Safety profile and outcome of mild therapeutic hypothermia in patients following cardiac arrest: systematic review and meta-analysis

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CRD summary

The authors concluded that mild therapeutic hypothermia was generally safe, for comatose patients, following a cardiac arrest, and it could improve their short- and long-term survival. Given the heterogeneity across studies, for mortality, and the small numbers of studies reporting adverse events, the authors' suggestion to interpret the findings cautiously should be heeded; the findings may not be reliable.

Authors' objectives

To assess the safety and efficacy of mild therapeutic hypothermia, for patients following a cardiac arrest.

Searching

Five electronic databases, including MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL), were searched, for English-language articles, from inception to June 2011. Search terms were reported. Reference lists of relevant reviews and studies were manually screened, and experts on therapeutic hypothermia were contacted.

Study selection

Eligible for inclusion were studies assessing the safety and efficacy (mortality, complications, or any adverse event or side-effect) of mild therapeutic hypothermia, for comatose patients following a cardiac arrest. Studies that reported only mortality had to be randomised or non-randomised comparative studies; other outcomes could be reported in studies of any design.

The included studies were conducted in the USA, Europe (four in the UK), Australia, Canada, Japan, or Korea. Where reported, patients had various initial cardiac rhythm problems, such as ventricular tachycardia, ventricular fibrillation, or pulseless electrical activity. Where reported, cooling methods were surface, invasive or both, with target temperatures ranging from 32 to 35 degrees. The duration of cooling ranged from four to 48 hours. Three studies were of children. Many studies excluded patients with certain conditions (reported in the review), and most included patients who had received medication-induced sedation and paralysis, as well as other medications, such as insulin, as needed.

Two reviewers independently screened studies for inclusion, with discrepancies resolved by consensus.

Assessment of study quality

Two reviewers assessed the quality of randomised controlled trials (RCTs), using the Jadad scale (maximum score 5), and used the Newcastle-Ottawa scale to assess the quality of other studies (maximum score 9). Case reports were not assessed.

Data extraction

Data were extracted, from studies with control groups, to calculate relative risks and 95% confidence intervals. Summary incidence rates were calculated, using data from studies of any design.

Two reviewers extracted outcome data; discrepancies were resolved by referral to a third reviewer.

Methods of synthesis

A fixed-effect model was used to pool the relative risks and 95% confidence intervals. Statistical heterogeneity was assessed using Cochran's Q and I^2; heterogeneity was considered significant if I^2 was over 50%.

Sensitivity analyses were performed to investigate statistical heterogeneity. Outcome differences between cooling methods and devices were reported. Subgroup analyses were conducted by study design, and initial cardiac rhythm problem, and for studies that only included children.

Summary incidence rates were pooled using published methods.

Results of the review

Sixty-three studies (12,839 participants; range one to 5,317) were included in the review: seven were RCTs, 14 were prospective cohorts, 12 were retrospective cohorts, and 30 were case series or reports. Most studies were of good quality; RCTs scored between 2 and 5 on the Jadad scale. Cohort studies scored between 6 and 9 on the Newcastle-Ottawa scale, while case series scored between 3 and 5.

Mortality: From 17 comparative studies, mild therapeutic hypothermia statistically significantly reduced in-hospital mortality (RR 0.86, 95% CI 0.83 to 0.89; 17 studies; I^2=67%), mortality at one month (RR 0.61, 95% CI 0.45 to 0.81; two studies; I^2=0), and mortality at six months (RR 0.73, 95% CI 0.61 to 0.88; four studies; I^2=0). The results from subgroup analyses were reported.

Complications and adverse events: The authors reported that most complications and adverse events were not statistically significantly different between treatment groups, with the exception of arrhythmia (RR 1.25, 95% CI 1.00 to 1.55; five studies) and hypokalaemia (RR 2.35, 95% CI 1.35 to 4.11; one small study). The results for arrhythmia were of borderline significance, and there was evidence of significant statistical heterogeneity (I^2=75%). Sensitivity analyses identified one study that was most responsible for this heterogeneity. Three studies reported that statistically significantly fewer patients in their control groups required vasopressors (RR 1.23, 95% CI 1.09 to 1.40; three studies, I^2=16%).

There were no statistically significant differences in adverse events between cooling methods (three studies). Other results, including pooled incidence rates, were reported in the review.

Authors' conclusions

Mild therapeutic hypothermia was generally safe, for comatose patients, following a cardiac arrest, and it could improve their short- and long-term survival.

CRD commentary

The review question and supporting inclusion criteria were clearly defined. Various sources were searched for relevant articles, but the search was limited to articles in English, creating potential for language bias. Appropriate methods were used to assess the quality of studies with different designs. Each stage of the review process was conducted in duplicate, minimising the potential for reviewer error and bias.

The outcome data from comparative studies were pooled, but it was unclear why a random-effects model was not used, given the substantial statistical heterogeneity for some outcomes. The authors acknowledged that some study designs had inherent limitations, which may have resulted in insufficient power, potential for selection bias, and confounding. They therefore suggested that their conclusions should be interpreted cautiously.

The authors' conclusions reflect the evidence, but given the heterogeneity across studies, for mortality, and the small number of studies reporting individual adverse events, the authors' suggestion to interpret the findings cautiously should be heeded; the findings may not be reliable.

Implications of the review for practice and research

Practice: The authors stated that clinicians should be aware of the possible complications of mild therapeutic hypothermia.

Research: The authors stated that further research was needed to identify the most effective and safest methods to induce hypothermia. Studies should assess the effects of mild therapeutic hypothermia for patients with non-ventricular fibrillation, the optimal temperature, and the effects in children.

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