Objectives

- Perinatal brain injury
- Neuroprotection in the neonate
  - Preterm
  - Term

Perinatal Brain Injury

- Important cause of DEATH and DISABILITY
- Lifetime
- Improvement in perinatal and neonatal care
  - Improved survival
  - No significant ↓ in neurologic disabilities

Perinatal Brain Injury

- No effective TREATMENT for perinatal brain lesions
- NEUROPROTECTIVE strategies
  - Cerebral Palsy
  - Cognitive Impairment
  - Others

Cerebral Palsy (CP)

- Motor impairment due to malformation/lesion in the immature brain
- Often accompanying impairments
  - Cognition, communication, sensation

Perinatal, Neonatal Mortality and Cerebral Palsy (Sweden), 1975-2002

Pathophysiology

- Periventricular white matter injury
  - Generally, <32 weeks

- Cortical and subcortical lesions
  - Term

Preterm Neuroprotection

- Antenatal
  - Magnesium
  - Antenatal steroids

- Neonatal
  - ? Caffeine
  - X Indomethacin
  - X Vitamin A

Brain Injury in the Term Infant

- Stroke
- Birth trauma
- Metabolic or genetic disorders

- Hypoxic ischemic encephalopathy (HIE)
  - One of the most commonly recognized causes of severe, long-term neurologic deficits in children
  - Death, cerebral palsy, epilepsy, cognitive, developmental and behavioral problems
  - Incidence: ~1.5 per 1000 live births
  - Large human and financial costs

Fetal Response - Circulatory

- Interruptions in placental blood flow is common BUT neurologic sequelae are infrequent

Perinatal HIE

- Evolving process
  - 1º energy failure during asphyxia
    - Necrosis
  - Precipitates a biochemical cascade
  - Latent phase lasting 6–24 hr
  - 2º energy failure leads to most of the cell death
    - Apoptosis

- Severity of 2º energy failure is correlated with adverse neurodevelopmental outcome
HIE: Primary Insult

- Primary insult
  - High energy metabolites depleted (energy failure)
  - Swelling
  - Accumulation of excitatory amino acids
  - Cell necrosis

HIE: Latent Phase

- Latent phase (6-15h)
  - Cerebral circulation and oxygenation restored
  - Cerebral oxidative metabolism normalized
  - Depressed EEG
  - Decreased cerebral blood flow

HIE: Secondary Energy Failure

- Secondary energy failure (1-10 days)
  - Delayed seizures
  - Cell swelling
  - Excitotoxin accumulation
  - Mitochondrial failure
  - Cell death (apoptosis)

HIE Injury Cascade

Stopping the Injury Cascade

Therapeutic Hypothermia

- Effect of delay after cerebral ischemia before starting cooling

Hypothermia

- Whole Body Cooling or Head Cooling
- Halts 2º cell death
- Low toxicity
- Hypothermia protected animal models subjected to asphyxia
  - Cooling within 6 hr (earliest best)
  - >24 hr of cooling (72 hr is better)
  - Brain surface needs to be cooled to <34°C

Therapeutic Hypothermia

- Outcomes up to 18 months

Cool Cap

- Arkansas Children’s Hospital (ACH) participated in the Cool Cap Trial
- FDA approved Olympic Cool Cap® on 12/20/06 with specific enrollment criteria
- Core (rectal) temp at 34.5°C ± 0.5°C for 72 hrs

Enrollment Criteria: A + B + C

A. GA ≥ 36wks + at least one (1)
   - Apgar ≤ 5 at 10min
   - Acidosis: pH <7
   - BD ≥ 16 mmol/L in any blood sample within 60min of birth

B. 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 papillary abnormalities
     - Absent or weak suck
     - Clinical seizures

C. aEEG/CFM Recording
   - of at least 20 minutes duration that shows either moderately or severely abnormal aEEG background (score of 2 or 3) or seizures

Supportive Care

- Radiant Warmer
- Monitor
- Ventilator
- Cool Cap

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Toll Free: 1-800-ACH-HELP
(1-800-224-4357)
Direct Line: (501) 364-6429
Acute Intrapartum Event Sufficient to Cause CP (ACOG)

- **Essential Criteria (all 4)**
  - Metabolic acidosis in fetal arterial cord blood (pH<7, BD≥12)
  - Mod-severe neonatal enceph ≥34wks GA
  - Spastic quad or dyskinetic type CP
  - Excluding other etiologies

- **Intrapartum timing (“0-48H”)**
  - Sentinel event
  - Fetal heart tracing
  - Apgar 0-3 beyond 5 min
  - Multisystem involvement within 72H
  - Early imaging: nonfocal cerebral abnormality

HIE and Outcome

Long-Term Follow-Up

- >40% of infants who receive therapeutic hypothermia still have abnormal outcomes

Future Directions

- Interventions affecting multiple sites are required
- Hypothermia affects multiple sites
- Inhaled Xenon
- Erythropoetin
- N-acetylcysteine
- Melatonin
- Anticonvulsants

Conclusion

- Neuroprotection in term neonates
  - Hypothermia
  - Adjunct strategies – currently under study
- Neuroprotection in preterm neonates
  - Periventricular white matter injury
  - No proven strategies