Neonatal Hypothermia: A Method to Provide Neuroprotection After Hypoxic Ischemic Encephalopathy

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The evolving progression of hypoxic ischemic encephalopathy has devastating effects accounting for approximately 23% of the four million annual neonatal deaths globally. Of infants who survive, 25% to 55% will suffer significant neurologic sequelae (*Pediatrics 2008*;121:648-649; author reply 649-650). Scientific evidence has demonstrated significant improvements in clinical and developmental outcomes through therapeutic hypothermia. Interventions initiated within a predefined "therapeutic window" showed decreased secondary cellular injury and aptotosis. The aim of this article is to provide an account of the hypoxic event at the cellular level describing the progression of injury that leads to ongoing neuronal cell damage and death. Historical accounts of experimental and clinical trials to date are provided, which describe scientific evidence used to develop standardized treatment protocols for hypothermia after hypoxic ischemic encephalopathy. Details of current protocols are also provided. Lastly, a focus on nursing interventions with symptom management is provided, giving supportive rationale to assist the bedside nurse when caring for these complex patients in an effort to potentially improve short- and long-term outcomes.

Keywords: Birth asphyxia; Hypoxic ischemic encephalopathy; Neonatal hypothermia; Perinatal hypoxia; Selective head cooling and total body cooling

The topic of neonatal hypothermia and its effect on perinatal asphyxia is widespread throughout recent literature. Well-designed experimental studies based on earlier work using animal models are now guiding our treatment with cooling protocols for term infants in neonatal intensive care units (NICUs) across the United States.[1] Multiple systematic reviews and meta-analysis are available to describe the journey from first attempts of cold submersion in the 1950s through the well-organized clinical trials that now define neuroprotection with hypothermia protocols.[2-5] Proposed recommendations for future research are often included in these works that include hypothermia trials on younger neonates (34–36 week of gestation) and combination therapies to augment the protective effect of hypothermia and longitudinal studies to best describe long-term outcomes after hypothermia. A missing piece of the literature to date involves implications for care of these infants provided by expert nurses in the NICU. Understanding the scientific rationale that directs our care for these specialized patients will lead to best practices at the bedside with the potential to impact clinical and developmental outcomes. The focus of this article begins with an understanding of perinatal asphyxia and hypoxic ischemic encephalopathy (HIE). A discussion of hypothermia treatment including the nursing care implications for these infants will follow; finally, an emphasis on the long-term developmental outcomes, providing nursing strategies that potentially will improve these severely affected infants.

Incidence and Impact of HIE

Hypoxic ischemic encephalopathy or perinatal asphyxia affects one to three per 1000 live births in the United States.[2,6,7] Previous research has focused on the prevention of this type of birth injury as well as the development of treatment strategies, including hypothermia, in an effort to reduce mortality and morbidity.[8,9] Until the development and adaptation of these therapies, the care provided to these infants was primarily supportive with mortality rates ranging from 10% to 60% and of those who survived, morbidity rates approached 25%. It has been reported that 15% to 28% of the incidence of cerebral palsy among children are the result of perinatal asphyxia and HIE.[2,10] However, long-term outcomes are often difficult to predict. Infants who are minimally affected usually do not qualify for aggressive initial hypothermic treatment and, yet, may have

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residual deficits from the anoxic injury with later demonstration of both poor motor function and cognitive delays.

Infants identified as moderately affected often meet criteria for and receive hypothermia to provide neuroprotection. These infants showed the most significant improvement when compared with control groups in initial clinical trials as well as follow-up studies.[2] Severely affected infants who also meet criteria for hypothermia treatment showed slight improvement in mortality rates; however, most infants in the initial studies continue to have significant long-term consequences.[8,9]

Pathophysiology of HIE

We understand from previous research (clinical and experimental) that primary cell death occurs within minutes after having a loss of oxygen before or during the infant's delivery (see Fig 1). The primary causes of the loss of oxygen or hypoxia are usually related to an unforeseen event before or at delivery, such as cord compression or shear; placental abruption; maternal physiologic compromise such as preeclampsia/eclampsia, temperature/infection, maternal hemorrhage, or delivery complications such as entrapment.[11]

The cerebral blood flow (CBF) of adults is typically maintained at constant levels despite fluctuations in the systemic blood pressure. However, in the infant, CBF autoregulation is not as responsive; therefore, when hypoxia occurs, the infant's initial systemic response is to maintain perfusion to the brain and end organs through a redistribution of cardiac output. This compensation is accomplished with increased heart rate (to increase cardiac output) and the endogenous release of epinephrine. Although initially effective, these measures can only maintain CBF for a short time (minutes), and when the hypoxic state persists, the systemic blood pressure falls and neuronal cells are damaged through progressive intracellular energy failure and eventual cell death via apoptosis.[8,12,13]

This progressive hypoxic state begins the rapid depletion of high-energy metabolites (anaerobic metabolism) and rapid depletion of adenosine triphosphate; hypoxic depolarization of cells; cytotoxic edema or cell swelling; and intracellular accumulation of calcium, extracellular accumulation of neurotransmitters (glutamate), and additional by-products of the necrotic tissue (see Fig 1).[14,15]

When the cerebral circulation and oxygenation are restored (reperfusion), the slow reduction of the metabolic acidosis occurs as evident by the slow recovery of previous impairment from cerebral oxidative metabolism. This is clinically demonstrated by reduced cell swelling or cytotoxic edema and the reduction of the excitatory amino acids that initially accumulated in the extracellular spaces (see Fig 1). It is now clear that although neuronal cell death occurs during this primary or first phase of hypoxia, it is the second or latent stage of the insult, which leads to global damage.[3] Infants who did not show recovery from the initial hypoxic as demonstrated by persistent and profound acidosis showed universally adverse outcomes.[16]

This second or latent stage of this process, which occurs 6 to 24 hours after the initial insult, is the recovery of cerebral circulation and oxygenation leading to a progression of inflammatory response and significant cerebral edema, onset of seizures, secondary cytotoxic edema, and additional cell death.[8,17,18] This particular injury has been described as an evolving process, but evidence so far describes a period between the first and second stage of injury as a "therapeutic window," which was based on earlier animal models using primarily fetal sheep and infant rats.[19,20] The critical timing of this latent phase has been a key finding during research using animal models.

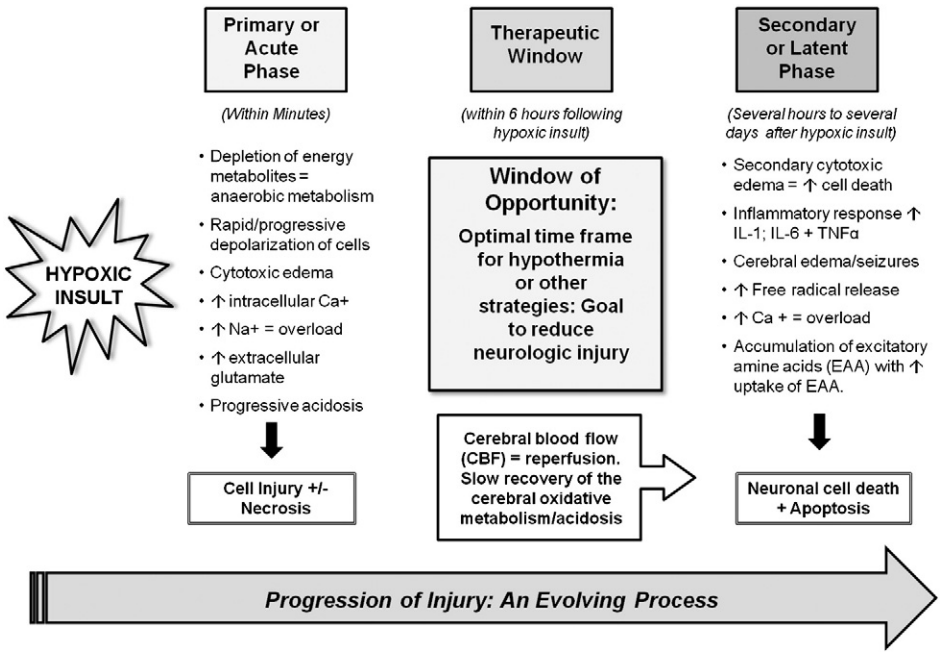

Fig 1. Pathophysiology of HIE.