Update on Hypoxic-Ischemic Encephalopathy and Cool-Cap Therapy

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Neonatal Asphyxia

- Neonatal asphyxia is a general term used for newborns deprived of oxygen long enough to cause apparent harm.
- Asphyxia can result in damage to most of newborn’s organs including heart, lung, liver, gut, kidneys and brain.
- The term “Asphyxia” is non-specific and draws the attention of medical malpractice attorneys.
- Perinatal depression is a more specific term.
Hypoxic Ischemic Encephalopathy

- Specific disorder characterized by clinical and laboratory evidence of brain injury due to hypoxia and/or ischemia

- Incidence is 2-10 per 1000 full term newborns
  - Cause of 23% of worldwide neonatal deaths

- Survivors can develop problems such as cerebral palsy, mental retardation, learning difficulties and other disabilities.
HIE Etiology

• 90% of events start prior to delivery
  – Placental Insufficiency/dysfunction (abruption)
  – Cord Compression
  – Fetal Hemorrhage

• 10% after delivery
  – Pulmonary/cardiovascular/neurologic abnormalities
Pathogenesis of HIE

**Therapeutic Window:**
- Hypothermia
- Other

**Primary energy failure (Minutes):**
- Na⁺ overload
- Excitotoxicity

**Reperfusion**

**Cerebral metabolism transiently recovers**
- Ca⁺⁺ overload
- ROS, NO

**Secondary phase (Hours to days):**
**Between 6-72 h after insult**
- Mitochondrial dysfunction
- Caspases activation

**Hypoxic ischemic brain injury**

**Immediate necrotic cell death**

**Delayed apoptotic cell death**
## Sarnot Classification of HIE

<table>
<thead>
<tr>
<th></th>
<th>State 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level of Consciousness</strong></td>
<td>Hyperalert</td>
<td>Lethargic or obtunded</td>
<td>Stuporous</td>
</tr>
<tr>
<td><strong>Neuromuscular Control</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle tone</td>
<td>Normal</td>
<td>Mild hypotonia</td>
<td>Fleccid</td>
</tr>
<tr>
<td>Posture</td>
<td>Mild distal flexion</td>
<td>Strong distal flexion</td>
<td>Intermittent decerebration</td>
</tr>
<tr>
<td>Stretch reflexes</td>
<td>Overactive</td>
<td>Overactive</td>
<td>Decreased or absent</td>
</tr>
<tr>
<td>Segmental myoclonus</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Complex Reflexes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suck</td>
<td>Weak</td>
<td>Weak or absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Moro</td>
<td>Strong; low threshold</td>
<td>Weak; incomplete; high threshold</td>
<td>Absent</td>
</tr>
<tr>
<td>Oculovestibular</td>
<td>Normal</td>
<td>Overactive</td>
<td>Weak or absent</td>
</tr>
<tr>
<td>Tonic neck</td>
<td>Slight</td>
<td>Strong</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Autonomic Function</strong></td>
<td>Generalized sympathetic</td>
<td>Generalized parasympathetic</td>
<td>Both systems depressed</td>
</tr>
<tr>
<td>Pupils</td>
<td>Mydriasis</td>
<td>Miosis</td>
<td>Variable; often unequal; poor light reflex</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>Tachycardia</td>
<td>Bradycardia</td>
<td>Variable</td>
</tr>
<tr>
<td>Bronchial and Salivary Secretions</td>
<td>Sparse</td>
<td>Profuse</td>
<td>Variable</td>
</tr>
<tr>
<td>GI Motility</td>
<td>Normal or decreased</td>
<td>Increased; diarrhea</td>
<td>Variable</td>
</tr>
<tr>
<td>Seizures</td>
<td>None</td>
<td>Common; focal or multifocal</td>
<td>Uncommon (excluding decerebration)</td>
</tr>
<tr>
<td>Duration</td>
<td>1-3 days</td>
<td>2-14</td>
<td>Hours to weeks</td>
</tr>
</tbody>
</table>
HIE Outcomes

• From Gluckman & Shankaran trials:
  – Moderate to severe HIE
    • 23-27% infants died prior to discharge from NICU
    • Overall mortality 18-22 months of age: 37-38%
    • Mental Developmental Index (MDI) at 18 months:
      – 85+ = 40%  70-84 = 21%  <70 = 39%
    • Physical Developmental Index (PDI) at 18 months:
      – 85+ = 55%  70-84 = 10%  <70 = 35-41%
  • Disabling cerebral palsy 30%
  • Epilepsy 16%
  • Blindness 14-17%
  • Severe hearing impairment 6%
Cooling Therapy

• Extensive experimental data suggest that mild hypothermia applied within 6 hours of injury is neuroprotective.

• Possible mechanisms:
  – Reduced metabolic rate & energy depletion
  – Decreased excitatory transmitter release
  – Reduced alterations in ion flux
  – Reduced apoptosis
  – Reduced vascular permeability, edema and disruption of blood-brain barrier function
Two Landmark Hypothermia Studies

• Shankaran et al, (NICHD Whole Body Hypothermia Study, NEJM 2005)
  – 239 infants with HIE >=36 weeks randomized: Death or moderate/severe disability at 18 months 44% in hypothermia group, 62% in control group, p=0.01. No increase in major disability among survivors with 19% of infants with cerebral palsy in hypothermia group vs 30% in control group, p=0.20.

• Gluckman et al, (Cool-Cap Selective Head Cooling, Lancet 2005)
  – 234 term infants with HIE and abnormal aEEG randomized: 55% in hypothermia group vs 66% in control group died or had severe disability at 18 months, p=0.1.
  – Subgroup analysis showed head cooling had little effect in infants with most severe aEEG changes but was beneficial in infants with less severe aEEG changes, p=0.009.
Hypothermia Treatment

- Summary of hypothermia data
  - No significant improvement in mortality
  - Reduction in death or severe disability with 7 infants needing to be cooled to prevent 1 bad outcome
  - No evidence of increased disabilities in survivors
  - No significant adverse events with cooling
New Treatment for Birth Hypoxia: Could It Have Been Used To Help Your Child?

Lack of oxygen at birth can frequently be avoided by good obstetric and neonatal care. You may want to investigate what happened to your baby and whether his or her injuries could have been prevented. Email or call us if we can be of assistance.

Infants suffering a lack of oxygen at birth who are then exposed to a new therapy involving cooling of either the infant’s head or whole body have a greater chance of reducing their risk of death or permanent brain damage, according to recent studies.¹

Prior to this treatment, infants who had suffered from a lack of oxygen at birth (also known as “perinatal asphyxia” or “hypoxic ischemic encephalopathy (HIE)”) had a high risk of death; those who survived had a substantial risk of permanent disability.²

More and more studies are showing, however, that except in the most severely affected infants, selective head cooling soon after birth could be a clinically feasible treatment in reducing the risk of disabling neurodevelopmental injuries to the basal ganglia area of the brain as a result of lack of oxygen at birth.³

For example, in one of the first pilot studies of whole body hypothermia involving 65 severely oxygen-deprived infants in the NICU, the overall death rate was 35%. However, among survivors with known developmental outcomes at 12 months, there were fewer infants with severely abnormal outcomes in the hypothermia group.⁴

In a more recent study, infants were treated with hypothermia before six hours of age. The treatment was continued for seventy-two hours. Death or moderate-to-severe disability occurred in 43 of 502 infants (8.6%) in the hypothermia group, compared to 64 of 503 infants (12.8%) in the control group. In the hypothermia and control groups respectively, the rate of cerebral palsy was 19 and 33%; the rate of blindness was 7 and 14%; the rate of hearing impairment was 4 and 6%; the total reduction in death or moderate disability at 18 months for the hypothermia group was 14%.⁵

Although the cooling therapy is not a “silver bullet” that can prevent all harm in infants who have suffered a lack of oxygen at birth, and the overall benefit (based on current studies) appears rather small, it clearly reduces the rates of death and disability.

¹. See reference 1 for more information.
². See reference 2 for more information.
³. See reference 3 for more information.
⁴. See reference 4 for more information.
⁵. See reference 5 for more information.
Tacoma General Hospital’s Program

- Natus/Olympic Medical Cool Cap System
  - Selective head cooling focuses treatment on brain
  - System is very user friendly and computer driven
Most Important Call

• Consult Neonatologist for Any Patient
  – Apgar score ≤ 5 at 10 min
  – Continued need for resuscitation
    • including endotracheal or mask ventilation, at 10 min after birth
  – Acidosis
    • defined as either umbilical cord pH or any arterial pH <7.00 within 60 min of birth
  – Base deficit ≥ 16 mmol/L
    • in umbilical cord blood sample or any blood sample within 60 min of birth (arterial or venous blood)

• Do not overheat infant awaiting transport!
  – Place temp probe over liver and set servo temp to 34.5 degrees C (94 degrees F)
Which Infants are Cooled?

- Newborns 36 weeks gestation or higher
- Newborns >=1800 grams
- Newborns <= 6 hours old. Studies ongoing are looking at longer windows to initiate cooling.
- Infant with moderate to severe encephalopathy consisting of altered state of consciousness (as shown by lethargy, stupor, or coma) and at least one of the following:
  - Hypotonia
  - Abnormal reflexes
    - including oculomotor or pupillary abnormalities
  - Absent or weak suck
  - Clinical seizures
aEEG Criteria

- Infant has amplitude integrated EEG / cerebral function monitor (aEEG/CFM) recording of at least 20 minutes duration that shows either:
  - Moderately/severely abnormal aEEG background activity (Score of 2 or 3)
  - Seizures
Amplitude-Integrated EEG
One Lead EEG to aEEG
Normal aEEG

- Normal: Upper margin of band of aEEG activity above 10 uV and lower margin of band of aEEG activity above 5 uV
- Moderately abnormal: Upper margin of band of aEEG activity above 10 uV and lower margin below 5 uV
- Severely abnormal: Upper margin of band of aEEG activity below 10 uV
Moderately Abnormal aEEG with Seizure

• Normal: Upper margin of band of aEEG activity above 10 uV and lower margin of band of aEEG activity above 5 uV
• Moderately abnormal: Upper margin of band of aEEG activity above 10 uV and lower margin below 5 uV
• Severely abnormal: Upper margin of band of aEEG activity below 10uV
Severely Abnormal aEEG

- Normal: Upper margin of band of aEEG activity above 10 uV and lower margin of band of aEEG activity above 5 uV
- Moderately abnormal: Upper margin of band of aEEG activity above 10 uV and lower margin below 5 uV
- Severely abnormal: Upper margin of band of aEEG activity below 10uV
Moderately Abnormal aEEG Group Benefits the Most

• Gluckman et al, (Cool-Cap Selective Head Cooling, Lancet 2005)
  – Subgroup analysis showed head cooling had little effect in infants with most severe aEEG changes but was beneficial in infants with less severe aEEG changes, p=0.009.
Cool Cap Protocol

- Set-up Wizard
- Temperature sensors
- Cooling cap
  - Starting cap temperature
  - Size selection
  - Placement
Cooling

- Monitored for 72 hours
- Rectal: 34.5°C  0.5°C
- Adjust cap water temperature as needed
- Radiant warmer
  - Turned off during induction
  - Turned on when rectal reaches 35.5°C
  - At ~100% output – 0.5°C above skin Temp
- 12-hour scalp checks
Monitoring

OLYMPIC COOL-CAP® SYSTEM

Cooling
Touch Pause before removing caps.

35.1°C Rectal
0.0°C Rate °C/hr

CONTINUING MEDICAL EDUCATION
MultiCare Women & Children's Grand Rounds
Seizure Management

- Infants with clinical evidence of seizure activity or electrical evidence on aEEG are started on anticonvulsants:
  - Phenobarbital 20 mg/kg IV over 15 minutes.
    - Target level initially 20, may be raised to 40 if seizure activity persists
  - Fosphenytoin (20 mg/kg of phenytoin equivalents) over 30 minutes.
    - Target phenytoin level initially 20
  - Lorazepam 0.1 mg/kg for breakthrough seizures
Novel Anticonvulsant: Keppra

- Keppra (levetiracetam) is an alternative agent recently gaining use in neonates
  - It is thought to impede nerve conduction across synapses.
  - Typical loading doses 10 mg/kg
  - Therapeutic concentrations 10-40 mcg/ml
  - Typical maintenance 10 mg/kg daily.
Adverse Effects of Cooling

• Potential Adverse Effects of Hypothermia
  – Increased oxygen consumption
  – Mild sinus bradycardia
  – Transient hyperglycemia
  – Prolongation of QT interval
  – Sclerema neonatorum (rare event)
  – Shivering
Rewarming

• Rewarm Wizard
  – Remove heat shield & cooling cap
  – Adjust radiant-warmer servo setting

• Passive rewarming
  – 4 hours at ~0.5°C per hour
  – 30-minute prompts for radiant warmer adjustments
Post Cooling

• Standard EEG obtained along with neurology consultation & physical therapy evaluation as appropriate.
• All patients are enrolled in the neurodevelopmental followup clinic.
Imaging with Hypoxic Ischemic Encephalopathy

- American Academy of Neurology, 2002 Guidelines recommend MRI imaging after cooling has completed.
  - 50% to 94% of infants with changes in the basal ganglia developed cerebral palsy, mental retardation and seizures at 1-2 years of age.
Tacoma General NICU Hypothermia Patients

- First patient cooled, June 2009.
- 22 Patients cooled thru end 2011
  - 2 patients remained ventilator dependent and support withdrawn on day 7 & day 11
  - 20 Patients discharged home, 1 required gastrostomy. Of survivors, hospital stays ranged from day 7 to day 45, median ~ 2 weeks of age.
Neurodevelopmental Outcome

- Epic provides electronic medical record with followup data.
- 12 Patients now >18 months old, followup evaluations on 9 available
  - 8/9 thought to have neurodevelopment within normal range for age
  - 1/9 judged to have moderate to severe cerebral palsy
Conclusions

• Hypothermia treatment has been shown to improve neurodevelopmental outcomes in infants born at 36 weeks or greater with perinatal depression

• Neonatology should be consulted on any infant born with birth depression especially if patient has been found to have a blood gas with pH <7 or base deficit >=16.
Bibliography

- Olympic Medical-A Division of Natus (2008) Olympic Cool-Cap System Hospital In-Service Training DVD

- Olympic Medical-A Division of Natus (2008) Olympic CFM 6000 : Infant aEEG Cerebral Function Training Hospital In-Service Training DVD
To obtain CME Credit, copy and paste link into browser to access post test/evaluation form.
www.surveygizmo.com/s3/798025/WCGR0212posttest

Next presentation: Cardiac Risk in Women
By Uma Krishnan, MD, FACC

Thursday, March 1, 2012, 6-7pm
Mary Bridge AV Conference Room
311 South L Street ~ Tacoma