Therapeutic hypothermia and the risk of infection: a systematic review and meta-analysis
Geurts M, Macleod MR, Kollmar R, Kremer PH, van der Worp HB

CRD summary
The authors concluded that cooling increased the risk of pneumonia and sepsis but found no convincing evidence of an increased overall rate of infections. This review appeared generally well conducted and despite the limitations found in the evidence the conclusions are probably reliable.

Authors' objectives
To evaluate whether therapeutic hypothermia in adults is associated with an increased risk of infections.

Searching
PUBMED, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to October 2012 for relevant studies in English, Dutch or German. Reference lists of included studies and Cochrane reviews were consulted. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) and quasi-RCTs that compared therapeutic hypothermia with control in adults were eligible for inclusion. Therapeutic hypothermia was defined as the intentional reduction of body temperature. All indications were considered. Studies with hypothermia as part of a procedure and studies in which the control group was actively managed to normothermia were included. Temperature modulation with antipyretics as the active treatment or local cooling without lowering of total body temperature were excluded. The primary outcome of interest was any infection. Secondary outcomes included pneumonia, urinary tract infection, sepsis and any other specific infection.

About one third of the trials used hypothermia as a procedure only. Most other studies involved patients with traumatic brain injury. Four studies involved patients with ischaemic stroke. One study involved patients with cardiac arrest. Most studies used surface cooling; duration varied depending on the indication.

Two reviewers independently selected the studies. Discrepancies were resolved through discussion.

Assessment of study quality
Two reviewers independently evaluated the quality of the studies using the Cochrane risk of bias tool.

Data extraction
Data on infection was extracted by two reviewers independently to calculate rate ratios (any infection) and risk ratios (specific infections) and 95% confidence intervals.

Methods of synthesis
A meta-analysis (random-effects model) was used to pool rate ratios and risk ratios. Heterogeneity was assessed using $I^2$. Publication bias was assessed using a funnel plot and Egger’s test. Subgroup analyses were conducted according to type of injury, duration of cooling, whether hypothermia was applied as part of a procedure, mode of hypothermia, use of mechanical ventilation, temperature achieved and use of prophylactic normothermia in the control group.

Results of the review
Twenty-three trials (2,820 patients, range 16 to 1,001) were included. Reported follow-up durations ranged from seven days to three months. Overall, the evidence was considered at high risk of bias due to a lack of information about methods of randomisation (11 out of 23 trials) and a lack of uniform and explicit definitions of infections. Few studies (five out of 23) reported that outcome assessors were appropriately blinded. The only study on patients with cardiac arrest was generally considered at low risk of bias. Other results of the quality assessment were reported.

Overall incidence of infections was higher in patients treated with hypothermia compared with control but the difference was not statistically significant (rate ratio 1.21, 95% CI 0.95 to 1.54; 23 trials).
Patients who underwent therapeutic hypothermia were at higher risk of pneumonia (risk ratio 1.44, 95% CI 1.10 to 1.90; 16 trials) and sepsis (risk ratio 1.80, 95% CI 1.04 to 3.10; six trials) compared to control. There was no statistically significant difference between intervention and control in risk of urinary tract infection. There was no evidence of significant heterogeneity across the studies ($I^2\leq33\%$).

The one study that included patients with cardiac arrest reported an increased risk of infection in patients treated with hypothermia but the difference was not statistically significant (rate ratio 1.40, 95% CI 0.97 to 2.02). Results of other subgroup analyses were reported.

**Authors' conclusions**

Cooling increased the risk of pneumonia and sepsis but no convincing evidence of an increased overall rate of infections was observed.

**CRD commentary**

The review question and selection criteria were stated clearly. Several bibliographic sources were consulted. Attempts were made to reduce reviewer error and bias throughout the stages of the review. Most of the included studies were small and several reporting and design limitations were identified. The synthesis methods appeared appropriate. A wide range of indications were considered. There was no evidence of significant heterogeneity in the main analyses.

This review appeared generally well conducted and despite the limitations in the evidence the conclusions are probably reliable.

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

**Practice:** The authors stated that clinicians should be aware that pneumonia and sepsis are common side effects associated with therapeutic hypothermia so that treatment can start early.

**Research:** The authors stated that future randomised trials of hypothermia should assess and report the occurrence of infections prospectively based on established definitions. They stated that future research should focus on identifying high-risk patients and on the effect of antibiotic prophylaxis.

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