Developmental Outcomes following Therapeutic Hypothermia Treatment in Neonates with HIE

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Learning Objectives

- Review incidence and impact of HIE
- Review pathophysiology of HIE
- Diagnosis of encephalopathy in term infants
- Hypothermia as neuroprotection
- Summary of 3 large randomized clinical trials
- Developmental outcomes
- How are we doing in our developmental clinics

Definition of HIE

"neonatal HIE is an acute, non-static encephalopathy caused by intrapartum or late antepartum brain hypoxia and ischemia." - Robertson, C, et. al.

Incidence

- Hypoxic ischemic encephalopathy or perinatal asphyxia affects 1-6 per 1000 live full term births
- 15-20% affected newborns will die in post-natal period. An additional 25% will sustain childhood disabilities
- 15-28% of the incidence of cerebral palsy among children are the result of perinatal asphyxia and HIE

Incidence

- Infant with moderate HIE
  - have a 10% chance of death
  - Those that survive have a 30% chance of disability
- Infants with severe HIE
  - Have a 60% chance of death
  - Most all that survive do so with a disability
**Impact of HIE**

- Neonates with mild encephalopathy do not have increased risk of motor or cognitive deficits.
- Neonates with severe encephalopathy have increased risk of death and increased risk of CP and MR amongst survivors.
- Neonates with moderate encephalopathy have significant deficits, memory impairment, visual motor or visual perceptual dysfunction, increased hyperactivity, and delayed school readiness.

**Criteria for Diagnosis of HIE with moderate/severe encephalopathy**

- Metabolic acidosis with a cord pH <7 or base deficit of ≥12.
- Early onset of encephalopathy.
- Multi-system organ dysfunction.
- Exclusion of other etiology such as trauma, coagulation disorders, metabolic disorders, and genetic causes.

**Pathophysiology of Neonatal HIE**

- Two phases that lead to brain injury.
- Primary or acute phase of energy failure.
- Latent phase or secondary energy failure.
- Therapeutic window duration about 6 hrs in near term infants.

**Hypothermia as Neuroprotection**

- A relatively small reduction in brain temp (1-6°C) of neonatal animals is associated with better maintenance of cerebral energy state during or immed. After ischemia and decrease release of excitatory neurotransmitters.
- Normalization of a decrease in protein synthesis, reduction in free radicals, and modulation of activation of microglia and cytokine production.
Hypothermia as Neuroprotection: Clinical Studies

- Whole body cooled NICHD trial (Shankaran et al, 2005)
- Cool Cap trial (Gluckman et al, 2005)
- Whole body cooled TOBY trial (Azzopardi et al, 2009)

NICHD (NRN) Study: Whole Body Hypothermia for Neonates with Hypoxic Ischemic Encephalopathy

- Randomized trial of hypothermia in infants gestational age >36wks before 6 hrs life with severe acidosis or perinatal complications with moderate/severe encephalopathy
- Controll group (usual care) vs Whole body cooling to 33.5 C for 72hrs, followed by slow rewarming
- Neurodevelopmental outcomes assessed @18-22 months of age
- 102 infants hypothermia group/106 controll group

NRN Study Results

- Primary Outcome: Death or moderate/severe disability
- Secondary outcomes:
  - Death
  - Death or disability
  - Survival
  - Bayley MDI score
  - Bayley Psychomotor Developmental Index score
  - Disabling Cerebral Palsy
  - Blindness
  - Severe hearing impairment

Conclusion: Whole body hypothermia reduces risk of death or severe/moderate disability in infants with moderate or severe HIE

Whole Body Hypothermia in Neonatal HIE

Death or Disability at 18 months

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypothermia Group (%)</th>
<th>Control Group (%)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>44 (43)</td>
<td>58 (55)</td>
<td>0.70 (0.54-0.90)</td>
<td>0.01</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>28 (27)</td>
<td>35 (33)</td>
<td>0.80 (0.64-1.00)</td>
<td>0.08</td>
</tr>
<tr>
<td>Death</td>
<td>10 (10)</td>
<td>16 (15)</td>
<td>0.65 (0.44-0.96)</td>
<td>0.03</td>
</tr>
<tr>
<td>Sria lSria l</td>
<td>2 (2)</td>
<td>4 (4)</td>
<td>1.00 (0.19-5.34)</td>
<td>0.99</td>
</tr>
<tr>
<td>Blindness</td>
<td>1 (1)</td>
<td>3 (3)</td>
<td>2.00 (0.3-12.9)</td>
<td>0.50</td>
</tr>
<tr>
<td>Severe hearing impairment</td>
<td>0 (0)</td>
<td>2 (2)</td>
<td>5.00 (0.1-30.0)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Moderate Hypothermia to Treat Perinatal Asphyxial Encephalopathy

- Randomized trial of infants who were <6hrs old with gestational age ≥36 wks and had perinatal asphyxial encephalopathy
- Intensive care plus whole body cooling to 33.5 C x 72 hrs vs intensive care alone
- Primary outcome was death or severe disability at 18 months of age
- 325 infants enrolled: 163 cooled/162 controll
TOBY Study Results

- No statistical significance comparing number infants died or survived with severe disability
- However, infants in cooled group had an increased rate of survival without neurological abnormality ($p<0.0003$)
- Among survivors, cooling resulted in reduced risks of cerebral palsy and improved scores on MDI and PDI of Bayley II and the GMFCS
- Conclusion: Induction of moderate hypothermia for 72 hrs in infants who had perinatal resulted in improved neurologic outcomes in survivors

Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial
Gluckman et al; Lancet 2005

- 234 term infants with moderate to severe neonatal encephalopathy and abnormal amplitude integrated EEG were randomly assigned to either head cooling for 72 hr, within 6 hr of birth at 34-35°C or conventional care
- Primary outcome was death or severe disability at 18 months
- Did not show statistically significant difference in primary outcome
- Head cooling had no effect in infants with the most severe aEEG changes, but was beneficial in infants with less severe aEEG changes

WCHOB Neonatal Hypothermia Treatment Protocol (10/21/2008)

- Standard treatment: Whole body cooling for term infants with HIE as per NICHD NRN Study
- Whole body cooling with Blanketrol to achieve esophageal temp of 33.5°C
- Cooling initiated within 6 hrs of birth and continued for 72 hrs with subsequent slow rewarming over 6-8 hrs.
WCHOB Neonatal Hypothermia Treatment Protocol

Inclusion Criteria:
- Clinical and biochemical criteria:
  - Gestational age ≥ 36 wks
  - Cord or neonatal (<1hr of age) blood gas with pH ≤ 7.0 or base deficit ≥ 16meq/l
  - History of acute perinatal event (e.g., Abruption, cardioresp. Arrest) with either APGAR score ≤ 5 at 10 min or Continued need for ventilation initiated at birth and continued for at least 10 min

WCHOB Neonatal Hypothermia Treatment Protocol (cont.)

Neurological Criteria: encephalopathy defined as the presence of one or more signs in at least 3 of the following 6 categories (see table):
- Level of consciousness
- Spontaneous activity
- Posture
- Tone
- Primitive reflexes
- Autonomic nervous system

The presence of moderate/severe encephalopathy defined as seizures OR presence of one or more signs in 3 of 6 categories will qualify the baby for cooling

Optimizing Hypothermia Study (cont.)

Outcome measures:
- Primary: Death or disability (either moderate or severe in extent) at 18-22 months of age
- Secondary: Normal infants, mildly disabled infants, mortality, cognitive outcome, cerebral palsy, disability by stage of HIE, visual impairment, hearing impairment, multiple disabilities acute adverse events, multiorgan dysfunction, neonatal seizures, MRI findings, length of hospital stay, rehospitalizations, growth parameters at follow up, Bayley III Motor score

Optimizing Hypothermia as Neuroprotection at <6hrs of Age for Neonatal HIE trial

Prospective, randomized multi-centered trial
- Same inclusion criteria

Study intervention: Infants will be randomized to either usual depth of cooling (33.5 C) or deeper cooling (32 C) and then to usual length of cooling (72hrs) or longer cooling (120 hrs)

Timetable: 10/2010 – 10/2015
Our Current Data

- Total No. pts cooled= 21 (since 10/2008)
- Total No. pts cooled in new study= 12 (since 4/2011)
- Group A (standard protocol): 9 pts
- Group B (research group): 12 pts
- Total No. pts death= 2 out of the 21 (9%)
  - 1 pt from each group

Out of the 19 surviving patients, 1 pt. never seen for developmental follow-up from Grp. A, and 4 from Grp. B still need initial dev. follow-up

Therefore, available data is based on 14 out of 19 surviving patients; 7 pts in each group

No available data at 18-22 month of age range: 4 lost to follow-up and 3 approaching age range

Initial developmental assessments done at corrected age range of 2month12days old to 4month5days old

7 out of 14 pts were already receiving therapy at initial visit

Initial Developmental Assessment

- CAT/CLAMS (capute scales)
- AIMS (Alberta Infant Motor Score)
- Gross Motor and Fine Motor Age
- Neurological exam: includes muscle tone
- History and Physical

Developmental Outcomes: Group A

<table>
<thead>
<tr>
<th>Grp A</th>
<th>CAT</th>
<th>CLAMS</th>
<th>GM/Aims</th>
<th>FM</th>
<th>Tone</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Nl/Nl</td>
<td>Nl/Nl</td>
<td>Nl/Nl</td>
<td>Nl/Nl</td>
<td>Nl/Nl</td>
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<tr>
<td>2*</td>
<td>Abnl/Abnl</td>
<td>Abnl/Abnl</td>
<td>Abnl/Abnl</td>
<td>Abnl/Abnl</td>
<td>Abnl/Abnl</td>
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<tr>
<td>3*</td>
<td>Abnl</td>
<td>Abnl</td>
<td>Abnl</td>
<td>Abnl</td>
<td>Abnl</td>
</tr>
<tr>
<td>4</td>
<td>Nl/Nl</td>
<td>Nl/Nl</td>
<td>Nl/Nl</td>
<td>Nl/Nl</td>
<td>Nl/Nl</td>
</tr>
<tr>
<td>5</td>
<td>Nl/Nl</td>
<td>Nl/Nl</td>
<td>Nl/Nl</td>
<td>Nl/Nl</td>
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<tr>
<td>6</td>
<td>Abnl</td>
<td>Abnl</td>
<td>Abnl</td>
<td>Abnl</td>
<td>Abnl</td>
</tr>
<tr>
<td>7</td>
<td>Nl</td>
<td>Nl</td>
<td>Nl</td>
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<td>Nl</td>
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Developmental Outcomes: Group B

<table>
<thead>
<tr>
<th>Grp B</th>
<th>CAT</th>
<th>CLAMS</th>
<th>GM/Aims</th>
<th>FM</th>
<th>Tone</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Abnl/Abnl</td>
<td>Abnl/Abnl</td>
<td>Abnl/Abnl</td>
<td>Abnl/Abnl</td>
<td>Abnl/Abnl</td>
</tr>
<tr>
<td>9*</td>
<td>Abnl/Abnl</td>
<td>Abnl/Abnl</td>
<td>Abnl/Abnl</td>
<td>Abnl/Abnl</td>
<td>Abnl/Abnl</td>
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<tr>
<td>10</td>
<td>Nl</td>
<td>Nl</td>
<td>Nl</td>
<td>Nl</td>
<td>Nl</td>
</tr>
<tr>
<td>11</td>
<td>Abnl/Abnl</td>
<td>Abnl/Abnl</td>
<td>Abnl/Abnl</td>
<td>Abnl/Abnl</td>
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<tr>
<td>12</td>
<td>Nl</td>
<td>Nl</td>
<td>Nl</td>
<td>Nl</td>
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<tr>
<td>13</td>
<td>Nl</td>
<td>Nl</td>
<td>Nl</td>
<td>Nl</td>
<td>Abnl</td>
</tr>
<tr>
<td>14</td>
<td>Nl</td>
<td>Nl</td>
<td>Nl</td>
<td>Nl</td>
<td>Abnl</td>
</tr>
</tbody>
</table>

Initial Outcomes

- Initial dev. Screens abnormal in 5/14 (36%)

Abnormal muscle tone: 11/14 but 1 with hypotonia (trisomy 21)

Pt #2: development more apparently delayed at subsequent visits
Developmental Outcomes (based on most recent exams)

<table>
<thead>
<tr>
<th>Grp.</th>
<th>Mental Index %</th>
<th>GM Index %</th>
<th>Tone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100%</td>
<td>71%</td>
<td>Mild incr.</td>
</tr>
<tr>
<td>2</td>
<td>54%</td>
<td>25%</td>
<td>R. Spastic hemi</td>
</tr>
<tr>
<td>3</td>
<td>77%</td>
<td>43%</td>
<td>Hypo</td>
</tr>
<tr>
<td>4</td>
<td>100%</td>
<td>100%</td>
<td>NL</td>
</tr>
<tr>
<td>5</td>
<td>100%</td>
<td>100%</td>
<td>NL</td>
</tr>
<tr>
<td>6</td>
<td>95%</td>
<td>93%</td>
<td>NL</td>
</tr>
<tr>
<td>7</td>
<td>97%</td>
<td>94%</td>
<td>Mild Incr.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grp. B</th>
<th>Mental Index %</th>
<th>GM Index %</th>
<th>Tone</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>100%</td>
<td>95%</td>
<td>NL</td>
</tr>
<tr>
<td>9*</td>
<td>11%</td>
<td>11%</td>
<td>Decr. L.E.</td>
</tr>
<tr>
<td>10</td>
<td>99%</td>
<td>100%</td>
<td>NL</td>
</tr>
<tr>
<td>11*</td>
<td>37%</td>
<td>54%</td>
<td>Mild to mod Incr.</td>
</tr>
<tr>
<td>12</td>
<td>100%</td>
<td>100%</td>
<td>NL</td>
</tr>
<tr>
<td>13</td>
<td>89%</td>
<td>99%</td>
<td>Mild Incr.</td>
</tr>
<tr>
<td>14</td>
<td>100%</td>
<td>99%</td>
<td>Mild mod increase</td>
</tr>
</tbody>
</table>

Our Outcomes
- Abnormal Mental or Gross motor index= 5/14 (35%)
- Mental Index% <70% = 3/14  (21%)
- GM Index%<70% = 4/14 (1 with trisomy 21) (28%)
- Initial abnormal muscle tone: 11/14 (78%)
- Subsequent eval abnormal muscle tone: 8/14; 3/8 with moderate increase in tone and 2/8 hypotonic and 3/8 with mild increase

Conclusions
- Difficult to interpret data because 18-22month data not yet available (earliest age at which major disability can be ruled out with a high level of confidence)
- Deaths: 2/21 or 9.5% (improved)
- Survive with disability: 5/14 or 36% (not improved)
- Survive with severe disability (index < 70%): 3/13 or 23% (improved)
- However, we have not delineated between those who had moderate or severe encephalopathy at birth

Conclusions
- Need to consider different developmental screening such as with Bayley III and GMFCS to be consistent with other studies
- Determine if Early Intervention needs to be initiated in all cases automatically
- Identify those at highest risk early on:
  - Consider TIMP (Test of Infant Motor Performance) score in NICU
  - Identify co-morbidities that affect outcome
Late Outcome Studies

- NICHD (NRN) study: Follow up at 6 – 7 years old from original study
- Cool Cap Study: also has follow up at 7-8 years post original study

Use of therapeutic hypothermia:

- Has significantly reduced the incidence of death
- Has significantly reduced the incidence of moderate or severe disability

Rehabilitation Services

Prior to discharge

- Occupational Therapy and Physical Therapy
  - provide and initial assessment, once the infant is stable
  - Meet with parents to provide developmental recommendations
- EIP referral
- Early Motor Clinic Appointment

Future F/U Plans

- Standardize developmental assessments prior to discharge
- Implement strategies to improve follow-up rates
- Formalize therapy recommendations at discharge
**Goals of Inpatient services:**

- Determine baseline developmental skills
- Establish initial level of outpatient therapy service
- Educate parents to importance of follow-up and developmental intervention

**Developmental follow-up**

- Robert Warner Center for children with special needs
  - Early motor clinic
- Early Intervention
- Out patient therapy services

**Goals of Outpatient Rehab**

- Monitor development
- Review and update level of therapy services
- Keep parents informed of infants developmental status
- Assess and provide recommendations for adaptive equipment