Evidence-Based Guidelines for the Effectiveness of Therapeutic Hypothermia and aEEG Monitoring for Hypoxic Ischemic Encephalopathy in Infants 35-42 Weeks Gestation

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Abstract

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Anoxic brain injury, or birth asphyxia, can lead to multiple reactions causing a change in brain function in neonates, known as hypoxic ischemic encephalopathy (HIE). An infant may return to normal, but brain injury can result in neuromotor or developmental delay, cerebral palsy, neurodevelopmental disability, or even death. Lowering core body temperature from 37 degrees Celsius to 33-35 degrees Celsius can lower the severity of damage. Therapeutic hypothermia (TH) lowers body temperature by the use of head, or whole body cooling. Hypothermia treatment is started when the neonate is less than six hours old, the temperature is maintained for 48-72 hours, with gradual rewarming to 37 degrees at a rate of 0.5 degrees per hour. Amplitude-integrated electroencephalography (aEEG) monitoring is often utilized at the bedside to determine the need for treatment, patient status during TH, as well as helping to predict long-term outcomes. Multiple randomized controlled trials (RCTs) implementing TH to treat moderate to severe have been performed in the past 15-20 years, demonstrating a continued decrease in mortality and long-term morbidity as evidenced by improved neurologic outcomes, physical and psychosocial health, and IQ scores.
Keywords: therapeutic hypothermia, head cooling, whole-body cooling, neonatal cold therapy, hypoxic ischemic encephalopathy, newborn, neonate, infant, term, amplitude-integrated electroencephalography, EEG, aEEG, , anoxic brain injury, birth asphyxia, seizures
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Introduction

According to reports by the World Health Organization, almost 4 million neonatal deaths occurred worldwide in 2006 (Neonatal and Perinatal Mortality, 2006). Of these, 7 deaths per 1000 live births were attributed to birth asphyxia, most of which were in underdeveloped countries. In the United States (U.S.), the mortality rate was 4.54 infant deaths per 1000 live births in 2005 (Hoyert, Kung, Murphy & Xu, 2005). Also in the U.S., death as associated with asphyxia was less than 1 per 1000 live births, or 2.7% of the neonatal death rate (Chirinian & Mann, 2011). Although precise figures are not available, birth asphyxia is considered the cause of 23% of worldwide newborn deaths. It is the fifth leading cause of death for children less than five years old. Asphyxia accounts for roughly 920,000 newborn deaths yearly and 1.1 million stillbirths worldwide. Greater than one million of those who survive develop problems including learning difficulties, mental retardation, cerebral palsy, or other disabilities (Bryce, Boschi-Pinto, Shibuya, & Black, 2005).

Birth asphyxia, or inadequate oxygen delivery, can cause a large number of reactions in the body, which lead to altered functioning of a neonate’s brain, known as hypoxic-ischemic encephalopathy (HIE) (Chirinian & Mann, 2011). The symptoms of moderate-to-severe HIE are almost always manifested at birth or within a few hours afterwards (Zanelli, 2012). The causes of birth asphyxia are often unknown, and damage may happen during the actual pregnancy. However, asphyxia may be caused by delay in respiration, obstruction of the airway, aspiration of meconium, congenital malformations, trauma from birth, uterine rupture, infection of the uterus, cord compression, and placenta abruptio (Chirinian & Mann). Outcomes of infants who survive range from normal functioning to death, but include possibilities of neuromotor or developmental delay, cerebral palsy, and neurodevelopmental disability (Chirinian & Mann). With severe HIE, death rates are 25-50%. Infants usually die within one week of birth due to organ failure or the decision to withdraw care. Others may die later from system-wide infection or aspiration pneumonia. Up to 80% of those who survive severe HIE end up with serious developmental disabilities, and 30-50% who experience moderate HIE will develop serious problems. Those with mild HIE are usually free of severe complications (Lawn, Shibuya, & Stein, 2005).
A therapy known as therapeutic hypothermia (TH) is increasingly being used in critical care units for infants, who during birth acquire an anoxic brain injury that leads to HIE. Therapeutic hypothermia has been experimented with for decades, but in the past 20 years it has emerged as a focus of renewed research. There is increasing evidence that TH is helpful in reducing brain injury and improving long-term neurological outcomes (Tagin et al., 2012). Early studies were performed on animals, such as pigs (Thoresen et al., 1995) and rats (Sirimanne et al., 1995). There have also been multiple studies using TH on adults with a history of cerebral injury due to cardiac arrest (Arrich, 2012; Horburger et al., 2012; Sanders, 2006). More recently studies were begun on neonates with HIE. Randomized controlled trials (RCT’s) were performed initially, with mixed results. Even among more recent studies there have been mixed results about the effectiveness of using TH, with some showing TH helpful for moderate HIE, while others appear to demonstrate better TH outcomes for severe HIE. It is essentially not ethically possible to perform RCT’s at this point, because there is a continued increase in evidence demonstrating improved outcomes for infants with both moderate and severe HIE. An increasing number of facilities are beginning to use TH as a standard of care. According to Doctor G. McDonald (personal communication, June 10, 2012), Sacred Heart Children’s Hospital in eastern Washington began using TH and amplitude-integrated electroencephalography (aEEG), or bedside EEG monitoring, as standard treatment for neonates with HIE, as recently as 2010.

Therapeutic hypothermia is defined as the lowering of core body temperature to 33-34 degrees Celsius or 91.4-93.2 degrees Fahrenheit (Chirinian & Mann, 2011). The cooling process is normally begun within six hours of birth. The infant remains cooled for 48-72 hours, then slowly rewarmed over 12 hours (with variations in studies, as low as 6 hours) to 98.6 degrees (37.0 degrees Celsius).

Hypoxic ischemic encephalopathy is categorized as a mild, moderate, or severe brain injury (Chirinian & Mann, 2011). Zanelli (2012) summarized the levels of injury of HIE. In mild injury, mild hypertonicity and behavioral abnormalities (poor feeding, irritableness, sleep disturbance) may be seen. Moderate injury exhibits as lethargy, hypotonia, slow or absent reflexes, apnea and seizures. Severe injury
is characterized by irregular breathing, heart rate and blood pressure, as well as coma, hypotonia, absent neonatal reflexes, eye disturbances and frequent seizures.

The majority of studies utilized TH on neonates only with moderate to severe HIE. Some questions to consider are, “How can health-care practitioners utilize TH to improve outcomes in neonates who have experienced moderate to severe HIE.” “How effective is aEEG in monitoring brain function in TH patients.” “What is the clinical progress of cooling therapies, and what remains to be studied?” The population of interest is neonates, ages 35-42 weeks gestation, in the neonatal ICU who are diagnosed shortly after birth with moderate to severe HIE.

The purpose of this paper is to examine evidence-based research on the protocols and effectiveness of TH in neonates with moderate to severe HIE. Concepts of interests are neonates with HIE, TH outcomes, and aEEG monitoring.

**Literature Search Strategy**

The WSU online library, PubMed, CINAHL (EBSCO), and Cochrane Library (Wiley) were searched using search terms of “hypoxic ischemic encephalopathy” and “neonatal cold therapy.” PubMed produced 556 results with the use of “hypoxic ischemic encephalopathy.” The search was narrowed to 227 articles by adding limiting terms of “humans,” “clinical trial,” “meta-analysis,” “practice guideline,” “randomized controlled trial,” “review,” “core clinical journals,” “history of medicine,” “MEDLINE,” “nursing journals,” “systematic reviews,” “all infant: birth-23 months,” and “published in the last 5 years.” These 227 articles were narrowed to 66 by finding articles that discussed EEG monitoring, HIE and TH. CINAHL produced 44 results with the term “hypoxic ischemic encephalopathy” and 16 results using the term “neonatal cold therapy.” These articles were narrowed even further into three concepts of interest consisting of, (a) outcomes of TH groups versus control groups (seven articles), (b) guidelines and criteria used to decide the need for TH treatment (two articles), and (c) the uses for aEEG monitoring (three articles). These articles were chosen due to their significant sample sizes, the recency of their publication, and the relevancy to the topic of interest.
Theoretical Framework

The theory of symptom management (TSM; Newcomb, 2010), constructed by faculty at the University of California, San Francisco in 2001, is considered a mid-range theory. This theory “provides a conceptual framework for detecting symptom management gaps, assessing management barriers, planning interventions and targeting areas for research” (Newcomb, 2010, p. 40). This theory was chosen because of its emphasis on symptom experience, symptom management strategies, and symptom outcomes. Part of the theory is self-care strategies, which may vary depending on the amount of stress a person is subjected to. The area of symptoms outcome includes outcomes of morbidity, mortality, emotion, function, self-care ability, quality of life and money. The TSM model is important in that it is the only model that allows for examination of specific plans for symptom management. Dodd et al. (2001) founded this theory on the following six assumptions:

- That the gold standard for the study of symptoms is based on the perception of the individual experiencing the symptom and his/her self-report.
- That the symptom does not have to be experienced by an individual to apply this model of symptom management. The individual may be at risk for the development of the symptom because of the influence (impact) of a context variable such as a work hazard. Intervention strategies may be initiated before an individual experiences the symptom.
- That nonverbal patients (infants, poststroke aphasic persons) may experience symptoms and the interpretation by the parent or caregiver is assumed to be accurate for purposes of intervening.
- That all troublesome symptoms need to be managed.
- That management strategy may be targeted at the individual, a group, a family, or the work environment.
- That symptom management is a dynamic process; that is, it is modified by individual outcomes and the influences of the nursing domains of person, health/illness, or environment (pp. 669-670).

The theory, historically applied to adults and providers, does not account for factors related to children such as their lack of autonomy, their inability to communicate well, and their rapid growth and
development (Newcomb, 2010). Newcomb suggests modifying the theory, by adding the roles of "communication" and "feedback" to make the theory more effective for children.

In working with neonates in the ICU, the health professional is caring for nonverbal patients, and may intervene by listening to reports from the infant’s parent or caregiver and by cueing in to an infant’s attempts at communication, such as crying, irritableness, or excessive sleepiness. Appropriate feedback may be evidenced by the provider achieving adequate pain control, monitoring temperature and other vital signs closely, and ensuring the infant is changed and fed. Therapeutic hypothermia may help prevent symptoms such as brain injury, seizures, and long-term developmental delay. The use of aEEG monitoring may provide information to help manage troubling symptoms such as subclinical seizures. As symptom management is a dynamic process, aEEG use evaluates brain function, helping providers determine whether therapy is effective or not, and helping to guide changes in treatment, or symptom management. Moderate to severe HIE may result in long-term poor outcomes such as cerebral palsy, so treatment must be started before these symptoms appear, with the hope of producing a better outcome as suggested in the TSM.

**Literature Review**

The following literature review is divided into three areas: outcomes of TH groups versus control groups, guidelines and criteria used to decide the need for TH treatment, and the uses for aEEG monitoring.

**Outcomes of TH Groups Versus Control Groups**

Jacobs, Hunt, Tarnow-Mordi, Inder, and Davis (2007) reviewed eight RCT’s of TH used on neonates 35-42 weeks gestation with HIE, finding that infants who received TH treatment had significantly improved quality of life (N=318), (RR=0.76; 95% CI: 0.65-0.89) compared to neonates with no TH treatment, but supportive care only (N=320). Quality of life was measured as improved development and survival at 18 months of age for term newborns with risk of brain damage. This article was a meta-analysis of eight RCT’s comparing the rates of death or major neurodevelopmental disability of children ages 18-22 months. Strengths of the analysis included sample size (N=638), the fact that only
RCT’s were included, and that similar findings were found in eight separate studies. Weaknesses were that the analysis consisted of only 638 out of a total of 829 infants on which studies have already been completed or are still in progress. Another weakness was that the studies were not double blind.

A large RCT was completed by Azzopardi et al. (2009), using 325 infants interspersed throughout 42 participating centers in the United Kingdom. This study is known as the total body hypothermia for neonatal encephalopathy trial (TOBY). Infants were divided into two groups, and total-body cooling was compared to normal temperature care for neonates with HIE. Azzopardi et al. concluded that the combined rate of death or severe disability was not significantly reduced by TH, but that neurologic outcomes did improve in those who survived. In the TH group, 42 neonates died and 32 survived with severe neurodevelopmental disability, or 74 patients out of a total of (N=163) infants. In the normothermic group 44 died, while 42 had severe disability, consisting of 86 patients out of a total of (N=162) infants (RR 0.86 for either group, 95% CI: 1.16-2.12; p=0.003). Infants who were cooled had a decreased risk of cerebral palsy (RR=0.67; 95% CI: 0.47-0.96; p=0.03), and improved mental and motor developmental scores. As in other studies that have been done, there were common minor cardiovascular and respiratory adverse effects, but none of these was considered to have been caused by TH. Strengths of the study were the large number of subjects, minimal loss to follow up, and that it was a RCT. A possible weakness was that the last follow-up was short at 18 months. The authors suggested the need for obtaining studies with longer follow-up times, such as when children are six or seven years old.

Jacobs et al. (2011) performed a RCT known as the infant cooling evaluation (ICE) trial. This was a multi-center, international study of 221 newborns 35 weeks of age or older with moderate to severe HIE. Their goal was to discover how safe and effective whole body hypothermia might be when using simple cooling techniques in relatively rural facilities. Dedicated retrieval teams were sent to the hospitals to evaluate whether the infants were eligible and to start TH treatment prior to transport. Due to various reasons, 13 of the 221 infants were ultimately excluded. Of those remaining, 55 of 107 infants (51.4%) with TH and 67 of 101 infants (66.3%) with normothermia either died or had major disability at the age of two years (RR=0.77, 95% CI: 0.62-0.98; p=0.03). Major disability included cerebral palsy, blindness,
deafness, and low motor and cognitive scores. Mortality rates decreased, and survival rates increased free of sensorineural problems for those who received TH. Adverse outcomes of TH were negligent. The study was in progress between the years 2001-2007. Strengths are that this study was a RCT, consisting of 28 centers, and was international, including Australia, New Zealand, Canada and the United States. Infants were assigned randomly by computer-generated numbers and then stratified to a study center by an independent statistician. Cooling was done by maintaining room temperature, only applying simple refrigerated gel packs if necessary. Jacobs et al. (2011) demonstrated that treatment can be done simply and cheaply, a method applicable for many developing countries, as well as smaller facilities. A limitation was that recruitment was stopped after 221 infants (goal was 300), because of increasing evidence of the effectiveness of TH for infants with moderate to severe HIE. Further, 19% of the recruited infants had mild HIE, which may reflect lack of a standard neurological assessment instrument, and a lack of formal certification for those who transported the babies (Jacobs et al., 2011).

A RCT was performed in Europe by Simbruner, Mittal, Rohlmann, and Muche (2010) on 129 infants. The trial took place in 24 centers between the years 2001 and 2006. Simbruner et al. concluded that TH provided a strong neuroprotective effect, decreasing the incidence of seizures in the newborn period, effective primarily in patients with severe HIE. Follow-up was conducted of 111 children, at 18-21 months of age, with primary outcomes of death or severe disability. The rates of death or severe disability were 51% in the TH group and 83% in the normothermia group (p=0.001; odds ratio: 0.21, 95% CI: 0.09-0.54; NNT: 4; 95% CI: 3-9). Those treated with hypothermia had a lower rate of disabling cerebral palsy, severe hearing loss that needed cochlear implants, and cortical blindness. Strengths of the study included the random assignment of patients to either normothermic or hypothermic treatment by the use of sealed envelopes, large study size, and the fact that the neurologists performing the six and 18 month follow-up were blinded to the original patient neurological status. A possible limitation was that the study was stopped sooner than planned due to ethical concerns for the subjects in the control group, as there was increasing evidence that TH was effective in reducing negative long-term effects of HIE. Further, this trial was not double-blind, nor was there follow-up past 18 months of age.
Zhou et al. (2010) performed a large multicenter RCT in China, finding that head cooling along with mild systemic TH for 72 hours, significantly decreased severe disability and death as compared to control infants who received supportive care only. Combined outcome of death and disability for head cooling and control groups was 31% and 49% respectively (odds ratio: 0.47; 95% CI: 0.26-0.84; p=0.01). Mortality rate was 20% and 29% (odds ratio: 0.62; 95% CI: 0.32-1.20; p=0.16), and severe disability 14% (11/80) and 28% (19/67) (odds ratio: 0.40; 95% CI: 0.17-0.92; p=0.01). Strengths were that this study was performed at 12 centers, included a large number of infants (194), was a RCT, partially blind (numbers randomly assigned by computer and given out over the telephone), with follow-up by certified staff that were blinded to the treatment group. Some limitations were that a significant number of infants were lost to follow-up, and that males made up a larger proportion of the study.

In 2005, Shankaran et al. completed a study of 208 infants, with a primary outcome obtained from 205 of these. Neonates were recruited from 15 centers by the National Institute of Child Health and Human Developmental (NICHD) Neonatal Research Network. The infants were at least 36 weeks gestational age, less than six hours from birth and had either moderate or severe encephalopathy. They may have experienced either severe acidosis or complications at birth with a need for resuscitation. The conclusion of Shankaran et al. at that time was that whole-body hypothermia was safe and that there was decreased risk of disability or death in infants with moderate or severe brain injury. Death or moderate-severe disability took place in 45 of 102 neonates (44%) in the TH group, with these same results occurring in 64 of 103 neonates (62%) in the control group. (RR 0.72; 95% CI: 0.54-0.95; p=0.01). In the TH group 24 (24%) children died, compared to 38 (37%) in the control group (RR 0.68; 95% CI: 0.44-1.05; p=0.08). There was no noted increase in major disability is those who lived. Cerebral palsy was seen in 15 of 77 (19%) in the group with TH, whereas it was seen in 19 of 64 (30%) in the control group (RR 0.68; 95% CI: 0.38-1.22; p=0.20). Strengths were that the study was large, consisting of (N=208) neonates, and there was no noted increase in moderate or severe disability at the 18-22 month follow-up. A possible weakness was that follow-up was only as far out as 18-22 months of age. Another possible
weakness was that the temperature was noted to be elevated on at least one occasion in more than one
third of the infants in the control group, which could have caused brain injury.

A long-term follow-up of the study completed by Shankaran et al. in 2005 is now available. In
this recent evaluation by Shankaran et al. (2012), participants were six or seven years old, and were
evaluated for neurologic outcomes, physical and psychosocial health; visuospatial, executive, attentive,
and cognitive function. Of the original 208 infants in the study completed in 2005, 190 were available for
follow-up. The primary outcome was death or IQ below 70. Of 97 children in the TH group, an IQ score
below 70 occurred in 19 (20%), and death in 27 (28%). Of 93 in the control group, an IQ score below 70
occurred in 17 (18%) and death occurred in 41(44%), with a statistical significance of (p=0.04).

Therapeutic hypothermia did not increase severe disability rates, and resulted in a fewer number of
deaths. This follow-up information supported the authors’ previous conclusion that TH should continue to
be used in term infants with HIE. The authors considered these results reassuring as TH is now currently
used in many centers worldwide and recommended by policymakers. Strengths of this study were the
number of patients available for follow-up. Limitations of the study were that it was not powered to assess
secondary outcomes, such as physical and psychosocial health, disability, and motor and cognitive
outcomes. Also, there may have been diminished statistical power due to the fairly high level of loss at
follow up (N=18).

Guidelines and Criteria for HIE Treatment

Studies prior to the 1980’s used moderate hypothermia of 28-32 degrees Celsius, instead of mild
hypothermia, 33-35 degrees Celsius, and treated patients for longer than a week. This resulted in an
increase in complications, leading to decreased popularity and use of TH (Bohn, Biggar, Smith, Conn, &
Barker, 1986). A short time later, studies done on rats (Busto et al., 1987), and canines (Leonov et al.,
1990), demonstrated improved outcomes with the use of mild hypothermia.

In 2010, Perlman et al., as part of the American Heart Association (AHA), formed a committee
that developed the International Consensus on Cardiopulmonary Resuscitation and Emergency
Cardiovascular Care Science with Treatment Recommendations. Perlman et al. recommended TH be
considered for infants with HIE. They suggested whole-body or selective head cooling, the use of clearly defined protocols, and treatment in a neonatal intensive care unit (NICU) that employed a care team composed of multiple disciplines. Protocols were recommended that had been used in a number of RCT’s, including starting TH within the first six hours of life, continuing treatment for 72 hours from birth, and a rewarming period of four or more hours (Azzopardi et al., 2009; Eicher et al., 2005; Gluckman et al., 2005; Lin et al., 2006; Shankaran et al., 2005).

Just after the previous guidelines were published, similar guidelines for TH use were developed and published by (a) the Working Group on Therapeutic Hypothermia for Neonatal Encephalopathy, Ministry of Health, Labor and Welfare (MHLW), Japan, and (b) the Japan Society for Perinatal and Neonatal Medicine (JSPNM). The goal of the authors of these two nationwide consensus practice guidelines was international dissemination (Takenouchi, Iwata, Nabetani, & Tamura, 2012). Included were criteria for beginning TH on neonates. The authors recommended TH be started on neonates >36 weeks gestational age with a birth weight >1800 grams. Of those infants, TH was to be started on those showing signs and symptoms of moderate to severe HIE, as evidenced by seizures, hypotonia, or coma, had 10 minute Apgar scores <5, continued to need resuscitation at 10 minutes of age, and had a blood pH <7.0 or base deficit >16 mmol/L. Target temperature was 33.5 +/- 0.5 and 34.5 +/-0.5 degrees Celsius for whole body and head only hypothermia respectively, with TH duration of 72 hours, and a gradual rewarming not faster than 0.5 degrees Celsius per hour. Long-term follow-up was consistently performed.

The Uses of aEEG Monitoring

Electroencephalography (EEG) is considered the gold standard to assess electrophysiological brain function (Spitzmiller, Phillips, Meinzen-Derr, & Hoath, 2007). Besides the traditional EEG, there are two other styles of EEG monitoring that may be used to evaluate infants. The type most often used with HIE is amplitude-integrated EEG (aEEG), which is a simplified EEG used to make it easier for non-EEG experts to review and interpret (Hellstrom-Westes, & Rosen, 2006). Amplitude-integrated EEG, or another style known as video EEG monitoring, may be used for continuous bedside evaluation during the time an infant is undergoing TH. Electroencephalography can detect brain improvement or decline during
TH, and is helpful for picking up subclinical seizures, or seizures that cannot be visually seen, that can harm the neonate. According to Nash et al. (2011), there is data coming to light suggesting that seizures might be related to an increase in brain damage after HIE. Thus, detecting seizures quickly and accurately is important to help protect and preserve brain function.

A study of 24 neonates with moderate to severe HIE, treated with TH (33.5 degrees Celsius for 72 hours) was performed in Sweden by Hallberg, Grossmann, Bartocci, and Blennow (2010), to research the correlation between aEEG use during TH and short-term neurologic outcomes. The authors found that the early use of aEEG monitoring, started shortly after birth and continued for the full 72 hours of TH, as well as during warming, accurately predicted neurological outcomes when the infants were evaluated again at four months and one year of age. The strength of the study is that the aEEG tracings were assessed by two independent researchers, blinded to patient status, who ultimately agreed on the aEEG interpretations. The small number of patients and short follow-up time are limitations.

Nash et al. (2011), in a retrospective study performed on 41 neonates, found that continuous video EEG monitoring, performed during hypothermia and rewarming, could accurately monitor seizures during TH and provide prognostic information on magnetic resonance imaging (MRI) results, after rewarming, for infants with moderate to severe HIE. The greatest prognostic value was at the point of mid-cooling (about day two of life), demonstrating the need and importance of continuous, or at least serial, EEG monitoring. Monitoring was begun within 12 hours of birth, and continued for approximately 90 hours. Electrographic seizures were seen in 34% (14/41), while 10% (4/41) of infants went into status epilepticus. Seizures were noted clinically in 57% (8/14) and were subclinical in 43% (6/14). Some strengths were that the person reading the MRIs was blinded to the clinical history of the infants, 41 infants were a relatively large research sample, and the results were compared to studies done on infants with HIE who had not received TH treatment. Possible weaknesses were that the design was not a double blind, RCT, and there was no long-term follow-up. In addition, some infants were referred from outlying hospitals, preventing researchers from starting video EEG monitoring at the same point in life.
Spitzmiller, Phillips, Meinzen-Derr, and Hoath (2007) completed a meta-analysis of eight studies, which included a total of 499 infants, concluding that aEEG was a useful and valuable tool for bedside use, helping providers to predict long-term neurodevelopmental outcomes in newborns with HIE. Information from aEEG monitoring was also found helpful in making care plans and structuring communication for parents and providers. An overall sensitivity of 91% (95% CI: 87-95) was noted, with a negative likelihood ratio of 0.09 (95% CI: 0.06-0.15) for aEEG monitoring to predict poor outcomes accurately. Early normalization of tracing was seen to lend to a better outcome than tracings that continued to remain severe. Early aEEG use was found to provide an objective way to identify infants to include in clinical studies using TH, as well as assist in predicting those most likely to respond to therapy. A strength was the large number of subjects (N=499). Weaknesses included that several of the studies were done in the mid-1990’s, and the results applied only to term neonates.

**Discussion**

**Significance to Nursing**

Caring for the neonate with HIE involves a multidisciplinary team of people to effectively manage and guide treatment to ensure the best outcome possible. Some of the challenges for nurses are how to maintain their level of competence, how to manage the risks and safety issues associated with TH and how best to help families go through this experience. Traditionally, keeping infants warm is a priority for nurses, with cold being the “enemy.” It is important that nurses caring for these neonates understand the reasons for cooling, while keeping in mind that a core temperature of less than 32 degrees Celsius is dangerous. During TH, the infant’s temperature must be monitored closely and strictly controlled. After 72 hours of TH, rewarming should be done slowly, at a maximum of 0.5 degrees Celsius per hour to ensure vasodilation does not cause hypotension. Parents should be encouraged to continue to interact with their child. They should be provided verbal information and handouts about what to expect during therapy, the benefits and possible side effects, the desired long-term outcomes, and the importance of regular clinical follow-up until two years of age. McGrath (2012) believes there are several important steps to consider in dealing with parents who have gone through the traumatic experience of having their
infant admitted to the neonatal intensive care unit. To begin with, the staff caring for the child must seek to form a partnership with his parents. To have an effective partnership, there must be mutual respect, a full sharing of information, the valuing of input from the family, and the joint making of decisions and goals. Parents must feel that their role is essential, which is demonstrated by the staff providing support, encouragement, and a true role for the family. The creation of a welcoming environment is also essential. Discharge planning best occurs when it is shared by both family members and staff. Parents must begin participating in their child’s caregiving the very day of admission to best facilitate the later transition to home. This will help to give them a sense of control, help with early parent-infant attachment, and increase their confidence in caring for the neonate. McGrath (2012) believes that the goal for transition to home should be “No discharge teaching on the day of discharge.” According to (Vandertak, 2009) the infant’s comfort must also be considered, with the provider ensuring the infant receives pain medication and sedation per protocol along with careful skin care. Hypoxic brain injury is evidenced by fetal distress and acidosis. To diagnose injury, aEEG, venous and umbilical blood gas analysis, and clinical exam are all performed on the neonate. Goals and outcomes to be monitored for the infants who receive TH include a decrease in severe disability, an increase in survival without neurological impairment, and an increase in Motor and Psychomotor Development Index scores.

Providers encounter multiple difficulties in making the decision to withhold or withdraw therapy from neonates with brain injury and comorbidities who may end up with severe neurological deficits. Guidelines from the National Institute for Health and Clinical Evidence (NICE), based in the United Kingdom, suggested that TH should be done only in units where the staff and clinicians have been specially trained to use the therapy, and also have sufficient experience in caring for critically-ill newborns (NICE, 2010).

Possible adverse effects of cooling are an increase in the number of infections, metabolic disturbances, blood hyperviscosity, and seizures, if rewarming is done too rapidly (NICE, 2010). Protocols should be set in place for the use of TH and the care of infants with HIE. To be effective, the protocol should address the three main areas of treatment: how to begin hypothermia; how to maintain the
neonate’s temperature; and how to re-warm the infant. Further important considerations include guidance on what equipment and methods are needed at each step, how long the treatment should last, how best to monitor during treatment, and possible adverse effects of TH (Abend et al., 2011).

Continuous aEEG monitoring for neonates with HIE, who are receiving TH treatment, provides an effective predictor for the early outcomes of MRI’s and accurately identifies seizures, almost half of which are subclinical or show up only on the aEEG with no outward signs and symptoms. However, according to Nash et al. (2011), the point of best prediction did not happen until mid-cooling, showing the importance and need for continuous monitoring, or at least sequential EEG’s.

A major side effect of TH is shivering, which increases the body’s oxygen use and its temperature and must be avoided. Shivering leads to muscle artifact and electrode movement. Treatment includes sedation and paralytics. Neonates with HIE must also be monitored for hypotension, blood coagulopathies, dysrhythmias and increased risk for infection while undergoing TH (Varon & Acosta, 2008).

Important needs to consider when using aEEG, is that it can be accessed from several sites in-hospital, as well as from places outside the hospital so that reviews of the readings can be made several times per day if necessary. To ensure proper evaluation for encephalopathy, sleep must be captured during the monitoring, which requires a minimum of one hour, and possibly up to three hours of monitor time. The aEEG equipment should be placed where the patient is consistently on video, but where the device will not be in the way of staff caring for the infant. Events that might change the readings of aEEG monitoring need to be considered, such as medications (especially seizure medications and those that alter mental status), physical contact, and machines. If live, synchronous video monitoring is unavailable, a bedside caregiver must be present to press event buttons or maintain written logs of all events and times of medication administration (Abend et al., 2011).

**Recommendations for Future Research**

Protocols for implementing and providing TH vary between institutions. The literature reviewed thus far does not suggest a consensus on what cutoff indicators should be used for deciding whether an
infant fits the criteria to receive TH. Some factors still not well studied include the most effective way to cool the infant, the best length of time to maintain hypothermia, the optimal temperature to maintain, the best rate for rewarming, and the best way to monitor the neonate’s temperature.

At this time there is a RCT in progress by Shankaran et al. (2012) examining the effectiveness of TH for mild HIE and preterm infants (32-36 weeks gestation), and comparing results when cooling is started after six hours of life as opposed to less than six hours. Future studies should examine the assessment and treatment of non-convulsive seizures on a neonate’s outcome (Abend et al., 2011). Further trials are also needed to compare whole body versus head only cooling, the best and safest methods needed to provide TH, and who will most likely benefit from treatment (Jacobs, Hunt, Tarnow-Mordi, Inder & Davis, 2007).

In preclinical studies on piglets, there was evidence that an increased depth of cooling results in improved neuroprotection after anoxic injury (Iwata et al., 2006). Shankaran et al. (2012) are currently conducting a RCT to evaluate the effectiveness of a deeper degree of cooling (32 degrees Celsius) and a longer time cooling (120 hours). As yet, no studies have been done to evaluate toleration of enteral feeds during treatment with TH (Vandertak, 2009). Thus, neonates are kept nothing by mouth until they are rewarmed. Once warm, slow-rate enteral feeds may be started, but with careful monitoring as these infants are at high risk for necrotizing enterocolitis (Zanelli, 2012).

Simbruner, Mittal, Rohlmann, and Muche (2010) used regular doses of morphine to help decrease discomfort and the stress caused by TH. They suggested further studies to validate the role and effects of morphine use. Simburner et al. (2010) also advocated for trials in which absolute control of temperature is maintained in both control and TH groups, as in this and other studies there have been multiple episodes of infants’ temperatures wandering out of target ranges. Each of these situations could have affected the outcomes and accuracy of the trials.

The use of aEEG monitoring is easily done at the bedside and is noninvasive. Continuous aEEG monitoring, even in hypothermia, can help with goals of care, seizure control and with the evaluation of a neonate’s prognosis. To help with future use of aEEG monitoring, consensus must be established
regarding its classification and nomenclature, and other similar studies should be done to validate these results. Clinicians and researchers are finding that seizures are associated with increased brain injury from HIE, and therefore assessing seizures accurately can help to protect the neonate’s brain. Continuous EEG monitoring will be an important part of future studies evaluating whether fast and effective seizure treatment will ameliorate the negative neurologic outcomes in newborns (Abend et al., 2011).
References


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