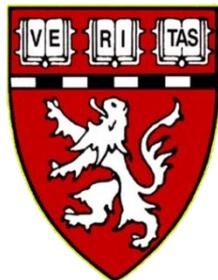


NICU Therapy – Brain Cooling

Hypothermic Therapy (HT) for Neonatal Hypoxic Ischemic Encephalopathy (HIE)



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Conflict of Interest Disclosure

I have no financial relationships with any commercial entity producing healthcare-related products and/or services relevant to this presentation.

HIE Definition

- *Moderate or Severe* HIE:
 - metabolic acidosis
 - cord pH <7.0 or base deficit \geq 12 mmol/L
 - early onset of encephalopathy
 - multisystem organ dysfunction
 - exclusion of other causes such as coagulation, metabolic and genetic disorders or maternal trauma

HIE Epidemiology

- Incidence: 1.5/1000 term births
- Mortality: 15 – 20%
- Morbidity: Overall, 25% long-term disabilities
 - *Mild* HIE: Low risk of motor or cognitive defects
 - *Moderate* HIE: significant motor deficits, fine motor disability, memory impairment, visual or visuomotor dysfunction, increased hyperactivity and delayed school readiness
 - *Severe* HIE: 85% die, high risk of CP, MR in survivors

HIE Pathophysiology - Damage Mechanisms

Two Phases

- Primary Energy Failure
 - ↓ CBF, O₂ substrates, high-energy PO₄ compounds (ATP), low tissue pH
 - Excitotoxic-oxidative cascade (excess neurotransmitter stimulation)
 - Loss of ionic homeostasis across membranes (depolarization), entry of intracellular Ca²⁺ → ↑NOS → ↑ RO/NS → mitochondrial disruption → apoptosis → necrosis
- Reperfusion: Therapeutic window = 6 hours
- Secondary energy failure
 - Continuation of excitotoxic-oxidative cascade
 - Activation of microglia— inflammatory response
 - Activation of caspases
 - ↓ growth factors, protein synthesis
 - Apoptosis—necrosis continuum

HIE Diagnosis

- History of pregnancy and intrapartum period
 - Events leading to compromised blood or oxygen supply to the fetus (placental abruption, amniotic fluid embolism, tight nuchal cord, cord prolapse/avulsion, maternal hemorrhage (placental abruption/accreta), trauma or cardiorespiratory arrest, uterine rupture)
 - Acute severe and sustained fetal decelerations
 - Maternal fever
- Neurologic examination c/w encephalopathy
- Laboratory
 - Placental pathology with evidence for infection.
 - Amplitude integrated electroencephalography (aEEG) (abnormalities at < 6 hours of age highly predict early childhood outcome)
 - Markers of renal, liver, cardiac and coagulation function and muscle injury.
- Imaging

HIE Therapies

- Prior: Supportive
 - Respiratory and cardiovascular support
 - Correction of metabolic disturbances
 - Anti-seizure medications
- Current: Neuroprotection
 - Hypothermia
- Future: Hypothermia + drugs

Evidence for Hypothermia for Neuroprotection:

Preclinical Studies

- Fetal and neonatal controlled animal models: cooling to 4 - 6C for 3 - 72 hrs is neuroprotective (NP) and well tolerated
- ↑ protection with ↓ temp (up to 28C). AE: Bradycardia and coagulation defects. ↑ HT may be detrimental; cooling to 30C is associated with ↑ metabolic derangements, death and cardiac arrest than cooling to 33.5C
- HT is NP by inhibiting many steps in the excitotoxic-oxidative cascade: inhibits the ↑ in brain lactic acid, glutamate, [NO] and epileptic activity
- HT ↓ protease activation, mitochondrial failure, ROS damage, lipid peroxidation and inflammation
- HT ↓ brain energy use, prolongs the latent phase, ↓ infarct size, ↓ neuronal cell loss, retains sensory motor function, and preserves hippocampal structures
- Optimal NP by HT may occur at different temps in cortical and deep gray matter
- HT may be cardioprotective: ↓ cardiac troponin 1 and ↓ ischemic lesions
- NP effects are reversible; resuscitation with 100% O₂ → ↑ brain injury and counteracts the NP effect of HT

Evidence for Hypothermia for Neuroprotection: Clinical Trials -1

- Six major RCTs of HT for neonatal HIE, infants born ≥ 35 - 36 weeks gestation, within the therapeutic window of 6 hours:
- **CoolCap** (n=234): Head Cooling
 - term infants with mod or severe encephalopathy and abnormal aEEG
 - cooled to 34C - 35C for 72 hours vs. conventional care
 - primary outcome: death or severe disability at 18 months occurred in 66% conventional care and 55% cooled group (adjusted [OR] [95% CI] 0.61 [0.34–1.09], P = .10).
 - Predefined subgroup analysis suggested that head cooling had no effect in infants with the most severe aEEG changes but was beneficial in infants with less severe aEEG changes.

Evidence for Hypothermia for Neuroprotection: Clinical Trials -2

- **NICHD (n = 208): Whole-body cooling**
 - term infants with mod or severe encephalopathy
 - cooled to 33.5C for 72 hours or usual care.
 - primary outcome: death or moderate or severe disability at 18 months occurred in 62% of the usual care group and 44% of the hypothermia group ([RR] [95% CI] 0.72 [0.54–0.95], P 5 .01).

Evidence for Hypothermia for Neuroprotection: Clinical Trials -3

- **Total Body Hypothermia for Neonatal Encephalopathy (TOBY) (n= 325): Whole body cooling**
 - moderate or severe encephalopathy and an abnormal aEEG.
 - Cooled to 33C - 34C for 72 hours or usual care.
 - primary outcome: death or severe neurodevelopmental disability at 18 months occurred in 53% of the usual care group and 45% of the cooled group ([RR] 0.86 [0.68–1.07], P = .17).
 - predefined secondary outcomes: survival without disabilities significantly higher in the cooled vs. the usual care group. The rate of CP was lower, and improved mental and psychomotor indices were noted in the cooled vs. the usual care group (P<.05).

Evidence for Hypothermia for Neuroprotection: Clinical Trials -4

- **Selective head cooling**, China (n=256)
 - 21% and 19% had mild encephalopathy in the cooled and usual care groups
 - cooled to 34C for 72 hours
 - primary outcome: death or severe disability at 18 months occurred in 49% control and 31% hypothermia group infants (OR 0.47 [0.26–0.84, P = .01])

Evidence for Hypothermia for Neuroprotection: Clinical Trials -5

- **European Network** (n= 129), Whole-body hypothermia
 - moderate or severe encephalopathy and an abnormal aEEG
 - Cooled 33C - 34.0C
 - all infants received morphine (0.1 mg/1 g) infusions.
 - primary outcome: death or disability at 18 months occurred in 51% of the cooled group and 83% in the usual group (OR, 0.21 [0.09–0.54], P = .001)

Evidence for Hypothermia for Neuroprotection: Clinical Trials -6

- **Infant Cooling Evaluation (ICE) trial:** (n = 221). Whole-body cooling
 - cooling initiated at the referral hospital after clinical diagnosis of encephalopathy
 - mild encephalopathy in 15% of the cooled and 23% of control infants
 - primary outcome: death or major disability at 24 months occurred in 51% of the cooled and 66% of control infants (RR, 0.77 [0.62–0.98]). The mortality rate was significantly reduced. Survival free of disability was increased in the cooled group
- Recent systematic reviews and meta-analyses have demonstrated that hypothermia improves survival and neurodevelopmental outcome at 18 months among term infants with moderate or severe HIE.
- No trials have been large enough to distinguish effects of HT on mod vs. severe HIE

Utility of MRI

- TOBY (40% trial participants)
 - HT was associated with ↓ lesions in the
 - basal ganglia or thalamus (OR, 0.36 [0.15–0.84], P = .02)
 - white matter (OR, 0.30 [0.12–0.77], P = .01)
 - abnormal posterior limb of the internal capsule (OR, 0.38 [0.17–0.85], P = .02)
 - Cooled infants had more normal scans and fewer scans that predicted 18-month neuromotor abnormalities.
 - Accuracy of prediction of death and disability by MRI was 0.84 (0.74–0.94) in the cooled and 0.81 (0.71–0.91) in the control group.
- NICHD Neonatal Research Network (65% trial participants)
 - Normal scans were noted among 52% of cooled and 35% of controls (P = .06).
 - Cerebral infarction detected in fewer cooled than controls (P = .02) as well as fewer anterior limb of the internal capsule abnormalities (P = .05) and posterior limb of internal capsule injuries (P = .06).
 - MRI brain injury pattern correlated with the outcome of death or disability and with disability in survivors at 18 months. Each point increase in the severity of the pattern of brain injury was associated with a 2x increase in the odds of death or disability.

Body vs. Head



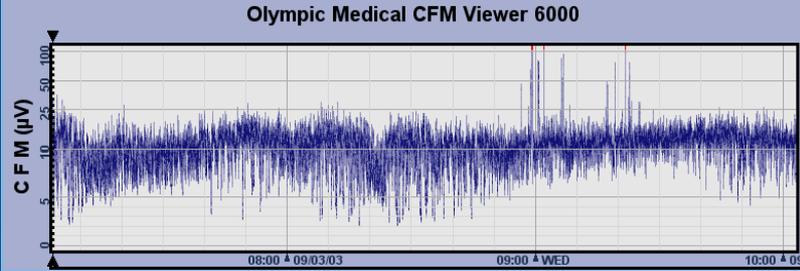
HT Inclusion Criteria

Brigham and Women's Hospital

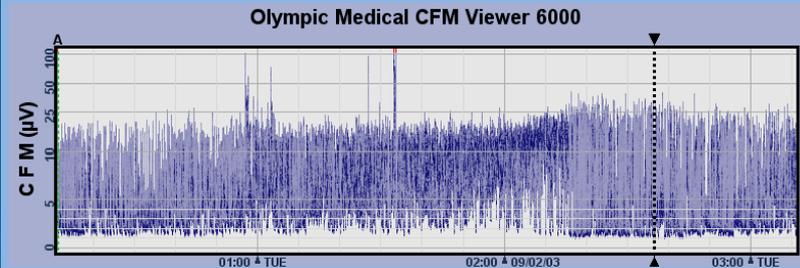
- Gestational age ≥ 36 weeks and birth weight ≥ 2000 gm
- Evidence of **fetal** distress as evidenced by at least one of the following:
 - history of acute perinatal event (e.g. abruption placenta, cord prolapse, severe FHR abnormality, variable or late decelerations)
 - BPP $< 6/10$ (or $4/8$) within 6 hours of birth
 - cord pH ≤ 7.0 **or** base deficit ≥ 16 mEq/L
- Evidence of **neonatal** distress as evidenced by at least one of the following:
 - Apgar score ≤ 5 at 10 minutes
 - Postnatal blood gas pH at < 1 hour ≤ 7.0 **or** base deficit ≥ 16 mEq/L
- Continued need for ventilation initiated at birth and continued for at least 10 minutes
- Evidence of neonatal encephalopathy by physical exam (by neurologist)
 - Abnormal Cerebral Function Monitor (CFM), with minimum of 20 minutes recording, one of the following:
 - Severely abnormal: Upper margin $< 10\mu V$
 - Moderately abnormal: Upper margin $> 10\mu V$ and lower margin $< 5\mu V$
 - Seizures identified by aEEG



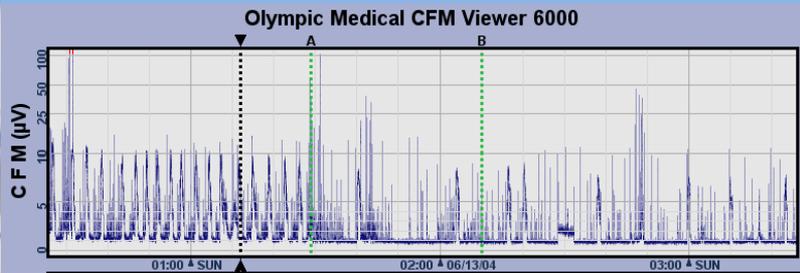
aEEG (CFM)



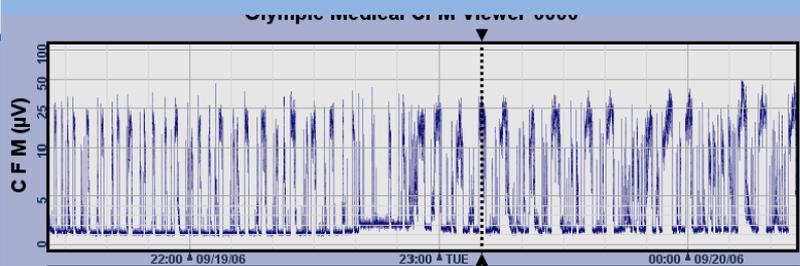
Normal trace



Moderately abnormal trace



Severe abnormal trace



Seizures

Future Therapies

Drugs that might augment neuroprotection by HT

- **Anticonvulsant or antiexcitatory**
 - Phenobarbital, topiramate, levetiracetam, memantine, xenon, magnesium, sulphate, bumetanide
- **Anti-inflammatory or antioxidant**
 - Sodium cromoglicate, minocycline, indometacin, melatonin, N-acetylcysteine, allopurinol, pomegranate polyphenols, 7-nitroindazole, 2-iminobiotin, necrostatin
- **Multiple mechanisms**
 - Erythropoietin
- **Growth factors**
 - Nerve growth factor, insulin-like growth factor 1, brain derived neurotrophic factor

Summary

- Therapeutic HT appears to be neuroprotective when initiated within 6 hours of birth in newborns with moderate to severe HIE.
- Cooling has become standard of care for infants with HIE, although more study is required to determine the optimal selection criteria and treatment protocol.
- Future therapy will involve HT + other neuroprotective drugs that can interfere with multiple steps in the two phase injury pathway.