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[Intervention Review]

Cooling for newborns with hypoxic ischaemic encephalopathy

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ABSTRACT

Background

Newborn animal studies and pilot studies in humans suggest that mild hypothermia following peripartum hypoxia-ischaemia 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). Randomised controlled trials evaluating therapeutic hypothermia in term and late preterm newborns with hypoxic ischaemic 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 randomised 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 recognisable 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 randomised controlled trials in this updated review, comprising 1505 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 to 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 to 10) (8 studies, 1344 infants). Cooling also resulted in statistically significant reductions in mortality (typical RR 0.75 (95% CI 0.64 to 0.88), typical RD -0.09 (95% CI -0.13 to -0.04); NNTB 11 (95% CI 8 to 25) (11 studies, 1468 infants) and in neurodevelopmental disability in survivors (typical RR 0.77 (95% CI 0.63 to 0.94), typical RD -0.13 (95% CI -0.19 to -0.07); NNTB 8 (95% CI 5 to 14) (8 studies, 917 infants). Some adverse effects of hypothermia included an increase sinus bradycardia and a significant increase in thrombocytopenia.

Authors' conclusions

There is evidence from the 11 randomised controlled trials included in this systematic review (N = 1505 infants) that therapeutic hypothermia is beneficial in term and late preterm newborns with hypoxic ischaemic 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 ischaemic encephalopathy if identified before six hours 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.

PLAIN LANGUAGE SUMMARY

Cooling for newborns with hypoxic ischaemic encephalopathy

There is evidence that induced hypothermia (cooling) of newborn babies who may have suffered from a lack of oxygen at birth reduces death or disability, without increasing disability in survivors. This means that parents should expect that cooling will decrease their baby's chance of dying, and that if their baby survives, cooling will decrease his/her chance of major disability. A lack of oxygen before and during birth can destroy cells in a newborn baby's brain. The damage caused by the lack of oxygen continues for some time afterwards. One way to try to stop this damage is to induce hypothermia - cooling the baby or just the baby's head for hours to days. This treatment may reduce the amount of damage to brain cells. This review found that there is evidence from trials to show that induced hypothermia helps to improve survival and development at 18 to 24 months for term and late preterm newborn babies at risk of brain damage. More research is needed to understand which infants need cooling and the best way of cooling, including duration of treatment and method of cooling.