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REVIEW

Hypothermia for the treatment of infants with hypoxic–ischemic encephalopathy

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Neonatal encephalopathy affects 2 to 5 of every 1000 live births and represents a major cause of mortality and long-term morbidity in affected infants. Hypoxic ischemic encephalopathy (HIE) is the major cause of encephalopathy in the neonatal period. Until recently, management of a newborn with encephalopathy has consisted largely of supportive care to restore and maintain cerebral perfusion, provide adequate gas exchange and treat seizure activity. Recent randomized controlled trials have shown that mild therapeutic hypothermia (cooling) initiated within 6 h of birth reduces death and disability in these infants. Cooling can be accomplished through whole-body cooling or selective head cooling. Meta-analysis of these trials suggests that for every six or seven infants with moderate to severe HIE who are treated with mild hypothermia, there will be one fewer infant who dies or has significant neurodevelopmental disability. In response to this evidence, major policy makers and guideline developers have recommended that cooling therapy be offered to infants with moderate to severe HIE. The dissemination of this new therapy will require improved identification of infants with HIE and regional commitment to allow these infants to be cared for in a timely manner.

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Introduction

Neonatal encephalopathy (NE) in term or late preterm infant is 'a clinically defined syndrome of disturbed neurological function in the earliest days of life manifested by difficulty with initiating and maintaining respiration, depression of tone and reflexes, subnormal level of consciousness and often by seizures.'[1] NE is estimated to occur in 2 to 5 of every 1000 live term births. Up to one-quarter of these infants experience moderate to severe cerebral injury.[2–4] Between 10 and 40% of affected infants will not survive and as many as 30% will exhibit significant long-term neurodevelopmental disability.[5] In developing countries, it is likely that the incidence is even higher, with fewer intact survivors. The financial, medical and social burdens of NE are poorly quantified, but undoubtedly substantial.

Historically, the presence of neonatal encephalopathy was considered *sine qua non* of hypoxic–ischemic injury or birth asphyxia surrounding the birth. More recently, more diverse diagnoses have been attributed as potential etiologies of neonatal encephalopathy.[6] Evidence from magnetic resonance imaging studies suggests that, although there may be antenatal risk factors that predispose to brain injury, the timing of the insult is almost always acute.[7] However, in only 25 to 35% of cases attributed to birth asphyxia is it possible to identify a clear contributing sentinel event in the intrapartum period.[8,9] Furthermore, implicated are antepartum insults, direct injuries or increased susceptibility to injury that occur well before the birth process, as well as congenital and metabolic birth defects.[1–3,10] Although the causes of neonatal encephalopathy are likely heterogeneous, a model of cerebral hypoxic–ischemic injury that begins *in utero* and extends into a recovery period is increasingly suggested and has been used as a model of study.[11]

Hypoxic ischemic encephalopathy (HIE) is the most well-recognized and studied cause of neonatal encephalopathy. HIE follows a disruption in cerebral blood flow and oxygen delivery to the brain, typically secondary to threatened or diminished placental blood flow and gas exchange. Many factors such as timing, duration and severity of the insult influence the progression and degree of injury. Severe acute hypoxic–ischemic injury rapidly results in neuronal death by necrosis, whereas less-severe but prolonged insult leads to greater apoptosis.[12,13] Brain injury is thought to occur in two phases, separated by a brief recovery or 'latent phase'.[14] If the oxygen deprivation is not corrected, predictable 'primary' cell death (necrosis) ensues in proportion to the nature and severity of the initial insult. After reperfusion, brain oxidative metabolism and cellular pH recover briefly during the 'latent period', which does not seem to extend for

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more than 6 h from the primary injury. The secondary or delayed phase of injury (apoptosis) that subsequently follows extends over several days.[15] This degree of secondary phase of energy failure and apoptosis is proportional to adverse neurodevelopmental outcomes at 1 and 4 years of age.[16,17] It is this time during transition from the recovery period into the secondary phase of injury that allows for a potential window for neuroprotection or diminution of injury.[18] This therapeutic window of opportunity exists during the period of time following resuscitation of infants injured by hypoxic–ischemic insults but before the secondary phase of injury.

Multiple possible mechanisms of injury exist. During the phase of primary cell death, the initial deprivation of gas exchange (oxygen delivery) and nutrients leads to a period of aerobic metabolism failure. Anaerobic glycolysis predominates and leads to excessive lactic acid production, depletion of high-energy phosphate compounds, such as ATP and phosphocreatine, and an inability to maintain cell membrane function.[19] This loss of cell membrane integrity and function manifests itself by a loss of electrolyte ionic gradients. Sodium, calcium and water shift intracellularly, leading to cell swelling and cell death (necrosis).[20] In parallel, potassium leaks out of the cell, inducing depolarization and subsequent release of the neurotoxic excitatory amino acid neurotransmitter, glutamate.[21] In addition, free fatty acids undergo peroxidation by free-oxygen radicals, and nitric oxide is produced, leading to neurotoxicity in susceptible neurons.[9,12] Mechanisms of injury during the secondary phase include iron accumulation, mitochondrial failure and injury from inflammatory mediators that initiate programmed cell death (apoptosis). The role of inflammation in hypoxic–ischemic brain injury is complex but it seems to exert both beneficial and deleterious effects after injury. Animal models suggest that certain inflammatory cytokines induce sensitization and potentiate injury after minor insults, whereas others have a direct toxic effect by inducible nitric oxide synthetase, free radical release and excitatory amino acid release.[11]

Until recently, management of a newborn with encephalopathy has consisted largely of supportive care to restore and maintain cerebral perfusion, provide adequate gas exchange and treat seizure activity. Recent randomized controlled trials have shown that mild therapeutic hypothermia initiated within 6 h of birth reduces death and disability in these infants.[22–24] The publication of these initial randomized trials showing efficacy of hypothermia in improving neurological and developmental outcomes in term infants with HIE has brought an enhanced interest in the etiology, recognition, management and outcome of these encephalopathic infants.

Therapeutic hypothermia

The single most promising intervention for infants with neonatal encephalopathy and hypoxic–ischemic injury is therapeutic hypothermia. The protective effect of hypothermia on infant asphyxia was initially noted by Westin *et al* in the mid 1950s and reinforced by reports of hypothermic near-drowning victims with surprisingly positive neurological outcomes.[25,26] Animal models of hypoxic–ischemic injury using fetal sheep, neonatal pigs and neonatal rats have shown benefits of hypothermia, including reduced neuronal loss, and improved survival and functional outcome.[27–32] Hypothermia is most effective if begun before the secondary phase of energy failure. These animal studies showed that the sooner cooling can be initiated after injury, the more likely it is to be successful. Although the various animal models vary with respect to the length of the therapeutic window, it is believed that the severity of the hypoxic–ischemic insult is inversely proportional to the length of this time window.[33] Although the animal data indicate that the 6-h window is not universal between species, expert opinion would indicate that cooling should be initiated as early as feasible (preferably within 2 h) and not later than 6 h.

The exact duration for which cooling should be provided is unknown. On the,basis of Gunn's work in fetal sheep, it is believed that hypothermia is beneficial until the end of the secondary phase of energy failure (48 to 72 h).[28,29,34–36] The use of 72 h provides a duration in which it is unlikely that the duration of cooling will limit the degree of neuroprotection. As a result, the trials of hypothermia in human newborns have continued cooling for 48–72 h after birth. No data exist in animal models to guide the rate of rewarming.

Two different methods of applying the concept of hypothermic therapy have been introduced: whole-body cooling and selective head cooling. The animal studies suggested that the ideal temperature for whole-body cooling was 32 to 34 °C, but that more modest reductions in temperature might be appropriate for selective head cooling (34 to 35 °C).[34] Although neither method has been demonstrated to be superior in animal or human models, each mode of cooling has unique properties. In a porcine model, selective head cooling resulted in larger observed temperature gradients, resulting in warmer deeper structures and a cooler brain periphery, whereas whole-body cooling was associated with more homogeneous cooling.[37] In addition, the degree of hypothermia affected the pattern of injury protection. Cooling to 33 °C preserved more neurons in the cortex and hippocampus and cooling to 35 °C preserved more neurons in the deep nuclear gray matter.[38]

Initial pilot studies in human newborns described reproducible approaches to both selective head and whole-body hypothermic therapy and confirmed the feasibility of such therapies.[39–44] Although these studies noted mild physiological changes in cardiovascular status and the potential for minor permutations in coagulation measurements, they showed that these changes were not clinically significant, that both methods of cooling were practical and that there were no major short-term consequences or complications to either method of cooling. On the basis of these

pilot studies, larger clinical trials in newborns (described below) have been performed.

Clinical trials of hypothermia in infants with moderate to severe HIE

Five large randomized controlled trials have been conducted, establishing the efficacy and safety of hypothermia for HIE. A total of 1117 infants have been enrolled in these studies. Two of these trials, the infant cooling evaluation (ICE) trial and the European network-induced hypothermia trial, were stopped early because of recruitment issues and/or loss of equipoise. The ICE trial enrolled infants using simplified entry criteria and intervention protocols that consist of application of 'Hot–Cold' gel packs.[45] The results from the ICE trial have been presented (PSANZ, Wellington 2010 and PAS, Vancouver 2010), but are not yet published, and also seem to show a significant improvement in primary outcome and survival without disability. The European Network trial also investigated systemic hypothermia using a cooling mattress and amplitude-integrated EEG (aEEG) entry criteria and is unique because its protocol prospectively required sedation of infants receiving cooling (http://www.neonatal-research.at/php/systemic_hypothermia_cooling_of_asphyxiated_babies,17614,4367.html). Follow-up results of the European Network trial of hypothermia have not been published. Because the evidence of efficacy is heavily weighted by the remaining three trials, we will discuss them in detail.

The Cool-Cap Trial used selective head cooling with mild systemic hypothermia for treatment of asphyxia and enrolled 234 infants.[23] Inclusion criteria included biochemical, clinical, neurological and aEEG data to select infants with moderate to severe asphyxia. The intervention consisted of a specially designed cap placed on the head of the affected infant through which cooled fluid circulated for 72 h, thereby lowering rectal temperature to 34°–35 °C versus normothermia in the control group. The primary outcome was death or severe disability at 18-month follow-up. Of the 218 (93%) infants available for follow-up, 66% of controls and 55% of cooled infants had an unfavorable primary outcome (odds ratio (OR) 0.61, 95% confidence interval (CI) 0.32, 1.09). Predetermined subgroup analysis based on degree of insult as measured by aEEG showed no evidence of benefit among infants with the most severe changes on aEEG, but a significantly improved primary outcome in less-affected cases (OR 0.42, 95% CI 0.22, 0.80). On further *post hoc* analysis, when baseline clinical severity was added to a logistic regression model, hypothermia was shown to provide a beneficial effect to the entire cohort (OR 0.52, 95% CI 0.28, 0.97).[46]

The second large randomized controlled trial was performed by the National Institute of Child Health and Human Development (NICHD) Neonatal Network (referred to as the NICHD trial). The NICHD trial enrolled 208 infants and tested the effects of systemic whole-body cooling in moderate to severe HIE.[24] Inclusion was based on perinatal history, neurological exam, clinical findings and biochemical evidence of asphyxia. No aEEG data were obtained before inclusion. Cooling blankets were used to maintain the esophageal temperature at 33 to 34 °C for 72 h versus normothermia in the control group. At 18-month follow-up, the primary outcome of death or moderate to severe disability was known for 205 (98%) infants. An unfavorable primary outcome was observed in 62% of controls and 44% of cooled infants (relative risk (RR) 0.72, 95% CI 0.54, 0.95). No significant differences in the rates of death or moderate to severe disability were noted in the moderately affected group or in the severely affected group when analyzed individually. In addition, the overall mortality rate in the control group was 37% and in the hypothermia group was 24% (RR 0.68, 95% CI 0.43, 1.01), which did not reach statistical significance.

The TOBY (total body cooling trial) trial enrolled 325 infants at 42 centers worldwide. The TOBY trial randomized infants with moderate to severe encephalopathy to either whole-body cooling or standard intensive care.[47] Of interest, this trial used similar entry criteria as the CoolCap trial: a stepwise process showing fetal distress, neonatal encephalopathy and also aEEG data. Infants randomized to the cooling intervention were removed from external heat sources to allow passive cooling and cooled using gel packs while on transport. Once the infants were admitted to a participating center, cooling blankets were used to keep the rectal temperature at 33 to 34 °C for 72 h versus normothermia in the control group. At 18-month follow-up, the primary outcome of death or moderate to severe disability was known for 323 (99%) infants. An unfavorable primary outcome was observed in 53% of controls and 45% of cooled infants (RR 0.86, 95% CI 0.68, 1.07). Among survivors, cooling resulted in reduced risks of cerebral palsy (RR 0.67, 95% CI 0.47, 0.96) and improved scores on the mental developmental index and psychomotor developmental index of the Bayley Scales of Infant Development II and the Gross Motor Function Classification System. No other significant improvements in neurological outcomes in the cooled group were noted.

Edwards *et al* have recently completed a meta-analysis of hypothermic therapy for HIE. This systematic review includes 10 randomized controlled trials, including the large (NICHD, Cool Cap and TOBY) trials noted above, with 767 enrolled infants for whom neurodevelopmental follow-up is available, comparing the use of therapeutic hypothermia with standard care in moderate to severely affected encephalopathic newborn infants with evidence of peripartum asphyxia.[48] In this review, there were three studies that used selective head cooling and seven studies that used whole-body cooling. The primary outcome measure is death or long-term major neurodevelopmental disability at 18 months of age. In this systematic review, meta-analysis included studies showing a significant reduction in the combined outcome of mortality or neurological disability at 18-month follow-up (typical RR 0.81, 95% CI 0.71, 0.93), as well as in single outcomes of mortality (typical RR 0.78,

95% CI 0.66, 0.93) and severe disability in survivors (typical RR 0.71, 95% CI 0.56, 0.91). This review suggests that cooling provides a statistically significant and clinically important reduction in the primary outcome. To prevent one infant death or survivor with major disability, typically one would need to treat only nine infants (typical risk difference (RD) −0.11, 95% CI −0.18, −0.04; number needed to treat (NNT) 9, 95% CI 5, 25). Incorporation of data from the ICE and European studies is important to refine our estimate of the effectiveness of cooling and to provide more information on the safety of therapeutic hypothermia.

Significant unanswered questions remain with regard to implementation of therapeutic hypothermia. Secondary analysis of data from the NICHD trial of whole-body cooling noted that among infants in the control (normothermia) group, 39% of infants had at least one documented febrile (esophageal temperature >38°C) episode.[49] In fact, 8% of all recorded temperatures in the control group were high. These elevated temperatures in the control arm are concerning, in part because of the regularity with which they present and also because of an increase in the odds that these infants would suffer an increase in the frequency of adverse outcomes. The odds of death or disability adjusted for level of encephalopathy, gender, gestational age and race among infants with recorded temperatures in the highest quartile was significantly elevated (OR 4.0, CI 95% 1.5, 11.2). Furthermore, the risk of death or disability increased fourfold for every 1°C increase in the average of the highest quartile of esophageal temperatures. It is unclear whether this association is causal or reflective of the inability of brain injured infants to self-regulate their temperatures.

Another area of concern with regard to the dissemination of hypothermia is the issue of transport. As cooling therapy is most effective when started early and as many affected infants are outborn (45% of enrolled infants in the NICHD whole-body cooling trial were transported), cooling while on transport will be necessary if this therapy is to be provided to infants born outside tertiary referral centers. Cooling in transport was performed using both passive and whole-body methods in several of the published reports of hypothermia. The TOBY trial included passive cooling (removal from external heat sources) for outborn infants in an attempt to reach target temperatures. This technique is gaining acceptance and has been reported while waiting on transport.[50] The ICE trial and the TOBY trial used cold gel packs and the pilot trial by Eicher *et al* used ice packs wrapped in wash cloths. The Eicher trial targeted a temperature of 33°C and reported acceptable variability: at 25 to 48 h the average difference between the high and low temperatures was 1.6 ± 0.6 °C.[43] However, another single center reported that 2 of 11 infants receiving whole-body cooling on transport had admission temperatures <30 °C.[51] Centers considering cooling on transport (active or passive) should monitor infant's temperature continuously while awaiting safety and efficacy results from ongoing trials.

Studies are underway to investigate the population that hypothermia may benefit. Given that it is difficult to identify and provide hypothermic therapy to outborn infants within 6 h of life, and given that the severity of the hypoxic–ischemic insult is inversely proportional to the length of the therapeutic window, whether initiation of cooling outside of 6 h of age is effective is an important question. The exact duration of the therapeutic window in humans is unknown and likely related to inflammatory influences, nutrition, brain maturation and genetic predisposition.[52] Reports from the TOBY registry and the Vermont Oxford Network (VON) Neonatal Encephalopathy Registry (NER) indicate that a sizable proportion of infants in a real-world setting receive cooling therapies after 6 h of age.[53,54] An NICHD study is currently enrolling infants who meet all inclusion criteria for cooling, but do not present until greater than 6 h of age with normothermia versus whole-body hypothermia (ClinicalTrials.gov, CT00614744). Likewise, safety and efficacy of hypothermia of infants born preterm is unknown. Accordingly, a trial on selective head cooling in preterm infants, born between 32 and 36 weeks of gestational age, is recruiting patients (ClinicalTrials.gov, CT00620711).

Management of a newborn with encephalopathy, apart from hypothermic therapy, consists largely of supportive care to restore and maintain cerebral perfusion, provide adequate gas exchange and treat seizure activity. Other neuroprotective interventions are being investigated. Multiple therapies that have shown promise in animal models include magnesium, inhibitory glutamate receptor antagonists, nitric oxide inhibitors, calcium channel blockers, platelet-activating factor antagonists, adenosinergic agents, growth factors, monosialoganglioside GM1, minocycline, xenon and erythropoietin.[11,18,55–59] Despite initial promise shown in animal models, none of these therapies have shown utility in human trials. Whether therapeutic hypothermia functions synergistically with other therapies or provides an opportunity for these or other therapies to work is unknown.

Reflecting the recent successful efficacy trials of hypothermia, a recent International Liaison Committee on Resuscitation (ILCOR) recommendation with regard to therapeutic hypothermia in neonates observed that as 'there is currently no other clinically proven treatment for infants with neonatal encephalopathy we propose that an interim advisory statement should be issued to support and guide the introduction of therapeutic hypothermia into routine clinical practice.' Recognizing the potential for use and misuse of hypothermic therapy, both the NICHD and the American Academy of Pediatrics have convened expert panels to address this issue. The NICHD has released an executive summary citing concerns regarding untested widespread use, and the American Academy of Pediatrics Committee on Fetus and Newborn has categorized the current state of the hypothermic therapy as investigational. Both groups cautioned that if therapeutic hypothermia is to be implemented outside of a trial, clinicians

should follow published trial protocols, ensure systematic follow-up of survivors and submit patient data to registries.[8,60]

Future randomized controlled trials of hypothermia versus normothermia will be difficult to perform as randomization to a normothermic control group could be construed as unethical.[61] Outside the confines of any trial, implementation of cooling is rapidly expanding into routine neonatal care. Registries are ideal for the study of actual standard medical practice and of 'real world' dissemination of a novel therapy, such as therapeutic hypothermia, outside of the narrow confines of a clinical trial. Currently, two registries therapeutic hypothermia exist. The VON NER was established in 2006 with the primary objective of characterizing infants born with NE. Secondary objectives include the identification of the antenatal and perinatal factors of these infants; description of the evaluations and medical treatments that these infants receive, and how treatment varies among centers; identification of the comorbidities and outcomes of these infants; and monitoring the introduction and dissemination of hypothermic therapy. The VON NER was conceived as a study of all late preterm and term infants with NE, including, but not limited to, infants treated with therapeutic hypothermia. Accordingly, the entry criteria of the VON NER are intentionally very broad in order to study the full spectrum of patients with NE. One other registry, the UK TOBY Cooling Register, captures data on neonatal hypothermia[53] and is the follow-up arm of the TOBY trial of therapeutic hypothermia that completed enrollment in November 2006.[22,47] The TOBY Register, similar to the VON NER, was designed after enrollment of the TOBY trial was completed and on recognition that many physicians were offering cooling out of the context of any trial. The TOBY investigators, therefore, created guidelines, informational material and Register forms to monitor the spread of cooling in the United Kingdom. Comparison of information in the VON and TOBY registries will be useful in understanding dissemination of this therapy when implemented strictly in accordance with a previous trial (TOBY) versus in a more broad clinical setting (VON).

Conclusion

Mild hypothermia has been proven to be effective in reducing death and major disability in infants with moderate to severe HIE. Although further follow-up will allow us to appreciate the impact of this therapy with greater precision, infants who present within the first hours after birth with signs and symptoms of moderate to severe encephalopathy should be cooled according to established protocols from previous randomized controlled trials. Successful dissemination of this new therapy will require improved identification of infants with HIE and the creation of systems that can institute therapy in a timely manner.

Conflict of interest

The authors declare no conflict of interest.

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