Therapeutic Hypothermia: Applications in the PICU

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Disclosure

I have no relationships with commercial companies to disclose.

Objectives

- Review the basic science of hypothermia and application in hypoxic-ischemic neuronal injury
- Summarize current clinical evidence for use of therapeutic hypothermia
  - Use in cardiac arrest, intrapartum asphyxia and traumatic brain injury
  - Limitations of available evidence
- Introduction to the goals and objectives of the THAPCA trials

Background

- Cardiac arrest (CA) in children is a tragic event associated with high mortality and poor neurological outcome
- Especially true of out-of-hospital (OH) CA
- CA in the in-hospital (IH) setting results in higher survival and neurologic sequelae are far less common in survivors

History of Hypothermia

- Concept developed in the 1950s
  - Hypothermic dogs survived 20 min of cardiac arrest
- 1960s Neurosurgery for large aneurysms under cardiac arrest
- 1970s Ascending aortic arch surgery
- Outcome: not good

Simplified scheme of the mechanism after ischemia
Neuroprotective Effects of Hypothermia

- In rat models: ↓ cerebral edema, blood brain barrier permeability, cerebral atrophy
- Lowers CBF and ICP
- Potential as an anticonvulsant
- 24hr hypothermia is safe

Evidence for Hypothermia in Pediatric Cardiac Arrest

- Hypothermic group
  - Target temp 30°C for 1 week
- Increased risk for neutropenia, sepsis, death in the hypothermia group
- No optimal core temperature determined
Hypothermia in Adult Arrest – European trial

- Randomized survivors OOH witnessed VF/VT with coma after ROSC
  - Goal was to cool to temp 32-34 °C within 4 hours of ROSC but median was 8 hours
  - Sedated and Intermittent NMB for shivering
  - Blinded assessment of outcome at 6 months
- 3551 patients screened and 275 studied (only 7.7% of total arrest population)

Hypothermia after Pediatric Cardiac Arrest

- CHOP, Retrospective cohort
- Children w/o CHD with ROSC
- 181 pts studied
  - 91% asphyxial cause; 55% in-hosp CA
- 40 pts received HT
- Similar mortality rates- 55%, p=1.0

Canadian Study

- 5 center, retrospective study
- 79 pts studied, 29 received HT
  - Cooled to 33.7± 1.3°C for 20.8± 11.9 hrs
- HT assoc
  - Higher mortality, longer duration of CA, more resus interventions, Higher lactacte, and ECMO use
- No signif stat diff in Mortality when adjusted CA duration, ECMO, propensity scores

Hypothermia after Pediatric Cardiac Arrest

- Hypothermia Pts
  - 78% survivors d/c home
  - Temp <32°C (15%); assoc with higher mortality
  - More unwitnessed CA and out hosp CA; Epi doses to ROSC
  - Received more Electrolytes
- Normothermia Pts (68% survivors)
  - 2x more likely to fever; and re-arrest

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Cool Cap Perinatal Asphyxia Study

- 25 Center study in term newborns with HI-encephalopathy
- Evaluated use of selective head cooling using dedicated device
- Random assignment w/in 6h of birth to head cooling for 72h or conventional care

Cool Cap Perinatal Asphyxia Study
- Inclusion: term infant with clinical evidence of mod to severe encephalopathy or seizures and evidence of perinatal HI
  - (Apgar ≤ 5 at 10 min or severe acidosis within 1 hr of birth) and abnormal aEEG within 6 hr
  - Rectal temp maintained at 34-35°C for 72 hr
- Primary outcome: death or severe disability at 18 mo


Hypothermia- Perinatal Asphyxia
- Logistic regression analysis controlling for pre-randomization severity of encephalopathy suggested a protective effect (p=0.05; OR 0.57; 0.32, 1.01)
- No effect in infants with most abnormal aEEG changes
- Adverse outcome reduced from 65.9% in controls (n=88) to 47.6% in cooled (n=84), p=0.01
  - ARR = 18.3%; NNT = 6 (95% CI: 3 to 27)


Whole Body Hypothermia for Neonatal HIE
- 15 center NICHD Neonatal Network trial of systemic hypothermia initiated within 6 h and continued for 72 h in neonates with HIE
  - 1st outcome: reduction of death or severe disability at 18-22 mo
  - Cooled with servo-controlled blanket; monitored rectal temp to target of 33.5°C
  - Controls at 36.5-37°C skin temp
  - Randomized block design at each center; 798 screened, 239 eligible and 208 enrolled


Whole Body Hypothermia for Neonatal HIE
- Included if significant acidosis (pH<7, BD> 16 mm/Hg) by umbilical cord or blood sample within 1 h of birth + acute perinatal event and either 10 min Apgar ≤ 5 OR assisted ventilation at birth and continued > 10 min
- Excluded if > 6 hrs, major congenital abnormality, moribund, severe growth retardation


Perinatal Hypothermia
Groups well matched at baseline
Randomized 234 with mod-severe HIE + abnormal amplitude-integrated EEG
1st outcome: death or severe disability
- < 6 hrs: 34.5±0.5°C
- Control-118, 66% poor outcome
- Hypo-116, 55% poor outcome

Bradycardia more common in HT group and scalp edema resolved without intervention.

NNT = 6 (95% CI, 3 to 27) for HIE therapy to prevent one death or severe disability
TOBY Study

- Prospective, multi-center, randomized neonatal trial in UK (325 pts recruited)
- Infants less than 6 hrs old, 36 weeks and perinatal encephalopathy
- Cooling 33.5°C for 72 hrs or 37°C
- Rewarming no more than 0.5°C/hr
- Primary outcome: death or severe disability (18 months)

TOBY Results

- Cooled group
  - 42 deaths, 32 survival with severe disability
- Noncooled group
  - 44 deaths, 42 survival with severe disability
- Either outcome: RR 0.86, P 0.17
  - Increased survival rate without neuro disability (RR 1.57; p=0.003)

Results

- Cooled infants increased survival rate w/o neuro abn (RR 0.67, P 0.003)
- Cooling had reduced risk for cerebral palsy (RR 0.67 P 0.03)
  - Improved developmental scores
- Adverse events similar in two groups
  - Hypotension, Plts, ICH, Coag time

Cochrane Collaboration

- Eight randomized trials reviewed
  - 638 term infants with moderate-severe encephalopathy and intrapartum asphyxia
- Results
  - Statistically significant reduction in combined outcome of mortality or major neuro disability to 18 mo
  - RR 0.76; RD -0.15, NNT 7
  - Adverse events: use of inotropes, thrombocytopenia

Cochrane Conclusions

- Therapeutic hypothermia beneficial to term infants with HIE
- Reduces mortality without increasing major disability in survivors
- Both large neonatal HI trials showed benefit in moderate HI encephalopathy group
  - Suggests that HT may not be effective if neuro injury severe
  - Ability to stratify by aEEG 24h/day is likely limited
- Incorporation of ongoing data needed to clarify effectiveness

Cardiac Arrest Hypothermia Summary

- Until recently, no tx shown to be efficacious for neuroprotection and survival in humans post CA
- In 2002, two adult RCTs from Europe & Australia of therapeutic hypothermia (TH) after VF OH CA reported improved outcome. (HACA, Bernard)
- In 2005, 3 RCTs for newborns with HIE, all reported improved outcomes. (Shankaran, Gluckman, Eicher)
Summary

- AHA guidelines
  - HT for comatose adult CA from ventricular arrhythmia shows neuroprotective benefit, but not convincing for PEA/asystole CA
  - Consideration of HT for coma survivors after pediatric CA
  - Large RCT studies for pediatric cardiac arrest
    - THAPCA study: Plan for 850 enrollment in ~30 centers

Hypothermia for other diseases?

- Can the data from adults and neonates be applied to other types of brain injury (trauma)?

Hypothermia Paediatric Head Injury Trial (HyP-HIT)

- Multi-center Randomized controlled trial of 24 hours of hypothermia therapy in Ped pts with severe traumatic brain injury (TBI)
- 17 centers in Canada, UK and France
- 225 patients enrolled

Hypothermia Paediatric Head Injury Trial (HyP-HIT) Outcome

<table>
<thead>
<tr>
<th>PCPC (primary outcome)</th>
<th>6 Months</th>
<th>Hypothermia n (%)</th>
<th>Normothermia n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCPC= 4-6</td>
<td>32 (31.4)</td>
<td>23 (22.3)</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>23 (21.3)</td>
<td>14 (12)</td>
<td>0.06</td>
<td></td>
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HyP-HIT Survival

P=0.04 (adjusted)
Conclusions

- Moderate hypothermia (32-33°C) did not improve functional outcome after 6 mo
- No statistically significant difference in mortality but worrisome trend
  - Increased mortality in hypothermia therapy (P=0.06)
- Increase in hypotensive episodes in hypothermia group during rewarming
- No difference in adverse events

Explanation for lack of effect?

- Diverse types of brain injury
- Hypothermia therapy is ineffective
- Better method to apply hypothermia therapy
  - Shorter time to implement therapy?
  - Longer duration? (>48hr)

Hypothermia Questions

- How to rewarm?
  - Worse outcome if rewarm rapidly
  - Management of shivering/stress response
- Which patients should be cooled?
  - Should cooling start in the field or at the referring hospital?

Hypothermia Questions

- How to monitor cooling?
  - Bladder, rectal or blood temp? Brain temp?
  - Frequent excessive hypothermia with surface cooling
- How should we manage shivering?
  - Counterwarming, buspirone, fentanyl
  - Use of NMB then need to monitor continuous EEG
- How to adjust medication in HT pts?

Application of Hypothermia

- No best method for induction of cooling
- Information on hypothermia protocol at UPENN site:
  - www.med.upenn.edu/resuscitation/hypothermia
- 106 protocols currently posted
Cooling Methods

- Surface Cooling
  - Body or regional cooling
- Extracorporeal cooling
- Endovascular cooling
- Cold IV infusions

Endovascular Catheters

Rate of Cooling

Survey of Pediatric Intensivists on Use of Therapeutic Hypothermia

- Surveyed for awareness and the usage of therapeutic hypothermia (143 PICU trained)
- Majority of physicians surveyed aware of:
  - Beneficial effects
  - Hypothermia not widely used (explicit protocols, lack of evidence)
- Randomized, clinical trial of induced hypothermia in children is ethical
- Therapeutic hypothermia should be studied in other ischemic insults
Therapeutic Hypothermia After Pediatric Cardiac Arrest (THAPCA) Trials

Research Question & Aims/Hypotheses

A. Primary research question:
   Does therapeutic hypothermia (TH) improve survival and long term neurobehavioral outcome following cardiac arrest (CA) in children?

B. Research hypotheses for THAPCA Trials are:
   1) TH will improve survival and neurobehavioral outcome following out-of-hospital CA in children (THAPCA-OH Trial) (similar to adult OH RCTs); and
   2) TH will improve survival and neurobehavioral outcome following in-hospital CA in children (THAPCA-IH Trial)

Study Design Summary

- Conceptually simple RCT(s)
  One intervention (Temperature)
  Two parallel trials (Out-of-Hospital; In-hospital)

THAPCA Trials

Inclusion/Exclusion Criteria

- Inclusions
  - Child requiring CPR (most compressions) > 2 minutes
  - Age 2 to 10 yr.
  - Mechanical ventilation after CA
  - CA not planned as part of surgical or other procedure
  - Parent speaks English or Spanish

- Exclusions
  - No informed consent < 6 yr.
  - CPR status
  - Terminal illness < 13 mos.
  - Consent must include documented NCS (mortality 5 or 6).
  - Localizes pain or loses command
  - Receiving ICD at time of CA (rare)

- Exclusions - continued
  - TBI or other severe trauma
  - Active and severe bleeding or exsanguination
  - Neurogenic with motor status HIE
  - Location in NICU
  - Prior CA > 2 min and > 6 hr previously during same hospitalization
  - ETP or NE > 2 mg/kg/min at time of consent/alignment
  - Core temperature < 32°C
  - CNS Tumor with radiation or chemotx
  - Propranolol degenerative enophthalmicity
  - Loss of skin integrity
  - Previously enrolled in THAPCA
  - Other misc (SCA (fit), congenital heart disease, hypothermia (hi))
Therapeutic Hypothermia (TH)

- **Induction Phase** -
  - As rapid as possible to goal temp 33.0°C
  - Ends when goal range (32-34°C) x 1 hr
  - R21 observed mild hypothermia contains after CA
  - Most cases young (16 min; IQ: >3-100)
  - Temp q 20 min (protocol: v1.1.10)
- **Maintenance Phase** -
  - Maintain (32-34°C) for 48 hrs; temp q 1 hr
- **Rewarming Phase** -
  - Slow rewarming to 36.8°C over at least 16 hr; temp q 30 min
- **Normothermia Phase** -
  - Maintain normothermia (36-37.5°C) through 120 hrs; temp q 4 hr

Therapeutic Normothermia (TN)

- **Induction Phase** - Normothermia.
  - Goal temp is 36.8°C, range 36-37.5°C
    - If baseline temp < 36.8°C, warm to goal range at rate of 1°C/2 hrs
    - NCTE = 36.8°C (oral), temp should have been increased by 0.5°C prior
    - If baseline temp >37.8°C (unintentionally), rapidly cool to goal 36.8°C
  - Phase ends when in goal range for 1 hr
  - Temp q 30 min
- **Maintenance Phase I** - Normothermia.
  - Maintain goal range of normothermia through 72 hrs
  - Temp q 1 hr
- **Maintenance Phase II** - Normothermia.
  - Maintain goal range of normothermia 73-120 hrs
  - Temp q 4 hr

Primary Outcome Measure

- Vineland (VABS-II) advantages
  - Well normed continuous measure
  - Recently updated with emphasis on young children (VABS-II)
  - Domain assessed
    - Communication (Receptive, Expressive, Written)
    - Daily living (Personal, Domestic, Community)
    - Social (Interpersonal Relationships, PlayLeisure Time, Coping Skills)
    - Motor (Gross, Fine)
  - May be retrospectively scored (i.e. pres- arrest baseline)
  - Age range - birth to 21 yr
  - Measures lower function abilities better than other tests
  - Widely utilized with English & Spanish versions
- Singo center (blinded to treatment group) to conduct
  - Johns Hopkins- KKI

Primary Outcome Measure

- Secondary outcomes
  - All cases
    - Survival at 12 mo. following CA
  - Change in neurobehavioral function from pre-CA baseline to 12 mo. measurement (VABS-II)
  - Neuropsychological battery score at 12 mo. evaluation
  - Neurological abnormality scores at 12 mo. evaluation (modified PRCA pediatric stroke scale)
Other Outcome Measures

- Safety outcomes
- All-cause 28 d mortality
- Incidence of culture proven infection within 7 d
  - Bacterial
  - Viral
  - Respiratory
  - Other
- Blood product requirement within 7 d post CA
- Arrhythmias within 7 d
Life Support Instruction Course

- Looking for Interested Residents
- Includes renewal of BLS and PALS and initial Instructor training resulting in AHA Certification
- Time Commitment: Approximately 12-15 hours in 3 to 4 hour sessions
- Maintaining Certification requires teaching 2 classes per year
- No cost to participants
- Asking for commitment to teach other residents as part of QI project

Interested?

- Contact Brad Scoggins, scogginsb@uthscsa.edu
- You'll never know something better than when you teach it!