Hypothermia for neonatal hypoxic ischemic encephalopathy: an updated systematic review and meta-analysis

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CRD summary
This review found that treatment with therapeutic hypothermia reduces the risk of death and major disability in newborns with moderate to severe hypoxic ischaemic encephalopathy. The review was generally well conducted and the authors' conclusions are likely to be reliable.

Authors' objectives
To evaluate the effectiveness of therapeutic hypothermia for newborns with hypoxic ischaemic encephalopathy.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and Oxford Database of Perinatal Trials were searched from June 2007 to May 2011. There were no without language restrictions. Search terms were reported. The strategy from a recent Cochrane review was used (see Other Publications of Related Interest). References from the previous review were checked.

Study selection
Eligible studies were randomised controlled trials in newborns with moderate to severe hypoxic ischaemic encephalopathy that compared treatment with therapeutic hypothermia to normothermia. Eligible trials were required to include data on death and disability at age 18 months or older. Trials of newborns with mild hypoxic ischaemic encephalopathy and trials with significant methodological limitations were excluded from the review.

The included patients presented with moderate to severe hypoxic ischaemic encephalopathy and were born at gestation times from at least 35 weeks. Some trials used total body cooling. Other trials used selective head cooling with mild systemic hypothermia. Random allocation and hypothermia were undertaken within six hours of birth. Therapeutic hypothermia was maintained for 72 hours except in one trial. Secondary outcomes included the individual elements of the primary outcomes and survival with normal neurological function.

The authors stated that study selection was performed by consensus.

Assessment of study quality
Methodological quality was assessed using the Cochrane risk of bias assessment tool for sequence generation, allocation concealment, blinding of outcome assessment, completeness of assessment, likelihood of selective reporting bias and likelihood of other biases.

The authors did not state how many reviewers performed the assessment.

Data extraction
Data were extracted by one reviewer to calculate risk ratios (RR) and 95% confidence intervals (CI) for the outcomes. The primary outcome was a composite of death or long-term (≥18 months) major neurodevelopmental disability defined as cerebral palsy, scores below specified levels on developmental scales, intellectual impairment, blindness or sensorineural deafness requiring amplification. Authors were contacted for clarification and missing information.

Methods of synthesis
Pooled risk ratios and 95% confidence intervals were calculated using a Mantel-Haenszel fixed-effect model. Number needed to treat (NNT) for benefit were calculated. Clinical heterogeneity was described narratively. Presence of statistical heterogeneity was assessed using $X^2$ and $I^2$. Subgroup and sensitivity analyses evaluated the impact of clinical factors, early cessation of treatment and methodological concerns on the outcomes. Potential for publication bias was evaluated using visual appraisals of funnel plots.
**Results of the review**

Seven randomised controlled trials (1,214 patients, range 31 to 325) were included in the review. The overall bias assessment indicated that three trials were unlikely to be at risk of bias, two trials had a low risk of bias and two trials had a moderate risk of bias.

Statistically significant benefits were observed in newborns treated with therapeutic hypothermia for the composite outcome of death or major neurodevelopmental disability at 18 months (RR 0.76, 95% CI 0.69 to 0.84 and NNT=7, 95% CI 5 to 10; I²=0%; seven trials). Significant reductions were observed in risk of death at 18 months (RR 0.75, 95% CI 0.63 to 0.88 and NNT=11, 95% CI 7 to 26; I²=0%).

Among newborns who survived to 18 months, therapeutic hypothermia was associated with statistically significant reductions in risk of major disability (RR 0.68, 95% CI 0.56 to 0.83 and NNT=8, 95% CI 5 to 16; I²=12%), cerebral palsy (RR 0.62, 95% CI 0.49 to 0.78 and NNT=8, 95% CI 5 to 16; I²=33%), developmental delay (RR 0.66, 95% CI 0.52 to 0.82 and NNT=8, 95% CI 5 to 18 patients; I²=25%) and blindness (RR 0.56, 95% CI 0.33 to 0.94 and NNT=23, 95% CI 12 to 207; I²=0%). No significant differences were observed for risk of deafness between newborns treated with hypothermia and newborns who maintained normothermia. Survival with normal neurological function was increased in the therapeutic hypothermia group (RR 1.63, 95% CI 1.36 to 1.95 and NNT=7, 95% CI 5 to 11; I²=0%; six trials).

The results of sensitivity and subgroup analyses were similar to the results for the primary analyses. No evidence of publication bias was identified by visual appraisals of funnel plots in the review.

**Authors’ conclusions**

 Therapeutic hypothermia was effective in reducing the risk of death or major disability at 18 months of age in newborns with moderate to severe hypoxic ischaemic encephalopathy. Importantly, the mortality rate was reduced without increasing disability rates in asphyxiated newborns.

**CRD commentary**

The review addressed a clear question. Criteria for study inclusion were defined and reproducible. Appropriate databases were searched without language restrictions. The reviewers examined potential for publication bias using validated methods. Steps were taken to minimise reviewer error and bias for study selection but were not reported for assessment of methodological quality and data extraction. Methodological quality was assessed using validated methods and the quality of the studies was observed to be generally good.

The authors’ decision to combine the results in a meta-analysis appeared justified by the lack of statistical heterogeneity observed in the results. Appropriate sensitivity and subgroup analyses were conducted to further determine characteristics of successful treatment on the basis of particular clinical factors (such as severity of encephalopathy at presentation and cooling method).

The review was well conducted and the authors conclusions’ regarding the evidence are likely to be reliable but the evidence base was rather small.

**Implications of the review for practice and research**

**Practice:** The authors stated that identifying newborns who were unlikely to respond to hypothermia therapy was required to individualise treatment decisions. Evidence from the review suggested that therapeutic hypothermia may be more beneficial in newborns with moderate hypoxic ischaemic encephalopathy. It remained appropriate for clinicians to be conservative when counselling parents regarding long-term neurological function as the evidence was limited to 18 months follow-up post-birth.

**Research:** The authors stated that research was required to find adjuvant treatments for therapeutic hypothermia and determine longer term effects of hypothermia treatment.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.