Policy: Cooling
Effective Date:

Kidz Medical Services
Whole-body Cooling for Hypoxic-Ischemic Encephalopathy

Purpose:
To provide the clinicians of Kidz Medical Services with guidelines for the consistent use of whole-body cooling (WBC) for the treatment of newborns with Hypoxic-Ischemic Encephalopathy.

Guideline:
I. Incidence of Hypoxic-Ischemic Encephalopathy (HIE):
   A. HIE due to acute perinatal asphyxia remains an important cause of death and neurodevelopmental deficits; perinatal asphyxia causes 19% of 5 million deaths annually.
   B. Infants with moderate HIE 10% of death, 30% risk of disabilities.
   C. Infants with severe HIE 50-60% die, many, if not all, survivors handicapped, 25-30% of survivors major disabilities.
   D. Peripartum asphyxia affects 3-5 per 1000 live births with subsequent moderate HIE, or severe HIE in 0.5-1 per 1000 live births.

II. Pathophysiology of HIE:
   A. Birth asphyxia is characterized by impaired gas exchange across the placenta and results in hypoxia, hypercapnia and eventually metabolic acidosis due to inadequate organ oxygenation and perfusion.
   B. The immature brain is highly resistant to hypoxia but if the asphyxiating process is allowed to continue the insult results in significant hypoxia-ischemia followed by neuronal injury and death.
   C. Neuronal death occurs in two phases following a reversible hypoxic-ischemic global insult.
   D. If the insult is severe, there may be immediate primary neuronal death related to cellular hypoxia with exhaustion of the cells high energy stores.
   E. After a latent period, the secondary phase of delayed neuronal death begins. The delayed phase is associated with encephalopathy and increased seizure activity and accounts for a significant proportion of the final cell loss even after very severe insults.
   F. The interval between the primary and secondary phase corresponds to a therapeutic window, during this time treatment may be applied to reduce brain injury.
   G. Exact duration of this window is not known, but studies have shown that neuroprotective effect of cerebral hypothermia diminishes and disappears if cooling is delayed beyond 6 hours.

III. Pathophysiology of therapeutic hypothermia:
   A. Brain cooling has a favorable effect on multiple pathways effecting brain injury:
      1. Reduces cerebral blood flow and metabolism.
      2. Inhibits glutamate and nitric oxide release.
      3. Reduces apoptosis.
      4. Stabilizes blood-brain barrier.
      5. Prevents seizures.
   B. Therapeutic hypothermia aims to lower the temperature of the deep vulnerable brain structures, to 32-34°C.
   C. Two methods are being evaluated in infants with HIE:
      1. Whole-body Cooling (WBC) - the brain can be cooled by cooling the body.
         a) WBC provides homogeneous cooling to all brain structures, including peripheral and central brain regions.
         b) Theoretical modeling of cooling investigating temperature distribution within the neonatal head found that the only situation that resulted in a significant reduction in deep brain temperature was when the core body temperature was lowered to 34°C.
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2. Selective head cooling (SHC):
   a) SHC provides greater cooling to the periphery of the brain than to the central brain structures.
   b) The rationale for SHC is that newborn head produces 70% of total body heat and systemic hypothermia may be physiologically harmful to sick infant.

D. The window of opportunity for cooling may be up to 6 hours or even longer in some circumstances, the degree of neuroprotection progressively declines if cooling is initiated more than a few hours after insult.

E. Given the propensity for hypoxic-ischemic injury to affect deep-brain structures such as the thalamus, internal capsule and basal ganglia in the human neonate, Kidz Medical Services recommends whole-body cooling to achieve a consistent reduction in brain temperature in such structures.

IV. Research studies:
   A. Early studies in the 1950s-1960s by Miller and Westin found hypothermia in treatment of asphyxia neonatorum in newborn animals and humans newborns improved survival without cerebral palsy or mental retardation. Despite their results, hypothermia did not become accepted therapy because it was not evaluated by randomized controlled trials (RCTs).
   B. National Institute of Child Health and Human Development (NICHD) 2005 workshop to evaluate status of knowledge regarding the safety and efficacy of hypothermia as neuroprotective therapy for HIE agreed that current evidence supports the conclusion that mild to moderate hypothermia holds promise for amelioration of neural injury after perinatal hypoxic-ischemic insult.
   C. Three RCTs that NICHD reviewed:
      1. Whole-body Hypothermia for Neonates with Encephalopathy (Shankaran et al):
         a) Randomized, controlled trial evaluated whether whole-body hypothermia initiated before 6 hours of age and continued for 72 hours in term infants with encephalopathy would reduce death or disability at 18 to 22 months of age as compared with infants given usual care.
         b) Results showed whole-body cooling to an esophageal temperature of 33.5°C initiated in first 6 hours of life and continued for 72 hours reduced the rate of death or moderate or severe disability in infants with hypoxic-ischemic encephalopathy (HIE).
      2. Cool-Cap Trial (Gluckman et al):
         a) Large randomized controlled study of selective head cooling with systemic hypothermia showed a benefit associated with selective head cooling among infants with moderate abnormalities on an amplitude-integrated electroencephalogram at enrollment.
      3. Eicher et al:
         a) Used whole-body cooling with surface ice packs and cooling blankets.
         b) Showed reduction in combined outcome of death and severe motor scores at 12 months in hypothermia group.
      4. No serious adverse side effects reported to date, although all 3 RCTs noted reversible cardiovascular effects, specifically sinus bradycardia and hypotension.
   D. NICHD conference identified significant questions that remain to be answered before universal implementation can be encouraged.
   E. American Academy of Pediatrics Committee on Fetus and Newborn 2006 concluded:
      1. Therapeutic hypothermia is a promising therapy that should be considered investigational until the safety and efficacy have been confirmed in additional human trials.
      2. Support completion of RCTs in progress.
      3. Additional trials needed that would define the most effective cooling strategies.
4. Registries of infants with perinatal encephalopathies should be established to facilitate data collection.

5. If therapeutic hypothermia is to be implemented outside of an RCT, clinicians should follow published protocols, ensure systematic follow-up of survivors validated neurodevelopmental tests, and submit patient data to national and international registries as they are established. Parents should be informed of the current status of hypothermia therapy and consent for the procedure obtained.

6. Long term follow up at least through early school age is essential.

F. The Cochrane Collaboration - Cooling for newborns with hypoxic ischaemic encephalopathy (review):

1. Eight RCTs were included in the review, comprising 638 infants with moderate/severe encephalopathy and evidence of intrapartum asphyxia.

2. Authors conclusions:
   a) Therapeutic hypothermia is beneficial to term newborns with hypoxic ischemic encephalopathy.
   b) Cooling reduces mortality without increasing major disability in survivors.
   c) Further studies were needed to determine the appropriated method of providing therapeutic hypothermia, including comparison of whole body with selective head cooling with mild systemic hypothermia.

3. Some adverse effects of hypothermia included an increase in the need for inotrope support of borderline significance and significant increase in thrombocytopenia.

V. Therapeutic Hypothermia:

A. An infant meeting clinical criteria, biochemical criteria I or II and neurologic criteria and does not meet exclusion criteria is eligible for body cooling.

B. Exclusion Criteria:

1. Inability to start therapy by six hours of age.
2. Major congenital abnormality.
3. Known chromosomal anomaly.
4. Less than 36 weeks gestational age.
5. Severe growth restriction (birth weight ≤ 1800g).
6. Refusal of consent of parents or neonatologist.
7. Infant in extremis (at the point of death) for which no additional intensive therapy will be offered by attending neonatologist.

C. Inclusion Criteria:

1. Clinical Criteria:
   a) Gestational age 36 weeks, 0 days or greater.
   b) Able to initiate body cooling procedure within 6 hours of age.
   c) History of acute perinatal event (severe fetal heart rate abnormality-late or variable decelerations, abruption placenta, prolapse cord, cord rupture, uterine rupture, maternal trauma, hemorrhage, or cardiorespiratory arrest).
   d) Apgar score of ≤ 5 at 10 minutes.
   e) Continued need for ventilation initiated at birth and continues for at least 10 minutes.

2. Biochemical Criteria I:
   a) Blood gas sample of umbilical cord blood or any blood during the first hour after birth:
      (1) pH of 7.0 or less or
      (2) a base deficit of 16 mmol per liter or more

3. Biochemical Criteria II:
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a) If during the first hour of life a pH was between 7.01 and 7.15, a base deficit was between 10 and 15.9 or a blood gas was not available, additional criteria required:
   (1) An acute perinatal event and
   (2) 10 minute Apgar score of 5 or less or
   (3) Assisted ventilation initiated at birth and continued for at least 10 minutes.

4. Neurologic Criteria:
   a) Once clinical and biochemical criteria met, if encephalopathy or seizures are present they are candidates for therapy.
   b) All infants undergo a standardized neurologic examination.
   c) Encephalopathy present if one or more signs in at least three of the following six categories:
      (1) Level of consciousness
      (2) Spontaneous activity
      (3) Posture
      (4) Tone
      (5) Primitive reflexes (suck, moro)
      (6) Autonomic nervous system (pupils, hear rate, respirations)
   d) The number of moderate or sever signs determine the extent of encephalopathy; if signs were equally distributed, the designation is based on the level of consciousness).

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<th>Criteria for Defining Moderate and Severe Encephalopathy</th>
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VI. Procedure for body cooling:
A. Body cooling will only be performed at hospitals with cooling blankets and written protocols and procedures.
B. See KMS Procedure for body cooling.
C. The whole body temperature is lowered by 3-4°C to 33.5°C (92.3°F) and maintained for 72 hours.

VII. Management of HIE:
A. Cornerstone of HIE is still supportive care:
   1. Establish adequate and rigorously control oxygenation and ventilation (hyperoxia and hypocapnia have been associated with adverse outcome of infants with HIE).
      a) Evidence on room air versus 100% O2 resuscitation remains insufficient.
      b) Important to control oxygen delivery, monitor O2 saturation and avoid hyperoxia.
   2. Restore circulation by appropriate, rapid and effective resuscitation.
   3. Maintain adequate systemic blood pressure and tissue perfusion.
5. Control seizures.
6. Correct electrolyte and acid-base disorders.
7. Avoid hyperthermia. (There is clear evidence that brain injury is more severe when fever is superimposed over hypoxic-ischemic insult)

VIII. Complications:
A. Cardiovascular effects: All trials noted reversible bradycardia and hypotension.
   1. Bradycardia:
      a) Reduced metabolic rate reduces cardiac output and heart rate.
      b) Heart rate is reduced by 14 beats per degree centigrade reduction in body temperature in the range of 37 to 33°C for infants (given not stressed, hypovolemic, anemic, or in pain).
   2. Hypotension:
      a) During rewarming, the vasoconstricted skin dilates and intravascular blood volume increases. If the vascular bed is underfilled, hypotension will occur.
      b) Give Volume of 0.9% NaCl or albumin at a dose of 10ml/kg if albumin level is low at discretion of the attending physician as soon as there is a drop of 5 mm Hg in MABP.
B. Skin Complications:
   1. Sclerema Neonatorum:
      a) Disorder of adipose tissue manifested by a diffuse, nonpitting induration of the affected tissue. The skin becomes cold, yellowish, mottled, and inflexible.
      b) Is known complication of inadvertent hypothermia and/or birth asphyxia, and rare cases were reported in infants treated with cool cap and whole body cooling.
      c) Sclerema eventually resolved as the infants recovered.
   2. Subcutaneous fat necrosis, erythema and cyanosis.
C. Seizures:
   1. Common complication of HIE.
   2. When treating seizures in infants being treated with WBC, remember that metabolism of Phenobarbital is reportedly slowed by WBC in infants with HIE.
      a) Requiring close monitoring of anticonvulsant levels
   3. Emergence and re-emergence of seizures have been observed during or after rewarming of infants treated with hypothermia.
D. Apnea:
   1. One study, apnea noted in 2 self-ventilating infants at beginning of rewarming, CPAP during the rest of rewarming was necessary and within hours of normal temperatures, CPAP discontinued.
IX. Management of asphyxiated infant in the delivery room:
   A. The overhead heater should be turned off during resuscitation as soon as adequate ventilation and heart rate are obtained.
   B. Active heat should be turned of in the transport incubator.
X. Management Issues while cooling:
A. Blood Gases:
   1. In ventilated infants who are cooled, adjust the normal Pco2 range, which at 37°C is 36-44mm Hg to 41-51 mm Hg.
   2. Avoid hyperoxia after asphyxia. Closely monitor FiO2 and saturation to keep within normal range.
   3. The effect of temperature on Po2 is different and smaller than for Pco2 during cooling, so adjustment in Po2 range not necessary, same for pH.
B. Ventilation:
   1. A reduction in metabolism (5-8% per degree C reduction in temp) is expected and desired effect of cooling and results in a decrease in CO2 production.
   2. To keep CO2 within suggested normal range during cooling, the ventilator frequency or tidal volume must be turned down to reduce minute volume.
   3. Secretions are stickier during hypothermia and cooled infants benefit from frequent turning, suctioning, and instillation of saline as needed.

C. PPHN:
   1. In published studies, the incidence of PPHN has been the same in cooled and noncooled groups.
   2. Administration of NO, using standard protocol, and cooling does not seem to be contraindicated.

D. Drug metabolism:
   1. Drugs metabolized by the liver, such as morphine and phenobarbital, have been shown to have higher levels in cooled group.
   2. If starting cooled baby on continuous infusions, consider running the “normothermic” dose for 6 to 12 hours and then reduce the dose until clinical signs of less drug effect appear, such as lack of sedation or paralysis.

E. Nutrition and Fluid Management:
   1. Large trials, withheld feedings during hypothermia.
   2. Start with clear fluids at 60ml/kg/day, followed by TPN by second day of life.
   3. Volume is increased as clinically indicated (cardiac and renal function). Asphyxiated infants receive volume in response to hypotension and the average actual volume on day 1 is usually 90ml/kg.
   4. Keep electrolytes within normal range. Obtain lytes every 12 hours and prn.
   5. Hyponatremia is the most frequent electrolyte abnormality in HIE due to the syndrome of inappropriate antidiuretic hormone caused by brain injury.
   6. There is conflicting experimental evidence as to whether magnesium is neuroprotective. Recommendations to keep Magnesium in normal range (level greater than 1) during cooling.

F. Inotropic Support:
   1. Trials did not find that cooled infants are more hypotensive than normothermic infants with same severity of asphyxia.
   2. If hypotensive, first correct hypovolemia. Give 10ml/kg of volume times two before starting inotropes.

G. Sedation:
   1. Sedation and paralytics may be used to prevent excess movement that could result in an increase in metabolic activity and body temperature.

H. Pain Management:
   1. Pain may be difficult to assess if paralyzed and/or sedated, care must be taken to detect subtle clues of pain, such as heart rate or blood pressure changes.

I. Coagulation:
   1. HIE and cooling may result in coagulopathies because the enzymatic reactions of the coagulation cascade are inhibited.
      a) Coagulation should be evaluated by obtaining a prothrombin time, activated partial thromboplastin time and fibrinogen at initiation of treatment and at regular intervals (usually 24 hours) during treatment or with changes in clinical status.

J. Nursing Care:
1. Bedside nurse should report changes in patient status, such as worsening condition and increased seizure activity.
2. Careful assessment of temperatures.
3. Vital signs monitored hourly.
4. Heart rate less than 100, mean arterial blood pressure less than gestational age, or capillary refill greater than 3 seconds should be reported.
5. Strict intake and output.
6. Minimal stimulation:
   a) Decreased light and noise, and decreased physical manipulation to prevent increased intracranial pressure.
   b) Cluster care activities.
7. Skin assessment at regular intervals:
   a) Frequency should be adjusted based on the infant’s clinical status.

K. Rewarming:
   1. After 72 hours of treatment, rewarm over a period of 6 hours.
   2. The blanket temperature is increased every hour by 0.5°C until 36.5°C is reached.

References:

Long, M. and D. Brandon, Induced Hypothermia for Neonates with Hypoxia-Ischemic Encephalopathy. AWHONN, the Association of Women’s Health, obstetric and Neonatal Nurses. 36. 2007. 293-298.