - Qualifies for exam
    - pH 7.01-7.15 OR Base def 10-15.9mEq/L
    - Qualifies for exam if either:
      - Acute event + Apgar ≤ 5 at 10min
      - Acute event + ventilation at birth for at least 10 min
    - pH > 7.15 OR Base def < 10mEq/L
    - Does NOT qualify for exam
Inclusion Criteria (cont’d)

- Moderate or severe encephalopathy, or Seizures
  - Certified study examiner
  - Modified Sarnat stages/caveats for the preterm
  - Need abnormalities in at least 3 of 6 categories
    - Level of consciousness
    - Spontaneous activity
    - Posture
    - Tone
    - Primitive reflexes
    - Autonomic function

- Level of consciousness must be abnormal
  - Important caveats for the exam of preterm infants
- Examine all infants even if they qualify by Sz
Exclusion Criteria

- Paralytic, sedative/hypnotic agents that obscure the exam
- Etiology of NE is likely not to be hypoxic-ischemic
- Major congenital anomaly
- Moribund and will not receive full intensive care
- Equipment or appropriate staff are not available
- Cooled to a core temperature < 34°C for > 1hr at the time of screening
- Unable to randomize by 6 hrs
- Infant to receive or receiving ECMO
- All blood gases (cord/< 1hr): pH > 7.15 and BE < 10mEq/L
- Unable to obtain consent/concurrence (parents/Attending, respectively)
Randomization and Stratification

• Telephone randomization via RTI to either hypothermia or control (non-cooled)

• Stratification variables:
  • Center
  • Degree of encephalopathy (moderate vs severe)

• If multiples qualify: randomize independently
Hypothermia Group

- Whole body hypothermia
- Induction and maintenance
  - CSZ Blanketrol 2 or Blanketrol 3 (in automatic control mode)
  - Tes placement: lower third of esophagus
    - May need to be placed orally if nasal passage is too narrow
    - CXR confirmation within 12 hrs
  - Maintain Tes at 33.5°C using servo control
  - Duration: 72 hours
  - Temperatures recorded each 15 min x 4hrs, each hr up until 12 hrs and then every 2 hrs
  - Keep NPO while being cooled
Hypothermia Group

• **Rewarming**
  
  • After 72 hrs of cooling, ↑ Te set point by 0.5°C/hr until Tes ≥ 36.5°C
  
  • When Tes ≥ 36.5°C and < 37.3°C for 4 consecutive hours, Tes probe can be removed
  
  • Resume temperature control via a radiant warmer or incubator
  
  • If the intervention is discontinued prior to completion, rewarming as outlined above is recommended
Control Group

• Tes placed in the lower third of the esophagus
  • Monitor Tes with CSZ Blanketrol in Monitor Only mode
  • CXR confirmation within 12 hrs
• Maintain Tes at 37.0°C (range of 36.5-37.3°C)
  • Adjust skin temperature set point if on servo control to maintain Tes
  • Adjust ambient air temperature if on manual control in an incubator per Tes
• Avoid elevated Tes
  • Follow algorithm of LH protocol for Tes > 37.3°C
• Monitor temperatures every hr x 12, then at 2 hr intervals until 108 hrs
Safety Monitoring

• There are no mandated blood tests
  • Record data ordered by the medical team
  • CUS is the only mandated test
    • Obtain prior to initiation of intervention (ideal) or within 24 hours of initiation
    • Local reading to be used
  • Other CUS are clinical decisions
    • CUS is recommended if Hct \( \downarrow \) by 10 percentage points ie 40 to 30% and is unexplained
Safety Monitoring

• Serial temperatures
• Metabolic: glucose, electrolytes, calcium, phosphorus
• Respiratory: pulmonary support, blood gases, acid-base, PPHN, hemorrhage, aspiration, CLD
• Cardiovascular: HR, BP, inotropes, arrhythmias,
• Renal: input/output, BUN, creatinine
• Neurologic: serial examinations (36hrs post initiation, 1d after rewarming, and at 38-40wks or prior to D/C or transfer), EEG, other imaging
  • MRI: at d10-17 (> d17 if unstable, < d10 if prior to D/C or transfer to a non-NRN facility)
Safety Monitoring (cont’d)

- Hematologic: CBC with platelets, clotting studies
- Infection: cultures, CXR, CRP
- Hepatic: liver enzymes, bilirubin
- Gastro-intestinal: NEC, feeding tolerance
  - Do not feed infants while being cooled
- Dermatologic: erythema, necrosis, sclerema, subcutaneous fat necrosis
- Esophageal probe: perforation, bleeding
Adverse Events

- ICH
- Arrhythmia
  - Requiring therapy
- Persistent acidosis
- Thrombosis
- Major bleeding
- Major skin changes
- NEC
  - Tes probe perforation, ulceration, bleeding
- Hyperglycemia
- Hypoglycemia
- PPHN after randomization
- ECMO
- Death
- Other
Discontinuation of Hypothermia

- Discontinuation of hypothermia
  - Need for ECMO
  - Withdrawal of consent (parent, Attending)
  - SAE: at the discretion of Attending after consultation with the site/study PI
  - Infants remain in the study

- Withdrawal of support/limitation of care
  - Decisions during the intervention period will be made by an Attending ± other Attendings and not the site/study PI
Follow-up

- Contact information to track patients
- Follow-up assessments at 18-22 months corrected age
  - Growth
  - Neurologic exam
  - Bayley Scales of Infant Development III
  - Obtain results of Ophthalmologic and Audiologic assessments
- Evaluations done by NRN personnel trained to reliability and blinded to intervention
Primary Outcome

• Death or disability (severe or moderate)
  • Severe disability:
    • Bayley III cognitive score <70 OR
    • GMF 3-5 OR
    • Blindness OR
    • Hearing loss (unable to understand commands in spite of amplification or cochlear implant)
  • Moderate disability:
    • Bayley III cognitive score 70-84 AND
    • GMF 2 OR
    • Seizure disorder OR
    • Hearing loss (follows commands with amplification or cochlear implant)
Secondary Outcomes

- Death up to 18-22 months corrected age
- Causes of death
- Severe and moderate disability only
- Components of moderate and severe disability
- Death or profound disability (lowest score on Bayley III)
- Survival with no impairment
- Safety issues
- Evolution of encephalopathy
- CUS abnormalities within 24hrs of enrollment
- MRI findings
Sample Size and Bayesian Analyses

• Primary analysis (sample size = 168)
  • After data lock
    • Either after 168 infants have completed the study or if the study is terminated for efficacy, futility or safety
  • Adjust for level of encephalopathy and gestational age at randomization
  • Determine posterior probabilities of > 0, > 10 and > 20% decrease in death/disability with 95% credibility intervals with different priors
## Interim Analysis Schedule

<table>
<thead>
<tr>
<th>Interim Analysis</th>
<th>Sample Size</th>
<th>Purpose</th>
<th>Primary Prior for RR</th>
<th>Endpoint</th>
<th>Stoppage Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>Safety</td>
<td>Neutral</td>
<td>Interim Safety</td>
<td>Pr((\Theta &gt; 1/X)) &gt; .999</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>Safety</td>
<td>Neutral</td>
<td>Interim Safety</td>
<td>Pr((\Theta &gt; 1/X)) &gt; .99</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>Safety</td>
<td>Neutral</td>
<td>Interim Safety</td>
<td>Pr((\Theta &gt; 1/X)) &gt; .98</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>Safety</td>
<td>Neutral Skeptical</td>
<td>Interim Safety</td>
<td>Pr((\Theta &gt; 1/X)) &gt; .95, Pr((\Theta &lt; 1/X)) &lt; .975</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>Futility</td>
<td>Enthusiastic</td>
<td>Primary Efficacy</td>
<td>Pr((\Theta &lt; 1/X)) &lt; .10, Pr((\Theta &gt; 1/X)) &gt; .925, Pr((\Theta &lt; 1/X)) &lt; .975</td>
</tr>
<tr>
<td>6</td>
<td>130</td>
<td>Futility</td>
<td>Enthusiastic</td>
<td>Primary Efficacy</td>
<td>Pr((\Theta &lt; 1/X)) &lt; .10, Pr((\Theta &gt; 1/X)) &gt; .90</td>
</tr>
</tbody>
</table>

Pr = posterior probability  
\(\Theta\) = relative risk favoring treatment group  
X = available data
Staged Analysis and Safety Monitoring

- Trial will be paused after the first 20 enrollees reach NICU discharge, alive in the NICU at 60 days or death by 60 days
- DSMC will review safety data to determine if resumption is indicated
  - Bayesian interim monitoring approach for systematic differences among groups for AE
- If continued, interim analyses per analysis plan
- Subcommittee: reviews study status, protocol violations, SAEs and temperature profiles 4x/yr
Questions?