Newborn & Infant Nursing Reviews 14 (2014) 77–81

Contents lists available at ScienceDirect

Newborn & Infant Nursing Reviews

journal homepage: www.nainr.com

Therapeutic Hypothermia for Treatment of Neonatal Encephalopathy: Current Research and Nursing Care

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ARTICLE INFO

Keywords:
Therapeutic hypothermia
Neonatal encephalopathy
Hypoxic-ischemic encephalopathy
Nursing

ABSTRACT

Neonatal encephalopathy, a condition resulting from perinatal asphyxia, occurs in 2.0–6.0 of every 1000 live births. Without treatment, prognosis is poor and resulting complications such as intellectual delay and cerebral palsy are often severe. Therapeutic hypothermia has emerged as an effective treatment for neonatal encephalopathy. Now, research is aimed at determining prognosis after encephalopathy and therapeutic hypothermia. Additionally, nurses play a large role in the identification and care of infants receiving therapeutic hypothermia and their families.

Neonatal encephalopathy (NE) is a condition that often results in serious health consequences including death, cerebral palsy, developmental delay, and seizure disorder.[1] The incidence ranges from 2.0 to 6.0 per 1000 live births, with higher incidence in poorer countries.[1] Therapeutic hypothermia (TH) has become the gold standard in treatment of NE due to its effectiveness in preventing death and major disability during the neonatal period. This paper aims to discuss the pathophysiology of NE, review current literature, and discuss nursing care of the cooled infant.

Search Methods

A comprehensive literature search was performed on CINHAL, PubMED, and Cochrane Collection databases. Key words and MeSH terms included therapeutic hypothermia, neonatal encephalopathy, hypoxic ischemic encephalopathy, MRI, aEEG, and nursing. Search results were limited to clinical trials and English language published in the last 5 years.

Pathophysiology

NE is a condition characterized by abnormal neurological function in the newborn period. Infants with NE may display an abnormal level of consciousness, altered muscle tone or reflexes, apnea or altered respirations, and sometimes seizures.[2,3] Hypoxic-ischemic encephalopathy (HIE) occurs when NE is the product of hypoxic-ischemic brain injury. HIE is the result of any event that causes decreased blood supply to the brain. Disturbed uteroplacental blood flow, placental abruption, tight or knotted nuchal cord, umbilical cord prolapse, and uterine rupture are risk factors.[3]

The disruption of blood flow and oxygen delivery that occurs in HIE causes a two phase reaction within the brain tissue that eventually causes brain injury.[3,4] Phase one, also known as primary energy failure, occurs when blood flow to the brain is disturbed and delivery of oxygen and other required substrates is impaired causing the brain to enter anaerobic metabolism.[4] Subsequently, brain tissue acidosis due to lactic acid buildup disrupts neuronal ability to maintain ionic balance, synthesize proteins, and regulate neurotransmitter release and reuptake.[5] One neurotransmitter in particular, glutamate, is a prominent excitatory neurotransmitter.[5] Buildup of excessive extracellular glutamate leads to a process called excitotoxicity where channels activated by glutamate remain open, causing persistent neuronal depolarization, allowing excess extracellular calcium into the cell resulting in cell death.[3,5,6]

Primary energy failure is relieved by the resolution of hypoxia-ischemia, leading to restoration of aerobic metabolism and reduced acidosis. However, reperfusion is followed by a secondary energy failure that usually occurs within 8–16 hours of primary failure.[5–7] Secondary energy failure is thought to be a product of mitochondrial damage, inflammation, the continued existence of surplus extracellular excitatory neurotransmitters, free radical damage, and oxidative injury culminating in premature neuronal apoptosis.[4–6] The timing and severity of secondary energy failure correlate with the severity of primary energy failure. Quicker onset and increased severity of secondary energy failure follow more severe primary failure.[5]

Therapeutic Hypothermia

Treatment of NE is aimed at disruption of the cascade of events leading to secondary energy failure and neuronal death.[8] TH is thought to diminish the severity of secondary energy failure by reducing the brain's energy utilization, decreasing free radical

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http://dx.doi.org/10.1053/j.nainr.2014.03.006
1527-3369/

production and release of extracellular excitatory neurotransmitters, and normalizing protein synthesis.[9,10] Combined, these effects lead to reduced neuronal apoptosis.[9,10]

Westin first reported the use of TH as treatment for asphyxiated infants in 1959.[4] Infants had improved neurological outcomes after being immersed in cold water to achieve core body temperatures of 23–25 °C for 20 minutes. However, clinical trials in the neonatal setting did not start in earnest until the late 1990s and early 2000s when pilot studies showed TH was safe for infants greater than 36 weeks gestation.[11,12] Then, in 2005, the results of the first multicenter phase III trial showed TH was both safe and effective for the treatment of mild and moderate NE.[12]

Since then, multicenter randomized controlled trials (RCTs) including the U.K.'s Total Body Hypothermia Trial (TOBY), Europe's "neo.nEuro.network" trial of whole body cooling, the National Institute of Child Health and Human Development's (NICHD) trial, and Australia's Infant Cooling Evaluation (ICE) encompassing over 1000 infants have commenced.[13–15] The results from these trials were published in the early to mid 2000s and since then several meta-analyses of these and other studies have been published that help to summarize the outcomes.[16–18] Edwards, et al. (2010) performed a meta-analysis of 10 clinical trials encompassing 1320 infants.[16] Their analysis showed lower rates of mortality, cerebral palsy, hearing and visual impairment, and neurodevelopmental delay in cooled infants. They concluded that the overall effect of TH is significant for preventing the primary outcomes of death and major disability as well as secondary outcomes such as cerebral palsy caused by NE. Shah (2010) reviewed 19 reports of 14 clinical trials of 1440 patients and found significant reductions in the risk of mortality or moderate to severe developmental delay.[18] Tagin, et al. (2011) reviewed 7 trials encompassing 1214 newborns and also found overall reduced risk of death and major disability along with cerebral palsy, developmental delay, and blindness.[19] Though there is some overlap in the studies included in these meta-analyses, they highlight the growing pool of evidence supporting the efficacy of TH.

Since the initial results of the large RCTs were published, subsequent follow-up studies were done on the surviving participants. Researchers were interested in whether TH provided long-lasting neuroprotection. The 18-month to 8-year follow-up results are summarized in Table 1. In general, TH was shown to reduce the incidence of death and major disability into childhood.[13–15,17,20]

Of particular interest are outcome measures of treatment subjects who are now reaching school age. Shankaran, et al. performed follow-up evaluations on 122 surviving subjects of the NICHD RCT.[20] They evaluated survivors on IQ and motor function, including classifying the level of cerebral palsy if present. At 6–7 years post treatment, they found no statistically significant difference in the rates of the composite outcome of death or IQ below 70 between the hypothermia and control groups. However, reduced mortality continued through age 6–7 years in the hypothermia group. Additionally, survivors had no significant increase risk of negative neurodevelopmental outcomes. These results suggest that TH safely provides long-term neuroprotection.[20]

New Topics in Therapeutic Hypothermia Research

Early research has shown that TH can be beneficial in the treatment of NE. However, researchers are now attempting to identify methods for real-time assessment of effectiveness of treatment and ways to predict outcomes. Knowledge pertaining to these topics could aid in counseling parents as well as finding complimentary treatments.

Imaging

Magnetic resonance imaging (MRI) is a useful tool for defining the extent of brain injury in infants following perinatal asphyxia. A main focus in current literature is research aimed at expanding the utility of MRI beyond diagnosis. Studies are now reporting evaluations of MRI in measuring the effectiveness of TH as well as predicting neurodevelopmental outcomes. Additional information is being sought to determine appropriate timing of scans and whether TH interferes with the reliability of MRI readings.

Shankaran, et al. (2011) compared MRIs performed at 44 weeks gestational age and categorized by pattern of injury to neurodevelopmental assessments at 18–22 months.[21] Because some patterns of injury did not fit into earlier defined systems of categorization, a method called the NICHD Neonatal Research Network (NRN) pattern of injury was created that classified injuries into six groups. The most common pattern of injury included damage to the posterior limb of the internal capsule (PLIC), the anterior limb of the internal capsule (ALIC), or the basal ganglia and thalami (BGT). Infants in the hypothermia group tended to have more normal appearing MRIs, normal PLIC and ALIC, and significantly fewer areas of watershed infarction. They found excellent correlation between the NICHD NRN pattern of injury categorization system and the primary outcome of death or disability at 18–22 months. Additionally, there was no statistically significant effect of age at time of scan on the prognostic utility of the NICHD NRN pattern of injury system.[21]

Rutherford, et al. (2010) and Cheong, et al. (2012) analyzed T1 and T2 weighted MRIs and performed sub-studies of infants in the TOBY and ICE trials, respectively.[22,23] Lesions were categorized into 1 of 5 patterns of injury as defined by Okeraefor, et al.[24] Cheong, et al. found moderate to severe injuries in certain regions to be prognostic of poor outcomes at 2 years of age.[23] In both studies, cooled infants were

Table 1
Outcomes at Greater Than 18 Months Post Treatment.

	CoolCaps[17]		Neo.nEuro. Network[14]		NICHD[20]		TOBY[13]		ICE[16]	
No./total no. (%)										
Age at follow-up	7–8 years		18–21 months		6–7 years		18 months		24–26 months	
	TH	C	TH	C	TH	C	TH	C	TH	C
Death	38	45	20/53 (37.7)	33/58 (56.8)	27/97 (28)	41/93 (44)	42/163 (26)	44/162 (27)	27/108 (25)	42/109 (38.5)
Cerebral palsy	NR		4/32 (12.5)	10/21 (47.6)	12/69 (17)	15/52 (29)	33/120 (28)	48/117 (41)	21/79 (26.6)	17/59 (28.8)
Visual impairment	NR		1/32 (3.1)	1/20 (5)	1/67 (1)	2/50 (4)	8/119 (7)	12/114 (11)	1/78 (1.3)	0/58 (0)
Hearing impairment	NR		0/30 (0)	2/17 (11.8)	3/6 (5)	1/50 (2)	4/114 (4)	7/108 (6)	2/79 (2.5)	2/58 (3.4)
Seizure disorder	NR		NR		7/67 (10)	8/50 (16)	12/116 (10)	16/116 (14)	NR	
Developmental delay	NR		7/33 (21.2)	13/23 (56.5)	19/70 (27)	17/52 (33)	34/115 (29)	50/110 (45)	17/73 (23.3)	14/50 (28)

TH = Therapeutic hypothermia group; C = Control Group; NR = Not reported.