PERSPECTIVE

Ethical Challenges in the Use of Therapeutic Hypothermia in Indian Neonatal Units

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Received: February 22, 2010; Initial review: March 11, 2010; Accepted: April 10, 2010.

Trials in developed countries have shown that therapeutic hypothermia reduces the risk of death or severe disability in infants with neonatal encephalopathy. Cooling has been adopted as a standard of care in some parts of the world. Some Indian neonatal units have considered or even embarked upon cooling encephalopathic term newborn infants. In this article we discuss some of the potential ethical questions that should be considered before introducing therapeutic hypothermia in an Indian setting. Evidence from previous trials may not be relevant given significant differences in the epidemiology of neonatal encephalopathy in countries like India. There is a possibility that hypothermia would be ineffective or harmful. The most appropriate way to answer these concerns would be to perform a large randomized controlled trial of cooling in India. However, such trials will also raise potential ethical challenges. Cooling may also affect decisions about treatment withdrawal, and may create uncertainty about prognosis. It may exacerbate ethical problems relating to lack of neonatal intensive care bed space.

Key words: *Cooling, Ethics, Therapeutic, Hypothermia, Hypoxia-Ischemia, Newborn, India*.

Therapeutic hypothermia (TH) for infants with neonatal encephalopathy (NE) has emerged in the last couple of years as one of the most promising new treatments in neonatology. Several large, multi-centre, randomized controlled trials have shown that TH reduces the risk of death or severe disability at 18-month follow-up in infants with moderate or severe encephalopathy(1-4). Meta-analysis of these trials indicates that TH reduces the risk of adverse outcome by approximately 15%, with a number-needed to treat of 6-8 infants(5-7).

Following the publication of the above evidence, cooling for infants with NE has been recommended or adopted as a standard of care in neonatal units in some countries(8-10). Yet the translation of this research into practice has been associated with significant debate and controversy(11-14), and the implementation of TH is associated with a number of ethical issues(13). There are issues relating particularly to the transition from experimental therapy to practice and the extrapolation of research evidence to clinical care. These issues may be even more apparent in developing countries like India. But there are also several issues relating to treatment limitation decisions in encephalopathic newborn infants, and the way in which these are potentially influenced by new treatments. This paper outlines some of the ethical considerations that may arise in relation to TH in an Indian setting.

STANDARD OF CARE

As the randomized controlled trials of TH were published in the mid 2000s, and it became clear that cooling was effective, a debate emerged about whether further trials were necessary, or whether,

indeed, it was even ethical to continue to randomise patients to normothermia(11-15). The stakes were particularly high because of the lack of other available treatments and the high rates of death and disability in infants with moderate or severe NE.

This debate was fundamentally about the level of certainty that is required of scientific evidence before it is sufficient to ground a change in standard practice(14). Mistakes can be made by the overenthusiastic or premature adoption of treatments that may be ineffective or even harmful, for example the liberal use of oxygen for premature infants, or steroids for chronic lung disease(16). On the other hand, delay in adopting treatments that have been proven to be effective and safe can lead to substantial preventable morbidity and morta-lity(17,18) (one example includes the considerable delay after evidence of benefit was demonstrated before antenatal steroids were used routinely for mothers at risk of premature delivery).

The standard of care debate about TH appears to have resolved, since normothermia-controlled trials have been stopped in developed countries(9); albeit TH has not been universally adopted(19). However, the issue of therapeutic cooling for transitional and developing countries raises several issues and dilemmas.

The biggest issue is that it may not be acceptable or safe to extrapolate evidence from trials performed in developed countries to Third World and transitional countries(20-21). There are differences in the epidemiology and outcome of NE in low-resource settings(22). For example, infants may have had a longer time since brain injury because of obstructed labor or out-of hospital delivery. There is a high incidence of bacterial sepsis and pneumonia in encephalopathic infants in India(23). Many of the more severely affected infants who require respiratory support and who were enrolled in previous trials would not survive in a transitional country setting(20-21). These differences, and others, could alter the safety or effectiveness of TH. Given the possibility that the new treatment would, in fact, cause harm, some have recommended that TH should *not* be adopted in India except in controlled trials, citing the ethical principle of non-maleficence(24).

Nevertheless, there may be a desire on the part of some pediatricians in India to adopt cooling in the hope that it would be effective(24). The greatest burden of NE falls in transitional and developing countries, where it is responsible for a large number of deaths and neuromotor disabilities(22,25). Doctors may be understandably reluctant to withhold a treatment simply on the basis that it has not been proven effective in low resource settings. After all, performing randomised controlled trials is expensive, and many medical treatments are never tested separately in developing countries. Withholding all medical treatments that hadn't been shown specifically to be effective in low resource settings would potentially exacerbate existing health care inequalities between developed and developing countries.

The issue becomes more complicated since in transitional economies like India there are substantial differences across the country in the standards of neonatal units, in the populations that they service and the resources available for care. In some tertiary care private centres in urban areas, the quality of NICU care in India may be at par with some neonatal units in the West where TH trials were conducted. And clinicians in these centres may feel justified in treating selected or suitable infants with TH, (there may also be perceived commercial advantages in offering this new treatment). Within the public health care system, particularly in level 2 neonatal centres, the concerns about extrapolating evidence from previous trials have greater relevance. However, this inconsistency in management protocols between various centres may, in itself, give rise to concerns, since some may worry that poorer patients are being given sub-standard care.

As in the debate about cooling trials in developed countries, the key question relates to balancing risks, benefits and uncertainty. One approach to uncertainty, and one way of analysing the debate is to draw on Bayesian theory(14). Briefly, our response to an intervention depends on the 'prior probability'. Where there is a high prior probability that a given treatment is effective, we are more likely to respond positively to the trial evidence that appears to support it. Conversely, where the prior probability is low, a single positive trial result may not be enough

(and should not be enough) to convince us to change an established practice. In developed countries the evidence from multiple clinical trials builds on existing (and strongly supportive) pre-clinical evidence(26). It is appropriate that hypothermia is used routinely for infants who would have met the criteria of previous trials. On the other hand, in developing countries there is considerable evidence that "non-therapeutic" hypothermia is associated with an increased risk of mortality in newborns(23, 27,28). Furthermore, the significant differences in the epidemiology of NE in these settings raise the distinct possibility that the safety and efficacy of TH in Indian neonatal units would be different from that evident in the trials conducted in developed countries.

There are two approaches that are of potential use in resolving debates about treatments that may or may not be effective. The first draws on the importance of patient autonomy - it involves informing patients (or parents in this case) about the uncertainty relating to new treatments, and the arguments for and against its use(29). This approach is particularly challenging for populations with little formal education and no prior exposure to concepts of research, statistical testing, or medical uncertainty. Even in developed countries parents involved in a controlled trial may have several misconceptions about randomisation and the research process despite informed consent having been obtained(30). The second approach would be to draw on the disagreement about treatment and the concept of clinical equipoise(32,32). In this setting, the best way to ensure that doubts are put to rest and Indian infants with NE are treated appropriately (either with or without cooling) would be to perform an appropriately powered, controlled trial.

ETHICAL ISSUES IN COOLING TRIALS

Given the genuine uncertainties about whether cooling would be effective and safe in less well resourced settings, there is a strong case for performing further randomised controlled trials(29). But some might have concerns that this would conflict with existing guidelines for performing trials in developing countries. The recently revised World Medical Association Declaration of Helsinki specifically indicates that comparisons with no treatment or placebo are only appropriate where there is no current proven intervention(33). However, the Declaration itself has been criticised on the grounds that it would prevent research that has the potential to improve the health and well being of patients in developing countries(34,35). Instead of a universal standard some have proposed that research participants should be offered, as a minimum, the best intervention currently available as part of a national public health system(36). In any case, as noted above, it could be argued that in low resource settings there is no currently proven treatment for NE(21).

If cooling trials are conducted in Indian centres, trial participants should be made aware of the results of previous research as part of the informed consent process. One issue worth considering is whether parents who do not consent to enrolment in such trials should be allowed to choose that their infant be cooled or given the conventional treatment. This may jeopardise enrolment, however, or even render a trial unworkable. Patients and parents are often biased towards new treatments – particularly where there is little or no existing therapy. The majority of parents interviewed following the UK extracorporeal membrane oxygenation (ECMO) trial had a preference for ECMO at the time of consent(30). Those who were allocated to conventional treatment exhibited intense disappointment and anger(30). In an Indian setting, enrolment may also be threatened if some centres offer (and advertise) cooling outside a trial.

A further question relates to the likely substantial cost of an adequately powered Indian cooling trial with appropriate follow-up. Such a trial would need to compete with other health priorities for funding. Some may feel that it would be better, for example, to devote resources to improving antenatal care and reducing the incidence of NE. On the other hand, given that infants are going to continue to be affected by NE even if antenatal care is improved, there is good reason to seek simple, effective ways of reducing the burden of this illness and the considerable ongoing health care costs for survivors. If a low-cost form of TH were shown to be effective and safe in an Indian trial it would have enormous significance for

the large number of infants with NE, both in India, and in other transitional and developing countries.

COOLING AND PALLIATIVE CARE

The other potential source of ethical conflicts or dilemmas relating to cooling is the impact of cooling on decisions about withdrawal of life-sustaining treatment. The majority of deaths in infants with HIE in neonatal units in developed countries follow decisions to withdraw treatment in the face of predicted poor prognosis(3,8,37,38). There are few studies of treatment limitation decisions in Indian neonatal units. Withdrawal of treatment appears to be generally accepted(39,40), though there is considerable legal ambiguity that may lead to confusion in the minds of doctors and inconsistency in management(41,42). Withdrawal of treatment in infants with HIE is often cited as particularly difficult because of uncertainty about outcome(43), but also because such decisions are based on potentially controversial judgements about future quality of life(44).

Firstly, TH may influence withdrawal of treatment by affecting the timing of decisions. In previous trials cooling was initiated within 6 hours of birth, continued for 72 hours, followed by slow rewarming over the next 6 hours. However, there is the possibility that by 80 hours of age or soon after, infants will have resumed spontaneous breathing and no longer be ventilator dependent. If neonatologists wait until cooling has been completed before making decisions about treatment withdrawal the "window of opportunity" may have been missed(45). This concern is not borne out in previous trials, since decisions to withdraw treatment occurred at similar times in cooled and non-cooled infants(2,3). Furthermore, there were fewer severely impaired infants among survivors in the three large cooling trials, implying that overall TH did not lead to the survival of a large number of impaired infants. Discussions about treatment should be initiated early in the most severely affected infants, whether or not they are cooled. In some infants it may be appropriate to withdraw treatment before completing the 72 hours of cooling.

Secondly, TH may influence decisions about withdrawing treatment by raising questions about prognosis. The majority of existing evidence about predicting outcome in infants with NE relates to infants who have not been cooled. It is possible that factors, previously strongly associated with adverse outcome, may be less reliable in a population of infants who are cooled. Doctors and parents usually seek a high degree of certainty of adverse outcome before deciding to withdraw treatment, and consequently if an infant has been cooled there may be reluctance to discontinue intensive care.

Recently published studies are helpful in this regard. They suggest that early assessment of severity either clinically(46) or with the help of amplitude integrated electroencephalogram (aEEG)(47) are less useful in cooled infants. Severe encephalopathy or burst suppression on aEEG at this stage was not uniformly associated with poor outcome in infants treated with TH(46,47). However, persistent severely abnormal neurological findings or aEEG abnormalities were strongly linked to adverse outcome(46,47). In another recent study cooling did not substantially change the relationship between various prognostic parameters including MRI findings. Infants who were cooled were less likely to have MRI evidence of injury, or had less severe patterns of injury, but those who had such patterns were still likely to have a poor outcome(48).

Third, TH may raise questions about withdrawing or withholding treatment in the setting of limited intensive care beds, and limited support for surviving disabled infants and their families(42,49). Cooling may make it possible to save the life of infants with severe NE. This is likely, however, to increase the pressure on neonatal intensive care capacity. It may mean, for example, that premature infants with respiratory distress are unable to be supported due to space constraints in the NICU. It will also highlight the difficult balance between the interests of the infant, and that of the family. Although TH may reduce the risk of disability in surviving infants with NE (and it is not clear yet whether it will in an Indian setting), it may also lead to substantial burdens on some families by leading to the survival of infants (with moderate or severe impairment) who would have died previously. TH has been used in conjunction with monitoring of aEEG and magnetic resonance imaging for

prognostication but these technologies are not available in low resource settings, or are likely to be in short supply. It is probably appropriate to provide cooling without these adjuncts, but it potentially makes prognostication and decision-making more challenging.

There is a range of other practical questions that are likely to be faced if TH is adopted. The equipment used for cooling in previous trials is expensive, and it is important that staff is adequately trained in its use. In some parts of the world this has led to the development of regional centres with expertise in cooling and referral of affected infants to the specialized units. However, such a system requires adequate infrastructure to transport sick encephalopathic infants to the cooling centres, which is unlikely to be available in many centres in developing countries. Furthermore it raises the question of cooling the infants during transport, something that has not been well studied, and is associated with a risk of over-cooling(50).

The other requirement for implementation of TH in developed countries is availability of adequate follow-up facilities and infrastructure to assess the safety and efficacy of the treatment (9, 51). However, this facility is unlikely to be available in most centres in resource poor countries except as part of a funded research protocol.

CONCLUSION

Although the development of TH for newborn infants with NE has the potential to prevent death and severe disability, its implementation is likely to raise a number of ethical challenges. There are unanswered questions about the safety and effectiveness of cooling in low resource settings. There is a need to exercise caution in the adoption of TH in Indian neonatal units until further trials have been performed. We suggest that there is a strong ethical argument in favour of such trials given differences in the epidemiology of NE in developing countries and the possibility that TH may be ineffective or even harmful.

ACKNOWLEDGMENTS

Sudhin Thayyil (Academic Neonatology, University College London) provided very valuable comments and support in the writing of this manuscript.

Contributors: DW conceived and drafted the article, he will act as guarantor. JW and MS were involved in analysis, critical revision and editing of the manuscript. The final manuscript was approved by all authors.

Funding and Conflict of Interest: DW is supported by an Oxford Nuffield Medical Fellowship, an Eric Burnard Fellowship, and Royal Australasian College of Physicians Astra-Zeneca Medical Fellowship. The funders had no involvement in this work. JW was one of the principal investigators of the Cool Cap trial. The authors have no conflicting interests.

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