

Cool heads: ethical issues associated with therapeutic hypothermia for newborns

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ABSTRACT Hypothermia is the first treatment for newborns with hypoxic-ischaemic encephalopathy with consistent evidence of a reduction in the risk of death or severe disability. This paper addresses a number of ethical and practical issues faced by clinicians as cooling moves from an experimental treatment into practice. These issues are not unique to therapeutic hypothermia. They include the extrapolation of evidence from trials to clinical care, as well as the impact of hypothermia on prognosis and withdrawal of life-sustaining treatment. Conclusion: Hypothermia is a promising new therapy, but further research will be necessary to help resolve some of the ethical concerns associated with its use in newborns with hypoxic-ischaemic encephalopathy.

Hypoxic-ischaemic-encephalopathy (HIE) is a major cause of neonatal death and of long-term disability.(1, 2, 3) Until recently the only treatment available has been supportive care. There has been considerable interest in potential neuroprotective strategies, the most promising of which is therapeutic hypothermia. This has been studied in a number of pilot studies, and in two large multi-centre randomised controlled trials (the CoolCap,(4) and National Institute of Child Health and Human Development (NICHD)(5)

trials). Three separate meta-analyses of hypothermia in HIE have recently concluded that therapeutic hypothermia is safe and that it significantly reduces death or significant disability compared with control infants.(3, 6, 7)

This paper outlines a number of ethical and practical issues associated with the introduction of hypothermia into the management of infants with HIE. There has been heated debate about the evidence for hypothermia, and whether or not it justifies its incorporation as a standard of care for HIE.(8-12) This sort of question is frequently seen with innovative therapies as they move from research into clinical practice.(13, 14) In addition hypothermia raises issues related to patient selection, prognostic certainty and treatment withdrawal. Finally there are questions about how further research into hypothermia should be conducted.

SHOULD COOLING BE THE STANDARD OF CARE?

One reason that proponents of hypothermia have argued for its widespread adoption is the magnitude of the potential clinical benefit. In the United States alone, its introduction has been estimated to potentially prevent death or severe disability in 1200 newborns per year. (3, 9) Poor

prognosis, and the absence of other effective treatments are strong incentives to the dissemination of promising therapies.(13) Others have advised caution in the adoption of hypothermia on the basis of a number of methodological limitations or concerns about the published trials.(10)

A certain wariness about procedural change, and a cautious approach to the adoption of new therapies is understandable in the context of the history of neonatology, and past mistakes that were attributable to over-enthusiasm.(15, 16) However the evidence for benefit of hypothermia is consistent and compelling; across the 4 published studies (506 infants), the relative risk of death or major disability was 0.76 (95% confidence interval (CI): 0.65-0.89).(6) Delayed adoption of effective therapies can also come at significant cost,(9, 17) and continuing to provide only standard supportive therapy is not risk-free. One possibility is that preference for it may be an example of the status quo bias, a cognitive bias in decision making that prefers the current state even when objective evidence would motivate a change.(18, 19)

This debate may be resolved by the publication of results from other trials. Follow-up data from at least a further 829 infants is anticipated to be available in the next 1-2 years.(6) In the meantime clinicians will need to address the important ethical question of how to weigh up the importance of scientific certainty against the chance of preventing disability and death in infants with HIE.(12)

One important, but neglected issue in the standard of care debate is the autonomy of parents,(20) and their involvement in decisions about cooling. In the opinion of this author, given the current evidence about hypothermia, failing to

at least discuss with parents the option of cooling (including transfer if necessary) would be unethical.

WHICH INFANTS SHOULD BE COOLED?

The published trials studied a subset of term infants who had neonatal encephalopathy, clear-cut evidence of perinatal hypoxia/ischaemia, and in whom cooling could be initiated within 6 hours of birth. It has been suggested that similar criteria be used for therapeutic hypothermia outside trials.(3, 21-23) This reflects a sensible approach to the application of the evidence to clinical care. However in practice there is likely to be some temptation to extrapolate the results of the published trials to infants who would not necessarily have met their strict entry criteria. For example infants who suffer a post-natal hypoxic event,(24) near-term infants with HIE, or infants (particularly those who have been transferred from another hospital) who have not had a chance to be cooled within the first 6 hours of life.(21)

The problem is not only that the published data do not answer the question of whether or not cooling would benefit such infants. It is also that better evidence to guide treatment may not be available in the foreseeable future because the number of infants in that group may be relatively small, while very large numbers are likely to be needed to show benefit. So difficult decisions may need to be made about how much to generalise from published trials,(16, 25) and whether or not to offer hypothermia outside the established guidelines. Given that mild systemic hypothermia appears to be associated with few adverse effects it may be justified to apply it more liberally than

was the case in published studies.(21) If long-term follow-up confirms the safety of hypothermia for newborn infants clinicians may be more comfortable using hypothermia outside the groups studied to date.

Even within the guidelines, decisions may need to be made. Not all term infants who meet strict criteria for HIE will necessarily benefit from cooling. Where the injury to the brain is too severe, or too well established, the outcome for an infant is still likely to be extremely poor.(21) The difficulty is in identifying these infants. Amplitude integrated electroencephalogram monitoring may be useful. In a prespecified subgroup analysis in the CoolCap trial, infants with severely reduced background activity or seizures on early aEEG had no benefit from hypothermia.(4) On the other hand, there is evidence that hypothermia may still be of benefit to infants with severe clinical encephalopathy, with some analyses pointing to a similar degree of improvement in the rate of death and disability as that seen in infants with moderate encephalopathy.(6, 21) There is good reason to be cautious about placing undue emphasis on subgroup analyses.(10, 26) At this point in time it is not possible to define with confidence which infants do not benefit from cooling.

COOLING AND PALLIATIVE CARE

One concern about cooling for infants with severe (and irretrievable) brain injury is that it may delay decision-making. The vast majority of deaths in HIE in many neonatal units follow decisions to withdraw life-support.(27, 28) Treatment protocols for hypothermia generally aim to cool for 72 hours, with a subsequent period of slow warming over at least another 4 to

6 hours.(4, 5) One concern is that this may delay discussions with parents about treatment limitation or withdrawal, with the potential to prolong suffering if an infant is in pain. (It should be noted that such infants are unlikely to be suffering greatly given the severity of their encephalopathy.) It may also make palliation more problematic, as by the time that 80 hours or more have elapsed, infants may have resumed spontaneous breathing. At this point infants may not die if mechanical ventilation is withdrawn, and parents and medical teams may be faced with substantially more difficult questions about whether or when to withhold other supportive measures.(29)

Fortunately this is not borne out by the published trials, as the institution of hypothermia did not appear to delay decisions about withdrawal of treatment. (4, 5) Furthermore, the meta-analysis shows a significant reduction in major neurodevelopmental disability in survivors who had been cooled,(6) which should allay concerns that cooling may lead to the survival of a large number of infants with severe impairment who would otherwise have died.

Worries about the effect of hypothermia on palliative care should not prevent the initiation of cooling in infants with severe HIE. However it will remain important that cooling does not delay discussions with parents about withdrawal of life-sustaining treatment from infants with evidence of profound brain injury. Indeed it may be appropriate in such circumstances for treatment to be withdrawn before the completion of 72 hours of hypothermia.

PROGNOSTIC CERTAINTY?

While hypothermia has been shown to improve outcome for infants with HIE, a significant proportion still die or survive with significant disability.(6) Determining prognosis for infants with HIE is a significant challenge, and multiple different predictive tools have been used to attempt to improve this.(30) An additional problem raised by the introduction of a new treatment for HIE is that almost all published studies of prognostic factors have been in infants who have not been treated with hypothermia. It is conceivable that features that have previously been closely associated with poor outcome might not be so specific in infants whose injury has been mitigated by neuroprotective strategies. A post-hoc analysis of the CoolCap study recently concluded that hypothermia modified the prognostic value of clinical grading of encephalopathy.(31) Further research into the influence of hypothermia on prognostic factors will be necessary, but in the meantime cooling will add an extra level of uncertainty in discussions with parents about prognosis and the advisability of continuing to provide intensive care.

ISSUES IN COOLING RESEARCH

There remain a number of unanswered questions about hypothermia for neonates with HIE.(11, 12) The long-term outcome is unknown, and it will be important to follow-up infants enrolled in the controlled trials.(2) Other questions include the ideal temperature to aim for, the duration of cooling, whether head-cooling or systemic hypothermia are more effective, and whether there are identifiable sub-groups that are not responsive to cooling.(23) Such questions do not require comparison with normothermia as a control (and indeed many would argue that it

would be unethical at this point to do so). Ideally treatments should be compared prospectively in multi-centre randomised trials, and the development of regional cooling centres with common protocols and universal follow-up may facilitate this. Centralisation of cooling would also help overcome the problem of lack of expertise with this therapy in smaller centres,(12) though it would have significant resource implications for transport services.

However the numbers of infants required may well make such comparisons impractical.(21) This has led to suggestions that infants treated with hypothermia be entered into national or international registries (eg the UK TOBY register)(32) and followed up prospectively.(11, 12, 21) It should be noted that such registries can be expensive, and that they are not universally available. Additionally, interpretation of data can be difficult in the absence of randomisation.(13, 33) On the other hand such observational studies may be critical in generating hypotheses and planning further trials, and enrolment of patients should be strongly encouraged.(34)

CONCLUSIONS

Hypothermia is the first treatment shown to improve outcome in infants with HIE. It is currently being introduced, or has been introduced in many centres around the world. The devastating outcome for many infants with moderate or severe HIE, as well as the fact that the majority of deaths follow decisions to withdraw life-support mean that any treatment for HIE is likely to lead to ethical concerns and questions.

This paper has highlighted some of the ethical complexities associated with the introduction of

hypothermia into practice. Given the evidence of benefit many (including this author) believe that it is no longer ethical in developed countries to treat infants with moderate or severe encephalopathy without cooling. However uncertainties about which specific infants will benefit (and which mode of cooling to use) are likely to be difficult to resolve. Delaying decisions about withdrawal of life-sustaining treatment could compromise palliative care in some infants. Treating infants with hypothermia may lead to uncertainty about prognosis.

Some of these issues may be resolved by further research, and this provides an important reason to continue to study hypothermia. Where possible infants should be entered into further trials, or a national registry so that the outcome of different protocols can be compared. It is also important to ensure that parents are fully informed of the benefits and potential drawbacks of cooling.

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Abbreviations: CI, 95% Confidence Interval; HIE, Hypoxic-Ischaemic Encephalopathy; MRI, Magnetic Resonance Imaging; NICHD, National Institute of Child Health and Human Development; TOBY Total Body Hypothermia

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