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The Iowa PERINATAL Letter

Cooling Newborns to Improve Outcomes:

Therapeutic Hypothermia for Neonatal Hypoxic-Ischemic Encephalopathy

Background

In the developed world, 1-2 infants per 1000 live births suffer some degree of post-delivery encephalopathy as a result of intrapartum asphyxia. Based on this incidence and with approximately 40,000 deliveries annually in Iowa, we can anticipate 40-80 newborns to be affected each year. Neonatal encephalopathy due to acute perinatal asphyxia (hypoxic-ischemic encephalopathy: HIE) is a clinical entity generally described as mild, moderate or severe in nature. Infants suffering a mild insult most usually do well in both the near and long term. However, those suffering a moderate degree of encephalopathy have a 10% risk of death and those who survive have a 30% risk of disability. Infants with severe encephalopathy have a 60% risk of death and survivors are most always disabled (1,2). Until recently, there has been no effective treatment to improve the outcomes of affected infants.

In addition to some smaller studies, there have now been three large randomized clinical trials published describing the effect of hypothermia to treat infants with moderate to severe HIE (3,4,5). These trials were based on studies demonstrating that neural damage after hypoxia-ischemia takes several hours to occur and that moderate hypothermia reduces cerebral injury and improves neurological outcome (6). Several additional studies employing hypothermia are underway and all studies are discussed and analyzed in a recent meta-analysis (7).

Hypothermia is induced either by selective head cooling with a "cooling cap" or by employing a cooling blanket to induce whole body hypothermia. The two selective head cooling trials did not demonstrate a statistically significant reduction in death or major neurodevelopmental disability as opposed to the whole body cooling trials that demonstrated a reduction in both death and major neurodevelopmental disability (8). Though the individual trials have not all demonstrated a significant decrease in death or developmental impairment in treatment groups the meta-analysis combining trials has demonstrated significant improvements in the combined outcome of death and disability (7, 8). This most recent meta-analysis (7), which includes the largest and most recently published study (5) determined that hypothermia reduced death and severe disability at 18 months of age by 19%, and increased survival with normal neurological function by 53% when examining the three largest trials that included 767 infants. The number needed to treat for these outcomes was 9 and 8 respectively (7). Additional analysis demonstrated significant reductions in survivors of severe disability, cerebral palsy and mental and psychomotor developmental index less than 70. When all 10 trials are combined (including 1320 infants) the relative risk of mortality is significantly reduced with cooling by 22%, with a number needed to treat of 14.

How do we identify candidates for hypothermia?

In determining which newborns might be candidates for induced hypothermia it is important to employ known criteria that have been used for selecting study populations. Otherwise there is absolutely no way to know if the therapy will be of benefit or detriment to a patient. See ADDENDUM for guidance.

All three tertiary care NICUs in Iowa employ the selection criteria used by the NICHD Neonatal Research Network study (4). Examples of the primary criteria that have been employed to select affected newborns include 36 weeks or greater gestation, an umbilical cord pH of 7.0 or less or a base deficit 16 or greater or these values in any blood sample in the first hour of life (see Addendum). If a blood gas is not available then evidence of an acute perinatal event indicated by late or variable decelerations, cord prolapse, cord rupture, uterine rupture, maternal trauma, hemorrhage, or cardiorespiratory arrest and either a APGAR score of 5 or less at 10 minutes or the continued need for assisted ventilation at 10 minutes of life are additional criteria employed (see Addendum). Clinical evidence of moderate to severe neonatal encephalopathy is also required. This diagnosis is made by careful neurological examination and requires the presence of one or more signs in three or more of the following categories: level of consciousness, spontaneous activity, posture, tone, primitive reflexes (suck or Moro) and autonomic nervous system (pupils, heart rate or respiration)(see Table 1).

How is hypothermia induced and maintained?

The three major hypothermia studies began cooling newborns within the first six hours of life. Two methods of cooling have been employed. The "CoolCap" trial (3) used selective head cooling whereas the other two studies used a cooling blanket that was servo controlled via a deep temperature probe. Consistent with the NICHD study, Iowa's Level III NICUs are using the systemic hypothermia model employing a cooling blanket and an esophageal temperature probe that results in a servo controlled system to achieve desired systemic tempera-

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tures. Infants who meet the above criteria for hypoxic-ischemic encephalopathy, and who are six or fewer hours of age, are cooled gradually per protocol to a core temperature of 33.5°C and maintained at that temperature for 72 hours. After 72 hours the infants are gradually rewarmed at a rate of 0.5 °C per hour until a normal temperature is achieved.

Complications associated with therapeutic hypothermia include:

Cardiac arrhythmia, bradycardia, persistent pulmonary hypertension, bleeding, skin changes.

Important considerations

Standard of Care

At the present time it is not correct to say that therapeutic hypothermia is the "standard of care" for the treatment of infants with neonatal encephalopathy. However, I believe that this issue is evolving and that therapeutic hypothermia for the treatment of hypoxic-ischemic encephalopathy may become the standard of care therapy in the future. In any case, therapeutic hypothermia is the only therapy proven to improve the outcome of newborns affected by hypoxic-ischemic encephalopathy. As such we have an obligation to do our best to provide this therapy to those who might benefit.

Where to Cool

It is recommended that therapeutic cooling be done in regional centers. Since the need for this therapy is relatively rare it is important to concentrate the experience in centers with the most resources. Since many of these infants exhibit seizure activity, centers with pediatric neurologists are desirable. Anecdotally, there have been a number of infants transferred to the University of Iowa Children's Hospital NICU with persistent pulmonary hypertension associated with cooling that was severe enough to consider the need for ECMO therapy versus discontinuation of the cooling therapy.

Timing of initiation of hypothermia

It remains unknown if there is benefit to beginning the cooling of infants beyond six hours of life. Animal studies clearly demonstrate that a therapeutic window exists during which there may be benefit to cooling therapy. However, this window has not been fully elucidated in humans. To address this issue, there is a randomized clinical trial of delayed initiation of therapeutic hypothermia currently underway by the NICHD Neonatal Research Network that enrolls eligible newborns that are 6-24 hours of age.

Similarly, it is unknown if there is benefit to cooling infants with neonatal encephalopathy due to causes other than hypoxic-ischemic insult such as infection, neonatal stroke or metabolic causes. Until future studies demonstrate benefit for infants with these issues, therapeutic hypothermia for these patients cannot be recommended.

Recommendations

1. Infants of 36 weeks gestation or greater with metabolic and physical evidence of hypoxic-ischemic encephalopathy should be transferred as soon a possible to a tertiary care center with a cooling program for therapeutic hypothermia.
2. After delivery and during transport maintain the infant's temperature at 36.5-37°C. Hyperthermia should be avoided as evidence suggests that increasing temperatures are associated with worsened outcomes of affected infants (9). **Since there is not good data to support a recommendation for active cooling during transport this is not recommended.** Some have suggested that passive cooling by transporting in a isolette that is not warmed should be done. However, this approach has not been tested and it will result in quite variable temperatures for the infant.

—Michael Acarregui, MD
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Table 1: Evidence for HIE

Moderate/severe hypoxic-ischemic encephalopathy (HIE) will be defined as either **seizures** or in the absence of seizures, the presence of signs in **3 of 6** categories from the neurological exam.

Category	Moderate Encephalopathy	Severe Encephalopathy
1. Spontaneous activity	Decreased activity	No activity
2. Posture	Distal flexion or complete extension	Decerebrate
3. Autonomic system		
Pupils	Constricted	Skew deviation/dilated/non-reactive
Heart rate	Bradycardia	Variable HR
Respirations	Periodic breathing	Apnea
4. Tone	Hypotonia (focal or general)	Flaccid
5. Primitive reflexes		
Suck	Weak	Absent
Moro	Incomplete	Absent
6. Level of consciousness	Lethargic	Stupor or coma

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8. Jacobs SE, et al. Cooling for newborns with hypoxic ischaemic encephalopathy (Review). The Cochrane Collaboration 2008.
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10. Addendum by Jonathan Klein, MD. Associate Professor of Pediatrics and Medical Director, University of Iowa Children's Hospital. Whole-body hypothermia for hypoxic-ischemic encephalopathy (HIE).

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ADDENDUM

Whole-Body Hypothermia for Hypoxic-Ischemic Encephalopathy (HIE)

Screening Criteria: Screen term infants for eligibility if they had poor respiratory effort at birth and needed resuscitation or appear encephalopathic.

Inclusion Criteria: Infants ≥ 36 weeks **and** > 1800 grams with P**erinatal Depression (Part A)** and **HIE (Part B)**.

Part A: Physiologic Criteria for Acute Perinatal Depression:

1) Cord gas or first postnatal blood gas at < 1 hour of age with either pH ≤7.0 or base deficit ≥ 16 mmol/L.

OR

2) If cord gas or first postnatal blood gas at < 1 hour of age has either a pH of 7.01 - 7.15 or a base deficit of 10 - 15.9 mmol/L or if a blood gas is not available then **the following additional criteria are required.**

a. An acute perinatal event (e.g., late or variable decelerations, cord prolapse, cord rupture, uterine rupture, maternal trauma, hemorrhage, abruptio placenta, etc.) **and either:**

   i. Apgar score of **≤ 5** at **10** minutes **or**
   ii. Need for ventilation initiated at birth and continued for at least 10 minutes

Exclusion Criteria:

a. Inability to initiate cooling by 6 hours after birth.
b. Known chromosomal anomaly (excluding Trisomy 21, Turners, etc).
c. Presence of major congenital anomalies.
d. Infants *in extremis* for whom no additional intensive therapy will be offered.

If an infant meets either criteria A1 or A2, proceed to Part B (neurological criteria and exam).

Part B - Neurological Criteria: Infants meet criteria if either seizures or HIE is present.

Evidence for HIE

Moderate/severe hypoxic-ischemic encephalopathy (HIE) will be defined as either **seizures** or in the absence of seizures, the presence of signs in **3 of 6** categories from the neurological exam.

Category	Moderate Encephalopathy	Severe Encephalopathy
1. Spontaneous activity	Decreased activity	No activity
2. Posture	Distal flexion or complete extension	Decerebrate
3. Autonomic system		
Pupils	Constricted	Skew deviation/dilated/non-reactive
Heart rate	Bradycardia	Variable HR
Respirations	Periodic breathing	Apnea
4. Tone	Hypotonia (focal or general)	Flaccid
5. Primitive reflexes		
Suck	Weak	Absent
Moro	Incomplete	Absent
6. Level of consciousness	Lethargic	Stupor or coma

Timing of the examination: The exam should be done in the first **1 - 3 hours of life** once the patient's cardiopulmonary status has been stabilized.

Performance of the neurological examination for Whole Body Cooling:

The neurological examination should take 10 - 15 minutes to complete and be performed by the attending and/or fellow. The exam is to be recorded in the admit note and performed in the following order: Spontaneous activity, posture, autonomic system, tone (via ROM), primitive reflexes and level of consciousness (response to stimuli).

Patients who have HIE as defined by seizures will still need to have a neurological exam for cooling performed and documented.

If the infant meets physiologic criteria A1or A2 and neurologic criteria B without exclusion criteria, then whole body cooling can be initiated by ordering "Cooling per protocol".

Reference

N Engl J Med 2005; 353:1574-84.

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