Hypothermia to treat neonatal hypoxic ischemic encephalopathy: systematic review
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CRD summary
This well-conducted review concluded that hypothermia is safe and effective at reducing death and moderate to severe neurodevelopmental disability in neonates with postintrapartum asphyxial hypoxic-ischaemic encephalopathy. The authors' conclusions appear reliable despite the differences between the studies and the lack of long-term data.

Authors' objectives
To compare the effectiveness and safety of hypothermia verus normothermia in neonates with postintrapartum asphyxial hypoxic-ischaemic encephalopathy (HIE).

Searching
MEDLINE, EMBASE, CINAHL and the Cochrane Library were searched up to December 2006; the search terms were reported. Abstracts from annual meetings of the Pediatric Academic Societies and the European Society of Pediatric Research were also searched, along with references from retrieved articles. No language restrictions were applied.

Study selection
Randomised controlled trials (RCTs) and quasi-randomised controlled trials comparing hypothermia (systemic or selective head cooling) for at least 24 hours with normothermia, in neonates with clinical, electophysiological or biochemical evidence of HIE, were eligible for inclusion. Further details of the specific evidence required for the diagnosis of HIE were given in the review. Half of the included studies assessed systemic cooling and half selective head cooling, usually down to between 33 and 35 °C. The individual patient inclusion and exclusion criteria varied between studies, but most studies only included neonates with an Apgar score of 5 or less 10 minutes after birth and a cord arterial blood pH of 7 or less. Eligible studies had to report survival without moderate to severe neurodevelopmental disability in infancy and childhood. A number of secondary outcomes including efficacy, safety and mortality were also specified (further details were given).

Two reviewers independently assessed each study against the inclusion criteria, and any disagreements were resolved by consensus or a third reviewer.

Assessment of study quality
Two reviewers independently assessed the validity of the studies using the following criteria: allocation concealment, method of randomisation and blinding of the outcome assessment. The completeness of follow-up was also reported. Any disagreements were resolved through consensus or by a third reviewer.

Data extraction
Two reviewers independently extracted the data from the studies. Any disagreements were resolved through consensus or by a third reviewer. For each study, relative risks (RRs), risk differences and the number-needed-to-treat (NNT) were calculated, along with 95% confidence intervals (CIs), for each outcome. Only efficacy data from children aged at least 12 months old (4 studies) were extracted, but safety data were extracted from all included studies.

Methods of synthesis
The studies were grouped by outcome and pooled RRs and NNTs calculated, along with 95% CIs, using a fixed-effect analysis. No statistical corrections were used to adjust for multiple analyses. Heterogeneity was assessed using the $\chi^2$ and I$^2$ statistics; funnel plots were also used. Pre-planned subgroup analyses were performed according to severity of HIE (moderate or severe), type of hypothermia (systemic or selective head cooling) and degree of hypothermia (moderate or mild). Further details were given.

Results of the review
Seven RCTs and a quasi-RCT were included in the review (n=650 in total). The efficacy analysis included only 3 RCTs and the quasi-RCT, but the analysis of safety included data from all 8 studies.
The overall methodological quality of the studies was described as 'acceptable'. Six studies used concealed allocation, none of the studies blinded the intervention, but three used one or more blinded assessments, and four reported the completeness of follow-up. One study had a 32% loss to follow-up.

Overall, there was a statistically significant reduction in death or moderate to severe neurodevelopmental disability associated with the use of hypothermia in comparison with the control group (RR 0.76, 95% CI: 0.65, 0.88). In addition, compared with the control, hypothermia showed a significant reduction in severe neurodevelopmental disability (RR 0.65, 95% CI: 0.48, 0.87), severe cerebral palsy (RR 0.64, 95% CI: 0.42, 0.98), life support withdrawn (RR 0.59, 95% CI: 0.36, 0.96) and the number of infants with a Mental Developmental Index less than 70 (RR 0.69, 95% CI: 0.50, 0.96). Significant benefits in favour of hypothermia were also seen in the overall death rate (RR 0.74, 95% CI: 0.58, 0.94), although the incidence of arrhythmia (RR 6.29, 95% CI: 1.43, 27.75) and thrombocytopenia (RR 1.51, 95% CI: 1.09, 2.10) were higher in the hypothermia group. There was no evidence of significant statistical heterogeneity for any of the above RRs.

Subgroup analyses were only conducted for the severity of encephalopathy due to the small number of included participants. Significant reductions in the combined outcome of death or moderate to severe neurodevelopmental disability were reported for patients with moderate HIE, but in patients with severe HIE the differences were not statistically significant.

The funnel plots suggested a lack of studies at the extremes of the point estimates and a clustering around point estimates, suggesting some minor heterogeneity.

Authors' conclusions
Hypothermia is safe and effective at reducing death and moderate to severe neurodevelopmental disability in neonates with postintrapartum asphyxial HIE.

CRD commentary
This well-conducted review used reliable methods and a quite extensive literature search to answer a clearly defined research question. There was little evidence of statistical heterogeneity, although the authors cautioned that there was some evidence of clinical heterogeneity in terms of individual study inclusion criteria, severity of illness, degree of hypothermia and outcome assessment. The limited numbers of often quite small studies also suggested that the statistical power of the heterogeneity tests and subgroup analyses was low, thus the authors' decision to limit their analyses because of this appears appropriate. Overall, despite the caution with regard to heterogeneity and the lack of long-term data, the authors' conclusions appear reliable.

Implications of the review for practice and research
Practice: The authors stated that hypothermia should be used 'for the treatment of postintrapartum asphyxial HIE within the first six hours after birth, in particular in infants with moderate encephalopathy being treated in centers with expertise and within the strict guidelines outlined in the protocols of these [the included] studies'. They also stated that parents should be informed about the known benefits in short-term outcomes, but also the lack of knowledge about long-term safety data.

Research: The authors stated that long-term follow-up of trial participants is required and that further research is needed to investigate the ideal initiation time for therapy, therapy duration, degree of hypothermia, duration of rewarming and the types of participants who most need this type of intervention. The authors highlighted three ongoing multicentre RCTs due to be completed by 2011 (see Other Publications of Related Interest nos.1-3).

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