Total Body Cooling & Hypoxic Ischemic Encephalopathy in the Neonate

Kaleidoscope 2017

LEIGH ANN CATES  PHD, APRN, NNP-BC, RRT-NPS, CHSE
NEONATAL NURSE PRACTITIONER- TEXAS CHILDREN'S HOSPITAL
ASSISTANT PROFESSOR- NEONATOLOGY- BAYLOR COLLEGE OF MEDICINE
OBJECTIVES

Survey the background of acute fetal hypoxic injury
Review pathophysiology of hypoxic ischemic encephalopathy (HIE)
Discuss potential sources of fetal hypoxia resulting in HIE
Explore crucial preparation strategies to limit HIE
Examine steps of resuscitation to limit HIE
Study key stabilization strategies to limit HIE
Assess the interventions & therapies to limit postnatal hypoxic injury
List outcomes and what is on horizon
NEONATAL ENCEPHALOPATHY

“a clinically defined syndrome of disturbed neurological function in the earliest days of life, manifested by difficulty with initiating and maintaining respiration, depression of tone and reflexes, subnormal level of consciousness and often seizures”

POTENTIAL SOURCES

PRE-PLACENTAL

Maternal
- Anemia
- Infections
- Chronic inflammation
- Cardiovascular disease
- Pulmonary hypertension
- Residing at high altitudes

UTERO-PLACENTAL

Abnormal implantation
- Acreta
- Procreta

PIH

Pre-eclampsia
- HELLP
- ECLAMPSIA

POST-PLACENTAL

Mechanical Compression
- Nuchal Cord
- Knot in cord
- Prolapsed Cord

Thrombotic Occlusion

Uterine Rupture

Abruption
POTENTIAL SOURCES

Nuchal Cord

Prolapsed Cord

Knotted Cord
POTENTIAL SOURCES

PROGRESSION OF PLACENTAL ABRUPTION
**PATHOPHYSIOLOGY**

Birth Injury - An injury that occurred during the process of birth

Birth Asphyxia - asphyxia that occurred during 2\textsuperscript{nd} and 3\textsuperscript{rd} stages of labor

Perinatal Asphyxia - asphyxia that occurred anytime between conception to first month of life

Hypoxic-Ischemic Encephalopathy (HIE) - encephalopathy from asphyxia

- does not imply time injury occurred
- does not imply the brain was “normal” before the injury
PATHOPHYSIOLOGY

Redistribution of fetal blood flow (heart, brain, adrenals)

- ↑ BP
- ↑ CBF

Loss of CBF Autoregulation
- ↓ BP
- ↓ CBF

Ischemic Brain Injury

- ↑ CO₂ ↓ O₂ ↓ Ph
- ↑ Lactate
- ↓ Glucose

INeRST

Therapeutic Window: Hypothermia Other

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

Reperfusion

Cerebral metabolism transiently recovers
- Ca²⁺ overload
- ROS, NO

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

Hypoxic ischemic brain injury

Interventions NEED TO BE WITHIN 6 hrs of insult

IMMEDIATE necrotic cell death

DELAYED apoptotic cell death
PATHOPHYSIOLOGY

- Blood supply to the brain and border zones

- Anterior cerebral artery
- Middle cerebral artery
- Posterior cerebral artery
- Carotid artery

- Arrows indicating areas of interest on the brain sample
Cell Death Post Hypoxic Insult

Primary energy failure – Necrotising

Latent Period

Secondary Energy Failure - Apoptotic

TIME 1.... 2 3 4 5 6...19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37....
PATHOPHYSIOLOGY

Cell Death Post Hypoxic Insult

Latent Period

Primary energy failure – Necrotising

Secondary Energy Failure - Apoptotic

TIME

1... 2 3 4 5 6... 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37...
PATHOPHYSIOLOGY

Appearance of Hypoxic Newborn

- Brain damage in the watershed zones
- Moderate to severe encephalopathy
  - Posturing
  - Poor sucking
  - Fisting
  - Seizures
- Normal arm bones
- Micro-hemorrhages of the lungs
- Hypoxic damage to the liver and kidneys
- Metabolic acidosis at the time of delivery
  - pH less than 7

Apgar scores = 0-3
- 1 minute after birth
- Apgar scores = 0-3
- 5 minutes after birth
PREPARATION STRATEGIES

Obstetrical

EXTERNAL FETAL MONITOR

INTERNAL FETAL MONITOR

Fetal Monitoring

Variable

Early Decels

Cord Compression

Accels

Head Compression

Late Decels

Ok, Maybe O2

Placental Insufficiency
STEPS OF RESUSCITATION
STEPS OF RESUSCITATION
KEY STABILIZATION STRATEGIES
INTERVENTIONS & THERAPIES

Criteria

≥ 35 weeks gestation

Biochemical evidence of Hypoxic Ischemic Event

* pH ≤ 7.00 or base deficit ≥ 16mmol/L
  * Cord gas
  * Blood gas in 1st hour of life
  OR
* Presence of acute perinatal event
  AND
* APGAR <5 at 10 min
  OR
* Need for resuscitation at ≥ 10 min of life
  AND
  Evidence of moderate to severe encephalopathy
  * Seizures
  * Abnormalities in 3 of 6 Sarnat criteria
INTERRUPTIONS & THERAPIES

Whole body

Head only
Therapeutic Hypothermia

- Must be initiated within 6 hours of birth
  - Includes passive cooling
- All external heat sources off
- Desired temp $33.5^\circ C \pm 0.1^\circ C$
- Monitor Temp Q15 min
- VS, & UOP Q hour
- Neuro assessment Q1 until goal temp achieved then Q4
INTERVENTIONS & THERAPIES

Therapeutic Hypothermia

- Daily Sarnat scores
- Continuous video EEG
- NPO with total fluids at 40-45ml/kg/day
- Reposition Q2
- Morphine drip
  - Adjust dose to limit shivering
- Continues for 72 hours
INTERVENTIONS & THERAPIES

Therapeutic Hypothermia

- **Recommended Labs**
  - **Glucose**
    - Admission, Q1 x6, Q12 x2, QD x 4
  - **CBC d/p**
    - Admission, Q day x3
  - **Blood Culture**
    - Admission
  - **PT, PTT, Fibrenogen**
    - Admission, Q day x3
  - **Arterial Blood Gases**
    - Admission, Q6 x 4, Q12 x2, QD x 3 (more PRN)
  - **LFTs**
    - Admission, Q day x3
INTERVENTIONS & THERAPIES

Therapeutic Hypothermia

- Cranial US 8-12 hours after cooling initiated
- Post Cooling MRI day 4-5 (no contrast)
INTERVENTIONS & THERAPIES

Complications

Arrhythmias
- Bradycardia
- Ventricular tachycardia

Persistent Acidosis

Bleeding

Subcutaneous fat necrosis

Death
INTERVENTIONS & THERAPIES

Rewarming

- Rewarm slowly after 72 hours
  - Monitor very closely
- Increase temp by 0.5°C Q hour
  - Until reached 36.5°C
- Once temp reaches 36.5°C for 1 hour
  - Turn on radiant warmer and set temp 0.4°C above babies skin temp
- Once temp reaches 36.5°C -37°C
  - Return to standard servo control protocol
INTERVENTIONS & THERAPIES

Follow-up

- Developmental Pediatrics Consult & evaluation prior to discharge
- Neurology Clinic post discharge
- Brain MRI at 1 year of age
  - Decreased Whole Brain Volume at Follow-up MRI
    Associated with Increased Unfavorable Neurodevelopmental Outcomes
- Developmental Clinic at 6 months, 1 year, and 18 months
  - Full Bayley exam
EVIDENCE

Prevent Fluid OVERLOAD & Cerebral Edema

- AVOID fluid boluses
- Do not worry about lack of urine output for DOL 1–2
- ADH/vasopressin is elevated during stressful labor

Schlapbach et al, BMC Pediatrics 2011, 11:38
Infants with HIE and Low PaCO2 Have Poor Outcomes

Lingappan, Kaiser, Srinivasan, Gunn Pediatr Res 2016 In press
PREVENT & TREAT HYPER/HYPOGLYCEMIA

6.2: aOR of hypoglycemia associated with an unfavorable outcome

2.7: aOR of hyperglycemia associated with an unfavorable outcome

Basu, Kaiser, Guffey, Minard, Guillet, Gunn Arch Dis Child Fetal Neonatal Ed2015

Hypoglycemia (≤40 mg/dL), n=27

- 55% hypoglycemic vs 16% normoglycemic infants had abnormal neurologic outcomes

- OR: 6.3; 95% CI: 2.6-15.3

Salhab et al, Pediatrics 2004; 114:361-366
EVIDENCE

TREAT SEIZURES EARLY

• HIE: most common cause of newborn seizures
• >50% of infants with HIE have seizures
  (subtle, multifocal clonic, focal clonic, etc.)
• Most common during the first 24 hours
• 60% have seizures within the first 12 hours
• Thus, early continuous EEG is imperative, for the initiation of early treatment
• Clinical Neonatal Seizures are Independently Associated with Outcome in Infants at Risk for HIE Brain Injury

Therapeutic Hypothermia is Beneficial

• Cooling improves survival without increasing major disability in survivors
• Therapeutic hypothermia should be used in infants $\geq 35$ weeks with moderate-to-severe HIE if begun within 6 hours of age

Therapeutic hypothermia resulted in reduction in....

• The combined outcome of mortality or major ND disability

Cochrane Review Cooling for Newborns with HIE (May 2012)
OUTCOMES

• About 50% of infants (mod-severe HIE) treated with hypothermia still die or have major ND disability
• Hypothermia offers ~15% risk reduction of death or disability
• Thus, refinements in hypothermia protocols, and additional treatment strategies are needed
• In infants with moderate encephalopathy (Stage 2 Sarnat) at day 4, those treated with hypothermia had a higher rate of favorable outcome than expected after standard care

Effect of Hypothermia on aEEG Prediction of Outcome in Infants with HIE

• PPV of an abnormal aEEG pattern at 3–6 hours was 84% for normothermia, 59% for hypothermia to predict a poor outcome

• Time to Sleep-Wake Cycle: better predictor for cooled infants (89%) vs 64% for normothermia

• **Infants with good outcome: normalized pattern by 24 hours in normothermia, normalized pattern by 48 hours in cooled infants

ON THE HORIZON

• Erythropoietin (EPO) - reduces apoptotic, inflammatory and oxidative brain injury following H-I

• Melatonin - antioxidant, anti-apoptotic, crosses the BBB, neuroprotective in animal models of asphyxia

• N-Acetylcysteine (NAC) - precursor of glutathione and can act as an antioxidant and a ROS scavenger

• Allopurinol - antioxidant, inhibitor of superoxide and hydrogen peroxide production

• Xenon - not FDA approved, anesthetic, NMDA antagonist, anti-apoptotic effects, neuroprotective in animals, crosses the BBB, very costly, needs a closed-circuit delivery and recycling system

• Tetrahydrobiopterin (BH4) - antenatal therapy, safe, no adverse effects, not teratogenic; Important cofactor for enzymes, such as aromatic amino acid hydroxylases

Robertson, Tan, Groenendaal, van Bel, Juul, Bennet, Derrick, Back, Valdez, Northington, Gunn, Mallard. Which neuroprotective agents are ready for bench to bedside translation in the newborn infant? 2012 J Pediatr 160(4):544-52
ON THE HORIZON

NICHD Neonatal Network will soon be beginning a randomized controlled trial of cooling in 33–36 week infants*

• *transfer and/or send infants to Hermann- study not yet begun
QUESTIONS????

Leigh Ann Cates
lacates@texaschildrens.org


Kaiser, J., Rhee, C. Dinu, D., Shivanna, B. (2016-17) Encephalopathy in Guidelines for the Acute Care of the Neonate Ed 24, Baylor College of Medicine, Houston, TX p. 115-117.


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