Therapeutic Hypothermia for Neonatal Encephalopathy: Experiences of a Medical Center in Northern Taiwan

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Background

- 2011: Neonatal Resuscitation Program (NRP)

  *Infants born at $\geq 36$ weeks gestation with evolving moderate to severe hypoxic–ischemic encephalopathy (HIE) should be offered therapeutic hypothermia within 6 hours following birth.*

- Therapeutic hypothermia (TH) in Taiwan: late 2010

- Some “grey case” situations exist in the practice of TH.
Objective

The purpose of the study is to describe our experiences in performing TH for neonatal encephalopathy in our NICU at Chang Gung Children’s Hospital.
Patients and Methods (1)

- Admitted to NICU at Chang Gung Children’s Hospital
- April 2011 and December 2012
- Enrolled patients were divided into three groups.

**Group 1:** Those who were fulfilled with the NRP criteria for TH. TH was initiated *within 6 hours of life.*

**Group 2:** Newborn infants with perinatal HIE who were treated with TH *beyond 6 hours of life.*

**Group 3:** Infants with GA < 36 weeks who had perinatal HIE or postnatal collapse. TH was initiated immediately after the events.
Population:
Taiwan: 23,350,000
Area:
Taiwan: 36,192 km²
Taoyuan County: 1,220 km²
Neonatal Department at Chang Gung Children’s Hospital

NICU: 37 beds
Intermediate ICU: 70 beds
Annual birth: 3000-4000
Whole body cooling therapy was used. (A cooling blanket system, Cincinnati Sub-Zero Blanketrol II)

Eligible infants were kept at 33-34°C (esophageal temperature) for 72 hours and re-warmed for at least 6 hours.
Neurodevelopmental outcome was evaluated at 6 and 12 months of age by using Bayley Scales of Infant Development, third edition (BSID-III).

Adverse outcome was defined as cognitive score<85, language score<79 and motor score<85.
Results
Group 1 (n=17): Eligible for NRP Criteria

- A total of 17 patients was enrolled (M:F=10:7).
- The 1-min and 5-min Apgar scores were $1\pm2$ and $3\pm2$.
- Gestational age: $38.3\pm1.3$ / Birth weight: $3305\pm774$
- HIE stage II: 8 / HIE III: 9
Source of Patients in-born vs. out-born

- In-born (4/17)
- Out-born (13/17)
Age at Initiation of Hypothermia Therapy

Overall 288±77 minutes
## Mortality of Patients in-born vs. out-born

<table>
<thead>
<tr>
<th>#</th>
<th>Gender</th>
<th>In-born</th>
<th>GA</th>
<th>BBW</th>
<th>VD/CS</th>
<th>AS (1)</th>
<th>AS (5)</th>
<th>CPCR (mins)</th>
<th>1st ABG pH</th>
<th>1st ABG BE</th>
<th>HIE stage</th>
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<td>Out-born</td>
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<td>2895</td>
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<td>0</td>
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<td>-20.8</td>
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<td>3565</td>
<td>VD</td>
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<td>1</td>
<td>12</td>
<td>6.5</td>
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<td>3530</td>
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<td>1</td>
<td>60</td>
<td>6.35</td>
<td>-29</td>
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Out-born (13/17)
HIE II/III s/p TH
N=17

Survivors
N=14

Survivors, Age > 6 M
N=9

6 M BSID-III
N=8

12 M BSID-III
N=6

Loss f/u
N=1
<table>
<thead>
<tr>
<th>#</th>
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<th>AS-1</th>
<th>AS-5</th>
<th>HIE</th>
<th>6M</th>
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</table>

- **Lost follow-up**
The cognitive, language and motor score were 91±27, 88±12, 88±17.
The cognitive, language and motor score were $100 \pm 17$, $88 \pm 11$, $81 \pm 21$. 
Group 2 (n=2): Infants > 6 hours

#1 The baby girl (GA 36 wks; BBW 2081 g; AS 5→ 6; perinatal HIE II) was treated with TH at 9 hours of life. She received peritoneal dialysis since 2 days of age, and died due to sepsis.

#2 The baby girl (GA 36 wks; BBW 2765 g; AS 0→ 1; perinatal HIE II) was treated with TH at 11 hours of life. BSID-II performed at 6 M showed PDI 108 and MDI 114.

The survival rate was 50% in this group.
Group 3 (n=3): GA<36 wks (& postnatal collapse)

#1 The baby girl (GA 33 wks, BBW 2180 g, AS 1→ 2, perinatal HIE II-III) was treated with TH within 6 hours of life. She was discharged and followed up at OPD regularly.
Group 3 (n=3): GA<36 wks & postnatal collapse

#2 The baby boy (GA 32 wks, BBW 1940 g, AS 4 → 9) developed sudden onset of bradycardia, cyanosis and received resuscitation at PMA 34 weeks. TH was performed within 6 hours following the event. Brain MRI was evaluated 4 days after the event and showed multiple periventricular abnormal signals and brain stem hyperintensities indicating acute periventricular infarcts and early subacute pontine infarcts. However, he developed infantile spasms at 6 months of corrected age.
Group 3 (n=3): GA<36 wks & postnatal collapse

#3 The baby boy (GA 25 wks, BBW 985 g) received resuscitation due to mechanical problem at PMA 34 weeks with weight of 2165 g. TH was performed within 6 hours following the event. He tolerated TH well.
Esophageal Temperature during Hypothermia Therapy

Infants with GA 33-36 weeks
The survival rate was 83% (14/17) in the group 1. [100% among HIE II and 67% (6/9) among HIE III]

The survival rate of infants with stage II HIE was higher if TH was started within 6 hours of life compared to that after 6 hours of life in the current study.

Among the survivors who has been evaluated at 6 months of age, all infants with HIE II had good neurodevelopmental outcome but only 25% of infants with HIE III had good neurodevelopmental outcome.
There is evidence of ongoing brain injury beyond the 6-hour therapeutic window; hence hypothermia as therapy for infants with stage II/III HIE who present after 6 hours of birth is being evaluated (NCT00614744).


In cases of inadvertent delay, it is still reasonable to commence cooling in infants aged between 6 and ~12 hours postnatal, given that possible lifelong benefits would outweigh the small risks.

Austin et al. Arch Dis Child Fetal Neonatal Ed 2012
Based on our experience, infants with GA < 36 weeks could tolerate TH. For an infant with GA 33-36 weeks with stage II/III HIE, it would not be unreasonable to offer cooling in full discussion with the parents.

*Austin et al. Arch Dis Child Fetal Neonatal Ed 2012*

One RCT is ongoing, evaluating hypothermia as neuroprotection for late preterm infants (NCT00620711). Currently, it is not recommend to cool infants with GA < 33 weeks.

Austin et al. Arch Dis Child Fetal Neonatal Ed 2012*
Discussion (3)

Our data did not show benefits of TH for infants with postnatal collapse.

Although no clinical trial has looked at TH following early postnatal collapse, these babies often have good evidence of HI brain injury on neuroimaging and so are likely to benefit from cooling.

*Austin et al. Arch Dis Child Fetal Neonatal Ed 2012*

*Foran et al. Arch Dis Child Fetal Neonatal Ed 2009*
Thank you!