The role of hypothermia in the management of severe brain injury: a meta-analysis

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Authors' objectives
To determine the effectiveness of hypothermia in the management of severe brain injury.

Searching
MEDLINE, the Cochrane Database of Systematic Reviews, EMBASE and the abstract centre for the American Association of Neurological Surgery and the Congress of Neurological Surgeons were searched (from 1966 onwards); the search terms were reported and there were no language restrictions. The reference lists of retrieved articles were checked and experts were consulted for details of further studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies of hypothermia in the management of severe head injury, compared with normothermia, were eligible for inclusion. In the included studies, the temperature of hypothermia ranged from 32 to 35 degrees C and the duration of hypothermia was between 24 hours and 14 days. The time to target temperature, where reported, ranged from 8 to 15 hours post-injury and the rewarming schedule varied between 12 hours and 5 days.

Participants included in the review
Studies of participants aged 10 years or older with post-traumatic head injury were eligible for inclusion. In the included studies, the majority of participants were men and the primary mechanism of injury was a motor vehicle accident.

Outcomes assessed in the review
There were no specific criteria for the outcomes, providing data were given from which relative risks or weighted mean differences (WMDs) could be calculated. The included studies reported a variety of outcome measures including the Glasgow Outcome Scale score, intracranial pressure, pneumonia, cardiac arrhythmia, prothrombin time and partial thromboplastin time.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies for inclusion. At the final selection stage, the reviewers were blinded to the authors' names, journal titles and funding sources.

Assessment of study quality
The assessment was based on the Jadad scale. Points were allocated for concealment of treatment allocation, randomisation, blinding of the outcome assessment, and the handling of withdrawals and drop-outs. The authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.

Data extraction
Data were extracted by reviewers blinded to the journal titles and authors' names. A standard form was used to extract the following study details: classification of head injury (Glasgow Coma Scale score), category of hypothermia (mild or moderate), ages of the patients, initiation and duration of hypothermia, extent of blinding, and outcomes reported. Outcome data were used to calculate an odds ratio (OR) or WMD with 95% confidence intervals (CIs) for each of the outcomes of interest.
Methods of synthesis
How were the studies combined?
The studies were combined in a meta-analysis for each outcome measure, using a random-effects model and weighting studies by the inverse of their variance.

Publication bias was assessed using funnel plots of effect size (Glasgow Outcome Scale score and cardiac arrhythmia) versus sample size.

How were differences between studies investigated?
Heterogeneity was assessed with chi-squared tests; the results were considered heterogeneous if the P-value was less than 0.2.

Results of the review
Seven RCTs, involving a total of 668 participants, were included in the review.

Four studies assessed the Glasgow Outcome Scale score. There was evidence of heterogeneity between the studies and no significant effect of hypothermia was found (OR 0.61, 95% CI: 0.26, 1.46, P=0.3)

Five studies assessed intracranial pressure, but only two had data available for the meta-analysis. The summary effect showed no significant effect of hypothermia (WMD -2.98, 95% CI: -7.58, 1.61, P=0.2), but there was evidence of heterogeneity.

Three studies, which were not significantly heterogeneous, reported on pneumonia and cardiac arrhythmia. There was no significant effect of hypothermia on either pneumonia (OR 2.05, 95% CI: 0.79, 5.32, P=0.14) or cardiac arrhythmia (OR 1.27, 95% CI: 0.38, 4.25, P=0.7).

Three studies assessed prothrombin time and partial thromboplastin time, of which only two provided data for statistical analysis. There was no evidence of heterogeneity. There was no significant effect of hypothermia on prothrombin time (WMD 0.02, 95% CI: -0.07, 0.10, P=0.7). However, the results for partial thromboplastin time (WMD 2.22, 95% CI: 1.73, 2.71, P<0.001) favoured normothermia over hypothermia.

No evidence of publication bias was found.

Authors' conclusions
The meta-analysis did not support the use of hypothermia in the management of severe head injury.

CRD commentary
The review question and inclusion criteria were clearly defined. Several electronic databases and other relevant sources were used in the search for primary studies. Two reviewers worked independently and were blinded to some study details, which should have minimised the introduction of errors and bias during the study selection and data extraction processes. Sufficient details of the primary studies were provided, and the methods used for the data extraction and statistical analysis were appropriate. Statistical heterogeneity was assessed, and clinical variation between the studies was discussed in terms of potential confounding factors. The limitations of the meta-analysis were discussed and, accordingly, the authors presented suitably cautious conclusions and recommendations.

Implications of the review for practice and research
Practice: The authors stated that their conclusions should not be used to define clinical practice as there were some limitations of the studies in the meta-analysis.

Research: The authors stated that a definitive and rigorously conducted RCT is urgently needed to assess the effectiveness of hypothermia in the management of post-traumatic brain injury.
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