PERSPECTIVE

Therapeutic Hypothermia for Neonatal Encephalopathy: Implications for Neonatal Units in India

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Therapeutic hypothermia has recently emerged from bench to bedside. Three large multicenter trials from industrialized countries and three independent meta-analyses have shown its efficacy in reducing death and disability following neonatal encephalopathy due a perinatal hypoxic event. Many neonatal units in well-resourced settings now offer hypothermia as standard care in neonatal encephalopathy. However, these results cannot be extrapolated to low resource settings due to differences in population, risk benefits and high cost. Use of therapeutic hypothermia in low resource settings should be considered experimental and should therefore be restricted to well equipped level 2 and 3 neonatal units. The safety and efficacy of hypothermia using novel low technology methods need to be examined in rigorously controlled multicenter randomized controlled trials in these neonatal units before it can be offered as a standard care, as the risks may outweigh the benefits. The current practice of maintaining normothermia should continue, until such evidence is available.

Key words: *Hypoxic ischemic encephalopathy, Neonate, Therapeutic Hypothermia.*

The recent emergence of moderate therapeutic hypothermia (TH) for neuroprotection from bench to bedside has generated significant media interest and prompted discussions among clinicians and academicians around the world(1). TH has been used for neuroprotection in a variety of settings including traumatic and hypoxic brain injuries, stroke and during cardiac surgery. It is most effective in neonatal encephalopathy (NE) following a perinatal hypoxic event and in witnessed cardiac arrests in adults and least effective in traumatic brain injury(1). A controlled reduction of core body temperature by 2-3ºC, initiated within 6 hours of birth and continued for 72 hours, followed by slow re-warming, results in a significant reduction in death and neurodisability following hypoxic ischemic encephalopathy (HIE)(2-6). Leaders in this field have therefore recommended greater uptake of this novel therapy and that it should become standard care in HIE(1,7).

Translational neonatal research at University College London (UCL) is primarily focussed on the development of novel neuroprotective therapies for preventing and treating perinatal brain injury. The incidence of NE is 10-20 times higher in low resourced settings compared to industrialized countries. Therefore a research priority involves developing low technology methods of neuro-protection and evaluating these through an extensive network of developing country partners. In this article we critically examine the evidence for use of TH and the applicability of this novel therapy to neonatal units in low resourced settings.

EVOLUTION, EVIDENCE BASE AND UPTAKE OF THERAPEUTIC HYPOTHERMIA IN INDUSTRIALIZED COUNTRIES

Very few therapies in the history of medicine have been subject to such a prolonged and rigorous basic science, translational and clinical evaluation, as TH

for NE(2-6,8-12)(***Table* I**). Three large multicenter trials from industrialized countries and 3 independent meta-analyses have shown efficacy of TH in reducing death and disability following NE(2,3). The magnitude of risk reduction for prevention of death and neurodisability [RR 0.76 (95% CI 0.65, 0.89)] shown by TH, as reported in the Cochrane Review is considerable(2), particularly for a devastating condition for which there has been no effective therapy until now. The efficacy of TH is comparable to the most evidenced-based neonatal therapies like prophylactic use of surfactant in preterm babies for preventing death and broncho-pulmonary dysplasia, and the use of antenatal steroids in preterm labour for preventing neonatal deaths. To put this into perspective, we need to consider that many interventions used in neonatal practice have no evidence base at all.

Three further whole body hypothermia trials [Infant Cooling Evaluation (ICE)], nnnhypothermia and Total Body Hypothermia (TOBY) were ongoing at the time of publication of the systematic review showing the beneficial effects of hypothermia(2). In view of this evidence, clinicians recruiting cases into the ongoing trials felt that it was unethical to allocate babies to the control arm (normothermia). Therefore, recruitment to these trials became difficult and they had to be stopped prematurely without achieving target sample sizes. The results of the largest of these trials, the TOBY trial(13) will be published in the near future. The proportion of infants with severe HIE in the TOBY trial was substantially higher than previous TH trials. Therefore, the overall efficacy of TH in TOBY trial may be less than previous trials, as TH is likely to be more effective in moderate NE, rather than severe. However, even if the differences in primary outcome do not reach statistical significance, it will be informative to update the meta-analysis by including this trial. If the benefit persists without increasing statistical heterogeneity, it would greatly strengthen the positive results of the Cochrane review. Outcome assessments of other two smaller hypothermia trials have not been completed, as yet.

TABLE I EVOLUTION OF THERAPEUTIC HYPOTHERMIA IN NEONATAL ENCEPHALOPATHY

Year	Place	Research	Impact
1983	UCL, London(8)	First human ^{31}P MR spectroscopy obtained in 7 newborns babies at UCL Hospital	Feasibility of direct study of energy metabolism in human brain demonstrated.
1984	UCL, London(9,10)	Phosphocreatine/ Inorganic Phosphorous ratios by ^{31}P MR, ratios normal soon after hypoxic injury, but declined on 2nd day in babies with HIE	Concept of delayed neuronal injury and secondary energy failure. Potential for window period was observed, during which neuroprotective therapy could be used.
1995	UCL, London(11)	Hypothermia reduced secondary energy failure following hypoxic brain injury in a piglet model, when administered within the window period	Similar findings were subsequently reported in other experimental models.
1998	New Zealand(12)	1st pilot randomized control trial of therapeutic hypothermia in 31 newborn infants with HIE	Demonstration of the proof of principal, feasibility. This was followed by 4 other pilot trials from US, Australia, Turkey and China
2005	US, UK, Australia, New Zealand (4-6)	3 separate multicenter randomized control trials in therapeutic hypothermia (2-Whole body cooling, 1-Selective head cooling)	Both whole body cooling trials showed significant reduction in the primary outcome (death and disability). No risk reduction was seen with selective head cooling.
2007		3 independent meta-analyses, including a Cochrane review showed significant reduction in death and long adverse neurodevelopmental outcome(2,3)	Recruitment into the 3 ongoing therapeutic hypothermia trials became difficult. ICE (*n*=218), nnhypothermia (*n*=129) and TOBY trial (*n*=325) stopped prematurely without achieving the target sample sizes.

Critics of TH point out that the hypothermia trials so far, have been small and underpowered(14). To date the collective sample size is only 638 cases. Following an extensive review of highly cited publications on efficacious interventions in medicine, Ioannidis, *et al.* reported that 32% of the studies were subsequently refuted(15). The studies that were highly cited and not refuted had a median sample size of 1542, as opposed to those that were either contradicted or claimed initially stronger effects, which had a median sample size of 624.

Furthermore, TH trials so far have relied on composite outcomes of death and disability and were not large enough to examine mortality and neurodisability separately in survivors. Moreover, the numbers were too small to perform any accurate subgroup analysis based on severity of NE, or to examine very long term outcomes beyond 2 years of age. The small size of the TH trials was not ideal, but was a pragmatic response to the difficulty in recruitment and low incidence of NE in industrialized countries. For example, the prematurely-stopped ICE and nnnHypothermia trial took 6 and 5 years to recruit 218 and 129 cases, respectively.

Several unanswered questions remain, such as which sub-group would benefit most from TH and what is the optimal level and duration of hypothermia. Use of TH has been shown to increase the window period for use of other adjuvant neuroprotective therapies. Several adjuvant hypothermia therapies have been proposed, of which Xenon appears to be most promising in experimental settings. Not every single issue related to hypothermia can be addressed in clinical randomized control trials, so evidence for many of these questions need to come from experimental research. Moreover, future clinical trials are very likely to use quantitative biomarkers as surrogate endpoints, rather than long term neurodevelopmental outcome, thus shortening trial sizes and duration. A Medical Research Council (MRC), UK-funded clinical randomized control trial of hypothermia versus Xenon +hypothermia is expected to start at UCL and Imperial College London (TOBY plus), in late 2009. Outcome measure for this trial is Lactate/N-acetyl cysteine peak area metabolite ratio by ^{1}H MR spectroscopy. Another National Institute of Child and Human Development (NICHD) funded study on 168 newborn infants exploring benefits of late TH started between 6-24 hours of birth, is now ongoing in US, but is expected to be completed only by 2013.

Most experts now agree that equipoise has been lost and no further trials of TH can be undertaken in industrialized countries using a normothermic control arm(7,16). The relationship between strength of evidence and clinical uptake is not linear in medicine and often this is related to cost-effectiveness, availability of the interventions and attitudes of clinicians and policy makers. Often a lag period of several years occurs between demonstration of beneficial effect in clinical trials and the adaptation of new practice. However, it is heartening to note that immediately following the completion of recruitment to TOBY trial in September 2006, a national registry was established in the UK to support and monitor neonatal units that wished to offer hypothermia as standard care in HIE(17). At present 53 % of level 3 neonatal units in the UK, including UCL, offer TH as standard care in NE(18). A recent survey showed that most neonatologists in the UK wished to offer TH in NE, but for the limiting factor of formidable cost of cooling equipments and lack of expertise(18). It is likely that by effective dissemination of research evidence, training and the development of less expensive cooling methods, most neonatal units in the UK will be able to offer TH in the near future.

IMPLICATIONS FOR NEONATAL UNITS IN INDIA

Neonatal encephalopathy from perinatal asphyxia is the single most important cause of neonatal mortality among hospital delivered infants in India and the incidence (14 per 1000 live births) is 15 times higher than in highly resourced settings(19). Though exact morbidity data are not available, it is likely a significant proportion of infants are left disabled for life. Clearly an intervention with a number needed to treat (NNT) of 7 for preventing death or disability would be of great benefit and potentially save thousands of lives and prevent disabilities. However, extrapolation of the research evidence from the hypothermia trials in industrialized countries to

Indian settings is complex and may not be appropriate for the reasons described below.

Safety of therapeutic hypothermia in low resource settings

The reported safety and efficacy data are based on administration of TH within strict protocols and often at centers of excellence with considerable experience in TH(20). This expertise was then gradually disseminated to small units. It is reassuring to note that no major safety issues have been reported from the UK national registry, that collects safety and efficacy data on routine clinical use of TH in smaller neonatal units in the UK(17,18). Hypothermia has been safely used in non-ventilated babies and no deterioration in respiratory function has been reported(21).

Nevertheless, the safety and efficacy when TH is offered in less resourced settings cannot be taken for granted. A major concern about the use of TH is the reported linear association of mortality and hypothermia observed in such settings. Mild, moderate and severe hypothermia at presentation to the hospital has been reported to have 39.3%, 51.6% and 80% mortality rates, respectively(22). When mild hypothermia was associated with perinatal asphyxia, the case fatality rate was more than 50%(22). Clearly, there is no evidence to suggest that the association is causal, but the possibility that it is so cannot be excluded. It has also been suggested that hypothermia may result in neutrophil dysfunction and increased risk of infection. TH trials did not show any increased risk of infection, but this could have been masked by use of intravenous antibiotics(2). Risk and benefits may be very different when facilities for early infection screening and treatment are not available.

Differences in severity of brain injury and implication of the window period

In low resourced settings, there is a higher incidence of unbooked pregnancies and late presentations, often in obstructed labour. Therefore, many of these infants may already have established brain injury due to prolonged periods and multiple episodes of intrauterine hypoxia, which may decrease the efficacy of TH. Incidence of intrauterine retardation and meconium aspiration syndrome is far higher in low resource settings. Response to hypothermia in small for date babies may be different to appropriate for date babies, due to potential threshold levels of TH(23). On the other hand, babies with very severe hypoxic injury may not make it to the neonatal unit in such a setting. Thus a natural selection may occur, where the NE babies admitted to neonatal units may have only mild to moderate brain injury. The efficacy of TH is expected to be higher with moderate brain injury, rather than severe brain injury, so, potentially, TH may appear more efficacious in reducing neurodisability in low resource setting.

The window period for initiation of TH is short (within 4-6 hours of birth)(24). Industrialized countries have well organized neonatal transfer systems to ensure initiation of TH within this window period. Lack of such an infrastructure in most places of India may preclude this therapy for extramural babies.

Impact of natural hypothermia in asphyxiated babies in low resource settings

Most newborn infants (65%-85%) are already hypothermic on admission to neonatal units in low resource settings(25). The effects of natural cooling in NE, though reported first in 1950's are not widely appreciated(26). Infants with perinatal asphyxia were found to have persistent hypothermia for first 16 hours of life compared to healthy controls(26). It is possible that this 'natural hypothermia' does have a neuroprotective effect and TH may be unnecessary.

Nevertheless, on admission to neonatal units, hypothermic babies are rapidly rewarmed(27). Again, such rapid rewarming is known to result in worsening of brain injury in experimental models. However, extrapolation to clinical scenarios are only speculative at present.

RECOMMENDATIONS FOR USE OF THERAPEUTIC HYPOTHERMIA IN LOW RESOURCED SETTINGS

Resources for neonatal care and health facilities vary widely in India. There are several well-resourced tertiary neonatal units both in the private and public sectors in India, where resources are in par with industrialized countries. However, most neonatal

care is provided in poorly resourced level 1 units and in the community. The NE population and risk benefits of TH in neonatal units in India are very different to industrialized countries. TH should be considered experimental and should not be offered as standard care, until more evidence is available. The current practice of maintaining normothermia should be continued, particularly in community and small neonatal units.

Considering the potential for a huge impact on neurodevelopmental outcome of this intervention, rigorous scientific evaluation of safety and efficacy is warranted. Evaluation of TH should ideally start in larger centers of excellence and, if shown to be effective, gradually cascade down to smaller units in India. Close monitoring of temperature to avoid fluctuations and careful screening and early treatment of infection is important when TH is being used.

A multicenter approach would be required to achieve adequate sample sizes for a rigorous randomized and controlled evaluation and networks similar to the National perinatal neonatal database (NNPD) may provide an ideal model. TH may be particularly relevant to neonatal units in Kerala, where almost all deliveries occur in hospital and infant mortality rates are comparable to industrialized countries.

Method of cooling and cost of cooling equipments

The cost of currently available cooling equipments (INR 5 Lakhs) is formidable and it is clearly inappropriate for low resource settings. Selective head cooling is more technically challenging than whole body cooling and may result in temperature gradients within brain(23). Moreover, the evidence base for TH is restricted to whole body cooling and not selective head cooling(2,5). Using ice packs cannot be recommended due to the potential for fluctuations in the brain temperature(28), which may adversely affect outcome.

A recent pilot randomized control in a large neonatal unit in Uganda, where temperatures are 26-28ºC throughout the year, showed effective TH using water bottles filled with tap water was possible(29). Cooling mattresses made of phase-changing material(30) (INR 7000) is a promising option for Indian conditions and can effectively maintain TH for 24-36 hours. The mattress needs to be recharged after this period, by keeping it in a refrigerator for a few hours. This mattress is currently being evaluated for TH during transport of HIE babies in the UK. An alternative is to make indigenously designed servo-controlled systems, which are likely to be substantially cheaper than the standard cooling equipments currently available.

In summary, the data on safety and efficacy of TH from industrialized countries cannot be extrapolated to the neonatal units in developing countries, including India, and the use must therefore be considered experimental. The medical profession is only too aware of situations where research evidence was prematurely applied with disastrous consequences, for example the increased incidence of cerebral palsy that followed steroid administration during the early neonatal period in preterm infants, or too late adoption of the research evidence – as in unnecessary recruitment of 17,500 patients in control arms for streptokinase trials for myocardial infarction ignoring existing evidence(31). A joint effort between the neonatologists in India and policy makers is required to ensure that the benefits of this novel neuroprotective therapy reaches the infants who require it most, whilst ensuring that they are not exposed to unacceptable risk.

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