A systematic review of cooling for neuroprotection in neonates with hypoxic ischemic encephalopathy: are we there yet?

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CRD summary
This generally well-conducted review assessed hypothermia for term neonates with hypoxic ischemic encephalopathy and perinatal asphyxia. The authors concluded that hypothermia is beneficial in reducing mortality and neurodevelopmental delay from 18 months, but that further research into specific cooling techniques is required. Due to issues with the primary studies, these conclusions should be viewed with some caution.

Authors' objectives
To assess therapeutic hypothermia for term neonates with hypoxic ischaemic encephalopathy (HIE).

Searching
MEDLINE, EMBASE, CINAHL, the Cochrane CENTRAL Register and the Cochrane Database of Systematic Reviews were searched to July 2006; the search terms were reported. No language restrictions were employed. The proceedings of the Pediatric Academic Societies were also searched and references of identified studies were checked.

Study selection
Randomised controlled trials (RCTs) of therapeutic hypothermia compared with normothermia in term neonates with perinatal asphyxia and HIE were eligible for inclusion. Studies of neonates with major congenital abnormalities were excluded from the review. HIE was defined by standardised neurological examination. Several criteria were used for the diagnosis of asphyxia (definitions were reported). Studies of both selective head cooling and whole body cooling were eligible. The primary review outcome was death or neurodevelopmental disability at ≥18 months of age. The secondary review outcomes were individual components of the primary outcomes and adverse events (definitions were reported). The definition of term neonates in the included studies ranged from 35 to 37 weeks' gestation. The age at which cooling commenced ranged from 120 to 330 minutes. Target temperatures ranged from 32.5 to 35.9 °C for the intervention groups and from 36.5 to 37.5 °C for the control groups, and were measured rectally or oesophagally. Follow-up in the included studies ranged from 12 to 22 months.

Three reviewers independently assessed studies for inclusion in the review.

Assessment of study quality
Validity was assessed using the following criteria: randomisation, allocation concealment, blinding and completeness of follow-up. Studies with high losses to follow-up or without long-term follow-up were included only for analyses of mortality and adverse events.

Three reviewers independently assessed the validity of the studies.

Data extraction
Data were extracted on primary and secondary outcomes to enable the calculation of relative risks (RRs) and risk differences (RDs) with 95% confidence intervals (CIs).

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
The studies were combined in a fixed-effect meta-analysis and pooled RRs and RDs, with 95% CIs, were calculated. A random-effects model was also employed, but the results were not reported. A priori subgroup analyses of selective...
head cooling versus whole body cooling were conducted. Statistical heterogeneity between the studies was investigated using the $I^2$ statistic. Where statistically significant results were found, the number-needed-to-treat (NNT) or number-needed-to-harm (NNH) were calculated.

**Results of the review**

Five RCTs (n=552) were included in the review.

All studies used appropriate allocation concealment and randomisation methods. Two studies blinded the outcome assessment and three reported adequate follow-up (93 to 98%).

Therapeutic hypothermia reduced the composite outcome of death or disability (RR 0.78, 95% CI: 0.66, 0.92; NNT 6, 95% CI: 5, 20; 5 RCTs, n=552). Mortality was also significantly lower in the hypothermia group (RR 0.75, 95% CI: 0.59, 0.96; NNT 11, 95% CI: 6, 100). The subgroup analysis revealed that there was a significant effect for the study using whole body cooling (RR 0.68, 95% CI: 0.48, 0.97; NNT 8, 95% CI: 5, 100; 3 RCTs), but not for the 2 RCTs using selective head cooling.

There was a significant effect of hypothermia on overall neurodevelopmental disability at ≥18 months of age (3 RCTs, n=449), but not on disabling cerebral palsy, developmental delay, blindness or loss of hearing (3 RCTs in each case). No statistically significant heterogeneity between the studies was reported.

Significant adverse events were sinus bradycardia (RR 7.42, 95% CI: 2.52, 21.87; NNH 13, 95% CI: 8, 20; 4 RCTs), thrombocytopenia (RR 1.47, 95% CI: 1.07, 2.03; NNH 8, 95% CI: 5, 50; 3 RCTs) and spontaneously resolved higher mean plasma glucose concentrations. There were no other significant differences in adverse events.

**Authors' conclusions**

Therapeutic hypothermia appears to have a beneficial effect on outcomes in term neonates with moderate to severe HIE, but further research is required to establish the safety and efficacy of specific cooling techniques.

**CRD commentary**

The review question and inclusion criteria were clear. The authors searched a number of relevant databases and other sources. This, together with a lack of language restrictions, makes it less likely that some relevant studies were not included in the review. The authors reported using methods to minimise reviewer bias and error in the selection of studies for the review and the assessment of validity, although it is not clear if these were also employed for the data extraction. An appropriate validity assessment was conducted. The decision to employ meta-analysis was appropriate, subgroup analyses were planned a priori, and statistical heterogeneity between the studies was appropriately assessed. This was a generally well-conducted review, although some of the included studies were very small, while others had problems with follow-up of patients. In view of this, and the level of clinical heterogeneity, the authors' conclusions should be viewed with some caution.

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

Practice: The authors did not state any recommendations for practice.

Research: The authors stated that further research on the efficacy and safety of specific cooling techniques for neonates with HIE is required, but noted that while currently ongoing trials will provide further evidence for a subsequent systematic review, it may be difficult to justify continuing RCTs where evidence of benefit is clear.

**Funding**

Not stated.

**Bibliographic details**

Other publications of related interest

Indexing Status
Subject indexing assigned by CRD

MeSH
Causality; Central Nervous System /physiopathology; Cerebral Palsy /epidemiology; Developmental Disabilities /epidemiology; Follow-Up Studies; Humans; Hypothermia, Induced; Hypoxia-Ischemia, Brain /mortality /physiopathology /therapy; Infant; Infant, Newborn; Survival Analysis; Treatment Outcome; Vision Disorders /epidemiology

AccessionNumber
12008009463

Date bibliographic record published
09/08/2008

Date abstract record published
03/11/2008

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.