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Review

Prediction of outcome methods assessing short- and long-term outcome after therapeutic hypothermia

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SUMMARY

Therapeutic hypothermia has significantly changed outcomes for newborns suffering neonatal encephalopathy. Outcome predictors established in the pre-cooling era may not automatically be transferred to the cooling era. This article reviews how the reliability of routinely used outcome predictors has changed. We summarize current knowledge about why this may be the case and when to best obtain and analyze different clinical, biochemical, and imaging outcome markers to predict outcome in cooled asphyxiated newborns.

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1. Introduction

Therapeutic hypothermia (TH) for the treatment of neonatal encephalopathy (NE) of hypoxic–ischemic (HI) origin is one of the major improvements in neonatal medicine in the past 15 years. TH became standard treatment in 2010 following the large randomized controlled trials (RCTs) showing that TH significantly reduces death or severe disability in moderately asphyxiated newborns compared to normothermia (NT) treatment [1].

The prediction of neurodevelopmental outcome remains one of the major challenges for clinicians treating newborns with NE, and for parents this is a key question. Great progress had been made in establishing significant associations between early assessments and outcomes in non-cooled newborns suffering from NE, some aiming at prediction of outcome within the first days after birth and others providing information later in the first two weeks. However, there are questions about whether methods used to predict neurodevelopmental outcome in the pre-cooling era can be relied upon, now that cooling is standard care. There are many reasons why this may not be the case:

- Nowadays, there is unfortunately too little concern about applying TH more widely in units and to infants not eligible for the original RCTs. Thus, current cooled cohorts may differ from those previously included in studies assessing outcome predictors.
- Conversely, some of the pre-cooling data include newborns who would have not fulfilled all the entry criteria to the RCTs, hence prediction of outcome may be different from those applicable to the RCTs' strict recruitment criteria.
- Cooling is now initiated much earlier than during the RCTs, when the median time to start TH was 4.5 h [1]. Even though the neuroprotective potency of TH may be best when initiated very early after HI [2], it is not clear whether all affected newborns benefit from early cooling.
- Newborns with early mild encephalopathy (not included in the RCTs) are now often being cooled, some of whom would have spontaneously improved very quickly and would be expected to have a good outcome without TH.
- When newborns are cooled, less injury may occur, so very early markers of injury and outcome used previously are likely to be different.
- TH will induce changes in metabolism affecting biochemical markers. Therefore, the development of injury may be delayed, and hence the optimal timing of outcome markers may change.

This review focuses on methods suitable for use as outcome predictors in the neonatal period for infants with NE of presumed HI origin. The aim is to assess their accuracy and reliability for predicting outcomes up to early childhood, comparing data from the recent pre-cooling era and data from the non-cooling arms of RCTs, to data from infants undergoing TH.

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1.1. Outcome definitions

1.1.1. Short term

This includes different degrees of encephalopathy and other neurological abnormalities persisting at least a week or more from birth, or death.

1.1.2. Longer term

This is usually assessed using standardized tests [mainly the Bayley Scales of Infant Development, 2nd edn (BSID-II) or the Griffiths Mental Developmental Scales (GMDS)] that evaluate a child's cognitive and language skills and fine and gross motor development, most usually at 18–24 months. Severe outcome is generally taken as a developmental quotient (DQ) < 70 or severe cerebral palsy (CP; Gross Motor Function Classification System levels 3–5) [3]. Other severe outcomes are central visual difficulties not corrected with spectacles, hearing impairments requiring aids, and seizures requiring anti-epileptic medication. Sometimes secondary microcephaly with a fall of >2 SD from birth in head circumference is included. At the age at which most outcome assessments have been done following NE, behavioral and more subtle communication difficulties are still hard to assess and cognitive problems may well be underestimated. As yet, the longest follow-up of cooled infants is from three of the RCTs at 6–8 years [4–6].

2. Predicting outcome in newborns suffering neonatal encephalopathy: pre-cooling vs cooling eras

Table 1 summarizes the different outcome parameters, and whether there is a difference in outcome predictors, differentiating between the pre-cooling and cooling eras.

2.1. Clinical assessment

The Apgar score is used worldwide to describe the newborn's physical condition based on heart rate, respiration, colour, muscle tone, and responsiveness (maximum score 10) at 1, 5, and 10 min after birth. In the pre-cooling era, Carvale et al. found that a 5 min Apgar score <5 was significantly associated with the occurrence of seizures in the neonatal period and abnormal neurodevelopmental outcome at 1 year of age in asphyxiated newborns [7]. However, the 5 min Apgar score was only used in two cooling trials (one small) as one of their entry criteria [8,9] and neither found an association between this score and death or disability in non-cooled or cooled newborns. The 10 min Apgar score was used in most of the RCTs as one of the entry criteria and is now established in most cooling protocols. In non-cooled asphyxiated newborns from the National Institute of Child Health and Human Development (NICHD) cooling trial, a 10 min Apgar of ≤4 was significantly associated with a poor neurodevelopmental outcome [10]. In cooled infants from the same study group, the 10 min Apgar score was used to discriminate newborns with regard to outcome [10]. Of 63 cooled newborns, 24 had a 10 min APGAR of 0–2, of whom 17 died or survived with severe disability at 18–22 months. When the cohort was assessed at 6–7 years, there were 11 children with a 10 min Apgar score of 0. Five had survived without disability, of whom three were cooled [4]. In a secondary analysis of the CoolCap study, a higher 10 min Apgar in the cooled group was associated with better 18 month outcomes on univariate, but not on multivariate, analysis [11]. In a small single centre study, Sarkar et al. found on multivariate analysis that nine of their 12 cooled newborns with a 10 min Apgar of 0 died, and the three survivors were globally delayed at 18–24 months [12].

In summary, the 10 min Apgar score seems to be less predictive in the cooling era compared to the pre-cooling era. Currently published data would not support using the Apgar score in isolation as an outcome predictor.

In 1976 Sarnat and Sarnat [13] published a three-point clinical grading system to stage the severity of encephalopathy, and this staging system has been shown to correlate significantly with neurodevelopmental outcome in non-cooled asphyxiated newborns studied between 24 and 40 months of age [14]. The maximum stage of severity may not be apparent until 12–36 h after birth and the most severe stage reached is that most predictive of outcome. An analysis of Sarnat scores before initiation and after 72 h of therapy, from cooled newborns in the CoolCap trial, showed that clinical assessment at randomization was less predictive of outcome in the TH group compared to that in the NT group [15]. They also showed that the greater the improvement in encephalopathy by day 4, the better the outcome in the HT group compared to the NT group [15]. As described by Thoresen [16] this may be due to an effect of sedation, as most sedatives are metabolized in the liver and will have longer half-lives at lower temperatures, thus increasing the risk for high drug levels and over-sedation, worsening the encephalopathy score during TH. In the NICHD cooling trial [17], cooled infants had a higher likelihood of improving their stage of encephalopathy within 24 h of birth. In a secondary analysis, stages of encephalopathy were evaluated at different time-points, i.e. at <6 h, during TH and at discharge [18]. They found, not surprisingly, that the persistence of severe NE at the end of TH and an abnormal neurological examination at discharge were associated with a greater risk of death or disability at 18 months of age.

The Thompson score, introduced in 1997 [19], is based on a neurological examination of nine signs with a maximum score of 22. A neurologically normal newborn scores 0. In non-cooled newborns, the Thompson score is highly predictive of outcome: a score >10 on day 3 has a positive predictive value (PPV) of 73% and a negative predictive value (NPV) of 94% for abnormal outcome, and a score >7 on day 10 has a PPV of 63% and a NPV of 100% for abnormal outcome [19]. A score of >7, assessed within the first 6 h after birth, was used as part of the entry criteria for the NICHD cooling trial [17]. In a secondary analysis of the NICHD cooling trial [20], they found that a score >16 within 6 h of birth was significantly associated with poor outcome. However, the PPV for infants with a score between 7 and 16 was low. Lally et al. found in 54 newborns, of whom 17 were cooled, that a score >7 within 6 h of birth poorly identified infants eligible for cooling as defined by a moderate or severe stage of encephalopathy 3 days after birth [21]. In a single centre study [22], cooled infants with a score ≥16 at 3–5 h after birth had a severely abnormal amplitude-integrated electroencephalogram (aEEG) at 6 h and an abnormal short-term outcome. In a subgroup analysis of the neo.nEuro.network hypothermia trial, a score of <5 on day 7 had a PPV of survival without severe handicap of 91% and a score of >10 was associated with a PPV of 100% for a poor outcome [23].

2.1.1. Neurological assessment

Whereas clinical assessment would be considered routine, such data are often missing from clinical notes and there are not many studies assessing the usefulness of a standardized neurological examination for predicting outcome. Mercuri et al. [24] showed it to be a good prognostic tool using the Hammersmith Neonatal neurological assessment in non-cooled asphyxiated newborns. The optimal time-point for predicting outcome was two or more weeks after birth [25], though a normal examination at any time was associated with a good outcome. In the cooling era, its outcome prediction may have changed, as many cooled newborns receive

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