Prophylactic hypothermia for traumatic brain injury: a quantitative systematic review

CRD summary
The review found that early prophylactic mild to moderate hypothermia improved mortality and functional outcomes after severe traumatic brain injury, especially when a long-term or goal-directed cooling strategy was used. In view of limitations in the review, including poor quality studies and possible publication bias (both acknowledged by the authors), some caution may be required in interpreting the findings.

Authors’ objectives
To evaluate the use of prophylactic hypothermia for traumatic brain injury.

Searching
MEDLINE, EMBASE, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, PapersFirst and Proceedings were searched to June/July 2007. Conference proceedings, abstracts and reference lists of reviews and relevant studies were searched. Search terms were reported in an online appendix.

Study selection
Randomised controlled trials (RCTs) of early prophylactic mild to moderate hypothermia compared with standard management for treating adults (aged 16 years or older) with acute severe non-penetrating traumatic brain injury (Glasgow Coma Scale Score 8 or less) were eligible for inclusion. Studies were required to report mortality as an outcome.

The depth of cooling in most of the included studies was 32° to 34°C (range 32° to 35°, where reported). Duration of cooling ranged from 24 hours to 14 days. Rewarming criteria varied; half of the studies did not initiate rewarming until intracranial pressure had normalised. Outcomes reported in the review were mortality, neurological outcome defined by the Glasgow Outcome Scale (GOS) and adverse events.

Papers were shortlisted by a single reviewer. Final study selection was conducted independently by two reviewers (apart from studies in Chinese, which were reviewed by a single reviewer and all five were excluded).

Assessment of study quality
Study validity was assessed by rating methods of allocation concealment and blinding of outcome assessment as adequate, unclear or inadequate. Studies where neither were adequate were rated as poor quality. It was not stated how many reviewers performed the validity assessment.

Data extraction
Neurological outcomes were dichotomised as good (GOS score 4 to 5) or poor (GOS score 1 to 3). Risk ratios (RRs) were calculated for dichotomous outcomes and mean differences for continuous outcomes, with 95% confidence intervals (CIs).

Two reviewers independently extracted data. Study authors were contacted for more information if necessary.

Methods of synthesis
Studies were combined using a random-effects model to calculate pooled risk ratios and 95% CIs. Absolute risk and number needed to treat (NNT) were calculated. Heterogeneity was assessed using $X^2$ and $I^2$ tests ($p<0.10$ and $I^2=50\%$ signified statistical heterogeneity).

Subgroup analyses were conducted to determine the impact of length of cooling, defined as either short-term (48 hours or less) or long-term/goal-directed (over 48 hours and/or continued until intracranial pressure was normal). Sensitivity
analyses were planned to determine the impact of excluding low-quality studies. Publication bias was assessed with a funnel plot.

**Results of the review**

Twelve RCTs were included (n=1,327, range 22 to 396). Four trials had adequate allocation concealment. Seven trials had blinded outcome assessment. Five studies were low quality. No studies blinded patients and caregivers.

Hypothermia treatment was associated with significantly lower mortality (RR 0.73, 95% CI 0.62 to 0.85, NNT=10, 95% CI 6 to 20; 12 RCTs) and greater likelihood of a good neurological outcome (RR 1.52, 95% CI 1.28 to 1.80, NNT=5, 95% CI 3 to 8; 10 RCTs) without exceeding cut-offs for statistical heterogeneity ($I^2$=0% and $I^2$=34%). Subgroup analysis by length of treatment, long-term or goal-directed treatment (eight RCTs) significantly improved both mortality and neurological outcomes; short-term treatment (four RCTs) did not significantly affect either outcome.

Various adverse events were reported in the intervention groups, including bradycardia (seven RCTs), hypokalaemia (six RCTs), thrombocytopenia (four RCTs) and hypotension (three RCTs) associated with hypothermia, and rebound in intracranial pressure associated with rewarming (three RCTs of short-term cooling).

The funnel plot was suggestive of publication bias; small negative studies were less likely to be published. Sensitivity analysis by quality did not change the overall findings.

**Authors’ conclusions**

Early prophylactic mild to moderate hypothermia improved mortality and functional outcomes after severe traumatic brain injury, especially when a long-term or goal-directed cooling strategy was used.

**CRD commentary**

The objectives and inclusion criteria of the review were clear. Relevant sources were searched for studies without limitation by publication and language status. Steps were taken to minimise the risk of reviewer bias and error by having more than one reviewer undertake data extraction; it was unclear whether this applied also to validity assessment and it appeared that initial study selection involved only a single reviewer. Appropriate statistical methods were used to combine the studies and assess and explore heterogeneity.

The authors noted that the review had shortcomings, including suboptimal study quality and possible publication bias. In view of these limitations in the review, some caution may be required in interpreting the findings.

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

**Practice:** The authors stated that evidence supported use of early prophylactic mild to moderate hypothermia in individuals with severe traumatic brain injury, to be commenced as soon as possible after injury regardless of intracranial pressure. They stated that the best results occurred with a long-term or goal-directed cooling protocol.

**Research:** The authors stated that there was wide scope for more research on prophylactic hypothermia for traumatic brain injury in pre-hospital and emergency department settings; they noted that five studies were ongoing. The authors recommended that more research in this field be conducted by Western researchers as most of the long-term studies were set in Asia.

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**Bibliographic details**

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.