Therapeutic hypothermia – Are we ready?

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Are we ready?

Depends!
Are we ready?

Questions

1. Why?
   – Science, evidence

2. Why not?
   – Practical difficulties, cost, ...

3. Should we?
   – Balance between why & why not?

4. How?
   – Solutions
Causes of child deaths

2nd common cause of neonatal deaths!

Liu, Lancet 2015
<table>
<thead>
<tr>
<th>Intervention</th>
<th>No. of studies</th>
<th>Type of Study</th>
<th>No. of infants</th>
<th>Long-term outcome</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium sulfate</td>
<td>1</td>
<td>Safety RCT</td>
<td>15</td>
<td>N.A</td>
<td>Higher dose: Hypotension; low dose: Resp. depression can occur. Better short term outcomes (CT scan, EEG and oral feeds by 14 days)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td></td>
<td>33</td>
<td>N.A</td>
<td></td>
</tr>
<tr>
<td>Allopurinol</td>
<td>1</td>
<td>RCT</td>
<td>22</td>
<td>? Available</td>
<td>No difference in the mortality &amp; long-term outcome. Insufficient evidence</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Systemic Review</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>1</td>
<td>Case-series</td>
<td>4</td>
<td>N.A</td>
<td>No RCTs so far</td>
</tr>
</tbody>
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## Asphyxia – Management

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<tr>
<td>Steroids</td>
<td>1</td>
<td>Case-series</td>
<td>?</td>
<td>N.A</td>
<td>No effects on cerebral perfusion pressure</td>
</tr>
<tr>
<td>Mannitol</td>
<td>1</td>
<td>RCT</td>
<td>25</td>
<td>N.A</td>
<td>No difference in the mortality</td>
</tr>
<tr>
<td>Opiate antagonists</td>
<td>1</td>
<td>RCT</td>
<td>193</td>
<td>N.A</td>
<td>No difference in HR/RR; Increased muscle tone of UL &amp; LL</td>
</tr>
<tr>
<td>Phenobarbital (prophylactic)</td>
<td>3</td>
<td>RCT</td>
<td>110</td>
<td>YES</td>
<td>No difference in mortality or long-term outcome</td>
</tr>
<tr>
<td>Phenobarbital (prophylactic)</td>
<td>1</td>
<td>Cochrane</td>
<td></td>
<td></td>
<td>Same; but all studies have methodological weakness</td>
</tr>
</tbody>
</table>
Asphyxia - Management

Management of moderately and severely asphyxiated neonates

Neonate with birth asphyxia
- Requiring bag and mask ventilation / chest compressions / intubation / drugs at birth
- Non-vigorous baby born through meconium stained liquor

Check vitals
- Temperature (avoid hyperthermia)
- Heart rate
- Capillary refill time (CRT)
- Skin color - vary pale / blue
- Respiratory rate
- Lower chest retractions
- Abnormal movements
- SpO2

Principles & Management

1. Maintain normal temperature
   - Avoid hyperthermia (temperature ≥37.5°C)
   - Consider therapeutic hypothermia if facilities and expertise are available
2. Maintain oxygenation and ventilation
   - Secure airway
   - Start oxygen by hood if SpO2 is low.
   - Target SpO2 90-95%
3. Maintain normal perfusion
   - Administer RBCs if perfusion is low
   - Transfuse if there is evidence of blood loss
   - Start inotropes if perfusion is low despite volume expansion

Accordingly
- Consider Phenobarbital

Only supportive care!
Therapeutic hypothermia

- Induction phase (start of cooling)
- Start of re-warming phase (<0.5 °C per hr)
- Post-re-warming phase (controlled normothermia)

Core (rectal or esophageal temperature °C)

- Phase I
- Phase II: Beginning of maintenance phase
- Phase III: 33.5 °C ± 0.2 °C

Elapsed time in hours

30 min
Timing of Pathological Events After Hypoxia-Ischemia

- Hypoxia-Ischemia
- Asphyxia
- Primary Death
- Cytotoxic Mechanisms
- Delayed Neuronal Death

Hypothermia is circled.
How it acts?

1. Energy depletion
2. Glutamate release
3. Glutamate reuptake
4. Free radical generation
5. Blocks downstream mech. of apoptosis/necrosis
6. Inhibits inflammation
Evidence

THE COCHRANE COLLABORATION®
Is it effective?

Reduces mortality/disability by 25%

Cochrane 2013
Is it effective?

Cochrane 2013

Reduces mortality alone by 25%

Review: Cooling for newborns with hypoxic ischaemic encephalopathy
Comparison: 1 Therapeutic hypothermia versus standard care: subgroup analysis by method of cooling
Outcome: 2 Mortality, by method of cooling

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<th>Study or subgroup</th>
<th>Hypothermia n/N</th>
<th>Standard care n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Weight</th>
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<tr>
<td>1 Selective head cooling with mild systemic hypothermia</td>
<td></td>
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</tr>
<tr>
<td>Gunn 1998</td>
<td>3/18</td>
<td>3/13</td>
<td></td>
<td>1.4%</td>
<td>0.72 [0.17, 3.03]</td>
</tr>
<tr>
<td>Akisu 2003</td>
<td>0/11</td>
<td>2/10</td>
<td></td>
<td>1.0%</td>
<td>0.18 [0.01, 3.41]</td>
</tr>
<tr>
<td>Cool Cap Study 2005</td>
<td>36/108</td>
<td>42/110</td>
<td></td>
<td>16.7%</td>
<td>0.87 [0.61, 1.25]</td>
</tr>
<tr>
<td>Lin 2006</td>
<td>2/32</td>
<td>2/30</td>
<td></td>
<td>0.8%</td>
<td>0.94 [0.14, 6.24]</td>
</tr>
<tr>
<td>Zhou 2010</td>
<td>20/100</td>
<td>27/94</td>
<td></td>
<td>11.2%</td>
<td>0.70 [0.42, 1.15]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>269</strong></td>
<td><strong>257</strong></td>
<td></td>
<td><strong>31.1%</strong></td>
<td><strong>0.78 [0.59, 1.04]</strong></td>
</tr>
</tbody>
</table>

Total events: 61 (Hypothermia), 76 (Standard care)
Heterogeneity: Chi² = 1.56, df = 4 (P = 0.82); I² = 0.0%
Test for overall effect: Z = 1.72 (P = 0.089)

2 Whole body cooling
|                   |                  |                  |                              |        |                              |
| Shankaran 2002    | 2/9              | 3/10             |                              | 1.1%   | 0.74 [0.16, 3.48]            |
| Eicher 2005      | 10/32            | 14/33            |                              | 5.5%   | 0.74 [0.38, 1.41]            |
| NICHD Study 2005 | 24/102           | 38/103           |                              | 15.2%  | 0.64 [0.41, 0.98]            |
| TOBY Study 2009  | 42/163           | 44/162           |                              | 17.7%  | 0.95 [0.66, 1.36]            |
| neo.nEURO Study 2010 | 20/53       | 33/58            |                              | 12.6%  | 0.66 [0.44, 1.00]            |
| ICE Study 2011   | 27/108           | 42/109           |                              | 16.8%  | 0.65 [0.43, 0.97]            |
| **Subtotal (95% CI)** | **467**       | **475**           |                              | **68.9%** | **0.73 [0.61, 0.89]**      |

Total events: 125 (Hypothermia), 174 (Standard care)
Heterogeneity: Chi² = 2.92, df = 5 (P = 0.71); I² = 0.0%
Test for overall effect: Z = 3.18 (P = 0.0015)

**Total (95% CI)**

|                   |                  |                  |                              |        |                              |
|                   | 736              | 732              |                              | 100.0% | 0.75 [0.64, 0.88]            |

Heterogeneity: Chi² = 8.32, df = 10 (P = 0.01); I² = 0.0%
Test (even with an increase of random effects): Z = 2.36 (P = 0.02)

Cochrane 2013
Is it effective?

Reduces disability by 33%
Why?

- Any other modality? - No
- Science - Yes
- Evidence - Yes

Standard of care!
Why not to use?
India: Peculiar situation

- Population differences
- Practical issues
- Cost
- Evidence
Population differences

Brain injury – begins *in utero*

• Maternal malnutrition/anemia
• IUGR
• Poor antenatal care
• Home deliveries – poor perinatal care

? Less beneficial

Wilkinson 2010
Population differences...

Sepsis

• Hypothermia
  – affects neutrophil function
  – Can worsen sepsis and pneumonia

• Difficult to differentiate sepsis and asphyxia

Uganda trial – Increased mortality!

Wilkinson 2010
Population differences...

Late referral and others

- Reach after 6 hours
- Most – multiorgan dysfunction
  - Kidneys
  - Heart
- Many – MAS and PPHN

Less effective; may be harmful

Wilkinson 2010
Practical issues

Adverse events

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>No. (%)</th>
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<tbody>
<tr>
<td>Cardiac arrhythmias</td>
<td>Nil</td>
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<td>Oliguria (urine output &lt; 0.5 mL/kg/h)</td>
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Needs 24-hr monitoring!
Cost

Cost – 5 to 30 lakhs!
Evidence in LMIC

Therapeutic Hypothermia for Neonatal Encephalopathy in Low- and Middle-Income Countries: A Systematic Review and Meta-Analysis

Shreela S. Pauliah¹, Seetha Shankaran², Angie Wade³, Ernest B. Cady⁴, Sudhin Thayyil¹*
## Evidence in LMIC

<table>
<thead>
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<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td>5 min Apgar &lt; 6 AND Cord pH &lt; 7.1 or base deficit &gt; 10 mmol/L AND encephalopathy</td>
<td>5 min Apgar &lt; 6 AND Cord pH &lt; 7.1 or base deficit &gt; 15 mmol/L AND encephalopathy</td>
<td>5 min Apgar &lt; 6 AND Cord pH &lt; 7 or base deficit &lt; 16 mmol/L AND need for resuscitation at 5 minutes of age</td>
<td>5 min Apgar &lt; 6 AND encephalopathy (Thompson score &gt; 5)</td>
<td>5 min Apgar &lt; 6 AND encephalopathy (Thompson score &gt; 5)</td>
<td>10 min Apgar &lt; 6 AND arterial pH &lt; 7 or base excess ≥ 12 meq AND encephalopathy</td>
<td>10 minute Apgar &lt; 5 AND Cord pH &lt; 7 and or base deficit of &gt; 18 meq/L</td>
</tr>
<tr>
<td><strong>Exclusion criteria</strong></td>
<td>Major congenital malformation, metabolic disorder, chromosomal abnormalities, congenital infection, transitory drug depression</td>
<td>Major congenital abnormalities, persistent pulmonary hypertension</td>
<td>Major congenital abnormalities, maternal fever &gt; 38°C, infection, rupture of membranes &gt; 18 hours or foul smelling liquor, other encephalopathy</td>
<td>Apnoea or cyanosis, absent cardiac output &gt; 10 min</td>
<td>Major congenital malformations, imminent death at time of randomisation</td>
<td>Major congenital abnormalities, no spontaneous respiration by 20 min, out born babies</td>
<td>Not described</td>
</tr>
</tbody>
</table>
Efficacy: Mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Cooled Events</th>
<th>Total Events</th>
<th>Standard Care Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>M-H, Random, 95% CI</th>
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<td>3</td>
<td>62</td>
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<td>13.0%</td>
<td>0.50 [0.13, 1.91]</td>
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<td>Bhatt 2006</td>
<td>3</td>
<td>20</td>
<td>5</td>
<td>15</td>
<td>14.3%</td>
<td>0.45 [0.13, 1.59]</td>
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<td>7</td>
<td>21</td>
<td>1</td>
<td>15</td>
<td>6.5%</td>
<td>5.00 [0.69, 36.50]</td>
<td></td>
</tr>
<tr>
<td>Thayyil 2012</td>
<td>4</td>
<td>17</td>
<td>2</td>
<td>16</td>
<td>10.1%</td>
<td>1.88 [0.40, 8.90]</td>
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<td>20</td>
<td>138</td>
<td>27</td>
<td>118</td>
<td>45.9%</td>
<td>0.63 [0.38, 1.07]</td>
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</tr>
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Total (95% CI) 301 266 100.0% 0.74 [0.44, 1.25]

Total events 39 45

Heterogeneity: Tau² = 0.09; Chi² = 7.14, df = 6 (P = 0.31); I² = 16%

Test for overall effect: Z = 1.13 (P = 0.26)

No difference in mortality!
### Safety: Sepsis

#### Risk Ratio

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Cooled Events</th>
<th>Total</th>
<th>Standard care Total</th>
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<tbody>
<tr>
<td>Akisu 2003</td>
<td>1</td>
<td>11</td>
<td>2</td>
<td>0.45 [0.05, 4.28]</td>
</tr>
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<td>17</td>
<td>0</td>
<td>7.00 [0.39, 125.99]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>90</strong></td>
<td><strong>89</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.98 [0.26, 3.61]</strong></td>
</tr>
</tbody>
</table>

Total events: 7 (Cooled) 6 (Standard care)

#### Heterogeneity

- Tau² = 0.28; Chi² = 2.47, df = 2 (P = 0.29); I² = 19%
- Test for overall effect: Z = 0.03 (P = 0.97)

**No difference in sepsis!**
No future?
Should we?
Population differences

Brain injury – begins *in utero*

- Maternal malnutrition/anemia
- Poor antenatal care
- Home deliveries
- IUGR

Improve antenatal care; facility births!

Research idea 1:
Efficacy of hypothermia in IUGR!
Population differences

Sepsis

• Hypothermia
  – affects neutrophil function
  – Can worsen sepsis and pneumonia

• Difficult to differentiate sepsis and asphyxia

Research idea 2:
Safety in asphyxia and sepsis!
Population differences

Late referral and others

• Reach after 6 hours
• Most – multiorgan dysfunction
  – Kidneys
  – Heart
• Many – MAS and PPHN

Early referral!
Practical issues

Level of intensive care

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Ensure monitoring, lab facilities, blood bank!
Cost

Low-cost devices!
Options

Low tech devices

• Water bottles
• Fans
• Gels
• Ice packs
• Phase changing mattresses
Cooling using ice packs

(a) Rectal temperature
Options

Cost: 125 000 INR!
## Evidence in LMIC

### Cooling Therapy in Low and Middle-Income Countries

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**Test for overall effect:** $Z = 1.13$ ($P = 0.26$)

---

**Small sample size!**
Part 13: Neonatal Resuscitation

2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

Myra H. Wyckoff, Chair; Khalid Aziz; Marilyn B. Escobedo; Vishal S. Kapadia; John Kattwinkel; Jeffrey M. Perlman; Wendy M. Simon; Gary M. Weiner; Jeanette G. Zaichkin

Resource-Limited Areas

Evidence suggests that use of therapeutic hypothermia in resource-limited settings (ie, lack of qualified staff, inadequate equipment, etc) may be considered and offered under clearly defined protocols similar to those used in published clinical trials and in facilities with the capabilities for multivariate intensive care and medical follow-up. 103-105, 13-14.
How?
## 4P for optimum TH

<table>
<thead>
<tr>
<th>Place</th>
<th>Personnel</th>
<th>Paraphernalia</th>
<th>Protocols</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <strong>Level-3 NICU</strong> (desirable)</td>
<td>• Trained Pediatrician • Nursing staff</td>
<td>• Radiant Warmer • <strong>Cooling device</strong> • <strong>Rectal probes</strong> for temperature monitoring • Multiparametric monitors • ABG machine • Mechanical ventilator • Glucometer • aEEG (desirable) • MRI (desirable)</td>
<td>• <strong>Timely identification of HIE</strong> • Ensuring TH within 6 h of birth • <strong>Evidence-based standard protocol</strong> for providing and monitoring TH • 24 x 7 monitoring • Standardized neurodevelopment follow-up • Continuing staff education</td>
</tr>
<tr>
<td>• Well established Level-2 NICU</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Bhat VB, IJP 2014*
Conclusion

• **Level-3 units**
  – *Start cooling* with adequate monitoring

• **Level-2 units**
  – *Establish* facilities required (monitoring; lab)
  – Low-cost devices (if monitoring feasible)
  – Early referral (if no facilities)
Conclusion

Therapeutic hypothermia – Make ourselves ready!