Cooling for Newborns with Hypoxic Ischemic Encephalopathy

Cochrane Abstract

Background: Newborn animal studies and pilot studies in humans suggest that mild hypothermia following peripartum hypoxia-ischemia in newborn infants may reduce neurological sequelae without adverse effects. **Objectives:** To determine the effect of therapeutic hypothermia in encephalopathic asphyxiated newborn infants on mortality, long-term neurodevelopmental disability and clinically important side effects. **Search Methods:** We used the standard search strategy of the Cochrane Neonatal Review Group as outlined in The Cochrane Library (Issue 2, 2007). Randomized controlled trials evaluating therapeutic hypothermia in term and late preterm newborns with hypoxic ischemic encephalopathy were identified by searching the Oxford Database of Perinatal Trials, the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, 2007, Issue 2), MEDLINE (1966 to June 2007), previous reviews including cross-references, abstracts, conferences, symposia proceedings, expert informants and journal handsearching. We updated this search in May 2012. **Selection Criteria:** We included randomized controlled trials comparing the use of therapeutic hypothermia with standard care in encephalopathic term or late preterm infants with evidence of peripartum asphyxia and without recognizable major congenital anomalies. The primary outcome measure was death or long-term major neurodevelopmental disability. Other outcomes included

adverse effects of cooling and 'early' indicators of neurodevelopmental outcome. **Data Collection and Analysis:** Four review authors independently selected, assessed the quality of and extracted data from the included studies. Study authors were contacted for further information. Meta-analyses were performed using risk ratios (RR) and risk differences (RD) for dichotomous data, and weighted mean difference for continuous data with 95% confidence intervals (CI). **Main Results:** We included 11 randomized controlled trials in this updated review, comprising 1,505 term and late preterm infants with moderate/severe encephalopathy and evidence of intrapartum asphyxia. Therapeutic hypothermia resulted in a statistically significant and clinically important reduction in the combined outcome of mortality or major neurodevelopmental disability to 18 months of age (typical RR 0.75 (95% CI 0.68–0.83); typical RD –0.15, 95% CI –0.20 to –0.10); number needed to treat for an additional beneficial outcome (NNTB) 7 (95% CI 5–10) (8 studies, 1,344 infants). Cooling also resulted in statistically significant reductions in mortality (typical RR 0.75 (95% CI 0.64–0.88), typical RD –0.09 (95% CI –0.13 to –0.04); NNTB 11 (95% CI 8–25) (11 studies, 1,468 infants) and in neurodevelopmental disability in survivors (typical RR 0.77 (95% CI 0.63–0.94), typical RD –0.13 (95% CI –0.19 to –0.07); NNTB 8 (95% CI 5–14) (8 studies, 917 infants). Some adverse effects of hypothermia included an increase sinus bradycardia and a significant increase in thrombocytopenia.

Reviewers' Conclusions

There is evidence from the 11 randomized controlled trials included in this systematic review ($n = 1,505$ infants) that therapeutic hypothermia is beneficial in term and late preterm newborns with hypoxic ischemic encephalopathy. Cooling reduces mortality without increasing major disability in survivors. The benefits of cooling on survival and neurodevelopment outweigh the short-term adverse effects. Hypothermia should be instituted in term and late preterm infants with moderate-to-severe hypoxic ischemic encephalopathy if identified before 6 h of age. Further trials to determine the appropriate techniques of cooling, including refinement of patient selection, duration of cooling and method of providing therapeutic hypothermia, will refine our understanding of this intervention.

Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG: Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database of Systematic Reviews 2013, Issue 1. Art. No.: CD003311. DOI: [10.1002/14651858.CD003311.pub3](https://doi.org/10.1002/14651858.CD003311.pub3).

Commentary

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The updated review of Jacobs et al. [1] provides further convincing evidence of the efficacy of moderate therapeutic hypothermia ($33\text{--}34^{\circ}\text{C}$) for term and late preterm infants with moderate or severe hypoxic ischemic encephalopathy (HIE). Therapeutic hypothermia results in both a statistically significant and clinically important reduction in mortality or major neurodevelopmental disability (fig. 1, 2). The number needed to treat suggests that for every 7 infants with moderate to severe HIE we treat, 1 will benefit by surviving without developmental disability.

The addition of several more studies allows insight into interesting secondary outcomes. Short-term adverse effects of hypothermia include an increase in sinus bradycardia and a significant increase in thrombocytopenia. There also appears to be more persistent pulmonary hypertension than clinicians were previously aware of. However, the benefits of cooling on survival and neurodevelopment far outweigh these short-term adverse events.

In the current update, Jacobs et al. report a significant decrease in the risk of MRI abnormalities in infants who received cooling (typical RR 0.73, 95% CI 0.60–0.89).

These MRI abnormalities are highly predictive of poor developmental outcome and may be an important biomarker as we try to further define treatment strategies for cerebral protection with hypothermia [2].

Practice regarding therapeutic hypothermia varies greatly from the practices defined in the clinical trials (for example, gestation 35 weeks upwards, cooling to $33\text{--}34^{\circ}\text{C}$ for 72 h starting within 6 h of birth). In preliminary results from the Vermont Oxford Network Neonatal Encephalopathy Registry, only 57% of the 2,457 cooled infants met the key eligibility criteria used in the randomized trials. In those infants who did not meet key eligibility criteria, 40% were cooled that did not have moderate or severe encephalopathy or seizures prior to cooling, 17% were <36 weeks' gestation and 60% had hypothermic therapy initiated after 6 h from birth [3]. Although the results regarding cooling are quite promising, it is somewhat disconcerting to see the diffusion of this technology without adequate study in these related groups of infants.

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References

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- 3 Pfister RH, Edwards EE, Soll RF, Bingham P, Inder TE, Nelson KB, Raju TNK, Horbar JD: Do infants treated with hypothermic therapy in routine practice meet the eligibility criteria from the original randomized trials? Platform Session: Neonatal Hypoxic Ischemic Encephalopathy & Neuroprotection. Washington, PAS, 2013.

Fig. 1. Therapeutic hypothermia versus standard care. Effect on death or disability in survivors assessed (by method of cooling).

Fig. 2. Therapeutic hypothermia versus standard care. Effect on death (by method of cooling).