New Developments in Whole-Body Cooling for Preterm Neonates: Where Do We Stand?

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Disclosures

• Nothing to disclose
• Off-label use of cooling
Objectives

At the conclusion of this talk, the learner should be able to

• Describe the stages of preterm brain development.
• Describe the stages of preterm brain injury.
• Recognize the basis of pre-clinical studies of cooling for premature brain injury
• Make a judgment call on the evidence of cooling for premature encephalopathy.
Vulnerability of Preterm Brain

- Decreased antioxidant defense systems
- Highly active dendritic and axonal growth
- Exaggerated inflammatory response of an immature immune system.

Preterm brain grows and injury has to be considered in a dynamic manner.
Preterm Brain Migration
Myelination Failure
Oligodendrocyte Development

Subplate Neurons

- 10-24 weeks
- 24-32 weeks
- 32-36 weeks
Cortical Development
Preterm Hemorrhage

- Injury to pre-oligodendroglia
- Injury to axons
- Decreased GABAergic neurons
Periventricular Leucomalacia

- Macroscopic injury
- Microscopic injury
- Timing of primary insult is unknown
Pathogenesis of Preterm Brain Injury

• Migrating GABAergic neuron
• Subplate neuron
• Pre-OL injury
• Axonal injury
• Thalamic injury
Sheep Studies

- Near term
- 120-129 days
- Bilateral carotid a. occlusion 30 min
- Halothane
- Scalp cooling

- Less cytotoxic edema
- Better EEG recovery
- Less neuronal loss in all regions

- Less reduction of oligodendroglia and MBP
- Less microglial activation

*PEDIATRICS 102: 1098-1106, 1998

*Scientific Reports 6:25178, 2016*
Sheep Studies

- Preterm
- 103-104 days
- Umbilical artery occlusion 25 min
- Halothane
- Scalp cooling

- Less neuronal loss in reticular formation, recovery in striatum, hippocampus, median nucleus. (cortical sparing insult)
- Recovery of oligos in PV WM
- Less apoptosis and microglial reaction

*J Physiol 578.2 (2007) 491–506*
Fetal Hypoxia-Ischemia

Gestation (Days)

0 22 25 29 31.5

Sustained Hypoxia-Ischemia

32=P1
Different Ages React Differently

- Rabbit fetal hypoxia-ischemia
- Same duration of H-I results in increased late perinatal deaths with increasing gestational age.

• Using death as an endpoint, it becomes impossible to determine the timing of the insult.

Uterine Rupture

- Retrospective study, chart review
- 461 cases of uterine rupture
- Perinatal deaths 15 (3.2%)
- Trial of labor 10/347 (2.9%) vs. no trial of labor 5/114 (4.4%)
- No long term follow up.

Uterine Rupture

• Prospective study
• 17,898 patients that had a trial of labor after C-section
• 124 cases of uterine rupture.
• Perinatal deaths 2 (1.8%)
• HIE 7 (6.2%)
• Umbilical arterial pH≤7, 23 (33.3%)
• No long term follow up.

Uterine Rupture

• Retrospective study
• 40,772 patients with C-section; 11,195 attempted VBAC.
• 36 cases of uterine rupture.
• 3 had abnormal neurodevelopmental outcome: only one CP, one seizure and delayed speech, one developmental delay. (8%)

Hypothermia in Term Infants

- Well tolerated
- Physiologic bradycardia
- Mild thrombocytopenia
- Possible increase in inotrope requirements

Cochrane Database Systematic Reviews 2013, Issue 1:CD003311
Preterm Thermoregulation

- High surface area to body weight ratio
- Muscular inactivity
- Inadequate sweating mechanism
- Immature heat regulation mechanism

Unlike adults, infants respond to cooling with intense nonshivering thermogenesis, which is associated with release of free fatty acids and increased oxygen consumption.
Skin Fat Less

- Little subcutaneous fat
- Less brown fat
Premature Hypothermia

- Higher mortality in VLBW infants
- Theoretical: hypotension, increase oxygen consumption, decrease surfactant production, increase pulmonary vascular resistance, or promote free fatty acid release. ADH suppressed, in rabbits decreased renal blood flow and GFR.
- Glucose: transient mild hyperglycemia, but in piglets, prolonged cooling needed higher glucose administration.
- Hypokalemia in sheep, corrects with warming
- Poor cortisol response to stress.
Hypothermia in NEC

- Prospective study of 26-30 week
- 15 NEC infants cooled vs 10 non-cooled
- Three temperature targets 35.5, 34.5, 33.5 for 48 h
- Inotropes in first 24 hr 13/15 vs 7/10.
- Death 2/15 vs 3/10.

- Hypothermia significantly impaired all parameters of blood clot dynamics.
- More blood transfusion 55 ml/kg in 33.5 deg group vs 7.5 ml/kg. (28.3 in 3 groups)
- FFP 39 vs 27 ml/kg, platelets 22 vs 6 ml/kg

*Pediatrics 2010;125:e300–e308*
Cooling cap Without Systemic Hypothermia

- 4 case studies
- Two 32, one 33, one 35 week
- Target scalp cooling temperature was reached only in one patient within 6 hours.
- One was unsuccessful.
- One death, all bad outcomes.
- Confirmed by unofficial reports in piglets of no benefit of this strategy to protect brain without systemic hypothermia.

*J Neonatal-Perinatal Med 8 (2015) 47–51*
Hypothermia 34-35 weeks

- Retrospective study of 31 preterm vs 32 term
- Population had less meconium, more abruption, more maternal indications for delivery.
- Death in 13% in preterm with 0 in term
- Rewarming 19% vs. 0 in term
- Hyperglycemia higher; hypoglycemia tendency to be higher
- Leucopenia higher
- Coagulopathy tendency to be higher
- MRI findings: more frequent, more severe, more WMI, more cerebellar injury in preterm

*J Pediatr 2017;183:37-42*
Limitations

• No control group of preterm babies without hypothermia
• No neurodevelopmental followup
Randomized Clinical Trial

- Whole Body Hypothermia For Moderate And Severe Hypoxic-Ischemic Encephalopathy In 33-35 Weeks.
- May 2015 – Oct 2020
- Primary Outcome: Death or moderate or severe disability [Time Frame: Birth to 18-22 months corrected age]
- Secondary Outcomes:
  - Number of deaths in the NICU and following discharge
  - Number of infants with moderate and severe disability [Birth to 18-22 months corrected age]
  - Differences in MRI findings after cessation of cooling/control obtained [Birth to 40 weeks corrected]
  - Neurological injury by cranial ultrasound within 24 hours of enrollment [Birth to 2 days of life]
Experience at CHM

- 35¹-36⁶ weeks gestation
- Cooling for NE

![Pie chart showing categories of outcomes: Normal (1), Severe (2), Death (2), Lost (6).]
Things to Consider

- It is not clear that the $36^1-36^6$ infant benefits from cooling.
- Some centers are cooling 35 week infants.
- The more premature the baby the systemic complications of hypothermia become a bigger problem.
- Increased deaths most probably will be a tradeoff to consider.