Acute severe birth asphyxia - what may be done to improve the prognosis after resuscitation.

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Introduction
There is currently only one specific therapy for infants suffering hypoxia-ischaemia during birth which has been subjected to large randomised trials with apparent success; induced therapeutic hypothermia. How strong is the current evidence supporting therapeutic mild hypothermia and should this intervention become standard care for asphyxiated newborns?

Experimental evidence of the value of post-insult cooling
Studies of mild hypothermia for neural rescue after perinatal asphyxia commenced when experimental studies in animals suggested that mild hypothermia applied soon after hypoxia-ischaemia lessened pathophysiological abnormalities and improved functional outcome [1]. Several studies confirmed that post-insult cooling reduced injury in immature animals [2-5]. The mechanism of protection is unclear, but hypothermia attenuates blood brain barrier damage; release of excitatory neurotransmitters is reduced; free radical production is lessened and IL-10 (an anti-inflammatory cytokine) is increased [6-12]. Hypothermia decreases the cerebral metabolic rate for glucose and oxygen and reduces the loss of high energy phosphates during ischaemia and prevents or ameliorates secondary cerebral energy failure [4;13]. Importantly, hypothermia influences apoptotic mechanisms within cells: caspase 3 activity is lessened and cytochrome c translocation is diminished, resulting in a reduction in apoptotic neurons [14-16]. Following global hypoxic or HI or traumatic insults mild hypothermia reduces damage in the cortex, thalamus and hippocampus. Treated animals also demonstrate preserved neurological functions. Although some of these benefits may diminish over time, the protection provided by post-insult hypothermia generally persists [17;18].

Clinical studies of neuroprotective hypothermia in adults
In the 1990s promising results were reported in preliminary clinical studies of mild hypothermia following traumatic brain injury. However, in recent meta-analysis and systematic review of all clinical studies of neuroprotection with mild hypothermia following traumatic brain injury, there was no evidence of benefit with hypothermia, and there was increased sepsis in cooled patients [19-21]. The few studies of therapeutic hypothermia following stroke were primarily intended to assess feasibility and no large prospective randomised study has yet been reported [22-25]. In contrast to the predominantly negative studies of therapeutic hypothermia following traumatic brain injury and stroke, preliminary reports suggesting that mild hypothermia after cardiac arrest improved neurological outcome were substantiated by two randomised, controlled studies published in 2002. In these studies, 12-24 hours of mild hypothermia resulted in an absolute risk reduction of 14-23% in adverse neurological outcome at 6 months [26;27].

Studies of mild hypothermia in newborns
Since accidental hypothermia in premature infants is harmful, the primary aim of preliminary clinical studies following perinatal asphyxia was to assess the safety of induced prolonged mild hypothermia [28-33]. Cooling is associated with physiological changes in cardiovascular parameters: the blood pressure rises and heart rate falls linearly with cooling [29;34]. Hypothermia may also alter clotting and biochemical and metabolic measurements but no clinically significant differences in blood viscosity, coagulation or acidosis were noted between cooled and normothermic infants [29;32;36].

Choosing appropriate criteria for selecting study subjects is critical to the success of clinical studies of novel treatments. Combining early neurological assessment with a record of the amplitude integrated EEG (aEEG), a simple form of single channel EEG monitoring, increases the positive predictive value for an abnormal outcome following asphyxia[37]. Therefore, some studies of neuroprotection with mild hypothermia have used a combination of clinical features together with a record of the aEEG to identify

those infants at high risk of developing progressively severe asphyxial encephalopathy [28;29;38;39]. In other studies only clinical selection criteria were used[32;33;40].

The first randomised controlled trial of therapeutic cooling after perinatal asphyxia has recently been reported in The Lancet [41]. Head cooling was achieved using a cap of coiled tubing filled with cooled fluid wrapped around the head. 234 infants with moderate to severe encephalopathy and an abnormal aEEG were randomized to either head cooling for 72 hours starting within 6 hours of birth, with the rectal temperature maintained at 34.5 ^{0}C, or to conventional care. After controlling for severity of encephalopathy determined by pre randomisation aEEG a protective effect of hypothermia was suggested (p=0.05, odds ratio (OR): 0.57 (0.32, 1.01)). In a subsidiary publication the group presented a further analysis in which severity of encephalopathy judged by clinical assessment prior to randomisation was included in the equation and in this case the treatment was effective ($p<0.05$)[38].

A similarly sized study employing whole body cooling to 33.5 ^{o}C for 72 hours in infants selected by clinical assessment without EEG has also been completed (the NICHD study)[40]. The relative risk reduction was 0.72 (0.55-0.93) and 0.77 (0.6-0.98) after adjustment by centre and severity of encephalopathy. Some preliminary studies which were not powered to detect an effect on neurological outcome have also reported outcome [33;42]; Eicher et al found that in 65 asphyxiated newborns cooling reduced death or severe disability following asphyxia [33].

Evaluating the evidence

Combining the results of the 'Coolcap'[41], NICHD[40] and Eicher[33] studies suggest that mild hypothermia is associated with a significant reduction in deaths and severe disability following asphyxia. However, there are major differences between these studies which might invalidate such combined analysis. The three studies differed in the method of selection of infants, so that the study groups may not be comparable, and in the method and duration of cooling, which probably resulted in diverse brain temperatures in cooled infants, and in the assessment of outcome. In these three studies the primary outcome measure was a combined outcome of death or disability, but the definition of disability varied between the studies. Whereas adverse outcome in the 'Coolcap' study only included infants with severe disabilities, those with Bayley's psychomotor developmental score (PDI) < 70 or Gross Motor Function (GMF) score 3-5 (non ambulant, sitting with support), the NICHD study included infants with less severe disabilities: a PDI 70-85 or GMF 2-5. Outcome was assessed at 18 months in the CoolCap and NICHD studies and at 12 months in the study by Eicher et al. We excluded the study reported by Battin et al from the speculative meta-analysis since this was an exploratory study of combination of head cooling with varying degrees of systemic cooling, and group sizes were small [42].

Is hypothermia is now a proven therapy which should become standard treatment in asphyxiated newborns? To answer this question we need to ask if there are flaws in the presented trial data. If the data are robust, is the level of proof sufficient to remove equipoise for parents and professionals.

Both the CoolCap and the NICHD studies were well constructed and executed trials with large professional organisations. CoolCap was industrially sponsored which raises a question mark in some observer's minds, but was carried out under rigorous protocols administered by the Federal Drugs Administration which maintain scientific standards in industrially-sponsored research.

The result of CoolCap is positive and encouraging, particularly when further data given by the researchers is considered [38], but there are some questions to consider concerning the analysis of the trial.

First, the trial was not blinded during treatment. This is inevitable given the nature of the treatment but it may increase the possibility of unintentional and unquantifiable bias.

Second, the trial used a composite outcome measure: death or severe disability. This is unavoidable and appropriate, but composite outcome measures are often regarded by statisticians as increasing the precision of a trial at the cost of also adding to the uncertainly of the result [45]. This is not a problem as long as the trial is correctly interpreted: i.e. that the result applies only to the composite outcome not to the components. In the current trial this means that we can make no statement concerning the effect of

cooling on brain injury, or the effect cooling on death, only on the effect of cooling on adverse neurological outcome or death. This is clearly important, but it is not completely satisfactory to be unable to assess whether the treatment achieves the simple clinical goal of reducing brain damage.

Third, and perhaps most importantly, neurological outcome for the trial infants was assessed at 18 months. It is generally believed that it is not possible to completely exclude a diagnosis of cerebral palsy at this age, and certainly impossible to accurately define all cognitive defects. There have been examples in the past of early neurological assessments providing an over-optimistic assessment of the effect of treatments on neurological outcome, such as the trial of different methods of cardiopulmonary bypass techniques carried out in Boston in the 1990's, where early assessment suggested that low flow bypass was superior to deep hypothermic cardiac arrest but this was less evident at later examination . Although it is unlikely that the18 month assessment in the CoolCap trial has markedly underestimated severe cerebral palsy or death, later outcome assessments are needed to be confident that the beneficial effect of treatment is sustained, in particular that 'normal' children do not develop disabling cognitive problems.

Finally, there is a statistical nicety in the analysis of the CoolCap study. The investigators stated in the trial design that they did not expect the treatment to be effective in the most severely asphyxiated infants, and quite properly defined *a priori* a subgroup analysis excluding these infants. However, many statisticians feel that subgroup analysis in general is a less robust approach than analysing the whole trial population for interactions which reveal the effect of severity. This analysis is not presented which some, although by no means all, observers feel may detract from the robustness of the analysis. The additional data presented goes a considerable way to address this problem [38].

The NICHD trial is currently presented only in abstract form, but it is clear that the study shares the problems of blinding, composite outcome measure and early neurological assessment. The experience from the studies of cooling in adults following head injury where inadvertent deviation from the target temperature may have confounded the results, cautions us to await the full presentation of the data before we can be confident of the results of this study.

So what is the appropriate assessment of the quality of available data in these two large randomised trials? In general the trials were well executed. The numbers needed to treat in both trials is broadly similar, and neither showed any severe adverse effect. However the residual concerns about methodology, assessment and control arms should probably concern us, and not only because in both trials the levels of significance achieved by the data are perilously close to the time-honoured 0.05 significance value. Small errors introduced by methodological concerns might abolish this technical level of significance.

Conclusions

The trials of hypothermic neural rescue therapy for infants with neonatal encephalopathy that have been recently reported are well constructed and analysed trials. The data are suggestive that either selective head cooling or total body cooling reduces the combined chance of death or disability after birth asphyxia. However, there are still unanswered questions about the treatments which mean that many professionals may still feel that further data is needed before health care policy changes can be made to make cooling the standard of care for all babies with suspected birth asphyxia.

Reference List

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