Hypothermia for Neonatal Hypoxic-Ischemic Encephalopathy
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Hypoxic-ischemic encephalopathy, HIE, loosely defined, is damage to the central nervous system from inadequate oxygen supply. Hypoxemia means a decrease in the amount of oxygen circulating in the blood. Ischemia is a condition in which there is insufficient blood flow to the brain. The consequence of hypoxemia and/or ischemia to the brain are injury, specifically alteration of the blood/brain barrier, compromised auto-regulation of cerebral blood flow, and cell injury/death to areas of the brain with a high glucose demand.

This is a significant health issue because HIE occurs in about 1-6/1000 live births in developed countries, more in under-developed countries. Nearly 15-20 percent of affected newborns die and an additional 25 percent sustain childhood disabilities. Different degrees of severity can be present and generally correlate with outcome. Infants with severe encephalopathy have an increased risk of death and an increased risk of cerebral palsy and intellectual disability among survivors. Neonates with moderate encephalopathy have significant motor deficits, memory impairment, visual motor or visual perceptive dysfunction, increased hyperactivity, and delayed school readiness. Infants with only mild encephalopathy do not have an increased risk of either motor or cognitive deficits.

Sadly, the management of HIE has historically been limited to supportive intensive care. Correction of pulmonary, hemodynamic, and metabolic disturbances, as well as treatment of seizures has been the backbone of care. However, none of these measures targets the underlying pathophysiology.

Currently there is no diagnostic test for encephalopathy due to hypoxia-ischemia. Essential criteria suggested as prerequisites for a diagnosis of HIE include: metabolic acidosis, with a cord pH less than 7 or a base deficit of at least 12 mol/L; early onset encephalopathy; multi-system organ dysfunction; and exclusion of other causes such as trauma, coagulation disorders, metabolic disorders, and genetic causes.

Many studies have validated that injury from hypoxia-ischemia occurs in two phases and that a therapeutic window exists between these two phases. The first phase of energy failure can be associated with obvious perinatal events: prolapsed umbilical cord, cord avulsion (separation), placental abruption or entrapped head. Such well-defined situations account for only about 25 percent of cases of HIE. Most infants with HIE do not have a clearly identifiable cause. The second phase of energy failure is thought to start about six hours after the first phase. Simply, it can be explained as reperfusion injury. Detailed description is beyond the scope of this paper. Interested readers are referred to references from Fellman and Gluckman.

The interval between the first and second phases of energy failure represents a therapeutic window. Since the 1950s there has been an interest in using hypothermia as a treatment for infants at risk from brain injury from HIE. Miller and Westin suggested that rapidly cooling asphyxiated infants to 23°-32°C would result in improved outcomes. The lack of technology and newborn intensive care units at that time made it difficult to provide such hypothermia and concomitant life support to newborns. Interest in this therapy was renewed in the 1990s when adults with post-traumatic brain injury, stroke, and cardiac arrest were treated with hypothermia. Initiation of therapies during this therapeutic window in perinatal animals has been successful in reducing brain damage. Based on studies on near-term fetal sheep, the therapeutic window is felt to be about six hours in length. The goal of neuroprotection during this time is to block or diminish secondary energy failure. Studies in fetal and neonatal animal models have demonstrated that cooling by a depth of 4°-6°C is both neuroprotective and well tolerated clinically.
Studies in infants have resulted in publication of three clinical trials, one large pilot study and two randomized, controlled trials. The controlled pilot study was performed at seven centers. A total of 65 infants had systemic whole body cooling to 33°C for 48 hours compared with infants maintained at normothermia (37°C). At 12 months of age, death or severe motor scores were noted in 52 percent of the hypothermia group versus 84 percent of the normothermia group.

The multicenter Cool Cap Study involved 243 infants with moderate or severe encephalopathy and abnormal aEEG amplitudes. They were either cooled to a temperature of 34°-35°C for 72 hours or maintained at normothermia. The cooling was achieved with selective head cooling and mild systemic cooling. Death or severe disability occurred in 66 percent of the control infants and 55 percent of the cooled infant. This did not reach statistical significance. Upon further analysis of the data, it was suggested that infants with less severe aEEG findings benefited from cooling whereas those with severe aEEG findings did not.

The National Institute of Child Health and Human Development (NICHD) Neonatal Research Network trial used whole-body hypothermia for infants with moderate to severe encephalopathy. They randomized 102 infants to 33.5°C for 72 hours and 106 control infants to conventional care. Death or moderate to severe disability occurred in 62 percent of controls and 44 percent of those treated with hypothermia.

A commentary in *Pediatrics*, the official journal of the American Academy of Pediatrics, March 2006, agreed with current evidence supporting mild hypothermia as a promising therapy following hypoxic-ischemic insult. A 2009 Cochrane Database analysis stated “therapeutic hypothermia for term infants with moderate to severe hypoxic ischemic encephalopathy results in a reduction in the composite outcome of mortality or long-term neurodevelopmental disability to 18 months of age.”

Ultimately, it is the long term outcome of those at risk that is even more important than outcome at one to two years of age. School-age outcomes are being evaluated in participants in the Cool Cap and NICHD trials. Other areas of active interest regarding HIE include studies looking at how to predict outcome after hypothermia, initiation of hypothermia after the six-hour therapeutic window, and use of hypothermia as neuroprotection in infants born at 34-36 weeks’ gestation.

**References**


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