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Hypothermia: Novel Approaches for Premature Infants

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Abstract

Hypothermia for hypoxic ischemic encephalopathy has recently permeated clinical practice for term infants. Speculation regarding a neuroprotective benefit of hypothermia for premature infants with HIE has been raised as a need for further research. Hypothermia for other indications including necrotizing enterocolitis with the hope of tissue preservation following injury is less well studied. A summary of evidence for hypothermia and premature infants is presented in this brief report.

Keywords

Infant; premature; hypoxic-ischemic encephalopathy; hypothermia; necrotizing enterocolitis

Background

Hypothermia was initially used for “asphyxia neonatorum” in 1955.¹ Until reports of the COOL CAP Trial,² NICHD whole body cooling trial,³ TOBY Trial⁴ and ICE trial,⁵ there were no therapies other than supportive measures for perinatal hypoxic-ischemic encephalopathy (HIE). HIE results in approximately 60% combined mortality and long term neurodevelopmental impairment with cooling for encephalopathy bringing this rate down to 40-50%. The American Academy of Pediatrics⁶ and The National Institute for Health and Clinical Excellence⁷ has published on this topic to guide clinicians.

The most recent meta analysis to date (Edwards)⁸ combines evidence from 10 trials (n =1320) and concludes that moderate hypothermia is associated with a consistent reduction in death and neurological impairment at 18 months of age in 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.

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Hypothermia for HIE in premature infants

Hypothermia has been studied in the large clinical trials²⁻⁵ in infants ≥ 36 weeks. In addition, the ICE trial⁵ and Eicher et al^{9,10} enrolled infants beginning at 35 week gestation. In addition, in a very early report, one 34 week gestation infant underwent cooling and was reported to have normal outcome at 18 months (Azzopardi, 2000).¹¹ Other reports of hypothermia outside of clinical trials for individual infants at 34 weeks are in the literature, but no long term outcomes were reported (Zanelli, Kilani).^{12,13} The Vermont Oxford Network (VON) encephalopathy registry results were recently reported showing that 2.4% of infants undergoing mild hypothermia therapy are < 36 weeks gestational age.¹⁴ This included a total of 12 of 495 cooled infants in the VON registry. There has not been a specific subgroup analysis of premature infants and outcome performed to date. An individual patient meta analysis using combined trial data and/or observational data could potentially shed light on the safety and effect of hypothermia at < 6 hours of age for HIE in this gestational age (< 36 week) subgroup.

Thus, the question of a lower gestational age (< 36 weeks) for cooling for HIE has not yet been answered. There is one pilot feasibility study¹⁵ underway to test the feasibility of the Olympic Cool Cap in infants 32-35 weeks gestation with encephalopathy in the first 6 hours of life [NCT00620711]. Inclusion criteria consist of intubated infants up to 6 hours of age, with at least one of the following criteria for HIE: Apgar of 0-3 at 1, 5 or 10 minutes due to hypoxia, pH < 7.0 , base deficit > 15 or need for continuous resuscitation due to hypoxia at 10 minutes. Further, the infants are required to have a physical exam with evidence of hypotonia, lethargy or seizures, indicative of evolving HIE. Infants are excluded if they have mild HIE, unexpected to survive, evidence of head trauma, intraventricular hemorrhage, weight less than 5th percentile for gestational age or imperforate anus. Participants will be followed at 6, 12 and 24 months of age.

Safety versus efficacy would need to be balanced for preterm infants. All infants are at risk for cold stress following delivery, and thermoregulation is a high priority for preterm infants. Prevention of hypothermia in preterm infants has recently been reviewed (McCall, Cochrane).¹⁶ Gunn and Bennet¹⁷ recently published a review concluding that carefully designed safety studies and potentially large randomized trials in preterm infants should be considered.

Necrotizing Enterocolitis and Mild Hypothermia

Necrotizing enterocolitis is a serious, multifactorial acquired gastrointestinal disorder predominantly affecting preterm infants. High mortality and morbidity are associated with necrotizing enterocolitis (NEC). NEC is oftentimes associated with multiorgan dysfunction due to complications of sepsis, coagulopathy, and respiratory compromise due to intra-abdominal distension.

Intestinal ischemic injury has been shown to occur in the piglet animal model following mild hypothermic stress.¹⁸ However, multiple other reports have shown that mild hypothermia may be beneficial in other animal models.¹⁹⁻²⁴ Mild hypothermia has been reported in a rat model of NEC to exert benefit with decreased mucosal damage and is associated with attenuation of depletion of high-energy phosphates and less production of lactate.¹⁹ Mild hypothermia in a rat model of NEC has been shown to decrease myeloperoxidase.²⁰ Further rat NEC model study has shown that hypothermia lessens malondialdehyde, a marker of lipid peroxidation²¹. Additional research in the same model has shown that hypothermia decreases the elevation of serum soluble intercellular adhesion molecule-1 (sICAM), presuming that hypothermia blunts tissue injury.²² Moderate hypothermia in the rat NEC model during laparotomy does not appear to affect energy

metabolism.²³ Finally, an animal model of intestinal ischemic and reperfusion with mild hypothermia to 32 to 33.0°C decreases intestinal injury and other organ dysfunction.²⁴ Thus, the animal studies of intestinal injury (modeling NEC) suggest that hypothermia during the reperfusion phase(s) may decrease oxidative stress, prevention of neutrophil infiltration as measured by less myeloperoxidase, and preserve energy metabolism.

The safety and feasibility of mild hypothermia in premature infants with NEC and failure of at least 3 organs was evaluated in a pilot study of 15 infants, with 5 neonates per group cooled to core temperatures of 35.0, 34.5 and 33.5°C respectively for 48 hours prior to re-warming to 37.0°C. (Hall).²⁵ A non-cooled group of 10 infants with NEC and multi-organ dysfunction were used as a comparison group. Gestational age at birth ranged from 24 -39 weeks, birth weight ranged from 0.6-2.4 kg and age of 3 to 66 days at study entry. No major clinical problems or adverse effects were noted during cooling or re-warming. There was a relationship between target core temperature and low heart rate, though felt not to be clinically significant. There was also a significant relationship between core temperature and pH and base excess ($p < 0.001$ and $p = 0.0030$, respectively), felt to be clinically a small and non-significant effect. There was also a longer time to clot formation, slower rate of clot formation and decrease in clot strength as assessed by thromboelastography in the cooled group; the authors report that no infant suffered an episode of hemorrhage during the study.²⁵ There were a total of 2 deaths in the cooled groups and 3 in the control group which compares favorably to higher NEC mortality rates previously published (Blakely).²⁶ The investigators conclude that based on the 15 infants that underwent cooling, mild hypothermia for 48 hours in preterm infants with advanced NEC appears safe and feasible. Additional investigation is warranted to further test safety as well as efficacy of mild hypothermia for NEC.

Summary and Conclusions

Clinical and laboratory data related to hypothermia as a neuroprotective strategy for HIE are rapidly accumulating; however gaps in knowledge remain in this field. Use of mild hypothermia in premature infants ≤ 36 week gestation infants with HIE has not been rigorously evaluated and deserves further investigation. A further opportunity for research appears in the NEC field in infants with multiple organ failure. Safety should be monitored closely in any upcoming trials. Hypothermia may hold promise in the future for additional clinical applications.

References

1. Westin B, Einhorn G. An experimental study of the human fetus with special reference to asphyxia neonatorum. *Acta Paediatr.* 1955; 44(Suppl 103):79–81. [PubMed: 13292215]
2. Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, Ferriero DM, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicenter randomized trial. *Lancet.* 2005; 365:663–70. [PubMed: 15721471]
3. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, Fanaroff AA, Poole WK, Wright LL, Higgins RD, Finer NN, Carlo WA, Duara S, Oh W, Cotten CM, Stevenson DK, Stoll BJ, Lemons JA, Guillet R, Jobe AH, National Institute of Child Health and Human Development Neonatal Research Network. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med.* Oct 13; 2005 353(15):1574–84. [PubMed: 16221780]
4. Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, et al. TOBY Study Group. Moderate hypothermia to treat perinatal asphyxial encephalopathy. *N Engl J Med.* 2009; 361:1349–58. [PubMed: 19797281]
5. Jacobs SE, Morley Colin J, Inder Terrie E, Stewart Michael, Smith Katherine R, McNamara Patrick J, Wright Ian M.R, Kirpalani Haresh M, Darlow Brian A, Doyle Lex W. the ICE Collaboration. The

- ICE Randomised Trial of Whole Body Hypothermia for Term and Near-Term Newborns with Hypoxic-Ischemic Encephalopathy (HIE). PAS. 2011 Publication 1172.1.
6. Blackmon LR, Stark AR. American Academy of Pediatrics Committee on Fetus and Newborn. Hypothermia Pediatrics. Mar; 2006 117(3):942–8.
 7. National Institute for Health and Clinical Excellence. Therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury. May. 2010 interventional procedure guidance 347 <http://www.nice.org.uk/nicemedia/live/11315/48809/48809.pdf>
 8. Edwards AD, Brocklehurst P, Gunn AJ, Halliday H, Juszczak E, Levene M, Strohm B, Thoresen M, Whitelaw A, Azzopardi D. Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data. BMJ. Feb 9.2010 340:c363. doi: 10.1136/bmj.c363. [PubMed: 20144981]
 9. Eicher DJ, Wagner CL, Katikaneni LP, Hulsey TC, Bass WT, Kaufman DA, et al. Moderate hypothermia in neonatal encephalopathy: Efficacy outcomes. Pediatric Neurology. 2005; 32:11–17. [PubMed: 15607598]
 10. Eicher DJ, Wagner CL, Katikaneni LP, Hulsey TC, Bass WT, Kaufman DA, et al. Moderate hypothermia in neonatal encephalopathy: Safety outcomes. Pediatric Neurology. 2005; 32:18–24. [PubMed: 15607599]
 11. Azzopardi A, Robertson NJ, Cowan FM, Rutherford MA, Rampling M, Edwards AD. Pilot study of treatment with whole body hypothermia for neonatal encephalopathy. Pediatrics. 2000; 106:684–94. [PubMed: 11015509]
 12. Zanelli SA, Naylor M, Dobbins N, Quigg M, Goodkin HP. Implementation of a “Hypothermia for HIE” program: 2 year experience in a single NICU. J Perinatol. 2008; 28:171–5. et. al. [PubMed: 18059465]
 13. Kilani RA. The safety and practicality of selective head cooling in asphyxiated human newborn infants, a retrospective study. J Med Liban. 2002; 50:17–22. [PubMed: 12841308]
 14. Pfister, Robert H.; Bingham, Peter; Carpenter, Joseph H.; Horbar, Jeffrey D.; Kenny, Michael J.; Inder, Terrie E.; Nelson, Karin; Raju, Tonse N.K.; Soll, Roger F. Hypothermia in Practice, Initial Observations from the Vermont Oxford Network. PAS Abstracts. 2011:2632.5.
 15. Walsh, W. Pilot Study of Head Cooling in Preterm Infants With Hypoxic Ischemic Encephalopathy. <http://www.clinicaltrials.gov/ct2/show/NCT00620711?term=infants+and+hypothermia+and+premature%27&rank=4>
 16. McCall EM, Alderdice F, Halliday HL, Jenkins JG, Vohra S. Interventions to prevent hypothermia at birth in preterm and/or low birthweight infants. Cochrane Database Syst Rev. Mar 17.2010 (3) CD004210.
 17. Gunn AJ, Bennet L. Brain cooling for preterm infants. Clinics in Perinatology. 2008; 35:735–748. [PubMed: 19026337] Schneider PA, Hamilton SR, Dudgeon DL. Intestinal ischemic injury following mild hypothermic stress in the neonatal piglet. Pediatr Res. 1987; 21:422–5. [PubMed: 3574994]
 18. Schneider PA, Hamilton SR, Dudgeon DL. Intestinal ischemic injury following mild hypothermic stress in the neonatal piglet. Pediatr Res. Apr; 1987 21(4):422–5. [PubMed: 3574994]
 19. Vejchapipat P, Proctor E, Ramsay A, Petros A, Gadian DG, Spitz L, Pierro A. Intestinal energy metabolism after ischemia-reperfusion: effects of moderate hypothermia and perfluorocarbons. J Pediatr Surg. 2002; 37:786–90. [PubMed: 11987102]
 20. Vinardi S, Pierro A, Parkinson EJ, Vejchapipat P, Stafanutti G, Spitz L, Eaton S. JPediatr Surg. 2003; 38:88–91. [PubMed: 12592626]
 21. Stefanutti G, Peirro A, Vinardi S, Spitz L, Eaton S. Moderate hypothermia protects against systemic oxidative stress in a rat model of intestinal ischemia and reperfusion injury. Shock. 2005; 24:159–64. [PubMed: 16044087]
 22. Vejchapipat P, Leawhiran N, Poomsawat S, Theamboonlers A, Chittmittrapap S, Poovorawan Y. Amelioration of intestinal reperfusion injury by moderate hypothermia is associated with serum sICAM-1 levels. J Surg Res. 2006; 130:152–7. [PubMed: 16154143]

23. Vejchapipat P, Poomsawat S, Poovorawan Y, Proctor E, Pierro A. The effects of moderate hypothermia on energy metabolism and serum inflammatory markers during laparotomy. *Pediatric Surg Int*. 2006; 22:66–71.
24. Stefanutti, g; Peirro, A.; Parkinson, EJ.; Smith, VV.; Eaton, S. Moderate hypothermia as a rescue therapy against intestinal ischemia and reperfusion injury in the rat. *Crit Care Med*. 2008; 36:1676–7. [PubMed: 18448939]
25. Hall NJ, Eaton S, Peters MJ, et al. Mild controlled hypothermia in preterm neonates with advanced necrotizing enterocolitis. *Pediatrics*. 2010; 125:e300–8. [PubMed: 20100756]
26. Blakely ML, Lally KP, McDonald S, Brown RL, Barnhart DC, Ricketts RR, Thompson WR, Scherer LR, Klein MD, Letton RW, Chwals WJ, Touloukian RJ, Kurkchubasche AG, Skinner MA, Moss RL, Hilfiker ML. NEC Subcommittee of the NICHD Neonatal Research Network. ostoperative outcomes of extremely low birth-weight infants with necrotizing enterocolitis or isolated intestinal perforation: a prospective cohort study by the NICHD Neonatal Research Network. *Ann Surg*. 2005; 241:984–989. [PubMed: 15912048]