Therapeutic hypothermia for hypoxic ischemic encephalopathy using low-technology methods: A systematic review and meta-analysis

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Introduction

• Decreased death or severe disability at 18 months (Edwards, et al. 2010, Jacobs, et al. 2013)

• ILCOR: should be the standard of care (Perlman, et al. 2010)
  - In accordance with high quality RCT
  - Hypothermia must be implemented in intensive care
  - Most studies used high-technology cooling devices

• Several centres use low technology methods

• BUT a recent systematic review showed NO reduction of mortality in low and middle income countries (Pauliah, et al. 2013)
  - Authors speculate low-technology cooling methods inadequate
  - NB: Studies with no access to ventilation/ICU were included
Objectives

• **We hypothesised:** Neonates with HIE will benefit if low technology therapeutic hypothermia is applied and commenced within 6 hours in an intensive care setting with mechanical ventilation available.

• **Objectives:** To systematically review the literature to determine the effect of low technology hypothermia vs standard care in ICU infants with HIE.
Methodology

• Standard Cochrane methodology (Higgins, et al. 2011)

• Written protocol - registered with PROSPERO

• Standardised data extraction sheet – two independent authors

• RevMan 5.1 software - fixed effects model

• Risk for bias was assessed independently by two authors
Inclusion Criteria and Outcomes

• Randomised controlled trials:
  - Low technology hypothermia vs standard care
  - Low technology: manual application of cooling bags/packs
  - Therapeutic hypothermia: core temperature < 35 °C

• Participants:
  - newborns ≥ 35 weeks and < 6 hours
  - nursed in an intensive care environment
  - objectively defined clinical assessment of encephalopathy
  - criteria describing intrapartum hypoxia (one of):
    - APGAR score of ≤ 7 at 5 minutes or later
    - pH < 7.0 and base deficit (BD) > 10 mmol/l
    - ongoing resuscitation for > 5 minutes
    - history of perinatal event
Outcomes

Primary outcome: Mortality (Primary admission)

Secondary outcomes: Abnormal neurology at discharge
- Mortality at 6–24 months
- Mortality or severe neurological morbidity at 6 – 24 months
Search Strategy

• PubMed, Cochrane CENTRAL and Scopus (November 2013)

• (P)atient Keywords: “newborn”, “infant”, “neonate”, “baby”, asphyxia”, “ischemia”, “hypoxia”, “encephalopathy” or “anoxia”

• (I)ntervention Keywords: “therapeutic hypothermia” or “cooling”

• Filters: “Randomised Controlled Trial”, “Editorial”, “Letter”, “Clinical trial”, and “Human”

• No language or publication date restrictions
Results
Selection of Trials

- 64 records (Cochrane Central)
- 80 records (PubMed)
- 132 records (Scopus)

169 unique records (duplicates removed)

- 28 full text articles assessed for eligibility

- 7 RCTs of low technology hypothermia

Three studies included:
- Jacobs, 2011
- Bharadwaj, 2012
- Joy, 2013

141 records excluded with title and abstract review

- 21 articles excluded (not low technology therapeutic hypothermia)

Four studies excluded:
- Akisu, 2003: Inadequate core cooling
- Inder, 2004: No mortality data
- Robertson, 2008: No intensive care
- Thayil, 2013: Limited inclusion criteria
## Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Country</th>
<th>Method</th>
<th>Target and duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacobs, 2011</td>
<td>221</td>
<td>International</td>
<td>RCT Soft, refrigerated gel packs</td>
<td>33.5 °C for 72h</td>
</tr>
<tr>
<td>Bharadwaj, 2012</td>
<td>124</td>
<td>India</td>
<td>Frozen cloth covered gel packs</td>
<td>33.5 °C for 72h</td>
</tr>
<tr>
<td>Joy, 2013</td>
<td>116</td>
<td>India</td>
<td>Soft refrigerated gel packs</td>
<td>33.5 °C for 72h</td>
</tr>
</tbody>
</table>
Primary Outcome: Mortality

Risk of Bias

- Overall risk: Low
Quality of Evidence: GRADE approach

- Gradeprofiler 3.6
- Inconsistency, indirectness, risk of bias, imprecision and publication bias
- **High**: Further research very unlikely to change estimate
- **Moderate**: Further research is likely to have important impact
- **Low**: Further research is very likely to have an important impact
- **Very low**: Very uncertain about the estimate
Mortality: Meta-analysis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>TH Events</th>
<th>TH Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baradwaj 2012</td>
<td>3</td>
<td>62</td>
<td>6</td>
<td>62</td>
<td>13.3%</td>
<td>0.50 [0.13, 1.91]</td>
</tr>
<tr>
<td>Jacobs 2011</td>
<td>23</td>
<td>110</td>
<td>35</td>
<td>110</td>
<td>77.8%</td>
<td>0.66 [0.42, 1.04]</td>
</tr>
<tr>
<td>Joy 2013</td>
<td>1</td>
<td>58</td>
<td>4</td>
<td>58</td>
<td>8.9%</td>
<td>0.25 [0.03, 2.17]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>230</strong></td>
<td><strong>230</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td><strong>0.60 [0.39, 0.92]</strong></td>
</tr>
</tbody>
</table>

Total events: 27 (TH) vs. 45 (Control)

Heterogeneity: Chi² = 0.86, df = 2 (P = 0.65); I² = 0%

Test for overall effect: Z = 2.37 (P = 0.02)

Mortality: Primary admission (High quality evidence)
Mortality at 6-24 months

High quality evidence
Neurological morbidity in survivors at discharge from primary admission

• Bharadwaj, 2012 + Joy, 2013: Amiel-Tyson
• Jacobs, 2011: Not sucking feeds at discharge

Moderate quality of evidence
Morbidity at 6-24 months

• Two studies published data – favoured hypothermia

• Data not pooled because of heterogeneity of assessment methods and timing
Adverse Events

• No significant differences in clinically important adverse events in individual studies
  - Mechanical ventilation
  - Arrhythmia
  - Hypotension
  - Bleeding
  - Sepsis
• Substantial heterogeneity in methods
Conclusions

• Low technology hypothermia combined with intensive care can significantly reduce mortality (NNTB 13) and reduce morbidity (NNTB 4) in survivors at discharge

• Positive outcomes not at the cost of a significant increase in clinically important adverse events in individual studies

• Our results are different to those reported by Pauliah in 2013: Emphasizing the environment is more important than the income level

• Further research needed to determine the safety and feasibility of therapeutic hypothermia in the absence of intensive care such as low-income countries
Cooling: “It is not about the bike”

Thank you