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Therapeutic Hypothermia for Neonatal Hypoxic Ischemic Encephalopathy: Effects on Neurodevelopmental Outcomes

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III. Abstract

Therapeutic hypothermia is a standardized protocol in the management of term- or near-term neonates who have suffered asphyxia in the perinatal period. Birth asphyxia, if sustained, may develop into a more serious condition known as hypoxic ischemic encephalopathy (HIE). Depending on severity, HIE is associated with adverse cognitive and neurodevelopmental outcomes, yet through various physiological mechanisms, hypothermia sustained for a 72-hour period has been shown to attenuate, or even prevent, permanent brain damage by decreasing cerebral energy demands. Unfortunately, cognitive and neurodevelopmental outcomes are difficult to prognosticate before or after completion of hypothermia protocol, but existing standards and technology allow for reliable prognostication up at 18 months of age. Currently, research is underway to identify certain imaging and biochemical modalities that may help predict cognitive and neurodevelopmental outcomes at various stages of childhood beyond 18 months of age, even before hypothermia is initiated, as well as to evaluate methods holding potential to strengthen hypothermia protocol as it presently stands.

IV. Introduction

Perinatal asphyxia is not an infrequent incidence, occurring between 1 to 2 per 1000 live births in the United States.[1,2] When asphyxia is sustained, hypoxic ischemic encephalopathy (HIE) may result. While the main sequelae of moderate to severe HIE are neuromotor delays, such as cerebral palsy (CP), which accounts for 20% of cases of neonatal HIE, cognitive impairments can also occur.[3] When compared to neonates who do not experience hypoxic insults in the perinatal period, neonates with at least a moderate degree of HIE have a 10% increased risk of death, and those that survive carry a 30% increased risk of neurodevelopmental disabilities.[4]

Hypoxic insults that progress to HIE in the perinatal period are caused by cerebral ischemia. This lack of blood flow to the brain leads to deficiencies in oxygen, adenosine triphosphate (ATP), and glucose, creating an environment reliant on the anaerobic metabolism of lactate to meet energy needs, which in excess, leads to acidosis. Additionally, HIE triggers a release of excitatory glutamate that may cause neuronal hyperexcitability, seizure activity, and/or neuronal cell injury and death. Excess glutamate also increases production of reactive oxygen species (ROS) and nitric oxide (NO). ROS recruit inflammatory cytokines and enzymes that degrade the blood-brain barrier, leading to cerebral edema and a resultant increase in intracranial pressure (ICP), as well as increase apoptosis of neuronal cells. NO promotes cerebral capillary leakiness, which also increases ICP.[1,2,5]

Mechanistically, therapeutic hypothermia, or cooling core body temperature below 37.5 degrees Celsius (°C), decreases cerebral demand for oxygen, ATP, and glucose, to ultimately decrease lactate production and thwart acidosis. This cooling process also decreases release of glutamate from the brain, thereby attenuating ROS and NO production, which preserves the integrity of the blood-brain barrier, maintains normal ICP, and decreases inflammation and neuronal apoptosis. Therapeutic hypothermia experienced resurgence in the medical community in the 1950s, for notably decreasing cerebral blood flow, oxygen consumption, and ICP in patients undergoing cardiac surgery. Clinical application of and research into therapeutic hypothermia waned until the 1980s, until experimentation with milder hypothermic temperatures (i.e., greater than 32°C) began, including pilot research into applications for neonatal HIE in the late 1990s. In 2010, therapeutic hypothermia become a standard of practice for neonates of at least 36 weeks gestational age who had sustained asphyxia within 6 hours of birth, to minimize neurodevelopmental sequelae associated with HIE.[1-8]

The objective of the current research is to evaluate the efficacy of therapeutic hypothermia in improving neurodevelopmental outcomes in neonates with HIE, specifically by: 1) exploring protocol-defining research into therapeutic hypothermia for neonatal HIE; 2) assessing subsequent neurodevelopmental outcomes at various stages in childhood; 3) examining the utility of certain imaging tests and biochemical measures at predicting neurodevelopmental outcomes before therapeutic HIE is initiated; and 4) reviewing potential mechanisms for strengthening current hypothermia protocol for neonatal HIE.

V. Background: Literature Review

Standardizing Cooling Protocol for Neonatal HIE

Before therapeutic hypothermia became standardized protocol for term or near-term neonates who had suffered perinatal asphyxia, intensive care unit level management was still indicated, along with maintenance of physiological parameters within normal range and treatment of seizure activity with anti-epileptic drugs. There were some experimental pharmaceutical treatments being used, such as phenobarbital for potential reduction of neurodevelopmental handicap at 3 years of age, or allopurinol, which was thought to improve electroencephalogram (EEG) activity and reduce formation of ROS. Nevertheless, there was a paucity of data exploring the long-term effects of said interventions, so there did not exist any standardized protocol before the advent of therapeutic hypothermia.[1,2]

After the resurgence of interest and research into utilization of therapeutic hypothermia in reducing cerebral metabolism in the late 1990s,[5] small-scale randomized controlled trials (RCTs) examining the effects of mild hypothermia (i.e., core temperature of 33.5-34.5°C) on neurodevelopmental outcomes in neonates who had suffered perinatal asphyxia were conducted, but participant sizes were insufficient to yield adequate power to determine effectiveness in

clinical application.[6-8] However, these initial studies did pioneer the methods for inducing hypothermia that would come to be used in protocol-defining RCTs: whole body and/or selective head cooling. The former provides homogenous cooling to peripheral and central brain structures, namely, the posterior limb of the internal capsule, white matter cortex, basal ganglia, and thalamus. The latter provides a greater degree of cooling to the periphery of the brain than to the central brain structures, so, it was found that whole body cooling, combined with a degree of head cooling, minimizes temperature gradient differences across the brain and facilitates more effective cooling to the deeper brain structures.[1-4]

Soon after the launch of these pilot studies, larger scale, multi-center RCTs of neonates with moderate to severe HIE assigned to hypothermia protocol, with matched controls receiving intensive care unit level management and euthermia, emerged.[1, 2,4,9] The Eunice Kennedy Shriver National Institute of Child Health and Human Development Research Network (NICHD NRN) [4] utilized whole-body cooling, and the CoolCap study employed selective head-cooling.[9] The Total Body Hypothermia for Neonatal Encephalopathy (TOBY)[1,2] began in 2002, and additionally summarized data from other RCTs, including NICHD NRN and CoolCap, to maximize participant size and study power, so the most effective assessment of therapeutic hypothermia in the setting of neonatal HIE and neurodevelopmental outcomes could be conducted.

Per TOBY, neonates that met criteria for therapeutic hypothermia were at least 36 weeks gestational age and admitted to the neonatal intensive care unit, with at least one of the following: a) Apgar score of less than or equal to 5 at 10 minutes after birth; b) continued need for mechanical ventilation at 10 minutes after birth; c) acidosis within 60 minutes of birth; and/or d) base deficit greater than or equal to 16 mmol/L in any blood sample within 60 minutes of birth. Next, moderate or severe encephalopathy was defined as an altered state of consciousness,

characterized by lethargy, stupor, or coma, and at least one of the following (Table 1): a) hypotonia; b) abnormal reflexes, including oculomotor and pupillary; c) absent or weak suck; and/or d) clinical seizures. Within 6 hours of birth, whole-body cooling was initiated, with a rectal or esophageal probe monitoring temperature at 33.5°C for a duration of 72 hours. After 72 hours, body temperature was raised gradually, at a rate of 0.5°C per hour, until 36.5°C was reached.[1,2,4,9]

Immediately following the re-warming phase, magnetic resonance imaging (MRI) scans of the brain were conducted, along with assessments of both cognitive outcome per the Bayley Scales of Infant Development II (BSID II) and neurodevelopmental disability per the Gross Motor Function Classification System (GMFCS). Additionally, evaluations to assess hearing and vision impairment, as well as the existence of CP and/or seizure disorders, were performed. An identical battery of examinations was also performed when study participants reached 18 months of age.[1,2,4,9]

Neurodevelopmental Outcomes at 18 Months of Age

The general results ascertained from TOBY and the aforementioned RCTs were that across both cooled and non-cooled groups, the combined rates of mortality and severe neurodevelopmental disability were similar, in both the neonatal period and 18 months after birth. However, when looking at the survivors in each group, those who had received cooling were significantly more likely to be neurologically normal at 18 months of age, when compared to euthermic matched controls. Additionally, hypothermia was found to significantly reduce the risk of CP when compared to neonates who had received euthermic cares. Additionally, in these protocol-defining RCTs, there were no significant differences found in mortality or adverse

outcomes between cooled and non-cooled neonates, pointing to the safety of therapeutic hypothermia in neonates with HIE.[1,2,4,9]

Neurodevelopmental Outcomes Beyond 18 Months of Age

Despite these RCTs officially defining therapeutic hypothermia as protocol for management of neonatal HIE, the size of these trials were not large enough to allow for assessment of neurodevelopmental outcomes beyond 18 months of age.[1,2,4,9] The minimum duration of follow-up required for accurately diagnosing neuromotor, neurosensory, and cognitive disability is 18 months of age, and long-term follow-up to at least 6 years of age is desirable for a detailed assessment of neurodevelopmental and cognitive functioning.[1,2]

Even so, to date, the most prospective examination of neurodevelopmental outcomes at later points in childhood comes from secondary analysis of data from the NICHD NRN RCT and its associated 6-7 year follow-up outcomes study. Natarajan et al. 2013 evaluated the potential positive impact of therapeutic hypothermia in neonates with low 10-minute Apgar scores (i.e., 0-3) on neurodevelopmental outcomes at 6 to 7 years of age. From the primary results of the NICHD NRN RCT, there was a 45% increase in the odds of death or disability at 18 months of age with each 1-point decrease in Apgar score at 10 minutes. This secondary analysis showed that of the survivors with 10-minute Apgar scores of 0 (n=11 out of 24), 5 survived without moderate to severe disability, and had either a normal or mildly impaired intelligence quotient, normal visuospatial development, normal executive functioning, and no CP at 6 to 7 years of age; of these 5 survivors, 3 had undergone cooling.[10]

Early Predictors of Neurodevelopmental Outcome Before Hypothermia Initiation

Even with cooling therapy, over 40% of neonates with moderate to severe HIE die or suffer moderate to severe disabilities, such as CP, intellectual impairment, and epilepsy.[11] As

such, clinicians are interested in early predictors of neurodevelopmental outcome before the initiation of therapeutic hypothermia, in order to provide the most accurate prognosis.[12] The most accessible methods with prognosticating potential are imaging techniques and biochemical markers.

MRI is currently accepted as the best method in the detection of perinatally-acquired brain lesions, and has been found to be predictive of abnormal neurodevelopmental outcome at 18 months of age, especially if performed within 8 days of birth.[1-3] However, in a more recent retrospective observational study, mild degrees of brain injury per MRI assessment in the perinatal period did not consistently equate to normal cognitive and language measures around 24 months of age.[13] Even so, MRI is still recognized as the optimal modality for imaging structural changes following cerebral insults in the perinatal period, as well as for prognosticating neurodevelopmental outcomes at later stages in childhood; yet, standardized cognitive and neurodevelopmental testing, as well as MRI imaging, should be done serially throughout childhood, to provide the most accurate assessments and prognoses.[12] Amplitude of the filtered electroenceophalogram (aEEG) records trends in brain activity over a period of at least 24 hours. This is useful in monitoring neonates, because they have underdeveloped brains with activity signals that are not reliably recorded on EEG, and at most, provide only a snapshot of brain activity over a 45 to 60 minute period. aEEG is being increasingly used to assess and prognosticate the severity of neonatal encephalopathy following hypothermia protocol.[12] Finally, cranial ultrasound is a portable, fast, and easily available imaging technique to assess brain abnormalities, and attractive in that it confers no radiation exposure to the neonate. While a normal cranial ultrasound is reassuring, an abnormal result is associated with a high false-positive rate when predicting neurodevelopmental outcomes.[12]

Aside from the early prognostic potential of imaging procedures, certain biochemical markers may also be helpful in predicting neurodevelopmental outcomes before the onset of therapeutic hypothermia in neonates with HIE. A good biomarker is one that can be detected easily, rapidly, soon after birth, and also elevates in proportion to the degree of insult.[12] Initial neonatal arterial pH, time to spontaneous respirations, and absence of intrapartum exposure to oxytocin have been associated with 70% of neonates admitted for therapeutic hypothermia, and who subsequently suffered severe brain injury, per abnormal brain MRI at 7-10 days after birth.[14] All of these variables, when measured soon after birth, have a high specificity and a high negative predictive value for prognosticating neurodevelopmental outcomes at 18 months of age.[12] Glial fibrillary acidic protein (GFAP), a protein found in astrocytes; and ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1), an enzyme found in dendrites, hold potential for reflecting the extent of neuronal injury, because they are released into circulation after breakdown of the blood-brain barrier following an ischemic injury. In a prospective cohort pilot study using data from NICHD NRN RCT, those with moderate to severe HIE had significantly greater concentrations of GFAP and UCH-L1 when compared to infants with mild HIE, yet GFAP was the only biomarker that correlated significantly with other indicators of multiple organ dysfunction, like low 5-minute Apgar scores, and at 6-24 hours of age, only GFAP was significantly more elevated in neonates with abnormal neurodevelopmental outcomes at 20 months of age.[12,15] Finally, creatine kinase brain band (CK-BB), an enzyme found in neurons and astrocytes; neuron-specific enolase (NSE), an enzyme found in neurons; and S100b, a protein in astrocytes and Schwann cells, are all biomarker specific for neuronal tissue, but they have not been shown to be consistently elevated in neonatal HIE or correlated with neurodevelopmental outcomes.[12] Currently, no biochemical marker has been identified that meets all necessary

parameters for early prognostication of neurodevelopmental outcomes before hypothermia initiation in neonates with HIE, so prognosis continues to depend on serial cognitive and neurodevelopmental evaluation, along with neurophysiological tests and cerebral imaging into childhood.[12]

Strengthening Current Hypothermia Protocol for Neonatal HIE

Regardless of therapeutic hypothermia being a standard of care for the management of neonatal HIE,[5] new neuroprotective therapies will be necessary to reduce the unacceptably high risk of adverse outcomes after HIE.[11] Although there were no significant differences found in adverse outcomes between cooled and non-cooled neonates in protocol-defining RCTs, hypotension, thrombocytopenia, prolonged coagulation times, and intracranial hemorrhage were still observed in both groups.[1,2,4,9] Therapeutic hypothermia does hold potential for adverse outcomes, independent of HIE, which can be described in a systems-based format. In terms of the cardiovascular system, there exists a risk for arrhythmias, but mainly at temperatures below 30°C. Additionally, the induction of peripheral vasoconstriction in the setting of hypothermia decreases venous return to the heart, which causes an increase in atrial natriuretic peptide and a decrease in antidiuretic hormone, leading to increased diuresis. In the pulmonary system, there is an increased risk for pneumonia, because hypothermia decreases the inflammatory response, and makes the neonate more susceptible to infection. Hematological changes include a dwindling platelet count at temperatures less than 35°C, and the impairment of the coagulation cascade at temperatures less than 33°C. From a gastrointestinal standpoint, hypothermia promotes ileus and delayed gastric emptying, which increases risk for small bowel obstruction, feeding intolerance, and difficulties with blood glucose management. As far as electrolyte and hormonal balance, hypothermia decrease serum potassium and insulin sensitivity. Pharmacokinetics are also

affected, in that hypothermia reduces the rates of tubular reabsorption and secretion of certain drugs, as well as inhibits the cytochrome P450 system.[5]

With these caveats to therapeutic hypothermia in mind, several studies have been conducted to better elucidate stronger safety parameters for, and potentially efficacy of, protocol as it currently stands in the management of neonatal HIE.[11, 16, 17] A small, open-level phase I clinical trial was conducted to evaluate the safety and pharmacokinetics of high-dose erythropoietin (EPO) given to neonates with HIE undergoing hypothermia, because high doses (i.e., 250-2500 U/kg) of EPO have been shown to be neuroprotective in animal models of neonatal HIE, specifically lowering rates of death and moderate to severe CP, when compared with hypothermia treatment alone.[11] In the open level, phase 1 clinical trial, 1000 U/kg EPO plus hypothermia only showed no worsening of neurodevelopmental outcomes when compared with hypothermia alone, per MRI assessment in the neonatal period.[11] A secondary analysis of data from NICHD NRN RCT sought to highlight an advantage associated with birth location and induction of hypothermia; neonates born outside of centers performing hypothermia were considered "outborn," while those born within centers performing hypothermia were considered "inborn." After analysis, birth location had no significant impact on neurodevelopmental outcomes after therapeutic hypothermia.[16] Finally, an observational study in neonates with congenital brain anomalies or syndromic diagnoses and HIE independent of said factors, evaluated any positive effects of hypothermia on neurodevelopmental outcome in a population that would not have otherwise met induction criteria. Three of the subjects (n=8) deceased in the neonatal period, and 3 out of 5 survivors had unfavorable neurodevelopmental outcomes, independent of HIE, when seen for follow-up at 26 months of age. Because congenital anomalies and syndromic diagnoses confer a possibility for adverse developmental outcomes independent

of HIE, risk versus benefit of therapeutic hypothermia induction in this population of neonates remains to be defined, necessitating larger RCTs with increased sample sizes.[17]

VII. Methods

The framework for the present research was assembled using a PubMed Keyword search: "does therapeutic cooling in neonates with hypoxic brain injury improve outcomes?" Literature review was filtered to include only clinical trials and reviews, from the years 2000 to 2017.

VIII. Discussion

IX. Conclusion

X. References

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XI. Appendices

Table 1[2]

Table 1. Criteria for Defining Moderate and Severe Encephalopathy.

Category	Moderate Encephalopathy	Severe Encephalopathy
Level of consciousness	Lethargic	Stupor or coma
Spontaneous activity	Decreased activity	No activity
Posture	Distal flexion, complete extension	Decerebrate
Tone	Hypotonia (focal or general)	Flaccid
Primitive reflexes		
Suck	Weak	Absent
Moro	Incomplete	Absent
Autonomic system		
Pupils	Constricted	Deviated, dilated, or nonreactive to light
Heart rate	Bradycardia	Variable
Respiration	Periodic breathing	Apnea

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