It’s Here! A Cool Therapy for Neonatal Brain Injury

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Grand Rounds
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A Cool Therapy for HIE

I. Case Report
II. Extent of the Problem
III. Definitions and Diagnosis of HIE
IV. Pathophysiology of HIE
V. Conventional management
VI. New Therapies for HIE
Phenobarbital
Room air resuscitation
Brain Cooling
VII. Quality Improvement at WCHOB NICU
Continuous Video EEG
Delivery Room O2 blenders
Systemic Hypothermia

Case Report

- Baby SS was a 2.6 kg AGA product of a 35 1/7 weeks gestation to a 41 yo healthy G4P1 female with an uncomplicated pregnancy until she presented by ambulance to an outlying hospital with severe abdominal pain and fetal bradycardia. Delivered by stat C/S at which time placental abruption was noted.
- DR: apneic, HR < 60, flaccid. Intubated, cardiac compressions, epi x1. Cord gas: pH < 6.8, PCO2 80’s, BE > 30. Gasping respirations at 4min of life. Apgars 1,4,4 @ 1,5,10 min; no spont movement until 30 min of life.

Outside hospital course
- Handbagged ventilation with 100% O2
- UVC, UAC placed, 20 ml/kg NSS
- Seizure onset at 1h of life 20 mg/kg phenobarbital
- Oozing blood noted –– PT/PTT/Fibrinogen obtained
- ABG at 1.5h of life: 7.03/24/173/23
- Serum glucose 163 mg/dl
- Partial correction with 2 mEq/kg NaHCO3 during transport

Arrival at WCHOB NICU
- Neuro exam: no spontaneous breathing, decreased tone and reflexes; gag present
- Cardiovascular: no murmur, adequate pulses, BP 52/24, HR 160
- Temp 36.6°C
- Labs
  - Na 133; BUN 19, Cr 1.5; INR 2.12; Hct 41.1; plt 179K, AST 315, ALT 48

WCHOB Course
- HIE – no spontaneous respiratory x 24h; vent x72h; no spontaneous movement x 36h
- Metabolic Acidosis – persistent for 3h
- Coagulopathy - FFP 30/kg over first 24h
- Glucose instability
- Seizures – initial EEG mildly depressed background; normal D3
II. Extent of Problem

Acute Perinatal Hypoxic-Ischemic Encephalopathy

- Postasphyxial encephalopathy
  - Incidence: 2-3 infants per 1000 live term births in developed countries
  - *Unchanged over last 20 years
- Moderate HIE
  - Mortality: 10%
  - Permanent Disability: 30% of survivors
- Severe HIE
  - Mortality: 60%
  - Permanent Disability: up to 100% of survivors

WCHOB Perinatal Regional Referral Center NICU

- HIE Incidence
  - Outborn and inborn: 16 infants per year on average
  - Range 12-24 per year
  - WNY total birth rate: 16,000/yr
  - 131 infants with moderate to severe HIE admitted to WCHOB 2002-2008

III. Diagnosis of HIE

- Criteria
  - Pertinent obstetric event
    - (e.g. uterine rupture, abruption, cord prolapse, maternal hemorrhage)
  - Measures of impaired placental gas exchange
    - (e.g. cord pH)
  - Poor adaptation at birth and need for resuscitation
    - (e.g. low Apgar scores)
  - Clinical encephalopathy
    - (e.g. low Sarnat scores)
  - Other organ system dysfunction

Severity of Perinatal Asphyxia

- Initial Markers of Severity
  - Neurologic exam – Sarnat classification, EEG background pattern
  - Degree of metabolic acidosis and time to correction
    - Cord gas and early infant blood gases
  - Degree of other organ involvement
    - renal compromise
    - transaminase elevation
    - cardiogenic shock

Sarnat Classification of HIE

- Sarnat I (Mild)
  - hyper-alert, staring, irritability, apnea, hypotonia, no seizures
- Sarnat II (Moderate)
  - depressed consciousness, lethargy, hypotonia, seizures
- Sarnat III (Severe)
  - stupor, flaccid, unresponsive, decerebrate, seizures uncommon
EEG in Infant with Severe HIE

Multi-system Organ Injuries

<table>
<thead>
<tr>
<th>Vulnerability</th>
<th>Clinical Presentation</th>
<th>Recoverability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Apnea, Hypotonia, Encephalopathy, Coma, Seizures</td>
<td>++</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Acute Renal Failure</td>
<td>+++++</td>
</tr>
<tr>
<td>Lungs</td>
<td>PPHN, ALI, ARDS</td>
<td>+++++</td>
</tr>
<tr>
<td>Liver</td>
<td>Transamnese Derangement, Congestive Heart Failure</td>
<td>+++++</td>
</tr>
<tr>
<td>Heart</td>
<td>Cardiogenic Shock, Valvular Regurgitation</td>
<td>+++++</td>
</tr>
<tr>
<td>Vascular</td>
<td>SIRS, capillary leak, sepsis</td>
<td>+++++</td>
</tr>
<tr>
<td>GI Tract</td>
<td>Feeding Intolerance, NEC</td>
<td>+++++</td>
</tr>
</tbody>
</table>

IV. Pathophysiology of HIE

1º Energy Failure:
- ↓ cerebral blood flow and O2/substrates
- ↓ ATP
- Tissue acidosis
- Acute intracellular derangements

2º Energy Failure: Reperfusion injury
- NO tissue acidosis
- Acute intracellular derangements

Brain Responses to Perinatal Asphyxia

Phases of Cerebral Injury

- Insult: Hypoxic-ischemic brain injury
- Latent: 6 to 15 h
- Secondary: 3 to 10 days
- Hypothermia: 6 to 15 h recovery
- Secondary: 3 to 10 days final cell death
Regional Patterns of Hypoxic-Ischemic Brain Injury

- **Vulnerable** (damage associated with Sarnat II)
  - Cerebral Cortex
  - Subcortex and White Matter
  - Deep Central Brain – Thalamus, Caudate Nucleus, Internal Capsule
  - Basal Ganglia
  - Hippocampus

- **More Resistant** (damage associated with Sarnat III)
  - Brainstem

- **Very Resistant** (damage associated with death)
  - Midbrain
  - Cerebellum

Progression of neuronal injury or loss in term infant with HIE.

- **5 days**
  - Diffuse high signal intensity throughout the basal ganglia and thalami.
  - Normal white matter appearance.

- **18 days**
  - Increased high signal intensity with low signal cystic components.
  - Persistent abnormal high signal intensity in the thalami and lentiform nuclei.
  - Considerable white matter atrophy.

- **7 months**
  - Persistent abnormal high signal intensity in the thalami and lentiform nuclei. Complete white matter atrophy.

Supportive Intensive Care

- **Correction of Hemodynamic and Pulmonary Disturbances**
  - Hypotension – pressor, inotrope support
  - Metabolic acidosis – NaHCO₃ if needed
  - Capillary leak/ SIRS – colloid support, steroids, free water restriction
  - Hypoventilation/Apnea – IMV support
  - PPHN – Nitric Oxide

V. Conventional Management of the Term Infant with HIE

VI. New Therapies for HIE
HIE Pharmacotherapy

- Phenobarbital 40 mg/kg
  - 31 infants moderate-severe HIE – randomized
  - seizure incidence
    - Phenobarbital – 9/15
    - Control – 14/16
  - 3 year normal neurodevelopmental outcome
    - Phenobarbital – 11/15
    - Control – 3/16
    - Hall, J Pediatr 1998

Brain Cooling

Nature’s Evidence for Hypothermia Neuroprotection

- Natural cooling occurs in asphyxiated infant: hypothalamus suppressed by encephalopathy
  - Asphyxiated newborns have decreased temperature to 34.5°C within 2h of birth
    - (2°C less than non-asphyxiated newborns) - Burnard 1958
  - Infants of "difficult deliveries" unable to generate heat as well as infants that had no difficulty - Brück 1961
  - Infants given GA require active warming compared with children and adults - Plattner 1997

Experimental Evidence for Hypothermia Neuroprotection

- Animal Studies
  - Favorable effect on multiple pathways contributing to brain injury
    - Excitatory amino acids - Thoresen, Neuroreport 1997
    - Cerebral energy state - Thoresen, Pediatr Res 1991
    - Nitric oxide production - Thoresen, Neuroreport 1997
    - Apoptosis – Edwards, Boreal Biophys Res Commun 1993

Adult Hypothermia Therapy

- Used in head trauma, stroke, and cardiac arrest

Potential Complications of Therapeutic Hypothermia

- Sclerema
- Multi-system organ damage
  - pulmonary hemorrhage, renal failure, DIC
- Hypovolemia
- Glucose instability
- PPHN
Potential Complications of Therapeutic Hypothermia

- Bradycardia, arrhythmia
- Hypertension
- Major venous thrombosis
- Refractory hypotension
- Sepsis
- Hypotension with rapid re-warming

Brain Cooling Trials in Infants with HIE

- Randomized controlled clinical trials
  - Total body cooling
    - Multi-center pilots – Azzopardi, Pediatrics 2002
    - Multi-center – Shankaran, NICHD 2005
    - Multi-center – TOBY, UK pending 2008
  - Cooling Cap (Plus mild systemic hypothermia)
    - Multi-center – CoolCap – Gluckman, 2005

Cooling Cap

![Cooling Cap Diagram](Laptook, Pediatrics 2001)

Total Body Cooling

![Total Body Cooling Diagram](Laptook, Pediatrics 2001)

NICHD Trial

- Initial Screening
  - ≥36 weeks gestation
  - Admitted to NICU ≤6h of life
  - Poor respiratory effort at birth and need for resuscitation
  - Diagnosis of HIE

NICHD Trial

- Eligibility Criteria
  - pH ≤ 7.0 or BE ≥ -16 mmol/l within 1h of life
  - pH 7.01 to 7.15, or BE -15 to 10 mmol/l within 1h of life or blood gas not available
  - Acute perinatal event including late or variable decels, cord prolapse, cord rupture, uterine rupture, maternal trauma, hemorrhage, or cardiorespiratory arrest
  - Either Apgar ≤ 5 @10min or assisted ventilation at birth and continued for ≥ 10 min
**Inclusion Criteria**

- Infants who met above criteria
- Presence of moderate or severe encephalopathy according to table

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### Criteria for Moderate and Severe HIE

<table>
<thead>
<tr>
<th>Category</th>
<th>Moderate Encephalopathy</th>
<th>Severe Encephalopathy</th>
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<tbody>
<tr>
<td>Level of consciousness</td>
<td>Lethargic</td>
<td>Coma</td>
</tr>
<tr>
<td>Spontaneous activity</td>
<td>Decreased</td>
<td>No activity</td>
</tr>
<tr>
<td>Tone</td>
<td>Hypertonic (normal)</td>
<td>Flaccid</td>
</tr>
<tr>
<td>Presence of moderate or severe encephalopathy</td>
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<td></td>
</tr>
<tr>
<td>Autonomic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pupils</td>
<td>Weak</td>
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<td>Brady asystole</td>
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**Whole Body Hypothermia Trial**

**Table 1. Behavioral and Neurodevelopmental Outcomes**

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**Table 2. Continuous Data**

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**Table 3. Hospital Course and Status at Discharge**

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Summary of Deaths and Survivor Outcomes in Hypothermia Trials

(n) = %; MDI @ 18-22 months

18-22 Month Outcomes: Hypothermia Trials

(n)%; Visual impairment = blindness

Hypothermia – Bottom Line

- 2 large randomized controlled trials of therapeutic hypothermia for term newborns with mod-severe perinatal HIE
  - ↓ combined outcomes of death and ND disability
  - Few adverse effects – mild and transient

Support for Hypothermia as Standard of Care

- AAP Committee on Fetus and Newborn and the NICHD - 2006
  - “…institutions who use hypothermia should employ a rigorous protocol, data collection, and neurodevelopmental F/U…”

- Perlman, Pediatrics 2008
  - “It is time to stop postponing the decision to accept hypothermia (at experienced centers that use established protocols) as an effective treatment. It is our duty to explain the benefits and unknowns of cooling and to offer this treatment to every eligible patient with moderate to severe neonatal HIE.”

NICU QI: How can we improve the outcome of the infant with HIE?

- New at WCHOB
  - Continuous Video EEG
  - Aspen room; remote 24h monitoring on V7
  - $45,000 September to Remember NICU Fundraising Event
  - Cochaired by Dr. Reynolds and NICU parents

- Oxygen blenders purchased for every DR
  - Enables resuscitation with optimal O2

- Brain Cooling
  - Passive hypothermia on transport
  - Total Body Cooling in the NICU

VII. Quality Improvement at WCHOB Perinatal Regional Referral Center
WCHOB Regional Perinatal Referral Center

- Total body cooling
  - Phase I: Initiation of passive cooling at referring site
    - Turn off warmer in DR and nursery
  - Phase II: Arrival of transport team
    - Transport in unheated isolette
    - Consider cool packs
  - Phase III: Arrival at WCHOB NICU
    - Place on cooling blanket for 72h

Appreciation to Drs. Vasanth Kumar and Vivien Carrion