Hypothermia treatment for traumatic brain injury: a systematic review and meta-analysis

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CRD summary
The authors concluded that in specific circumstances hypothermia may reduce mortality and increase the likelihood of a favourable neurological outcome in adults with traumatic brain injury: more research is needed. Although the review was well conducted in many respects, these conclusions may need to be regarded cautiously, given the rather limited search and the questionable quality of the primary studies.

Authors' objectives
To evaluate the safety and effectiveness of hypothermia for treating adults with traumatic brain injury (TBI).

Searching
Four previously published systematic reviews were hand searched for relevant studies (see Other publications of related interest). Search strategies in these reviews included searches (to September 2002) of MEDLINE, EMBASE, the Cochrane Library, Current Contents, Science Citation Index, Dissertation Abstracts, the specialist trials register of the Cochrane Injuries Group, and the proceedings of scientific meetings. A supplemental search of MEDLINE (2002 to June 2007) was also conducted. Search terms were provided. The search was restricted to published articles in English.

Study selection
Randomised controlled trials (RCTs) of adults with TBI that compared therapeutic hypothermia with standard care on admission to hospital were eligible for inclusion. It was required that at least 85% of participants in each trial were aged 14 years or more. The review outcomes were all-cause mortality (primary effectiveness outcome), favourable neurological response (i.e. the proportion of participants achieving a Glasgow Outcome Scale score of four or five at defined time points) (secondary effectiveness outcome), and safety (rates of arrhythmia and pneumonia).

Participants in the included trials were 73% male, the mean age was 37 years and 61% were Asian. The baseline Glasgow Coma Score was 5.6 (where reported). The method of delivering hypothermia differed across trials, as did the time to induction, duration and depth of cooling, site for temperature monitoring intervention and re-warming rate. Duration of follow up ranged from 120 hours to 24 months.

Two reviewers independently selected trials for inclusion, with disagreements resolved by consensus.

Assessment of study quality
The following aspects of study validity were considered: randomisation methods, allocation concealment, similarity of comparison groups at baseline, blinding of outcome assessment, sample size, use of intention to treat analysis, follow-up rate and associated ongoing comparability of groups.

Two reviewers independently extracted data using a pre-specified form. They were masked to author and journal. Disagreements were resolved by consensus and/or in discussion with a third masked reviewer.

Data extraction
Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated from the number of events in the control and intervention groups of each trial.

Two reviewers independently assessed study validity, with disagreements resolved by consensus. They were masked to author and journal.

Methods of synthesis
Data were pooled using random effects models to obtain pooled RRs and 95% CIs. Statistical heterogeneity was
assessed with the $\chi^2$ test. Pre-specified and post-hoc subgroup analyses were conducted to examine the effects of clinical and methodological differences between the studies, such as cooling temperature (pre-specified), use of barbiturates for control of intracranial pressure (ICP) and trial duration (the latter two both post-hoc). The effects of individual components of trial quality were explored in sensitivity analyses. All independent variables were treated as dichotomous. Final analyses included only the RCTs which reported that there were no significant differences between groups at baseline.

**Results of the review**

Thirteen RCTs were included in the review (n=1,339; sample size 10 to 396).

Quality/sensitivity analysis by quality

Only one RCT reported using an adequate method of randomisation and none reported adequate allocation concealment. Nearly all analysed at least 97% of randomised participants. Nine RCTs reported that at baseline there were no statistically significant differences between the groups in demographic or prognostic characteristics. Sensitivity analysis showed stronger treatment effects in trials with statistically significant differences at baseline, or where this information was not reported.

**Hypothermia versus conventional treatment**

**Mortality:**
In the eight RCTs (n=781) that studied comparable groups, mortality was 20% lower in the intervention group, but this finding was not statistically significant (RR 0.80, 95% CI: 0.59, 1.09). Inclusion of all 13 studies resulted in a significant benefit for hypothermia (RR 0.74, 95% CI: 0.63, 0.88).

**Favourable neurological outcome:**
In the eight RCTs that studied comparable groups, a favourable outcome was 25% more common in the intervention group, but this finding was not statistically significant (RR 1.25, 95% CI: 0.96, 1.62). Inclusion of all 13 studies resulted in a significant benefit for hypothermia (RR 1.37, 95% CI: 1.11, 1.69).

Subgroup analyses (8RCTs) showed that for both the above endpoints favourable outcomes were most likely when hypothermia was maintained for more than 48 hours (mortality: RR 0.51, 95% CI: 0.33, 0.79; favourable neurological outcome: RR 1.91, 95% CI: 1.28, 2.85; 3RCTs) and when administration of barbiturates for ICP control was not part of standard management (mortality: RR 0.58, 95% CI: 0.4, 0.85; favourable neurological outcome: RR 1.79, 95% CI: 1.27, 2.52; 4RCTs). Significant benefits for hypothermia were also associated with longer trials (over one year).

**Adverse events**
Fewer than half of the RCTs reported this outcome. Pneumonia was significantly more common within 12 months in the hypothermia group than among controls (RR 2.37, 95% CI: 1.37, 4.10), especially in RCTs involving barbiturate administration (RR 6.45, 95% CI: 2.47, 16.85). No significant association between hypothermia and arrhythmia rates was reported.

**Authors' conclusions**
Current evidence suggests that in specific circumstances hypothermia may reduce mortality and increase the likelihood of a favourable neurological outcome in adults with traumatic brain injury. More research is needed.

**CRD commentary**
The objectives and inclusion criteria of the review were clear and several relevant sources were searched for studies, but the restriction to published studies in English meant that the review was prone to publication and language biases. Steps were taken to minimise the risk of bias and error by having more than one reviewer independently undertake study selection, data extraction and validity assessment, and relevant criteria were considered in the assessment of validity. There was some inconsistency between the text and table with respect to study validity. The statistical techniques used to combine trials and assess for heterogeneity seem appropriate, but where statistically significant heterogeneity was evident (in the meta-analysis of neurological outcomes) it was not noted in the text or explored further. Potential publication bias was not assessed, despite the exclusion of unpublished studies. Trial quality was strongly taken into account in the interpretation of results and the restriction to studies without significant baseline differences between groups seemed justifiable, although some such differences might arise by chance and their impact.
is unquantifiable. Also the quality of the remaining studies was questionable, given the absence of any studies reporting adequate allocation concealment. Although the review was well conducted in many respects, the authors’ conclusions may need to be regarded cautiously, given the rather limited search and the questionable quality of the primary studies.

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

Practice: the authors stated that hypothermia, preferably maintained for over 48 hours, is an option for treatment of TBI. It should be used only with caution, as potential benefits may be offset by an increased risk of pneumonia. The authors suggested restricting the use of hypothermia to patients initially responsive to standard ICP-lowering therapy.

Research: the authors stated that more evidence from well conducted trials is needed in this area. Future research should take account of real-life aspects of recovery such as return to work, driving and independent living.

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