Therapeutic Hypothermia for Neonatal Encephalopathy:

Preparation for Transport to Cooling Center

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Abstract

Asphyxia, or hypoxic ischemic encephalopathy (HIE) remains a serious condition that causes significant mortality and morbidity in the neonatal population. Studies suggest that induction of mild hypothermia can result in significantly improved neurodevelopmental outcome in neonates. Timing of the initiation of hypothermia following brain injury is critical. Many neonates who meet the criteria for hypothermia are born in remote hospitals that do not provide cooling therapy or the high level of care required for the complex needs of asphyxiated neonates. Since the therapeutic window for neuroprotection is six hours, adding the time for transport could result in delays that may lead to suboptimal outcomes. Some centers have implemented passive cooling prior to and during transport to minimize this delay. Eligibility criteria are discussed to assist in referral decision for hypothermia therapy. This article also reviews recommended guidelines for providing optimal benefit to infants who require remote transport to a cooling center.

Key Words: hypoxic-ischemic encephalopathy; therapeutic hypothermia; passive cooling; asphyxia; transport

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Hypoxic-ischemic encephalopathy (HIE) is a term used to describe the condition resulting from reduced oxygen to the brain, before and/or during the delivery of an infant and can result in major brain injury (Zanelli, Stanley, & Kaufman, 2009). HIE occurs in 1 to 6 per 1,000 term births in developed countries. Death occurs in approximately 15% to 20% of affected infants, and another 25% develop childhood disabilities (Shankaran, 2010). Chronic conditions that may result from HIE induced brain injury include mental retardation or learning disabilities, seizures, blindness, cerebral palsy, hearing impairment, and other mental and psychomotor deficits (Zanelli, et al., 2009; Glass & Ferriero, 2007).

Until recent years, treatment of HIE in neonates was limited to supportive care with ventilation, perfusion, prevention of hypoglycemia and hyperthermia, and treatment of seizures (Glass & Ferriero, 2007). Three multicenter randomized controlled trials published in 2005, demonstrated a significantly improved neurological and developmental outcome with induction of mild hypothermia in infants at least 36 weeks gestation who were born with HIE (Fairchild, Sokora, Scott, & Zanelli, 2010; Eicher et al., 2005a; Eicher et al., 2005b; Gluckman et al., 2005; Shankaran et al., 2005). These studies showed that induced hypothermia following asphyxia reduced the risk of death and severe disabilities assessed at 18-22 months of follow-up (Hallberg, Olson, Bartocci, Edqvist, & Blennow, 2009).

"Therapeutic hypothermia is an intensive care treatment which is delivered by either selective head, or total body cooling" (British Association of Perinatal Medicine, n.d.).

According to several studies, one of the key factors that influence the beneficial effect of hypothermia is the time between the asphyxial event and the induction of hypothermia. For

maximum benefit, hypothermia should be implemented as soon as possible and within 6 hours after the insult (Hallberg, et al., 2009). There is concern that efficacy is diminished with increased time from insult to cooling (Anderson, Longhofer, Phillips, & McRay, 2007).

Many neonates who meet the criteria for hypothermia are born in remote hospitals that do not provide cooling therapy or the high level of care required for asphyxiated neonates. It is essential that these infants be transferred to a neonatal intensive care unit (NICU) that has access to multidisciplinary subspecialty education, diagnostic interpretation and treatment to provide for the complex medical needs of these infants (Fairchild, et al., 2010; British Association of Perinatal Medicine, n.d.). Since the therapeutic window for neuroprotection is six hours, adding the time for transport could result in delays that may lead to suboptimal outcomes (Fairchild, et al., 2010). Preparation of the neonate with HIE for transport is a key intervention strategy for the prevention of further brain injury and neurological insult. Educating referring providers regarding how to initiate therapeutic hypothermia is paramount to a successful program (Fairchild, et al., 2010).

Diagnosis of Encephalopathy

It is imperative that neonates with risk factors for HIE be promptly identified and carefully monitored within the first few hours of birth (Zanelli, et al., 2009; Long & Brandon, 2007). HIE can be described as mild, moderate or severe. The grading system most commonly used is the Sarnat scale developed by Sarnat and Sarnat in 1976 (see Appendix). The Sarnat Scale utilizes clinical and electroencephalogram findings (I, II, III = mild, moderate, severe). When only clinical findings are used, the grading system is called the Modified Sarnat Score (Sarnat & Sarnat, 1976).

Currently, there is no clear diagnostic test for HIE (Shankaran, 2010). Diagnosis of HIE is based on a combination of the infant's birth history, clinical signs, and lab testing (Long & Brandon, 2007). The first step in diagnosing HIE is obtaining a detailed history of the antepartum, intrapartum, and postpartum periods. Evaluation should be made of any event that is likely to compromise blood or oxygen supply to the fetus. A history of placental abruption, uterine rupture, amniotic fluid embolism, tight nuchal cord, cord accident, maternal hemorrhage or trauma, sustained fetal bradycardia or prolonged labor should be considered as significant events. A history of maternal fever is crucial because the risk of neonatal encephalopathy is increased with moderate temperature elevation in the mother. Determination of the presence of infection is important (Shankaran, 2010).

Since hypothermia treatment should be induced within 6 hours of the asphyxial event, the health care provider must quickly assess the status of the neonate and determine if established criteria for hypothermia treatment is met (Long & Brandon, 2007). Once HIE is suspected, the referring provider should contact the accepting provider at the cooling center to where the infant will be transferred. Discussion regarding eligibility criteria, neurological examination, interim treatment, and arrangement for transport should be initiated (Fairchild, et al., 2010).

Eligibility for Hypothermia Treatment

According to current research, hypothermia treatment should be reserved for term or near-term infants (≥ 36 weeks gestation) admitted at less than 6 hours of age with moderate to severe birth asphyxia or depression. Throughout the literature, the standards are highly specific regarding inclusion or exclusion of a neonate into the hypothermia treatment regimen (Glass & Ferriero, 2007). The following eligibility criteria are taken from the National Institute of Child Health and Human Development Neonatal Research Network, 2010 protocols:

Inclusion Criteria

Infants will be evaluated in two steps; evaluation by clinical and biochemical criteria (Step A), followed by neurological exam (Step B).

A. All infants will be evaluated for the following:

1. History of an acute perinatal event (i.e. abruption placenta, cord prolapse, severe FHR abnormality: variable or late decelerations).
2. An Apgar score ≤ 5 at 10 minutes
3. Cord pH or any postnatal blood gas pH at ≤ 1 hour ≤ 7.0.
4. Base deficit on cord gas or any postnatal blood gas at ≤ 1 hour ≥ 16 mEq/L.
5. Continued need for ventilation initiated at birth and continued for at least 10 minutes.

Based on the above criteria infant's meeting specific parameters shall be categorized as either A1 or A2 (see table 1)

Table 1

IF BLOOD GAS IS AVAILABLE:	**IF BLOOD GAS IS NOT AVAILABLE, *OR* pH 7.01 to 7.15, *OR* BASE DEFICIT 10 TO 15.9 mEq/L**
A1 Infant should have (#3 or 4 from above) • Cord pH or first postnatal blood gas within 1 hour of age with pH ≤ 7.0 *OR* • Base deficit on cord gas or first postnatal gas within 1 hour of age at ≥ 16 mEq/L	A2 Infant should have: (#1 and 2 or #1 and 5 from above) • Acute perinatal event **and either** • An Apgar score ≤ 5 at 10 minutes *OR* • Continued need for ventilation initiated at birth and continued for at least 10 minutes

Once infant meets either A1 or A2, proceed to step B, the neurologic examination.

B. The presence of moderate/severe encephalopathy defined as seizures **OR** presence of one or more signs in **three of the six** categories: level of consciousness, spontaneous activity, posture, tone, primitive reflexes and autonomic system (see table 2).

Table 2

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

The neurologic examination will be performed by a physician examiner. If infant meets criteria A1 or A2 and criteria B and does not meet exclusion criteria, the infant is eligible for whole body cooling.

Exclusion Criteria

a. Inability to initiate cooling by 6 hours of age.

b. Presence of known chromosomal anomaly.

c. Presence of major congenital anomalies.

d. Severe intrauterine growth restriction (weight <1800g).

e. Infants in extremis for which no additional intensive therapy will be offered by attending neonatologist.

The Cool-Cap Clinical Trial (selective head cooling) and the National Institute of Child Health and Human Development Neonatal Research Network (NICHD) Whole Body

Hypothermia Trial used different entry eligibility criteria. The distinguishing difference was the use of the amplitude integrated electroencephalogram (aEEG) in the Cool-Cap Trial.

According to the British Association of Perinatal Medicine, aEEG is "a helpful though not essential tool for obtaining evidence of cerebral depression. Initiation of cooling should not be delayed awaiting aEEG data and indeed could be initiated in infants showing poor response to resuscitation at an early stage while they are being evaluated further" (British Association of Perinatal Medicine, n.d.). The Swedish national guidelines for induced hypothermia in newborns state that amplitude-integrated EEG is not mandatory to initiate hypothermia treatment (Hallberg, et al., 2009).

Recommendations for Care Prior to Transport

Standard Care

Management in the delivery room follows standard Neonatal Resuscitation Program (NRP) guidelines. If significant clinical asphyxia is apparent, the radiant warmer should be turned off as soon as effective breathing and heart rate are established, according to Chakkarapani & Thoresen, (2010). Rectal temperature monitoring should be initiated no later than 20 minutes following delivery (Chakkarapani & Thoresen, 2010). The target temperature range for therapeutic hypothermia is 33 to 34^{o}C (Fairchild et al., 2009; Hallberg et al., 2009). Active heating and hats are discouraged to avoid hyperthermia which is associated with a higher risk of adverse outcomes (Zanelli et al., 2009; Shankaran, 2010; Chakkarapani & Thoresen, 2010).

Treatment of HIE is supportive and adequate ventilation and perfusion, fluid management, and normoglycemia are the goals (Zanelli, et al., 2009; Glass & Ferriero, 2007).

Many infants with severe HIE require ventilator support. The focus of ventilation is to prevent hypoxia, hyperoxia, hypercapnia, hypocapnia, and to maintain blood gases and acid-base status in physiological ranges. Hypocapnia and hyperoxia particularly have been associated with worse neurodevelopment outcomes (Zanelli et al., 2009; Chakkarapani & Thoresen, 2010).

To avoid decreased cerebral perfusion, a mean blood pressure of 35-40 is indicated. Hypotension is common in infants with HIE and should be treated promptly. Dopamine and Dobutamine are often required to maintain perfusion in infants with HIE (Zanelli et al., 2009).

Fluid restriction is usually recommended for infants with HIE until renal function can be evaluated. Fluid management must be individualized based on clinical course and urine output.

Glucose and electrolyte levels should be maintained in a normal range. Hypoglycemia and hyperglycemia may affect neuroprotection and lead to further brain damage. Hypoglycemia (< 40 mg/dL) contributes significantly to adverse neurological outcomes (Zanelli, et al., 2009; Shankaran, 2010). Magnesium levels should particularly be maintained within normal limits at ~1mmol/L. Unacceptable hypotension and respiratory depression can result from high magnesium (>2.5 mmol/L.) Magnesium can increase the threshold for shivering which causes the production of heat (Chakkarapani & Thoresen).

Infection should be assessed and addressed. An exclusion criterion for cooling does not include infection (Chakkarapani & Thoresen, 2010).

Seizures are common in infants with HIE and may compromise homeostasis and should be treated early and controlled as fully as possible (Shankaran, 2010; Zanelli et al., 2009). Studies also suggest that seizures may accentuate brain injury (Zanelli et al., 2009). Current recommendations for treatment of seizures are Phenobarbitol and/or Keppra. Discussion with the physician at the cooling center will guide the referring provider to preference of drug.

Therapeutic Hypothermia

According to the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (2010), the current recommendations are that active therapeutic hypothermia should only be utilized under published protocols or as part of continuing controlled clinical trials. Cooling was not recommended by either the NICHD nor the CoolCap trial prior to arrival at the cooling center (Gluckman, et al., 2005; Shankaran et al., 2005).

It has long been known that infants who are asphyxiated lose temperature more quickly than non-asphyxiated babies (Hallberg et al., 2009; Burnard & Cross, 1958; Bruck, 1961). Some infants will passively cool to a core temperature in the 33 to 34^{o}C range if left uncovered at room temperature.

As a result of a 4 year study, Fairchild et al. (2010), recommends in cases of acute perinatal distress with suspected HIE, that the radiant warmer be turned off during the initial stabilization and neurological assessment. Should the suspicion of HIE prove to be unsupported by the neurological examination, routine thermoregulation can be assumed. If eligibility criteria are met for hypothermia therapy, passive cooling (external heat sources removed) may be continued until the arrival of the transport team with close monitoring of the baby's rectal temperature. Because of the time it takes to transport an infant with HIE to a cooling center; initiation of hypothermia treatment may exceed the limited therapeutic window for neuroprotection. With this approach, neuroprotective temperatures are reached hours sooner than waiting until arrival at the cooling center (Fairchild et al., 2010).

Efforts should be made to avoid excessive cooling. The target temperature range is 33 to 34^{o}C (Fairchild et al., 2009; Hallberg et al., 2009). Active cooling is discouraged by this study group, until arrival of the transport team, due to complications that may arise, such as excessive

hypothermia which can result in compromise of the cardiovascular, respiratory, hematologic, and immune systems (Fairchild et al., 2010).

A study published by Hallberg (2009), showed that passive cooling by turning off active warming devices before and during transport is possible and successfully reduces the rectal temperature. This achieves an earlier initiation of hypothermia. Continuous monitoring of the rectal temperature is mandatory when utilizing this strategy (Hallberg et al., 2009).

Summary

Therapeutic hypothermia is an emerging therapy in the treatment of neonatal HIE. Many sites are utilizing this therapy (Barks, 2008). "It appears that passive cooling can be an early adjunct to therapeutic hypothermia (Anderson et al., 2007). Further study is needed to discover the most efficient utilization of this treatment. Providing long-term follow-up to establish benefits to infants who received hypothermia treatment is critical for evaluation of this therapy. "Reducing the neurologic devastation associated with HIE is critical to improving the outcomes of this special population" (Long & Brandon, 2007). This therapy could result in alleviating financial as well as social burdens that families and infant with HIE may endure (Zanelli et al., 2009).

While it is prudent to manage medically very ill infants in cooling centers, further use of this treatment would be enhanced by education of clinicians at referring hospitals regarding the entry criteria for hypothermia treatment, diagnostics, neurological evaluation, and initiation of early cooling prior to transport team arrival (Chakkarapani & Thoresen, 2010; Fairchild et al., 2010).

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Appendix

Mild HIE – Sarnat Stage I

- Hyper-alert
- Eyes wide open
- Does not sleep
- Irritable
- No seizures
- Usually lasts ≤ 24 hours

Moderate HIE – Sarnat Stage II

- Lethargy (difficult to rouse)
- Reduced tone of the extremities and/or trunk
- Diminished brainstem reflexes (pupil/gag/suck)
- Possible clinical seizures

Severe HIE – Sarnat Stage III

- Coma (cannot be roused)
- Weak or absent respiratory drive
- No response to stimuli (may have spinal reflex to painful stimuli)
- Flaccid tone of the extremities and trunk (floppy)
- Diminished or absent brainstem reflexes (pupil/gag/suck)
- Diminished tendon reflexes
- EEG severely abnormal (suppressed or flat EEG with or without seizures)

Adapted from Sarnat, H. B., & Sarnat, M. S. (1976). Neonatal encephalopathy following fetal stress. A clinical and electroencephalographic study. *Archives of Neurology, 33*(10), 696-705.