Therapeutic Cooling after Perinatal Asphyxia

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Case presentation

• Full term, presenting in active labor
• Decreased fetal movement noted earlier in day
• FHRM: Non-reassuring fetal status
• Repetitive variables and late decelerations
• Emergent C-section
• Floppy, cyanotic, no respiratory effort
• HR<60 -> compression. Intubated 2’ apnea
• APGARs 1, 4, 5
• UA 6.9/-20; low initial blood glucose

Case: seizure and Rx cooling effects

MRI (day 4) – b/l watershed injury & deep gray nuclei
• Perinatal asphyxia occurs 6/1000 live births.

• Moderate to severe hypoxic ischemic encephalopathy (HIE) in 0.5-1/1000 live births. (Levene MI, Lancet 1986)

• HIE has 10-20% mortality (Dixon, 2002)

• 25-60% of survivors have long-term neurodevelopmental sequelae (Robertson, 1989).
  • CP, MR, LD, Epilepsy

• In the US, intrauterine hypoxia and birth asphyxia is 10th leading cause of neonatal death.

• Worldwide estimates:
  ✓ 4-9 million newborns suffer birth asphyxia/year.
  ✓ 1.2 million deaths or ~23% of all neonatal death
  ✓ 1.2 million severe disability.

What's in a name?

- Hypoxia
- Hypoxemia
- Ischemia
- Asphyxia
- Asphyxia neonatorum
- Birth asphyxia
- Intrapartum asphyxia
- Perinatal asphyxia

What's in a name?

- Hypoxic ischemic encephalopathy (HIE)
- Perinatal depression
- Neonatal encephalopathy

  • Describes CNS dysfunction in the newborn period from all causes, including HIE and BA
  (ACOG Opinion, No 326, December 2005: Inappropriate Use of the Terms Fetal Distress and Birth Asphyxia)

  • Use of term birth asphyxia has declined

Cooling targets neonatal brain injury from discrete perinatal events (within 12 hours of birth).
Criteria for acute intrapartum hypoxic event sufficient to cause cerebral palsy

1.1: Essential Criteria (must meet all four)
1. Evidence of metabolic acidosis (pH<7 and BD ≥12mmol/L) in cord UA blood obtained at delivery.
2. Early onset of moderate to severe neonatal encephalopathy (in infants >34wk GA).
3. Spastic quadriplegia or dyskinetic-type cerebral palsy.
4. Exclusion of other identifiable causes (eg, trauma, coagulopathy, ID, genetic).

Criteria for acute intrapartum hypoxic event sufficient to cause cerebral palsy

1.2: Non-specific but suggestive criteria in close proximity to L&D (e.g., 0-48 hrs)
1. Sentinel hypoxic/ischemic event immediately before/during labor.
2. Sudden/sustained fetal bradycardia or loss of FHR variability with persistent, late, or variable decels.
3. Apgars scores of 0-3 beyond 5 min
4. Onset of multisystem involvement within 72 hours (eg, kidney, liver, etc.)
5. Early imaging study showing evidence of acute nonfocal cerebral abnormalities.

Background:
Cerebral Palsy

- 8-10,000 babies/yr in the U.S.
- 1 in 3 very low BW infants
- Term babies with HIE more severely impaired
- Two-thirds children with CP mentally impaired
- One-third of children with CP have seizures
- Cost of care in US ~ $30 billion per annum

Centers for Disease Control and Prevention
National Institute of Neurologic Disease and Stroke
March of Dimes Foundation

Cooling to the rescue?

Newsweek
This Man Was Dead.

SHOCK: Doctors Freeze Baby For Four Days
What’s going on here?

Latent period represents a therapeutic “window of opportunity” between an asphyxia event and secondary phase of impaired energy metabolism and injury.

Major variants of FT neonatal brain injury

Mechanisms of injury and repair unique to newborn brain

Mechanisms of brain injury in term neonates

“Biphasic nature of cell death”

(Glückman PD, et al. Dev Med Child Neurol ’92)

Primary neuronal death

- Hypoxia
- Cytotoxic edema
- PAF in CSF
- Mitochondrial failure
- Accumulation of excitotoxins
- Active cell death (apoptosis)
- Nitric oxide synthesis
- Free radical damage
- Activated microglia
- Extracellular glutamate
- NMDA receptor activation
- Intracellular Ca++

Secondary phase

- Hyperemia
- Cytotoxic edema
- PAF in CSF
- Mitochondrial failure
- Accumulation of excitotoxins
- Active cell death (apoptosis)
- Nitric oxide synthesis
- Free radical damage
- Activated microglia
- Extracellular glutamate
- NMDA receptor activation
- Intracellular Ca++

Latent period

0 hrs 6 hrs ...

Animal Models

- Animal models began to support potential benefit for mild-moderate hypothermia (33-34°C ~ 92-93°F) in neonates after birth asphyxia.

- Term and preterm animal models for hypothesis
Safety Studies

- Pilot studies confirmed safety of neonatal cooling.
  - Azzopardi et. al (TOBY), Pediatrics, 2000
  - Shankaran S, et. al. (NICHD), Pediatrics, 2002

- Adverse effects (in pilot trials) were transient and reversible.
  - Sinus bradycardia
  - Increased blood pressure
  - Increased oxygen requirement

- Enrollment criteria for pilot studies were all similar.

Therapeutic Cooling Trials

- Enrollment Criteria:
  - >37wk GA
  - Need for resuscitation
  - Acidosis at birth (pH<7.0 or BE > -14)
  - Moderate-severe ncephalopathy (+/- aEEG/EEG evidence)

- Protocol:
  - Cooling (head vs body) to 33-34 °C
  - 48-72 hours
  - Continuous monitoring
  - Neuroimaging
  - Follow-up

- Now over 8 major RCT of neonatal cooling for BA.

Major RCT of Neonatal Cooling

- 6 RCT of Cooling with 18-24 mo follow-up
  - Cool Cap (Gluckman, et al, Lancet, 2005)
  - NICHD (Shankaran, et al, NEJM, 2005)
  - China Study Group (Zhou WH, et al, J Peds, 2010), n=194
  - neo.nEURO.network (nnn) (Simbruner, et al, Pediatrics, 2010)
  - ICE (Jacobs, et al, ’08) *Protocols and prelim data only

- Only two studies (NICHD & China Group™) showed significant reduction in primary outcome of death or disability at 18-24 months.

Cooling Trials: Meta-analyses

- Schulzke, et al, BioMed Central (BMC) 2007

- Mortality data available from 10 RCT: n= 1320
- 18 mo Follow-up data from 3 RCT: n=767
- Two pending trials w/ 18 mo f/u: n=221 (ICE) + n=129 (nnn)
Primary outcome: Death or disability (BMJ ‘10)

- Meta-analysis of primary outcome: Death or disability at 18 mo
- RRR of 0.81 (95% CI 0.71-0.93, p=0.002)
- NNT = 9 (95% CI 5-25)

Edwards AD, et. al., BMJ, Feb 2010

Caveats

- Risk of neurodevelopmental sequelae and mortality remains high (not a cure)
- Expectations can be unreasonably high
- Still awaiting 6–year follow-up data
- Cooling is performed in varied settings
  - cooling with water bottles possible…


Consensus Statements

- 2006 AAP Committee on Fetus & Newborn (Blackmon LR, Starks AR, Pediatrics, 2006)
- 2005 ILCOR Statement (Circulation, 2005)
- Recommend centers only use therapeutic hypothermia:
  - Under rigorous protocols
  - With systematic collection of patient data
    * large encephalopathy data registries (eg, VON, CPQCC)
  - With long-term neurodevelopmental follow-up.
‘08 Revised ILCOR Guidelines

Recent review of 2005 ILCOR recommendation that cooling be used only after cardiac arrest but not after neonatal resuscitation.

With additional robust RCT data with a mean NNT between 6 and 8, now recommend therapeutic hypothermia be offered as routine clinical practice (standard of care).


Cooling programs in California

- 146 NICU’s in California
- 14 Cooling Programs (as of October 31, 2009)
  - Child. Hosp. & Rsch. Ctr, Oakland (wbc) - Kaiser, Oakland (wbc)
  - Child. Hosp. Orange County (CC) - UC Irvine (wbc)
  - Lucille Packard CH/ Stanford (wbc) - UC Davis (wbc)
  - UC San Diego (wbc) - Rady CH, San Diego (wbc)
  - Sharp Mary Birch Hosp for Women (wbc) - Calif Pacific Med Ctr, SF (wbc)
  - UCSF (wbc) - Santa Clara Valley MC, San Jose (wbc)

Compiled by Bhatt DR, Ramanathan R, Kahle R, and Durand D

- Contact information and protocols available on CAN website:
  - http://www.canneo.org/

Protocols, Document and Guidelines

1. Cooling after birth asphyxia
   - Inborn patients
   - Outborn patients
   - Transport protocol
2. Family Information sheet
3. Outreach/NCPeTS Tipsheet
4. Seizure management
5. Neuro Exam checklist
6. Neuromonitoring guidelines
**Eligibility Criteria for Therapeutic Cooling**

Eligibility criteria to be considered for cooling:

1. Infants ≥ 36 weeks gestational age and ≥ 1100g of birth weight
2. Presence of one or more of the following:
   - Low Apgar scores (<5 for ≥ 10 minutes
   - Prolonged resuscitation at birth
   - Severe acidosis
     - pH < 7.0 (cord gas)
     - pH < 7.2 (1st patient gas)
   - Abnormal base excess
     - < -12 mmol/L in cord or 1st patient blood gas within 60 minutes of birth.

**Exclusion Criteria for Cooling**

- Presence of any of the following:
  - Preterm birth (<36 weeks gestation)
  - Other congenital anomalies
  - Neurocutaneous syndrome
  - Severe congenital heart defect
  - Severe congenital malformations
  - Neonatal sepsis
  - Neonatal encephalopathy
  - Severe acidosis on cord or first patient gas

**Early Patient Identification**

- Consider ASAP after concerning neo resuscitation
- Any staff member (MD, NNP, RN) may identify patients as candidates for cooling.
- Automatic "panic values" may trigger evaluation.
  - UCSF Clinical Labs notify MD if cord/1st pt blood gas:
    - pH: <7.0 (cord gas) or <7.2 (1st patient gas)
    - Base excess: < -12 mmol/L
- If any question, call a regional cooling center to discuss case (and document call).

**Clinical / Diagnostic grey zones**

- At risk babies with initial hypotonia can recover “good tone” – which exam counts?
- Encephalopathy may be evolving (“hyperalert state”).
- Severe acidosis on cord or first patient gas can recover with first/follow-up gas.
  - Is the 1st gas enough evidence of injury risk?
  - Is the rapid correction enough to reassure low risk?
Cooling on transport

Fairchild K, et al., Therapeutic hypothermia on neonatal transport: 4-year experience in a single NICU. J Perinatol, 2010

Whole Body Cooling Systems
e.g., CSZ Blanketrol III®

Monitoring in the NICU

- **Vital Signs** (HR, BP, RR, SaO2, TCO2, NIRS)
- **Clinical lab tests**, e.g.:
  * blood gas, glucose/electrolytes, lactate
  * coag panel
  * liver/renal function labs
- **Standard video EEG** (72 hours + 24 hours)
- **amplitude integrated EEG** (aEEG) / CFM

Cool Cap® System

The only on-demand nitroglycerin-amine treatment for severe congenital heart disease
Amplitude-integrated EEG (aEEG) Cerebral Function Monitor (CFM)

- Limited channel bedside neuromonitor
- Easy to use
- Allows checking of:
  - Background pattern
  - Response to treatment
  - Some seizure detection
- Full EEG still gold standard

Key considerations

- Core temperature monitoring
  - Turn off external heat sources ASAP
  - Begin passive cooling
  - Obtained initial blood gas and clinical details
  - Call regional cooling center
- Establish access
  - Umbilical lines (UVC/UAC) or PIV/RAL
- Provide adequate sedation (avoid shivering)
  - Continuous Morphine infusion or boluses

Key considerations

- Medical management of co-morbidities
  - FEN (glucose, calcium, sodium/potassium)
  - Respiratory
    * Hyperventilation/Hyperoxygenation
    * Meconium Aspiration Syndrome
    * Persistent Pulmonary Hypertension (PPHN)
  - Cardiovascular
    * Bradycardia
    * Hypotension
  - Hematologic
    * Coagulation disorders
  - Infectious

Key considerations

- Neurological issues
  - Seizures (clinical vs. sub-clinical)
  - Neuromonitoring
  - Sedation
  - Neuroimaging
Neonatal seizures are common

- Neonatal Seizures are common and often suggest underlying brain injury or dysfunction.
- Birth is most common time of life to have seizures
  - 0.95/1000 term births in California (OSWHPD database)


- Associated death or cerebral palsy
  - 16% death
  - 39% impaired (mental retardation, cerebral palsy)
  - Epilepsy


Neonatal seizures are important

Assessing neonatal brain injury by MRI

- MRI done after 72 hr cooling
- ~ DOL #4-5
- Injury patterns can predict outcomes and severity.

Neonatal neurocritical care: Experience and resources can matter

- Transport
- Seizure detection
- Acute critical care with multi-organ failure
- Complications and side effects
- ECMO
- Palliative care support
Complications in high-risk patients

• Multi-organ failure/ischemia-reperfusion injury
  Sarkar et al., J. Perinatol, 2009

• Other complications of cooling from clinical trials
  – Thrombocytopenia
  – Need for vasopressors (Butin et al., Pediatrics, 2009)
  – Sinus bradycardia (physiologic)
  – Glucose metabolism (hyper/hypo)
  – Prolonged PT/PTT (physiologic) with normal fibrinogen
  – Skin changes (Shankaran S, et al, NEJM, ’05) (Hogeling, et al, Peds Derm, ’10)

Future developments in cooling

• **Late Hypothermia for HIE Trial** (NICHD trial)
  • 6-24 hrs after injury
  • 96 hours of hypothermia
  • 17 centers (Stanford Univ in CA) – Completion Mar 2014
    ClinicalTrials.gov: NCT00614744

• **Head cooling in Preterm infants with HIE (pilot)**
  • <36wk, but >32wk GA after HIE and <6hours old
  • Industry sponsored, open label, safety trial
  • Vanderbilt/Northwestern - Completion Feb 2010
    ClinicalTrials.gov: NCT00620711

Summary

• Major RCT’s and meta-analyses consistently show cooling reduces death &/or disability and outcomes to 2 years.

• Mortality for asphyxia remains high.

• Consider cooling early. Contact a regional cooling center to discuss possible cases.

• Clinical experience and resources can matter.

• Advances in neuromonitoring, imaging and evidenced-based care make neonatal neurointensive care possible.

• In the future, emphasis on new adjuvant therapies and health service research.
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Our patients and their families