To cool or not to cool? Hypothermia treatment outside trial criteria

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ABSTRACT
Most infants undergoing therapeutic hypothermia for hypoxic-ischaemic encephalopathy fit the clinical criteria used in the main randomised controlled trials. Many infants who would not strictly qualify for trial entry may nevertheless benefit from hypothermia. These may include infants presenting with postnatal collapse, infants with neonatal stroke and moderately preterm infants. Given the relative safety and potential lifelong benefits of hypothermia treatment, all patients who may benefit from cooling should receive it in a timely and consistent manner. This article reviews several clinical scenarios where cooling may be considered for neuroprotection and provides practical management guidance based on available evidence. The authors emphasise the importance of clear communication with parents and of maintaining national registers to record practices.

Therapeutic hypothermia is now the standard of care for moderate to severe hypoxic-ischaemic encephalopathy (HIE) endorsed by the National Institute for Health and Clinical Excellence in 2010.1 The large randomised controlled trials (RCTs) of hypothermia shared similar, well-defined entry criteria for enrolment of infants with moderate/severe HIE, and good evidence of efficacy exists only for such infants.2–4 A growing body of evidence now supports therapeutic hypothermia for neuroprotection in diverse adult patient groups, including following cardiac arrest,5,6 stroke and traumatic brain injury.7 In paediatric patients, hypothermia appears safe but its efficacy remains to be proven.8,9 In neonatal medicine, with incorporation of research findings into clinical practice, there has been a perhaps inevitable ‘drift’ towards cooling infants who may not have met qualifying entry criteria for trial enrolment but who clinicians feel might benefit.

This paper reviews several ‘grey case’ situations arising in everyday clinical practice where provision of hypothermia is contentious but where pragmatic guidance may be helpful. The guidance we now present follows a review of the latest available evidence.

INFANTS WITH APPARENTLY MILD NEONATAL ENCEPHALOPATHY
Eligibility for enrolment into the major clinical trials required evidence of significant fetal compromise (Apgar score ≤5, ongoing resuscitation at 10 min, metabolic acidosis with pH of <7.0 and/or base deficit >16 mmol/l within 60 min of birth) and ongoing clinical encephalopathy.2–4 Infants with normal neurology or only mild encephalopathy (grade 1 HIE: duration <24 h characterised by hyper-alertness, uninhibited Moro and stretch reflexes) and a normal amplitude-integrated EEG (aEEG) on cerebral function monitoring (CFM) were excluded from the major RCTs. There is little evidence that mild encephalopathy is associated with subsequent neurodevelopmental problems,10 and without evidence that therapeutic hypothermia benefits this patient group it is difficult to recommend that these infants are cooled at present.

We would caution, however, that a minority of neonates with significant perinatal asphyxia appear deceptively well in the first hours of life. HIE is an evolving syndrome and the postnatal clinical condition may deteriorate with time due to progressive secondary energy failure. While no single method of assessment is completely reliable in evaluation of severity, a combination of clinical and neurophysiological assessment has the best predictive value.11 For infants admitted with apparently mild encephalopathy, we therefore recommend careful clinical observations and documented neurological examinations for at least 12 h, accompanied by continuous aEEG monitoring to ensure that deterioration is identified early and permits hypothermia therapy to be instituted in a timely manner.

INFANTS <36 WEEKS GESTATION
Preterm infants may be identified using similar biochemical and neurological HIE screening criteria as used in term infants, and epidemiological studies suggest a significant number of these infants may potentially benefit from hypothermia therapy.12,13 Sick preterm infants have been shown to tolerate prolonged periods of hypothermia: a pilot study of hypothermia (33.5–35.5°C) in preterm infants with advanced necrotising enterocolitis and multi-organ dysfunction (birth gestation range: 26–30 weeks) showed no increased mortality or morbidity.14 Studies in late preterm animal models confirm the safety and efficacy of cooling.15 A pilot study is currently examining the safety and feasibility of selective head cooling in infants of 32–35 weeks gestation.16

While awaiting publication of further data, we consider that where there is a clear history of a hypoxic-ischaemic insult (eg, placental abruption) in an encephalopathic infant between 35 and 36 weeks gestation who meets appropriate HIE screening criteria it would not be unreasonable to offer cooling in full discussion with the parents. We would presently not recommend cooling infants <33 weeks gestation given that the
mechanism of brain injury following a hypoxic-ischaemic insult differs in more preterm infants and considering the paucity of evidence suggesting benefit. Furthermore, the risks of increased morbidity from mild hypothermia treatment in very preterm asphyxiated infants may significantly outweigh any hypothetical benefits.

INFANTS >6 H OLD

The experimental studies tended to cool immediately after the hypoxic-ischaemic insult. It was impractical to cool infants in clinical trials immediately from birth and so an arbitrary 6 h window allowed for assessment, parental consent and randomisation of patients. No significant differences in neurodevelopmental outcomes were apparent between those cooled earlier versus later within this window, but the trend favoured earlier cooling. Experimental studies show a lack of benefit with delayed cooling. Training and education should focus on early identification and prompt cooling of all infants who may benefit. Nevertheless, in cases of inadvertent delay, we believe that it is still reasonable to commence cooling in infants aged between 6 and ~12 h postnatal, given that possible lifelong benefits would outweigh the small risks. An RCT is currently assessing late-onset therapeutic hypothermia versus normothermia in infants starting at 6–24 h postnatal.

INFANTS PRESENTING WITH POSTNATAL COLLAPSE

Although no clinical trial has looked at hypothermia following early postnatal collapse, these babies often have good evidence of hypoxic-ischaemic brain injury on neuroimaging and so are likely to benefit from cooling. Similarly, young infants presenting with other conditions associated with hypoxic-ischaemic brain insults, such as near-miss sudden infant death syndrome and near-drowning, should likewise be considered for cooling and CFM may help guide assessment for cooling and response to treatment in such infants.

INFANTS PRESENTING WITH NEONATAL STROKE

Most neonates with arterial ischaemic stroke are in good condition at birth and present with seizures (usually focal) at ≥12 h of age. However, stroke can mimic HIE in newborns. A recent study found 15/315 (5%) neonates with encephalopathy were cases of stroke and five had received therapeutic hypothermia. None of the five cooled ‘stroke’ infants had seizures, whereas 7/10 untreated stroke infants did so. Furthermore, the cooled infants had a better neurodevelopmental outcome, suggesting potential treatment effects of therapeutic hypothermia in perinatal stroke. However, early diagnosis of stroke remains a challenge: ultrasonography can be unreliable and although CFM with bi-hemispheric aEEG monitoring capability may raise suspicions when there is marked asymmetry in aEEG background and unilateral seizures, early conventional EEG has not proven helpful in differentiation. By the time the diagnosis is made via MRI the ‘therapeutic window’ has probably been missed. If diagnostic tools are developed to detect stroke at an earlier stage, then therapeutic hypothermia may emerge as a promising treatment.

For an infant cooled because of suspected HIE where an early revised diagnosis of neonatal arterial ischaemic stroke is made, we consider that it would be reasonable to persevere with cooling for a full 72 h period. Presently, there are no randomised trials of cooling in cases of neonatal arterial ischaemic stroke and so definite evidence of benefit is lacking.

OTHER CLINICAL SITUATIONS

Infants admitted with low arterial cord pH <7.0 who appear clinically well

An arterial cord pH <7.0 correlates with an increased risk of hypoxic-ischaemic brain damage and cerebral palsy. Some infants born with severe metabolic acidosis respond well to resuscitation and may not initially appear encephalopathic. These infants do not qualify for cooling. However, short and long term outcome data are lacking for such infants and they may be at a higher risk of early morbidity such as seizures. Pending further studies of this group, we consider that it is reasonable not to cool these infants but recommend their close observation for up to 24 h, ideally with concomitant CFM.

The encephalopathic infant whose clinical condition improves within 6 h of birth

An infant whose clinical condition improves within 6 h of birth and who is no longer encephalopathic is unlikely to have been eligible for entry into the large cooling RCTs. Careful neurological assessment is essential to demonstrate that the infant is not encephalopathic and if cooling has been commenced, it may be reasonable to re-warm the infant slowly. A concurrent normal aEEG tracing in this situation would provide further reassurance. These infants should be observed carefully over the next 24 h, preferably also with CFM. The infant with evidence of perinatal asphyxia, perhaps initially hypotonic, who apparently rapidly recovers clinically but in whom aEEG is unavailable to confirm functional cerebral recovery, presents a potential pitfall.

The encephalopathic infant whose clinical condition improves after 6 h of birth

An encephalopathic infant whose clinical condition improves later than 6 h postnatal should continue to be cooled for a full 72 h period. These infants would have qualified for entry into the cooling trials and would be in a good prognostic group with hypothermia treatment. Curtailing the proven treatment prematurely is not indicated and may be damaging.

The infant who develops ‘rebound’ seizures during or immediately following rewarming

Seizures are associated with delayed energy failure and the re-emergence of seizures during rewarming could suggest that delayed energy failure is ‘reactivated’. Theoretically, maintaining cooling for a further 24 h may limit brain injury; however, there is presently no evidence that prolonging the total duration of cooling to 96 h improves neurodevelopmental outcome. A clinical trial investigating longer and deeper cooling for HIE is in progress.

Infants in whom the diagnosis of HIE is uncertain

HIE has a wide spectrum of presentation and diagnosis is sometimes difficult because other encephalopathies may mimic HIE. A detailed perinatal history is vital and thorough examination and investigations should exclude infective, metabolic and other causes, especially when atypical features are present. The decision to continue cooling if another diagnosis is made can be challenging because neonates with other encephalopathies often tolerate labour and delivery poorly and they may well have a component of hypoxic-ischaemic damage that could be ameliorated by cooling. Therapeutic hypothermia may be continued on a case-by-case basis, depending on the underlying diagnosis and overall prognosis.
CONCLUSIONS

The treatment of HIE is evolving rapidly with new trials looking at adjunct therapies and different clinical groups. Treatment criteria and patient groups are likely to evolve and expand in the future and more clinical studies are urgently needed for the many grey case situations, though this may prove challenging given the relatively small numbers individually affected.

The safety of therapeutic hypothermia in a wide range of patient groups has been well documented. Patients who fall outside the established strict trial criteria should not automatically be excluded if it can be argued that treatment may be beneficial.

As with all guidance where the evidence base is limited, we believe that the decision to offer cooling should be based on senior clinical judgement where any potential benefits of hypothermia outweigh the known risks. We recommend that all grey case patients are discussed with clinicians in the regional cooling centre before cooling is initiated, continued or curtailed.

Provenance and peer review

Competing interests

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