Newborn & Infant Nursing Reviews 16 (2016) 20–24

Contents lists available at ScienceDirect

Newborn & Infant Nursing Reviews

journal homepage: www.nainr.com

Hypoxic-Ischemic Encephalopathy (HIE): A Review for the Bedside Nurse of a Complex Clinical Problem

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ARTICLE INFO

Keywords:
Asphyxia
Birth injury
Cooling
Hypothermia
Neuroprotection
Newborn

ABSTRACT

Hypoxic-ischemic encephalopathy (HIE) is a potentially devastating complication related to events in the prenatal and/or intrapartum period that lead to a depressed infant, or worse, a stillbirth. Prompt recognition of risk factors for HIE is required, followed by rapid delivery of the infant to ensure an optimal outcome. Clinical indicators can be applied to determine which infants are at risk of compromised long-term developmental outcomes and are helpful in guiding bedside care. Cooling is the standard of care when complications from HIE are expected, but it has not eliminated the sequelae in all cases. Novel adjuncts to cooling are being developed, with a common theme of neuroprotection. This article will focus on key aspects of clinical care that are important for the bedside nurse to recognize and understand, and will present information on the current standard of care, as well as provide insight into future directions that are currently under investigation.

"Crash C-section North OR": a message that comes across the pager system and prompts immediate action and concern. Everyone's heart rate is up, with one important exception; that of the infant pending birth. He emerges limp, floppy, pale, apneic, and with a barely perceptible heart rate, so a "full court press" is initiated according to the Neonatal Resuscitation Program (NRP) guidelines.[1] A skilled team is present to support this infant at birth, including a nurse and a neonatal nurse practitioner. They note that the infant does not respond to stimulation, and based on the understanding that this indicates secondary apnea, proceed with positive pressure ventilation which is followed by improvement in the heart rate to over 60 beats per minute, making chest compressions not needed. Nonetheless, this infant remains hypotonic and apneic, so he is intubated and the decision is made to admit to the NICU for ongoing assessment and care, and so begins a common scenario that leads to the diagnosis of "HIE" or "hypoxic-ischemic encephalopathy", a diagnosis that is made in up to 1.5 in 1000 live births in developed countries.[2] In this review, we will cover the pathophysiology of HIE, its diagnosis and medical management, and touch on some of the emerging concepts in HIE research.

Clinical Presentation of HIE

Hypoxic-ischemic encephalopathy, or HIE, occurs when there is a combined effect of both hypoxia and ischemia in the perinatal period. A typical harbinger of HIE is fetal distress in a monitored fetus, in which there is bradycardia and a characteristic non-reassuring pattern of the fetal heart rate tracing. When this scenario occurs, it is imperative that the obstetrical care providers move to immediate and emergent delivery of the infant. Significant delays may lead to a compromised infant, and in the worst case scenario, stillbirth.

The clinical description of the infant with HIE has been standardized since the 1970s based on a systematic analysis of affected infants of >36 weeks of gestational age by Sarnat and Sarnat.[3] At that time, the disorder was referred to as "asphyxia" but due to attempts at greater precision in the diagnostic criteria, and concerns of litigation when there was no medical fault, we now prefer to use the term "HIE", while "asphyxia" has largely been retired.[4] Three stages have been defined in the untreated infant.[3] In Stage 1 (mild), the infant is hyperalert, with normal tone but overactive reflexes. The suck is weak, and there is a generalized sympathetic nervous system state with mydriasis, tachycardia, reduced oral secretions, and a normal electroencephalogram (EEG). Stage 1 is typically present for up to 24 hours. Stage 2 (moderate) is associated with a lethargic or obtunded infant, with mild hypotonia, a posture with strong distal flexion, overactive reflexes, and the presence of myoclonus. The suck is typically weak or even absent, the Moro is incomplete, the oculovestibular reflex is overactive, and there is a strong tonic neck reflex. In contrast to Stage 1, the autonomic function in Stage 2 is parasympathetic, with the infant having miosis (constriction of the pupil), bradycardia, profuse secretions, and even diarrhea. Seizures are common, and may be focal or multifocal, and there is an abnormal EEG characterized by a low voltage pattern interrupted by focal seizures. Stage 2 typically has its onset at 24 hours and continues for two to 14 days. Stage 3 (severe) presents within hours and potentially lasts for weeks, the infant is stuporous and flaccid, with a decerebrate posture. Reflexes are decreased or absent, and there is no myoclonus. Both suck and Moro are absent, as are oculovestibular and tonic neck reflexes. Autonomic systems are depressed, and the pupils are often

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http://dx.doi.org/10.1053/j.nainr.2015.12.005
1527-3369/

unequal and have a poor light reflex. Seizures are uncommon, and the EEG shows a periodic pattern that evolves into being isopotential, i.e., with minimal variation from baseline. In ambiguous cases, the assistance of a pediatric neurologist can be key in determining the stage of HIE, and in guiding appropriate therapies.

Clinical Course and Pathophysiology

The injury incurred in HIE evolves over days to weeks, and involves multiple phases.[5] It is anchored in a loss of adequate cerebral blood flow leading to a loss of homeostasis in fetal brain glucose and oxygen levels. This may occur as a result of placental abnormalities such as abruption, prolapse of the cord, utero-placental insufficiency, or uterine rupture, and leads to compromise of the vasculature resulting in anaerobic metabolism in the fetus. This can lead to altered auto-regulation of the cerebral blood flow, that when accompanied by systemic hypotension, increases the risk of acidosis and ischemic brain injury.[6] Shoulder dystocia is another potential key sentinel event. Acutely, the infant will manifest low Apgar scores and a metabolic acidosis, a condition associated with excitotoxicity, or the process by which reduced delivery of glucose and oxygen to the brain leads to energy depletion, acidosis, and cell death.

HIE is a leading contributor to death in the neonatal period (birth to 28 days of life), and a major contributor to seizures in the term infant.[7] HIE is associated primarily with neuronal and white matter injury in the brain.[6] Brain injury occurs as a result of energy failure at the cellular level which then becomes reliant on anaerobic metabolism, resulting in the accumulation of lactic acid and depletion of adenosine triphosphate (ATP).[8] Perturbation of the normal cellular homeostasis leads to an altered distribution of sodium, calcium, and water, and contributes to a release of excitatory neurotransmitters, and eventually, free radical production, oxidative stress, and mitochondrial dysfunction.[6] Cell death occurs which may follow several specific pathways, but the mechanism of "auto-phagy" may actual be a protective mechanism that benefits brain cellular homeostasis.[6] A more chronic phase of HIE is based on inflammation that likely undermines brain plasticity and the appropriate growth of neurons and synapse formation, and may also alter the blood–brain barrier.[6]

The Standard of Care: Hypothermia

It is important for care providers even in non-tertiary centers to recognize that an infant may be at risk of having HIE, and to refer the infant promptly to a center where hypothermia therapy, better known as "cooling", may be implemented. Aside from the clinical aspects of optimizing patient care, failure to refer and initiate cooling in a timely manner has become a new area for malpractice litigation.[4] Oftentimes these births occur at centers remote from NICUs that perform cooling, so considerations must be made as to whether so-called "passive cooling" should be initiated by the birth hospital team. Passive cooling entails either down-regulating or turning off the radiant warmer, with close monitoring to assure that the infant's temperature remains in a low, but safe range, as an infant whose temperature is too low may also be at risk of harm.[9] Consultation with the accepting neonatal team in the tertiary care center is critical in making a decision to implement passive cooling. Active cooling is performed only in tertiary care centers. Novel technologies are making servo-controlled active cooling available on transport, assuring that infants receive optimal cooling within the window of time when it is most likely to be effective.[10,11]

Once a determination has been made that the infant has a diagnosis of HIE, clinical staging must be performed to determine whether the infant is likely to benefit from cooling. Cooling is a process by which the infant's temperature is controlled for an interval of 72 hours. Meticulous bedside nursing care is a key cornerstone in the successful implementation of a cooling protocol, and is described in detail below. In the whole body cooling approach studied by NICHD, the target temperature is 33.5 °C.[11] Selective cooling of the head has also been successfully performed in the "Cool Cap" and other studies.[12] Cooling is currently only provided to infants ≥36 weeks gestational age, and who have Stage 2 or 3 encephalopathy.[11] Infants with mild HIE will recover without need for cooling. Consultation with a pediatric neurologist may be helpful in determining the infant's stage of HIE, and whether cooling will likely be beneficial. Other criteria applied in determining which infants are appropriate for cooling include: initiated within 6 hours of birth, severe acidosis at birth or within the first hour of life (pH <7.15, base deficit >10), 10 minute Apgar score ≤5, assisted ventilation initiated at birth and continued for at least 10 minutes, and an acute perinatal event known to be associated with HIE.[11]

Some studies have also included the aEEG, or amplitude integrated EEG, as a criterion for cooling, based on the finding of an abnormal aEEG study.[12] The aEEG is a point-of-care bedside test that does not require a pediatric neurologist to interpret, and can be a helpful tool for bedside nursing staff in determining the likelihood of seizure activity. Rather than a full montage of electrodes as is used in the standard EEG, a single channel is recorded that is compressed in both amplitude and time to make it simpler to interpret (see accompanying paper by Sievert for more information on the use and interpretation of the aEEG in HIE).[13]

Nursing Care

Infants with HIE have multi-organ and multisystem problems that arise from the original hypoxic-ischemic insult.[14–16] As a result, management of these infants is complex and requires a coordinated team effort, most effectively within a NICU/tertiary care center. Although it is the medical team that determines the diagnosis and treatment plan, it is the expertise of the nursing staff that assures the successful implementation of that plan.

The initial acute management starts with delivery room resuscitation and stabilization. Effective NRP provides initial steps in alleviating tissue hypoxia and promoting cerebral perfusion/oxygenation. In HIE, temperature management is key to optimizing outcomes. Care should be taken to make sure that the infant is not overheated during resuscitation/stabilization.[17–20]

If the infant needs to be transported to a tertiary care center, passive cooling on a radiant warmer to a body temperature of 36 °C axilla until the transport team arrives is recommended. Care should be taken that the infant's temperature does not exceed 37 °C. Active cooling should only be done in a tertiary care center. Therapeutic hypothermia must begin within 6 hours of birth for effective neuroprotection. Cooling is less effective if started after 6 hours of life, after the onset of seizures, or in infants with the most severe EEG changes before therapy.[12,17–19,21–26]

Establishing and maintaining spontaneous or assisted ventilation, supporting adequate perfusion, preventing hypotension, hypoxia and acidosis, avoiding rapid alterations in cerebral blood flow and systemic blood pressure, and minimizing severe apneic and bradycardic episodes, are all of top priority during the initial management of HIE. In addition, neurologic status needs to be continuously monitored and any deviations from normal should be meticulously documented.[17,18,20] Fluid management is critical for treating the cerebral edema and for managing the alterations in renal function; fluids may need to be severely restricted to 40–60 mL/kg/day. Documenting every mL of fluid administered, including medications, is important throughout the initial phases of acute management.

Implementing Cooling Therapy

Once the decision is made to initiate hypothermia, meticulous care is required to provide the treatment safely and efficiently. Infants undergoing a cooling regimen require strict attention at the bedside as they may need rapid responses to emergencies such as acute respiratory failure and/or seizures.

There are currently two distinct approaches used to provide cooling for newborns: selective head cooling and whole body cooling. Selective head cooling is achieved with a special cooling cap applied directly to the infant's head. In contrast, placing the infant directly onto a cooling blanket is used for whole body cooling. Both approaches are effective;