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Neonatal Hypothermia: What are we waiting for?

Summary

With the publication of three randomized controlled trials demonstrating modest beneficial effects of hypothermia for treatment of hypoxic-ischemic encephalopathy in the term or near-term neonate in 2005 [1-4], neonatal clinicians must confront several questions: Does hypothermia "work"? Should our NICU use hypothermia, or refer potentially eligible infants to a center that offers hypothermia? How should they be cooled? Is cooling safe? Who should be cooled, or not cooled? In this commentary I will address each of those questions in a way that may help practitioners to make an informed judgment.

Does hypothermia "work"?

The short answer to this is "yes, but it's no silver bullet". There was a substantial burden of death and disability in the cooled groups of all three trials. The long answer is complex, and should be addressed by carefully considering and comparing the major publications.

First, the results of the CoolCap trial, presented in *The Lancet* [3] have contributed to questions about the efficacy of neonatal hypothermia in general, and of selective head cooling in specific. It was an *a priori* hypothesis of the CoolCap trial that infants with more severe injury at enrollment, as reflected in the amplitude-integrated EEG (aEEG) score, would be less likely to respond to cooling. In that paper, a pre-specified stratification of patients according to severity of aEEG abnormality at the time of enrollment led to the conclusion that head cooling was effective in decreasing death or severe disability (with an NNT of 6, 95% CI 3-27) in the large *a priori* subgroup of infants that had an "intermediate" abnormal aEEG that did not meet the criteria for the most severe abnormality, but cooling was ineffective in the smaller subgroup of infants with severely abnormal aEEG (severe suppression plus seizures) [3]. The erroneous assertion that this *a priori* subgroup stratification constitutes a post-hoc analysis persists in editorial and public comments by individuals not involved in the design or the FDA regulation of the CoolCap trial. Also frequently voiced is the incorrect notion that the *a priori* "intermediate" group lacked statistical power. By Fisher's exact test, with no adjustment for differences in baseline characteristics, a treatment effect was demonstrated in the "intermediate" group. Thus, by definition, there was sufficient statistical power to detect an effect. Additional CoolCap efficacy data, presented at the FDA Neurologic Devices Panel review of the Olympic Cool Cap device in June 2005 has not been widely disseminated, although it is in the public record (<http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4162t1.htm>). To

evaluate the primary outcome of death or severe disability at 18 months, and to take into account differences in baseline characteristics, at the time of trial approval the FDA had requested that the investigators perform a 6-factor logistic regression, which adjusted for chance baseline differences in aEEG background, aEEG seizure status, age at randomization, 5-minute Apgar score, birth weight and gender. The logistic regression analysis presented in the *Lancet* adjusted for only three factors, aEEG background, aEEG seizure status, and age at randomization, with a marginal treatment effect ($p=0.05$, odds ratio = 0.57, 95% CI 0.32-1.01, NNT=8.5). In contrast, according to the pre-specified six-factor logistic regression originally requested by the FDA, there was a significant treatment effect in the entire study population ($p=0.042$, odds ratio = 0.53).

The NICHD Neonatal Research Network body cooling trial, published in the *New England Journal of Medicine*, reported that cooling was effective in decreasing death or moderate or severe disability, with an NNT of 6, even after adjusting for study center and severity of encephalopathy at randomization [4]. To compare the results of this and the CoolCap trial, it is important to review differences in their designs. First, there were important differences in primary outcomes. The broader definition of “bad outcome” used in the Network trial (death or *moderate or severe* disability) than that used in the CoolCap trial (death or *severe* disability) made it easier statistically for the Network trial to detect a between-group difference. Second, there were important differences in temperature management of control infants. Experimentally, higher core temperature potentiates hypoxic-ischemic brain injury [5]. In the CoolCap trial control infant rectal temperatures were actively managed to a narrow goal of 37.0 ± 0.2 °C. In contrast in the Network trial, thermoregulation in the controls was targeted to an abdominal skin temperature of 36.5-37.0 °C initially, and “subsequent adjustments were made according to usual care at each center.” As a result, 39% of controls had at least one core temperature >38 °C. The Network investigators recently presented a *post-hoc* analysis of core and skin temperature data in their control group, indicating that the range of median core temperatures in their controls was 36.3-38.9 °C. Furthermore, an increase in only 1 °C in peak core temperature was associated with a 3.6-4-fold increase in death or disability [6]. Thus, many of the controls in the body cooling trial had higher core temperatures than the controls in the CoolCap trial. This meant that there was less of a core temperature differential between treatment groups in the CoolCap trial than in the Network trial, again making it easier to detect a between-group difference in the Network trial than in the CoolCap trial. Finally, there were differences in patient populations. Both trials recruited infants with moderate-to-severe encephalopathy, but the CoolCap trial added aEEG criteria after clinical examination. The result of this step was that the CoolCap trial excluded many infants with moderate encephalopathy that would have been enrolled in the Network trial. At our center, the aEEG step excluded one infant for every infant enrolled, and over the entire trial 98 infants were excluded at the aEEG step. As a result of this difference in selection strategies, the outcome in the control group of the CoolCap trial was worse (66% death or *severe* disability) than the outcome of the control group of Network trial (62% death or *moderate or severe* disability, but only 56% death or *severe* disability). Both the differences in inclusion criteria and in control group outcomes indicate that the CoolCap population had a greater mean baseline severity of injury, i.e. severely injured infants who were *a priori* less likely to respond to

hypothermia were over-represented in the CoolCap trial, *vs.* the Network trial. Note that the NNT in the large “intermediate” *a priori* subgroup in the CoolCap trial was the same as the NNT in the NICHD Neonatal Research Network (NRN) trial (i.e. 6).

Also contributing to questions about the efficacy of neonatal cooling may be the fact that the body cooling trial of Eicher *et al.* [1] was published in a journal that is less widely read than the *Lancet* and the *New England Journal*. Although described as a pilot trial, it enrolled 65 patients, and had sufficient power to detect a treatment effect on the primary outcome of death or severe disability at one year. Although there were differences in trial design compared to the Network trial (e.g. cooling initiated during transport with ice packs, lower target rectal temperature range of 33.0 ± 0.5 °C, only 48 hours cooling, 35 week gestation threshold), this smaller randomized trial nonetheless adds to the body of evidence in support of the efficacy of hypothermic rescue therapy.

With three trials that demonstrate a reduction in the combined outcome of death or disability, what are we waiting for?

We can no longer claim lack of a meta-analysis; one published in March 2006 based on the results of the three trials discussed above demonstrated a significant effect of cooling on the combined outcome of death or disability [7]. Some ask, are three positive trials sufficient? For those investigators participating in the ongoing randomized trials, the answer must be “no”. Many clinicians are concerned that cooling will only save severely handicapped children who would otherwise have died. The existing evidence does not support this. None of the three published trials shows increased disability in the survivors, and in the CoolCap trial there was a trend towards less disability in cooled infants of the “intermediate” group. Furthermore, none of the trials demonstrated a reduction in mortality alone. It is to be hoped that future meta-analyses of cooling trials will include evaluation of the effect on mortality and disability taken separately. Statistical purists will argue that it is not proper to separate disability from death in trials that were designed with a combined outcome. If we accept that, then some will never feel they have the answer to the question “Does cooling work?” until a trial is designed with the power to detect an effect on disability alone. In the meantime, one could wait for results from the TOBY, ICE, and neo.nEuro.network trials, to provide more information on disability, but all three trials also have combined primary outcomes, of death or disability (at 18 or 24 months).

Some critics claim that all the published cooling trials are biased because the NICU caregivers were not blinded. Even if non-cooled blankets or caps were used on controls, short of prohibiting physicians and nurses from touching study patients for 48-72 hours it is simply impossible to mask NICU caregivers to treatment in these trials. Thus, readers have a choice: they can believe that site investigators made their best efforts to blind the neurodevelopmental evaluators, or not.

Should our NICU use hypothermia, or refer potentially eligible infants to a center that offers hypothermia?

Centers that have not participated in one of the major trials first need to decide whether the accumulated data in support of cooling are convincing. It is noteworthy that the published NNTs are as good as or better than those for many interventions that are accepted practice in most perinatal centers.

Leading voices in the field have become quite circumspect in their public pronouncements, cautioning against uncontrolled use of cooling outside one of the established protocols [8]. Unfortunately, the degree of circumspection is such that some practitioners have taken away the message that hypothermia is ineffective. There are good reasons for caution; uncontrolled hypothermia in the neonate has serious life-threatening consequences. Anecdotes of "seat of the pants" hypothermia gone awry have circulated by word of mouth in recent years. Yet, for modest hypothermia, as practiced within the two larger published protocols, no safety concerns have yet arisen (see below).

Against this background of public expressions of reservation it is informative to compare those words *vs.* the actions of investigators that participated in the recently published trials. Many of us, including this author and the lead author of the Network trial, who caution against uncontrolled adoption of cooling, have lost equipoise, and we are now cooling babies who meet the eligibility criteria of our original trials, with or without informed consent, and without randomization. Several centers (including the author's center) that participated in the CoolCap trial have offered brain cooling for over two years, under an FDA-authorized continued access protocol, in which over 150 babies have been enrolled. More recently, many centers that participated in the Network body cooling trial have begun cooling eligible babies. Such loss of equipoise is not universal. Many experienced investigators have chosen to continue entering patients in randomized trials; note, however, that they all practice outside the United States.

If your center is convinced that the evidence supports cooling, you then have to decide whether you want to cool babies, or to transfer them to a cooling center. If you decide to cool them in your own unit, then how should you cool them?

How should we cool? Head or Body Cooling?

After considering the differences in design of the two larger trials, there is no convincing evidence that one method of cooling is more effective or less risky than the other. For NICUs that did not participate in the original trials, the practical problem is not in deciding whether to head cool or to body cool. The real problem is the lack of a commercial device or a detailed published protocol for either. As of this writing, the "Cool Cap" device is not yet on the market. Preliminary indications are that the marketed version of the Olympic Cool Care System will be designed to facilitate safe use by the infrequent user, utilizing touch screen technology and on-screen prompts; it remains to be seen whether or what sort of training program the FDA will require. "Body Cooling", as practiced in the Network trial, utilizes FDA-approved equipment, the Cincinnati Subzero Blanketrol II ®, (already available in many hospitals) but for an indication and in a manner for which it was not originally approved. While the Network cooling protocol is published in the "Methods" of two papers, in the absence of training courses or publicly available detailed protocols, many may be hesitant to embark on body cooling. How many of us would recommend attempting insertion of an umbilical arterial catheter after only reading about it in a brief paragraph? If a center decides to adopt body cooling, this should be done by carefully developing a protocol based on the published papers, public presentations, and discussion with experienced trial centers.

If your NICU has decided to transfer encephalopathic neonates to another center for possible cooling, then advanced planning and close communication with that cooling center is essential to ensure timely transfer; if feasible, time will be saved if the referring hospital takes responsibility for the transport. Referring hospitals should consider protocols to avoid conditions that might have a negative impact, such as hyperthermia, hypoglycemia, hypocarbia, hypoxia, and hypotension.

Is cooling safe?

The answer from the two larger trials is "yes," within the published protocols, but these are still critically ill infants. Many suffer from post-hypoxic-ischemic multi-organ system failure, with life-threatening complications that require the full resources of a level III NICU. To say that cooling is "safe" is just to say that cooled infants were no sicker than control infants. Sinus bradycardia is a uniform physiologic response to either method of cooling; it is reversible after the end of cooling, and not associated with altered blood pressure. Some reversible skin changes occurred with both methods of cooling: sclerema in a few cases in the body cooling trial, and scalp swelling beneath the cap in the CoolCap trial.

Who should be cooled?

All trials to date incorporated infants with moderate to severe hypoxic-ischemic encephalopathy. Such infants should continue to be considered for cooling. We must also consider a second question: “*Who should not be cooled?*” There are two separate parts to this question: (i) Are there babies that are too severely affected to be cooled? and (ii) Should we use aEEG to exclude babies that are “too good to cool”?

For the first question, available evidence suggests that hypothermia will probably stand the best chance of benefiting infants that are not the most severely affected at the outset. Undoubtedly there are infants, even within 5.5 or 6 hours of birth, whose injury has evolved to the point of irreversibility, who will not benefit from any form of cooling. However, it is not clear that we have rapid, reliable methods, usable by the majority of neonatologists, to distinguish these infants in the short time during which we must decide to cool or not to cool. Until we have such tools, we may have to err on the side of treating, and trust that we and our pediatric neurology colleagues will still be capable, after re-warming, of recognizing a baby for whom continuing intensive care is futile.

No direct evidence is available to address the second question. aEEG screening was used in the CoolCap trial, ostensibly to exclude babies who were at sufficiently low risk of adverse outcome that they should not be exposed to the risk of a novel therapy (i.e., to enhance specificity of selection). Unfortunately, the specificity of aEEG for that purpose, in the hands of relatively novice users, is uncertain. Indirectly, retrospective comparison of the patient populations and results of the Network and CoolCap trials raises the possibility that some moderately affected infants who may benefit from cooling might be excluded by use of an aEEG step. However, the digital aEEG devices in use today are more sophisticated than the analog Lectromed CFM used in the CoolCap trial. The new monitors permit detection of aEEG artifacts (e.g., ECG artifact) that might have led to the exclusion of patients with suppressed EEG activity from the original CoolCap trial. Now that we have evidence that cooling is safe and effective, the future role of the bedside EEG monitor might be to enhance sensitivity of detection of infants that could benefit from cooling, but this hypothesis has yet to be tested. Use of the CFM to increase specificity (i.e., to exclude patients from treatment) may no longer be necessary outside the context of a randomized trial.

What does the future hold?

All the data are not in. The three published trials only present 12-24 month neurodevelopmental outcome; school-age follow-up, to confirm the “durability” of cooling's benefits, is only in the planning phase. Patients are still being recruited to at least three large randomized trials of hypothermia, which will aid in our estimation of the degree of benefit of cooling, and which will address some important practical questions. Should we cool babies during transport to a definitive regional “cooling center”? Although the results of Eicher's “pilot trial” are encouraging, this question is not answered by the CoolCap or Network trials, but will be further addressed by both the Infant Cooling Evaluation (ICE) trial underway in Australia, New Zealand and Canada,

and by the TOBY trial in Europe. This investigator is sometimes asked, "Should we start using aEEG as an adjunct to selection for body cooling?" We may find the answer from the TOBY trial, which uses a newer generation of digital aEEG in a selection process otherwise identical to the CoolCap trial, to recruit patients for body cooling. Another question, posed by the members of the FDA expert panel in June 2005, was "is it really necessary to screen all head cooling candidates with aEEG?" No published trial has prospectively asked that question. Yet, comparison of the results of the CoolCap and Network trials might lead one to consider cooling all infants with moderate encephalopathy. Not to be forgotten is cost, which is not addressed in any of the published trials, but which will be an issue for centers wishing to purchase the Cool Care System for head cooling, or the Blanketrol for body cooling. No cost-effectiveness analysis of either technique has been presented. It is reasonable to ask why we need expensive devices to cool babies, when we know they are notoriously susceptible to hypothermia; can we not just use a pragmatic low-tech solution like turning down the incubator or warmer, or use fans or ice packs? The ICE trial uses such a pragmatic approach, but only a preliminary report of imaging findings in a small number of patients from that trial is available [9].

Conclusion

Hypothermic "rescue" of neonates with HIE is a therapy in evolution. In a small number of experienced centers, it is a novel therapy that has become "standard care" (without randomization), but it is not yet the "standard of care". Clearly, reasonable people differ in their evaluation of the evidence. Randomized trials will continue until that is no longer the case, and at least one trial (ICE) is open to additional centers. Even if the majority of neonatologists were convinced of the efficacy of hypothermia, there remains the practical barrier of access to a device or a public protocol. Hypothermic "rescue" will not be able to complete the transition to "standard of care" until the current barriers to access are resolved.

References

1. Eicher, D.J., et al., *Moderate hypothermia in neonatal encephalopathy: efficacy outcomes*. *Pediatr Neurol*, 2005. **32**(1): p. 11-7.
2. Eicher, D.J., et al., *Moderate hypothermia in neonatal encephalopathy: safety outcomes*. *Pediatr Neurol*, 2005. **32**(1): p. 18-24.
3. Gluckman, P.D., et al., *Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial*. *Lancet*, 2005. **365**(9460): p. 663-70.
4. Shankaran, S., et al., *Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy*. *N Engl J Med*, 2005. **353**(15): p. 1574-84.
5. Fukuda, H., et al., *Postischemic hyperthermia induced caspase-3 activation in the newborn rat brain after hypoxia-ischemia and exacerbated the brain damage*. *Biol Neonate*, 2003. **84**(2): p. 164-71.

6. Laptook, A.R., *Adverse outcome increases with elevated temperature for infants provided usual care following hypoxic-ischemic encephalopathy (HIE)*. *Pediatr Res*, 2006. **59**: p. 5755.2.
7. Edwards, A.D. and D.V. Azzopardi, *Therapeutic hypothermia following perinatal asphyxia*. *Arch Dis Child Fetal Neonatal Ed*, 2006. **91**(2): p. F127-31.
8. Higgins, R.D., et al., *Hypothermia and perinatal asphyxia: executive summary of the National Institute of Child Health and Human Development workshop*. *J Pediatr*, 2006. **148**(2): p. 170-175.
9. Inder, T.E., et al., *Randomized trial of systemic hypothermia selectively protects the cortex on MRI in term hypoxic-ischemic encephalopathy*. *J Pediatr*, 2004. **145**(6): p. 835-7.