Therapeutic hypothermia and prevention of acute kidney injury: a meta-analysis of randomized controlled trials
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CRD summary
The review found that in trials of therapeutic hypothermia that assessed kidney outcomes, therapeutic hypothermia did not appear to reduce acute kidney injury or need for dialysis and was associated with lower mortality. These conclusions should be regarded with some caution due to the poor quality of included trials and the lack of trials specifically designed to measure kidney outcomes.

Authors' objectives
To assess the effect of therapeutic hypothermia on development of acute kidney injury and mortality.

Searching
MEDLINE (to February 2011) and ClinicalTrials.gov were searched with no language restriction. Search terms were reported. Abstracts from the annual scientific meetings of the American Society of Nephrology were searched from 2000 to 2010. Reference lists of relevant reviews were also checked.

Study selection
Eligible studies were randomised controlled trials (RCTs) of adults undergoing therapeutic hypothermia compared with normothermia. Trials had to report acute kidney injury (primary outcome) or other kidney outcomes (such as serum creatinine, creatinine clearance, need for dialysis). The secondary outcome was all-cause mortality.

The age of participants in the included studies ranged from 29 to 69 years; most (53% to 95%) were men. The population setting in nearly all studies was traumatic brain injury, out-of-hospital cardiac arrest or cardiopulmonary bypass. The mean duration of cardiac arrest (where relevant) ranged from 22 to 103 minutes. The cooling technique was most commonly fluid infusion (usually blood and/or crystalloid), which lasted from 23 to 5,760 minutes. The hypothermic target temperature was 26°C to 34°C for most studies. None of the studies had kidney endpoints as a primary outcome. Definitions of acute kidney injury varied (where reported), but usually involved a change in creatinine and/or serum creatinine. Mortality was reported at differing follow-up times, ranging from postoperative to 90 days follow-up (where stated).

Two reviewers independently selected the studies.

Assessment of study quality
Trial quality was assessed with a modified Jadad scale, which allocated up to 5 points for adequacy of randomisation, blinding and study attrition. Trials were rated as poor (0 to 1 point), fair (2 to 3 points) or good (4 to 5 points).

The authors did not state how many reviewers conducted the assessment.

Data extraction
Data to permit the calculation of Peto odds ratios (ORs) were extracted for dichotomous outcomes and mean differences in change from baseline for continuous outcomes, with 95% confidence intervals (CIs). Where trials included more than two intervention groups, separate analyses were conducted for each group. Primary study authors were contacted for further information if necessary.

Two reviewers independently extracted the data, with disagreements resolved by discussion with a third reviewer.

Methods of synthesis
Trials were combined to calculate pooled odds ratios and 95% confidence intervals, using a fixed-effect model for most analyses. Heterogeneity was assessed using $X^2$ and $I^2$. Trials with no events in either group were excluded from the analyses.
Subgroup and sensitivity analyses were conducted to evaluate the effect of population setting, cooling technique, infusate type, trial quality, sample size, and statistical model. Meta-regression was used to explore other clinical variables.

Publication bias was assessed with funnel plots.

**Results of the review**

Nineteen RCTs with 2,218 participants were included in the review. Sample sizes ranged from 23 to 291 participants. One trial was good quality, 11 were fair quality, and seven were poor quality. Only 12 trials described an adequate randomisation method. Only seven trials reported the number of drop-outs and described use of intention-to-treat analysis.

Event rates were low; some studies had no events in either group. There was no significant difference between therapeutic hypothermia and normothermia in rates of acute kidney injury (OR 1.01, 95% CI 0.68 to 1.51; 12 RCTs; 1,839 participants; I² =0%), serum creatinine (five RCTs; 522 participants), creatinine clearance (three RCTs; 141 participants), or need for dialysis (three RCTs; 509 participants). Therapeutic hypothermia was associated with a significant reduction in the mortality rate (OR 0.69, 95% CI 0.51 to 0.92; 16 RCTs; 2,077 participants, I²=0%).

In meta-regression for the outcome of acute kidney injury, lower target cooling temperature was associated with lower odds of injury (p=0.01). However, the findings were no longer significant if a trial that delivered infra-renal arterial cooling of 15°C was excluded. Duration of therapeutic hypothermia or duration of cardiac arrest did not have a significant effect. The results of other sensitivity and subgroup analyses were also reported.

There was some asymmetry in the funnel plot for the primary outcome.

**Authors' conclusions**

In trials of therapeutic hypothermia that assessed kidney outcomes, therapeutic hypothermia did not appear to reduce acute kidney injury or need for dialysis, but was associated with lower mortality.

**CRD commentary**

The objectives of the review were clear. Some relevant sources were searched for studies without restriction by language or publication status, but only two databases were searched. There was some suggestion of publication bias, so it was possible that some trials may have been missed. It was unclear whether quality assessment was carried out with sufficient attempts to minimise reviewer bias and error.

No details were given about the quality of individual trials, but the overall quality of the evidence appeared low. Appropriate methods were used to combine the trials and to assess and explore differences between them. As the authors noted, the review was limited by lack of a consistent definition of acute kidney injury in the primary trials, differing target cooling temperatures, and small sample sizes. They also acknowledged that the review did not address safety outcomes and that analysis of mortality rates was restricted by the exclusion of trials not reporting kidney outcomes. Very low event rates in the included trials meant that the confidence intervals were wide.

The authors' conclusions should be regarded with some caution due to poor trial quality and a lack of trials specifically designed to measure kidney outcomes.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that future trials should examine whether hypothermia prevented acute kidney injury in the setting of major cardiovascular surgery and out-of hospital cardiac arrest. Future trials should aim to identify the optimum cooling temperature and should monitor for adverse effects.

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