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Review

Who should we cool after perinatal asphyxia?

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SUMMARY

Three ongoing challenges have arisen after the introduction of therapeutic hypothermia (TH) as standard of care for term newborns with moderate or severe perinatal asphyxia: (i) to ensure that the correct group of infants are cooled; (ii) to optimize the delivery of TH and intensive care in relation to the severity of the encephalopathy; (iii) to systematically follow up the long-term efficacy of TH using comparable outcome data between centers and countries. This review addresses the entry criteria for TH, and discusses potential issues regarding patient selection, and management of TH: cooling mild, moderate, and very severe perinatal asphyxia, cooling longer or deeper, and/or starting with a greater delay. This includes cooling of patients outside of standard trial entry criteria, such as after postnatal collapse, premature infants, those with infection, and infants with metabolic, chromosomal or surgical diagnoses in addition to perinatal asphyxia.

1. Introduction

In 2010, the International Liaison Committee on Resuscitation (ILCOR) published guidelines [1] that term-born infants with signs of moderate or severe perinatal asphyxia should be offered therapeutic hypothermia (TH). Many countries, including the UK, also published similar national recommendations; the National Institute for Health and Clinical Excellence (NICE) [2], and the British Association of Perinatal Medicine (BAPM) [3]. All western countries now have TH as "standard of care" after moderate and severe perinatal asphyxia. Many centres had introduced this practice already in 2007 when the UK lead TOBY trial had finished recruiting. These recommendations on how to administer TH, and to whom, were based on a large number of preclinical studies, pilot [1,4–7] and smaller clinical studies [8], in addition to the first three large trials: CoolCap, NICHD and TOBY [9–11].

Before discussing "who should we cool?," it is important to define "who did we cool?" in the above studies, which provided the scientific basis of TH becoming the standard of care. Importantly, it is unknown whether cooling would have been (or will be) effective in infants who did not fulfill those trial entry criteria.

The researchers behind the first TH trial, the CoolCap trial, developed a 72 h treatment protocol [6], which was further tested for feasibility and safety in two studies [12,13]. Based on animal experiments from a range of species at human term equivalent age [postnatal day 7 for rats, day 0 for pigs, and near-term (117–124 days of gestation) for fetal sheep], the optimal temperature, duration, and time window of cooling were defined to achieve long-term neuroprotection [14].

This three-day protocol has, with minor changes, been used since 2010 in the developed world, as part of the ILCOR guidelines. In encephalopathic infants, cooling should start within 5.5–6 h of birth, core temperature should be kept at 34.5°C (CoolCap) or 33.5°C (NICHD and TOBY), and cooling should last 72 h, followed by rewarming at a rate of 0.5°C/h. The CoolCap trial used a cooling cap combined with moderate body hypothermia to a rectal temperature (T_{rec}) of 34.5°C [9]. Seetha Shankaran then led the first whole-body cooling (WBC) trial (NICHD) using a cooling blanket, with a target oesophageal temperature of 33.5°C [10]. Later, the TOBY trial led by Denis Azzopardi also applied WBC [11], which since 2007 has become the preferred cooling method. There is no evidence that either method is better. However, servo-controlled WBC gives stable temperatures, and is less labor-intensive to apply. The entry criteria for the first six trials to select infants with encephalopathy of hypoxic–ischemic origin are presented in Table 1. One important difference between trials is whether (amplitude-integrated) electroencephalogram (aEEG)/EEG was one of the entry criteria used to document how the brain is affected, and the severity of the insult.

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The NICHD trial, which do not use aEEG, had the most stringent definition of "abnormal neurology" to ensure that the infants were encephalopathic. All three trials aimed to recruit infants with moderate or severe perinatal asphyxia, and excluded those with mild perinatal asphyxia (classified as SARNAT grade 1 or a normal aEEG pattern), as these infants were thought to have good outcome with standard care. Those recruited using aEEG also classified the severity of the depression of the aEEG background activity between moderate and severe.

A narrowly defined patient group gives the best chance of detecting a treatment effect if there is one, and thus there were numerous exclusion criteria as listed in Table 1. When the first three trials (comprising nearly 800 patients) were analysed together, the number needed to treat (NNT) for the primary outcome (death or disability) and secondary outcome (the number surviving with normal function) was nine and eight, respectively. In the six trials listed in Table 1, only CoolCap reported any patients (3%) that had mild encephalopathy at entry (they may have had subclinical seizures). The other trials did not report any with mild encephalopathy.

Recently, long-term follow-up from the first three trials at age 6–8 years has been published [15–17]. The TOBY trial was the only study large enough to have power to confirm that 72 h TH, starting within 6 h of birth, offered long-term neurological protection [17], with an NNT of eight. This number gives great scope for improving outcome. At 18 months, 50% of cooled infants had poor outcome defined as death or severe disability, compared to 66% in NT infants [18]. In addition to investigating additional treatment strategies, major emphasis should be put on investigating whether we are using the optimal TH treatment protocol. Uniform follow-up with comparable methods (ideally the same) is necessary, and here lies a major responsibility at national and international levels. Specifically, it seems to be easier to obtain funding for treatment than for follow-up.

Table 1 shows the entry criteria and outcome in six different trials. Note that three trials did not use aEEG or EEG (Criterion C) for entry – only Criteria A and B. All doctors who recruited patients for the NICHD trial were formally trained and certified in assessing neurology.

Unfortunately, the patients who did not meet the entry criteria in any of the large randomized controlled trials (RCTs) were not followed-up, so we missed the opportunity to study the outcome of those screened but not treated. This question could still be answered if large centers followed up, and reported, those screened but not cooled. There is evidence that mild derangements at birth, such as Apgar scores <7 at 1 min, reduce IQ by 8 points at 18 years of age [19], and that "grade I encephalopathy" survivors have worse behavioural outcomes at 10 years of age than matched children with no encephalopathy [20]. However, we do not know whether it might also be harmful to electively intubate, ventilate, sedate and cool infants for three days who are not encephalopathic (or mildly encephalopathic) after birth. Recent observational studies of cooled infants have seen outcomes that are more favorable than those presented in the RCTs (<50% poor outcome in the cooled group) [21–23]. It is possible that infants currently recruited have milder encephalopathy than those in the original trials. Overall mortality in published trials (Table 1) is also likely to be dependent on local practices for redirecting care, and may not purely represent the effectiveness of TH.

2. Comparing current with previous outcome data

All large trials published before 2010 used death and disability, assessed by Bayley II and the Gross Motor Function Classification System (GMFCS) at age 18 months, as primary outcome. Since 2006, Bayley III, a further-developed version of the Bayley examination, has been used. On examining 61 cooled infants with both tests, we found Bayley III scores to be higher than Bayley II by 10–15 points (one standard deviation = 15 points), which will result in better outcome if reporting uncorrected Bayley III results compared with Bayley II [24].

3. Broader entry criteria for cooling

We have expanded our local entry criteria for cooling since December 1st, 2006. Using prospective data collected over a six-year period in our regional cooling centre, we compared complications and outcome between infants who were cooled but who did not fulfill the standard inclusion and exclusion criteria as set out in the CoolCap/TOBY protocol ($n = 36$) with 129 infants who did fulfill the standard entry criteria (Table 2) [25]. The six subgroups cooled outside of standard entry criteria were infants who started cooling later than 6 h of age, moderately preterm infants (34–35 weeks of gestation), infants with postnatal collapse, major cranial hemorrhage, congenital cardiac disease, and surgical conditions. For each group, clinical details and outcome are presented. When comparing outcome between the 36 infants included outside trial criteria with those 129 that met traditional trial entry criteria, poor outcome was 36 vs 35%. One group stands out with worse outcome: five infants with major hemorrhage, of which four had a subgaleal hemorrhage, and one a large intraventricular hemorrhage during rewarming. Two died, and two had poor developmental outcome. The fifth had a very mild diplegia, with normal cognition. Our local advice is now not to cool infants with cranial bleeds until hemorrhage and clotting are under control, and then apply milder TH, e.g. T_{rec} 35°C. Currently, there are no experimental data behind this advice other than our own clinical experience.

Another much-discussed subgroup is that of infants with postnatal collapse. We cooled 10 such infants who fulfilled the A (except Apgar), B, and C entry criteria after the collapse [25]. They were a sick group of patients (Table 2). Fifty percent were hypoglycemic, 90% needed inotropic support, and 90% had seizures. One infant had a metabolic disorder (very long-chain acyl-CoA dehydrogenase deficiency) diagnosed after rewarming, and was developmentally within the normal range. Fortunately, cooling is likely to reduce the levels of toxic metabolites [26]. Of the subgroup with postnatal collapse, none died, and 38% had poor outcome. We continue to assess asphyxiated infants for TH if they do not fulfill the standard criteria on an individual basis. Parents are informed, and participation requested on the basis that infants are treated outside standard criteria. We have not had infants with a known chromosomal diagnosis when starting cooling, though one patient was later diagnosed with a chromosomal deletion. Another child who fulfilled criteria A and B was not cooled, as the aEEG was normal. He was diagnosed with the neonatal form of myotonic dystrophy at a few days of age, with the mother and grandmother having the same diagnosis.

Table 2 (data summarized from Smit et al. [25]) shows the demographic data and outcome from 129 infants recruited as advised in the CoolCap/TOBY protocols, and 36 infants recruited outside these criteria. Data from the 36 infants were grouped according to those criteria that were not implemented.

4. Effective time window for TH

The original decision for the CoolCap trial to start within 5.5 h of age was based on Gunn's thorough animal experiments in fetal sheep [27]. This important time window was then found to be the same as in a very different preclinical model, the seven-day-old rat [28]. Experimentally, the effectiveness of TH improves with an