Neonatal Hypoxic – Ischemic Encephalopathy

Treatment Approaches from Evidence

Dr. Nguyen Pham Minh Tri – NICU – Children’s Hospital 2
Content

1. Introduction
2. HIE and Hypothermia
3. Other combination treatments
4. Conclusion
HIE in the world

- Major public health issue
- 23% of the total 4 M deaths in the world
- 20% of global incidence of cerebral palsy

Lawn JE et al, Lancet 2005
Etiologies of HIE

- **Maternal**
  - Cardiac arrest
  - Asphyxiation
  - Severe anaphylaxis
  - Status epilepticus
  - Hypovolemic shock

- **Fetal**
  - Fetomaternal haemorrhage
  - Twin to twin transfusion
  - Severe iso-immune haemolytic disease
  - Cardiac arrhythmia

- **Uteroplacental**
  - Placental abruption
  - Cord prolapse
  - Uterine rupture
  - Hyperstimulation with oxytocic agents
<table>
<thead>
<tr>
<th>HIE severity and morbidity/mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moderately severe</strong></td>
</tr>
<tr>
<td>- 1-3 / 1000 livebirths</td>
</tr>
<tr>
<td>- Severe handicaps: 30-50% (epilepsy, cognitive impairment, CP…)</td>
</tr>
<tr>
<td>- Mild handicaps: 10-20%</td>
</tr>
<tr>
<td>- Normal outcome at 2y: 30-40%</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Early evaluation of HIE

- Early, **repeated** clinical examination: **Sarnat staging+++**
- Clinical investigations:
  - **EEG**: early, continuous recording / standard EEG or aEEG
  - **Ultrasonography**: easy but non specific, *as early as possible*
→ Short term prognosis. **HYPOTHERMIA?**
  - **MRI**: standard sequences + Diffusion +/- DTI + MR Spectroscopy: *btw day 3 - day 8 +/- day 10-15*
→ Long term outcome.
# Sarnat grading scale for HIE

<table>
<thead>
<tr>
<th></th>
<th>Grade 1 (mild)</th>
<th>Grade 2 (moderate)</th>
<th>Grade 3 (severe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of consciousness</td>
<td>Irritable/hyperalert</td>
<td>Lethargy</td>
<td>Coma</td>
</tr>
<tr>
<td>Muscle tone</td>
<td>Normal or hypertonia</td>
<td>Hypotonia</td>
<td>Flaccid</td>
</tr>
<tr>
<td>Tendon reflexes</td>
<td>Increased</td>
<td>Increased</td>
<td>Depressed or absent</td>
</tr>
<tr>
<td>Seizures</td>
<td>Absent</td>
<td>Frequent</td>
<td>Frequent</td>
</tr>
<tr>
<td>Complex reflexes</td>
<td>Normal</td>
<td>weak</td>
<td>Absent</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Good</td>
<td>Variable (80% ) Normal</td>
<td>High mortality and neurological disability (50% Death 50% major sequelae)</td>
</tr>
</tbody>
</table>
Amplitude EEG features in HIE

HIE and MRI features

- Basal ganglia and thalami
- Cortical enlighting
- Post limb of internal capsule
- White matter

Rutherford et al., Lancet 2010
Figure 1: Mechanisms of evolving neural injury in HIE
HIE and energy failures

- First energy failure during HIE
- Rapid recovery
- Secondary energy failure after 6-12h post HIE
- Mitochondrial insult
- Cell death and apoptosis

The ratio of inorganic phosphate (Pi) to phosphocreatine (PCr) is validated marker of mitochondrial function.
Brain metabolism is normal following resuscitation but deteriorates later.

Hypothermia: concept

- To induce a stable central temperature around 33.5 ± 0.5°C
- Before 6 hours of life
- In the most stable manner
- For a 72h duration
- Progressive and cautious rewarming 0.2°C / h
Hypothermia: cellular effects

- cerebral metabolism → edema
- energy utilization
- cytotoxic amino acid accumulation (glutamate) and nitric oxide
- platelet-activating factor → inflammatory cascade
- secondary neuronal damage and cell death
- extent of brain damage
- blood brain barrier disruption
Experimental evidence supporting therapeutic hypothermia

• Hypothermia applied after HIE:
  – Reduces elevation of dopamine, free fatty acid and glutamate
    • Stroke 1989; 20:904-10.
  – Preserves cerebral energy metabolism
  – Reduces the delayed increase in extracellular glutamate
    • Neuroreport 1997; 8:3359-62
  – Reduces the secondary rise in cortical impedance (cytotoxic oedema)
    • Pediatrics 1998; 102:1098-1106
  – Inhibits apoptotic cell death
    • Neuropathol Appl Neurobiol 1997; 23:16-25
Hypothermia

Head cooling or total body cooling
Hypothermia criteria

- Perinatal event leading to HIE
  - GA ≥ 36 wg et BW ≥ 1800 g
  - Postnatal age < 6 hours

Biological and/or clinical markers for HIE at birth?

- YES

Clinical signs of neurological disorder linked to HIE?

- YES

Therapeutic hypothermia

- Acidosis
  - pH ≤ 7
  - Base deficit ≥ 16 mmol/l
  - Lactate ≥ 11 mmol/l

- Apgar score ≤ 5 à M5

- No spontaneous breathing at M10

- Resuscitation at birth

- Clinical signs of HIE (Sarnat)

- If possible, abnormalities:
  - EEG
  - aEEG (staging)
Beneficial effect of hypothermia according to HIE severity

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hypothermia</th>
<th>Normothermia</th>
<th>Weight, %</th>
<th>Risk Ratio M-H, Fixed (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants With Moderate Encephalopathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azzopardi et al, 2009</td>
<td>20/65</td>
<td>30/67</td>
<td>17.9</td>
<td>0.69 (0.44-1.08)</td>
</tr>
<tr>
<td>Gluckman et al, 2005</td>
<td>28/62</td>
<td>39/69</td>
<td>22.3</td>
<td>0.80 (0.57-1.13)</td>
</tr>
<tr>
<td>Gunn et al, 1998</td>
<td>4/10</td>
<td>1/5</td>
<td>0.8</td>
<td>2.00 (0.30-13.51)</td>
</tr>
<tr>
<td>Jacobs et al, 2011</td>
<td>26/61</td>
<td>34/51</td>
<td>22.4</td>
<td>0.64 (0.45-0.91)</td>
</tr>
<tr>
<td>Shankaran et al, 2005</td>
<td>22/69</td>
<td>30/63</td>
<td>19.0</td>
<td>0.67 (0.43-1.03)</td>
</tr>
<tr>
<td>Simbruner et al, 2010</td>
<td>6/19</td>
<td>9/15</td>
<td>6.1</td>
<td>0.53 (0.24-1.15)</td>
</tr>
<tr>
<td>Zhou et al, 2010</td>
<td>9/41</td>
<td>19/41</td>
<td>11.5</td>
<td>0.47 (0.24-0.92)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>327/162</td>
<td></td>
<td>100.0</td>
<td>0.67 (0.56-0.81)</td>
</tr>
<tr>
<td>Total events</td>
<td>115</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 3.75; P = .71; I^2 = 0%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $z = 4.27; P &lt; .001$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Infants With Severe Encephalopathy | | | | |
| Azzopardi et al, 2009 | 54/98 | 56/95 | 26.8 | 0.93 (0.73-1.19) |
| Gluckman et al, 2005 | 28/40 | 32/35 | 16.1 | 0.77 (0.61-0.96) |
| Gunn et al, 1998 | 2/3 | 3/3 | 1.6 | 0.71 (0.31-1.66) |
| Jacobs et al, 2011 | 25/30 | 24/27 | 11.9 | 0.94 (0.76-1.15) |
| Shankaran et al, 2005 | 23/32 | 34/40 | 14.2 | 0.85 (0.66-1.09) |
| Simbruner et al, 2010 | 21/34 | 39/43 | 16.2 | 0.68 (0.51-0.90) |
| Zhou et al, 2010 | 22/38 | 27/35 | 13.2 | 0.75 (0.54-1.04) |
| Subtotal (95% CI) | 275/278 | | 100.0 | 0.83 (0.74-0.92) |
| Total events | 175 | | | |
| Heterogeneity: $\chi^2 = 5.12; P = .53; I^2 = 0\%$ |
| Test for overall effect: $z = 3.46; P < .001$ |

Tagin et al., Cochrane 2012

NNT 6-8
Beneficial effect of hypothermia according to cooling technique

Tagin et al., Cochrane 2012
Normal outcome following hypothermia for HIE

Tagin et al., Cochrane 2012
Impact of hypothermia on MRI findings

THERAPEUTIC HYPOTHERMIA reduces basal ganglia and WM lesions
BUT has NO effect on cortical damage

Rutherford et al., 2009
Mid- long-term outcomes: neurocognitive/behavior scales

• **12-30 months: Bayley**
  – (Eicher & al., 2004; Jacobs & al., 2011; Shankaran & al., 2005)

• **6-7 years: WPPSI-III / WISC-IV / NEPSY / M-ABC**
  – (Marlow & al., 2005; Shankaran & al., 2012)

• **9-10 years: WISC-III / M-ABC / CBCL**
  – (de Veries & Jongmans, 2010)
Childhood outcomes after hypothermia for HIE

- **Objective**
  - Long term evaluation (6-7 y) of infants having experienced hypothermia for HIE

- **Methods and patients**
  - 208 infants with HIE 2-3 at birth
  - 93 controls (6y8m) vs 97 hypothermia (6y7m)
  - 18 lost (15% of surviving)

Shankaran et al., NEJM 2012
Childhood outcomes after hypothermia for HIE

- **Results**
  - **Hypothermia (n = 97)**
    - 27 deaths (28 %)
    - 5 lost (5 %)
    - 12/69 CP (17 %)
    - 1/67 blindness (1 %)
    - 3/63 deafness (5%)
  - **Controls (n = 93)**
    - 41 deaths (44 %)
    - 13 lost (14 %)
    - 15/52 CP (29 %)
    - 2/50 blindness (4 %)
    - 1/50 deafness (2%)

Shankaran et al., NEJM 2012
Childhood outcomes after hypothermia for HIE

• **Results**
  – Hypothermia
    • 19/70 IQ < 70 (27 %)
    • 2/48 dysexecutive functions (< 70) (4 %)
    • 2/53 visuo-spatial impairment (< 70) (4 %)
  – Controls
    • 17/52 IQ < 70 (33 %)
    • 4/32 dysexecutive functions (< 70) (13 %)
    • 1/36 visuo-spatial impairment (< 70) (3 %)

Shankaran et al., NEJM 2012
Hypothermia + neuroprotective agents

Robertson et al., 2012
Promising candidate molecules to be associated with hypothermia

Robertson et al., 2012

<table>
<thead>
<tr>
<th></th>
<th>Melatonin</th>
<th>Epo</th>
<th>NAC</th>
<th>Epo mimetics</th>
<th>Allopurinol</th>
<th>Xenon</th>
<th>Vit C&amp;E</th>
<th>Memantine</th>
<th>Topiramate</th>
<th>Adenosine A2A rec antag</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Easy to use</strong></td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>7</td>
<td>4</td>
<td>9</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td><strong>Regimen</strong></td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>8</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td><strong>SAE</strong></td>
<td>10</td>
<td>8</td>
<td>10</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td><strong>Toxicity</strong></td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>7</td>
<td>10</td>
<td>8</td>
<td>8</td>
<td>10</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td><strong>Benefits</strong></td>
<td>8</td>
<td>8</td>
<td>3</td>
<td>6</td>
<td>3</td>
<td>8</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td><strong>FDA approval</strong></td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td><strong>Total score /50</strong></td>
<td>45</td>
<td>43</td>
<td>40</td>
<td>38</td>
<td>36</td>
<td>34</td>
<td>33</td>
<td>27</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td><strong>Rank % score</strong></td>
<td>1 (90%)</td>
<td>2 (86%)</td>
<td>3 (80%)</td>
<td>4 (76%)</td>
<td>5 (72%)</td>
<td>6 (68%)</td>
<td>7 (66%)</td>
<td>8 (54%)</td>
<td>9 (50%)</td>
<td>10 (44%)</td>
</tr>
</tbody>
</table>
Conclusion

• HIE trigger is poorly understood → public health issue

• More than 1M deaths and 2M infants with neurocognitive impairments / year

• Therapeutic hypothermia is feasible, safe in referral centers and efficient at mid-term if initiated before 6h of life … but impact in long-term outcomes?

• Hot topics for neuroprotective strategies

• … the future → combination of hypothermia + other pharmacological agent(s)