Neuroprotection in Newborn Heart Surgery

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Roadmap of Presentation

- Newborn heart surgery (NBHS) as a model of “planned and deliberate” ischemia-reperfusion
- chronic neurodevelopmental sequellae
- PVL most common neuropathology
- Patient-specific factors related to outcome
- Ideal population for neuroprotection trial: you know ahead of time when the “insult” will occur
- Prior neuroprotection trial (allopurinol)
- Future neuroprotection trials (e.g. caffeine & topiramate)

Congenital Heart Defects: Background

- CHD occurs in 8/1000 live births
- ~32,000 patients born each year in US with CHD
- ~11,000 newborn/infant interventions
- 3 basic forms of CHDs:
  - Mild: no surgery needed
  - Moderate: eventually needs surgery
  - Severe: needs newborn heart surgery (NBHS) example: hypoplastic left heart syndrome (HLHS)
Neurological Sequels in NBHS
Traditional Concepts

- Stroke
- Seizures
- Altered Consciousness
- Choreoathetosis

Traditional Concepts:
*Simple* Model of Brain Injury

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Totally Healthy Brain ➔ Acutely Injured Brain ➔ Chronically Injured Brain

Newborn Heart Surgery
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Hypoplastic Left Heart Syndrome

Congenital Heart Defects

Hypoplastic Left Heart Syndrome

(Half-a-Heart-Syndrome)

EASTERN SYMPHONY

Cardiopulmonary Bypass
As Mortality Falls, Increased Concerns About Long-Term Outcomes

TGA: Corrected Bayley Scores –Not Improved Over Time!
Neurodevelopmental Consequences of NBHS: Is the glass half-empty or half-full?

- Significant reduction in Bayley scales of infant development (PDI < MDI < Normal)
- ADHD and disorders of higher executive function
- Visual-motor integration deficits
- Fine and gross motor incoordination
- Reduced IQ by about ½ SD
- About 30% require special education/ancillary services
- Resembles outcome of the premature population!!
- ROLE of PVL!!!
PVL Most Common Form of Neuropathology

“In all infants dying after cardiac surgery, irrespective of the modality, cerebral white matter damage was the most significant lesion in terms of severity and incidence, followed by a spectrum of gray matter lesions”

Traditional Concept:

The Real Action is in the OR!

Pre-Operative MRI Measurements of Cerebral Blood Flow (CBF)

- Perfusion MRI was accomplished by pulsed ASL-pMRI
- Gradient applied to neck and T1 relaxation measured at brain

(Licht, JTCVS 2004)
Pre-Operative CBF Values in CHD

Normal perfusion = 50ml/100gm/min

CHD mean perfusion

Pre-Operative Factors:
Microcephaly and Aortic Morphometry
Microcephaly and Aortic Morphometry

(Shillingford et al. Card of the Young, 2007)

Cardiac Output Falls During the 1st Post-operative Night

(Wernovsky JTCVS 1995)

Mild PVL
Moderate PVL

Composite View: PVL Occurs Within the Cerebral Watersheds

Impact of PVL on Post-Natal Brain Growth

(N = 34/52 with PVL) (Licht 2005)

(unpublished data, CHOP 2004)
Patient-Specific Factors Related to Developmental Outcome in a Clean Population

- 2 ventricle heart; single operation
- 103 males, 85 females (n=188)
- Median gestational age: 39 wk (28-42)
- Median birth weight: 3175 gm (739-5140)

(Gaynor et al JTCVS 2007; 133:1344)

Bayley Scales of Infant Development-II at 1 year of Age

(Gaynor et al JTCVS 2007; 133:1344)

Variance in MDI and PDI

<table>
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<tr>
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<th>MDI</th>
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<th>PDI</th>
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<tr>
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<td>$r^2$</td>
<td>$p$</td>
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<tr>
<td>Patient Factors</td>
<td>0.2006</td>
<td>0.0008</td>
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<td>Intraoperative Factors</td>
<td>0.0951</td>
<td>0.011</td>
<td>0.1264</td>
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<td>DHCA (Y/N)</td>
<td>0.0281</td>
<td>0.0213</td>
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<td>Postoperative LOS</td>
<td>0.0423</td>
<td>0.0045</td>
<td>0.0829</td>
<td>&lt;0.0001</td>
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Patient Factors: gender, ethnicity, birth weight, birth head circumference, APGAR 1, APGAR 5, genetic exclusion, APOE genotype
Intra-operative Factors: weight at surgery, cooling time, DHCA time, CPB time, lowest NP temp, HCT

(Gaynor et al JTCVS 2007; 133:1344)
Patient-Specific Factors Related to Outcome

- Specific type of CHD
- Genetic conditions (suspected or confirmed)
- Maturity (pre-term, term, > 1 month)
- Apo-E polymorphisms
- Other genetic factors strongly suspected

Blueprint of a Neuroprotection Trial in Newborn Heart Surgery

Allopurinol Neurocardiac Protection Trial

- Advantages of neuroprotection in NBHS
  - Can evaluate the baby before the “insult”.
  - Drug administered as a RCT in a timely fashion.
  - Risk stratification
  - Can measure the dose of the obvious “insult”: the durations of CPB, HTCA, need for re-operation, etc.
  - Short-term and long-term endpoints of interest can be observed prospectively

(Clancy et. al. Peds 2001; 108:61)
Allopurinol Neurocardiac Protection Trial

- 350 neonates with CHDs who needed NBHS
  - Stratified into two large “risk” groups:
    - HLHS (highest risk of death, seizures, etc.)
    - Non-HLHS (all other forms of CHDs, considered to be at lower risk).
- Allopurinol administered before, during and after surgery.
- Efficacy endpoints: death, seizures, coma or cardiac events.

Major conclusions from the study:
- Allopurinol did not reduce the risk of death in either risk stratum (HLHS or non-HLHS)
- Allopurinol significantly protected the higher-risk HLHS survivors from seizures, coma and cardiac events (~50% reduction).
- Allopurinol did not protect the lower risk non-HLHS stratum survivors from seizures, coma and cardiac events.
- Allopurinol did not reduce PVL or improve short-term developmental outcomes

HIE vs. NBHS

<table>
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<th>Pre-partum period</th>
<th>Intra-partum labor &amp; delivery period</th>
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<tr>
<td>HIE</td>
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<tr>
<td>NBHS</td>
<td>Pre-operative period</td>
<td>Intra-operative period</td>
<td>Post-operative period</td>
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Topiramate for HIE/PVL

• Possible Mechanisms of Neuroprotection:
  – Blocks developmentally regulated AMPA receptors
  – In HI newborn rat pup models, prevents white matter injury, improves their neuromotor performance, blocks acute seizures, and reduces post-natal epilepsy (“anti-epileptogenic”)

Topiramate Neuroprotection for HIE

Logistic Regression Model for Moderate to Severe CP in Preterm Infants

Topiramate and White Matter Neuropottection in the Premature Infant

Robert Clancy, MD
Jan. 17, 2008

Glutamate Receptor-Mediated Oligodendrocyte Toxicity in Periventricular Leukomalacia: A Protective Role for Topiramate

Topiramate Prevents PVL and Improves Motor Outcomes in a Rat Pup WM Injury Model

Caffeine Neuroprotection in Premature PVL by Blockade of A1 Adenosine Receptors

Protective Effects of Caffeine on Chronic Hypoxia-Induced Perinatal White Matter Injury

Better Outcomes in Babies Rx’d with Caffeine for Apnea of Prematurity

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<th></th>
<th>Caffeine</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Dead or any disability</td>
<td>40.2%</td>
<td>46.2%</td>
<td>0.008</td>
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<tr>
<td>CP</td>
<td>4.4%</td>
<td>7.3%</td>
<td>0.009</td>
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<tr>
<td>Cognitive delay</td>
<td>33.8%</td>
<td>38.3%</td>
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Specific Neuroprotection Trial in Newborn Heart Surgery

NEUROPROTECTION
- Fetal Brain Development
- Birth
- Pre-operative
- Intra-operative
- Post-operative

Caffeine vs Placebo

Special Thanks to my CHOP Colleagues!

Bill Gaynor
Gil Wernovsky
Susan Nicolson
Tom Spray
Rick Ittenbach
Bob Zimmerman
Dan Licht
Becky Ichord
Dennis Dlugos
Renee Shellhaas
Nick Abend
Courtney Wusthoff