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Hypothermia for Hypoxic Ischemic Encephalopathy in Infants $\geq$ 36 weeks

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Abstract

Hypoxic ischemic encephalopathy is a serious condition affecting infants which can result in death and disability. This is a summary of pathogenesis of HIE, animal studies of cooling for hypoxic and ischemic models, human hypothermia trials, and the American Academy of Pediatrics publication on hypothermia for HIE. Hypothermia for neonatal HIE is continuing to evolve as a therapy. Studies, gaps in knowledge and opportunities for research are presented herein.

Background

Perinatal hypoxic ischemic encephalopathy (HIE) is a serious brain injury affecting 0.5–1/1000 live births in the United States on an annual basis. HIE can result in death or serious impairment in survivors. HIE has a variety of causes including acute perinatal events such as uterine rupture, placental abruption, and cord prolapse. Other causes of interrupted uterine and fetal blood flow and or hypoxia can also result in HIE.

Until publication of the COOLCAP (cooling of head with a cap) and NICHD whole body cooling trials, there were no therapies other than supportive measures for perinatal HIE which results in approximately 60% combined mortality and long term neurodevelopmental impairment in neonates. Hypothermia was used for “asphyxia neonatorum” initially in 1955.¹ In the past several years systematic animal and human studies have been carried out to address the safety and efficacy of cooling in HIE.^{2—16}

Two large trials have been completed showing beneficial effects of cooling in HIE.^{17—18} Other trials are in the final stages of completion and publication.^{19—20} NICHD held a workshop on the topic of HIE and cooling.²¹ The American Academy of Pediatrics has published on this topic to guide clinicians.²²

Pathogenesis of HIE

Evaluations of animal models including fetal sheep, newborn mice, rat pups, piglets, and nonhuman primates^{2—7, 9, 12, 13, 15, 16, 23—24} with timed hypoxic-ischemic injury have been

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performed and been reviewed.^{25, 26} It should be noted that hypoxia and ischemia can be well-controlled in laboratory studies; this is not necessarily the case in infants as the HIE may be acute, chronic or acute imposed on a chronic injury. Once the injury occurs, there is a reperfusion that occurs that can result in resolution of the initial hypoxia or ischemia, or result in further injury. The initial period is known as the latent phase and the secondary phase can involve further injury depending on the duration and severity of the initial event.

Lack of oxygen and nutrients results in anaerobic glycolysis, utilization of high-energy phosphate reserves, increased permeability of cell membranes, increases in lactic acid, calcium, free radicals and excitatory neurotransmitters such as glutamate, in the extra cellular environment; and deterioration of cell function. If the hypoxia and ischemia are severe, apoptosis can occur. There can also be ongoing neuronal injury and cell death which can occur over short and long time periods following the insult. Latent and secondary injury as a result of hypoxia and ischemia can vary across species. Individual differences based on the type, severity and pattern of injury exist.

Animal studies of hypothermia and neuroprotection

Animal studies have provided the basic structure for translation into clinical trials. Cooling performed within 90 minutes up to < 6 hours in fetal sheep showed benefit.^{5,6,9,16} Studies in other models also show that cooling is beneficial based on pathology, imaging and tests of learning after hypoxic and/or ischemic brain injury.^{2-4, 7, 12, 13, 15}

Clinical Trials

In 1955 Westin et al¹ showed that hypothermia was beneficial in perinatal asphyxia. Pilot studies^{8, 10, 11, 14, 27, 28} were undertaken largely for feasibility and preliminary safety evaluation. The pilot studies showed short term safety and feasibility for providing hypothermia and led to large, randomized controlled trials of cooling. Two large trials^{17,18} and a smaller trial^{27,28} were published in 2005, paving the way for translation of experimental hypothermia to become a potential therapy for infants with HIE.

The CoolCap trial, which was conducted in 25 international centers enrolled 234 infants with acute perinatal HIE.¹⁷ The inclusion criteria were: ≥ 36 weeks gestation; an Apgar score < 5 at 10 min after birth or a continued need for resuscitation at 10 min after birth; or a pH < 7.0 or base deficit > 16 mmol/L in the umbilical blood or venous blood sample within 60 min of birth; and a modified Sarnat score plus amplitude integrated EEG (aEEG) criteria consistent with a diagnosis of moderate to severe HIE.

The selective head cooling group ($n = 116$) underwent mild systemic hypothermia induced with a cooling cap device in which cold water was circulated at a temperature of 33.5°C . The rectal temperature was maintained between $34^{\circ} - 35^{\circ}\text{C}$ for 72 hours and the infants were re-warmed at a rate $< 0.5^{\circ}\text{C}$ per hour. The control group received usual neonatal intensive care ($n = 118$) under a radiant warmer servo-controlled to infant's abdominal skin temperature (maintained at $36.8-37.2^{\circ}\text{C}$).

The primary outcome was death or severe disability which occurred in 55% in the cooled infants and 66% in the controls (odds ratio 0.61; 95% CI 0.34–1.09, $p=0.1$). Outcome information was known on 93% of the study population. A logistical regression analysis controlling for baseline aEEG severity, presence of seizures and age at randomization indicated a possible treatment effect from hypothermia (odds ratio 0.57, 95% CI 0.32–1.01, $p=0.05$). In a pre-defined subgroup analysis of level of HIE (pre-randomization aEEG changes), the investigators found a significantly improved outcome (odds ratio 0.42; 95% CI, 0.22–0.80, $p=0.009$) in the less severe cases ($n=172$). No evidence of benefit was seen in infants with the severe findings in

the pre-randomization aEEG (n=46), Post-hoc analysis showed a significant protective effect from hypothermia was observed for the entire cohort (odds ratio 0.52, 95% CI 0.28–0.70, p=0.04) when baseline clinical severity was added to the regression model.²⁹

The NICHD Neonatal Research Network enrolled 208 infants ≥ 36 weeks gestational age from 16 Neonatal Research Network (NRN) centers, and tested the effect of whole body cooling in moderate to severe HIE.¹⁸ Eligibility criteria included a pH ≤ 7.0 or a base deficit of 16 mmol per liter or more in an umbilical cord blood sample or any blood gas within the first hour of life. If pH was between 7.01 and 7.15, a base deficit was between 10 and 15.9 mmol per liter, or a blood gas was not available, additional criteria were required for consideration of eligibility. These additional criteria consisted of an acute perinatal event and either a 10 minute Apgar score of ≤ 5 or assisted ventilation initiated at birth and continued for at least 10 minutes. Once these criteria were met, all infants had a modified Sarnat neurological examination performed by a trained examiner.¹⁸ Infants were eligible if moderate or severe encephalopathy was found on the examination or seizures were documented. Infants randomized to whole body hypothermia (n=102) were placed on cooling blankets such that the esophageal temperature was reduced to and maintained at 33.5 ± 0.5 °C for 72 hours (with no external heat source) followed by re-warming by on-site research personnel using the Cincinnati Sub-Zero System, while the control infants (n=106) were given standard intensive care.

At 18–22 months of age, the primary outcome status was known for 205/208 (98%) infants; death or moderate/severe disability occurred in 44% (45/102) of hypothermia group and 62% (64/103) of control group infants (risk ratio 0.72; 95 % CI, 0.54–0.95, p=0.01) indicating six infants need to be treated on average to result in one additional infant with a better outcome. Twenty-four infants (24 percent) in the hypothermia group and 38 (37 percent) in the control group died (risk ratio, 0.68; 95 percent confidence interval, 0.44 to 1.05; P=0.08). There was no increase in major disability among survivors; the rate of cerebral palsy was 15 of 77 (19 percent) in the hypothermia group compared with 19 of 64 (30 percent) in the control group (risk ratio, 0.68; 95 percent confidence interval, 0.38 to 1.22; P=0.20). Moderate disability was noted among 3 infants (2 hypothermia, 1 control group infant). The frequency of adverse event rates was similar in the hypothermia and control groups.

A multicenter, randomized controlled hypothermia pilot of 66 infants was published in 2005.²⁷ Infants were ≥ 35 weeks gestation, ≥ 2000 grams birth weight, ≤ 6 hours after birth or hypoxic ischemic insult with one of the following clinical signs and two neurological findings. The clinical signs were cord pH ≤ 7.0 or base deficit ≥ 13 , initial blood gas pH < 7.1 , Apgar score ≤ 5 at 10 minutes, continued resuscitation after 5 minutes, fetal bradycardia with heart rate < 80 beats/minute lasting at least 15 minutes, or post natal event with oxygen desaturation < 70 % or arterial oxygen tension < 35 mm Hg for 20 minutes with evidence of ischemia (including chest compressions, hypotension, hemorrhage). Two findings of neurologic evidence of hypoxia-ischemia included posturing, seizures, autonomic dysfunction, abnormalities of tone, reflexes or state of consciousness. Hypothermia was administered using plastic bags filled with ice and wrapped in a wash cloth applied to the head and the body for approximately 2 hours and subsequently a CSZ cooling blanket set at 33 ± 0.5 °C for 48 hours. Rewarming occurred at a rate of 0.5° C per hour.

The combined outcome of death or severe motor scores at 12 months of age was 52% in the hypothermia group compared with 84% in the normothermia group (p = 0.019). The authors concluded that this study provides important data for clinical trial design with respect to hypothermia for HIE.

The most recent meta analysis to date³⁰ combines evidence from 8 trials^{8, 14, 17, 18, 20, 27, 31, 32} (n = 638) and concludes that therapeutic hypothermia is beneficial to term newborns

with HIE. Cooling reduces death without increasing major disability in survivors. Further, benefits of cooling on survival and neurodevelopmental outcome outweigh the short-term adverse effects. It is acknowledged that data from ongoing and completed randomized trials (n = 829 additional study subjects) will be important to provide more information on the safety and efficacy of therapeutic hypothermia, but could also alter these conclusions.

Additional Clinical Trials

In the Total Body Cooling trial (TOBY) from England¹⁹ infants with moderate-to-severe HIE have been randomized to receive whole body cooling or standard intensive care. Recruitment and follow up have been completed and preliminary results are beneficial.³³ The trial design features and the entry criteria for the TOBY trial are similar to those of the CoolCap trial¹⁷ except for the method of cooling. Thus, upon completion, the findings from the TOBY trial can be effectively compared with those of CoolCap to assess the relative benefits from whole body versus selective head cooling in HIE. Such comparisons would be of great value, since these trials will constitute two of the largest cohorts of infants studied under an identical enrollment protocol.

The Infant Cooling Evaluation (ICE) trial aims to enroll infants from a wide geographic region, using simplified protocols.²⁰ Hypothermia is achieved by turning off the ambient heating systems and by applying “Hot-Cold” gel packs (at 10° C) around the infant’s head and over the chest, so that the rectal temperature is reduced to 33°–34° C. Recruitment is completed and follow up is in the final phase for this valuable cohort of infants.

Safety and Secondary Issues

Secondary outcomes have been published from the large trials. Eicher et. al²⁸ carefully collected adverse event information in their 66 patient hypothermia pilot study. The hypothermia treated group had more frequent bradycardia and lower heart rate measurements, longer use of vasopressors, higher prothrombin times, lower platelet levels, and higher rates of seizures. The authors state, however, not all statistically significant adverse events observed with moderate hypothermia are clinically significant. Continued monitoring of adverse events is required to facilitate understanding of effects of hypothermia.

Elevated temperature in standard NICU care infants in the NICHD trial showed adverse outcome.³⁴ Adverse outcomes were more likely in infants who had suffered HIE and subsequently had higher body temperatures. It remains unclear whether the brain injury resulted in higher temperatures or if higher temperatures contributed to adverse outcome. The CoolCap trial³⁵ also showed that pyrexia defined as body temperature > 38 ° C was associated with adverse outcomes.

The CoolCap study showed reassuring results that mild hypothermia did not affect arterial BP or initial treatment with inotropic agents or volume administration.³⁶ There was a slower withdrawal of these therapies in cooled infants in the CoolCap trial. The CoolCap study also showed that lower encephalopathy grade, lower birth weight, greater amplitude-integrated electroencephalographic (aEEG) amplitude, and absence of seizures were associated with better outcomes.

In the NICHD whole body hypothermia trial, safety outcomes including inotropic support, blood transfusion, platelet transfusion, volume expansion, use of nitric oxide, and use of extracorporeal membrane oxygenation (ECMO) were similar between both the cooled and control groups.³⁷ Non-central nervous system organ dysfunction was also similar between the two arms of the trial.

American Academy of Pediatrics Commentary

The Committee on Fetus and Newborn published a commentary²² in 2006 summarizing available evidence for mild to moderate hypothermia for perinatal HIE. At this point in time (2006), uncertainties including ongoing trials and longer term follow up (beyond 2 years of age) existed and are still present today. The AAP commentary concluded that if hypothermia is implemented outside of clinical trials, published protocols should be used, infants should have follow up and parents should be informed of the current status of hypothermia therapy.²²

Continued Gaps in Knowledge

In spite of rapidly accumulating clinical and laboratory data related to hypothermia as a neuroprotective strategy for HIE, gaps in knowledge remain in this field. Longer-term impact of hypothermia for HIE remains unknown. The COOLCAP and NICHD trial participants are being followed through school age.^{38,39} Results from these longer term follow up studies as well as results from the TOBY Trial and ICE Trial will provide more information for evidence-based guidelines for care of infants with HIE.

The roles of standard EEG or aEEG in selecting subjects for potential hypothermia treatment need to be further assessed and refined. Similarly, the value of continuous monitoring of EEG activity during treatment, and of EEG prior to discharge and at specific times during follow-up for prognostic evaluation need to be evaluated. Some data have been reported on use of aEEG but prognostic use is controversial.⁴⁰⁻⁴²

The role of standard imaging including magnetic resonance imaging (MRI) in selecting subjects for potential hypothermia treatment and predicting outcome in patients has been explored, but needs further assessment.^{40,43} The effect of cooling on perinatal brain injury and modification of brain injury evident on MRI is likely to add to the knowledge base.^{40,43}

Exact cooling strategies including depth, duration and re-warming approaches are also areas for which information and refinement are needed. Further, the optimal mode of cooling, i.e. head versus whole body, is not clearly defined.

Implications for clinical practice

The AAP commentary concluded that based on the available evidence and the known gaps in knowledge at the current time, therapeutic hypothermia, if offered, should be done using one of the published protocols.²² Appropriate follow up needs to be in place for infants undergoing hypothermia for HIE. Longer term follow up is unknown.²²

Summary and Conclusions

HIE can be a lethal or devastating disease. Until the advent of cooling for HIE, there was no therapy other than supportive NICU care. Cooling offers promise. Additional trial results may help to direct care of these critically ill infants. Longer term follow-up which is underway in two large trials, CoolCap study and NICHD whole body cooling study, may shed light on long-term effects of cooling therapy for HIE.

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