Warm versus cold cardioplegia for heart surgery: a meta-analysis
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CRD summary
This review concluded that cold or warm cardioplegia used in cardiac surgery resulted in similar clinical outcomes. Warm cardioplegia resulted in more favourable postoperative cardiac index and enzyme-release outcomes. As data came from studies of generally poor quality that used techniques that may not have reflected current practice, the authors’ conclusions should be treated with caution.

Authors’ objectives
To compare the effects of warm cardioplegia to cold cardioplegia for myocardial protection during heart surgery.

Searching
PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to March 2009. Search terms were reported. Bibliographies of relevant articles and conference proceedings were checked. Only studies published in English were sought.

Study selection
Randomised controlled trials (RCTs) that compared warm cardioplegia (including lukewarm) to cold cardioplegia, as both initial induction and reperfusion solutions, in adults who underwent cardiac surgery were eligible for inclusion. Trials in which warm cardioplegia was used only in the induction stage or as terminal warm reperfusion (hot-shot) were excluded. Trials on people who underwent heart transplant were excluded.

Primary outcomes of interest were all-cause in-hospital death, perioperative myocardial infarction (proven by electrocardiogram and/or enzyme). Other outcomes included low output syndrome, postoperative use of intra-aortic balloon pump (IABP), stroke, atrial fibrillation, cardiac index and concentrations of creatine kinase-MB (CK-MB) and cardiac troponin (cTn).

Most participants in the included studies underwent coronary artery bypass graft (CABG) and others isolated valve surgery or combined CABG/valve surgery; some trials used partial or complete internal mammary artery (IMA) grafting and some used proximal vein grafts implanted with side-biting clamp. Warm blood and either cold blood or cold crystalloid were used as cardioplegic agents; where reported, warm cardioplegia ranged from 28°C to 37°C and cold cardioplegia from 4°C to 15°C; timing was continuous and intermittent and routes were antegrade and retrograde. Year of study publication was from 1992 to 2005.

The authors did not state how papers were selected for the review.

Assessment of study quality
Quality was assessed using the Jadad score of generation of allocation sequence, allocation concealment, investigator blinding, description of withdrawals/dropouts and efficacy of randomisation. The maximum score was 10.

The authors did not state how the validity assessment was performed other than that any disagreements were resolved by consensus.

Data extraction
Data were extracted independently and disagreements were resolved by consensus.

Relative risk (RR) and 95% confidence intervals (CI) were calculated for dichotomous data and weighted mean differences (WMD) and 95% CI for continuous data.
Methods of synthesis
Pooled odds ratios and 95% CI and WMD and 95% CI were calculated using a random-effects model.

Heterogeneity was assessed using $X^2$ and $I^2$.

Sensitivity analyses excluded trials that did not clearly report temperatures of cardioplegia and trials that used lukewarm cardioplegia. Subgroup analyses were based on use of different cold cardioplegia solutions (cold blood versus cold crystalloid).

Metaregression was used to investigate possible effects of publication year, quality score, type of surgical procedure, IMA grafting, proximal vein grafting with side-biting clamp and route (antegrade, retrograde) and timing (continuous, intermittent) of cardioplegia.

Publication bias was investigated using Egger's weighted regression test.

Results of the review
Forty-one RCTs (5,879 participants) were included. Study size ranged from 17 to 1,732 participants; 27 studies fewer than 100 participants and two studies contributed 2,733 participants.

Quality scores ranged from 4 to 7. Methods of randomisation and allocation concealment were unclear in most studies.

There were no differences between warm and cold cardioplegia for the outcomes of all cause mortality (18 RCTs), myocardial infarction (24 RCTs), low output syndrome (10 RCTs), IABP support (14 RCTs), atrial fibrillation (eight RCTs) and stroke (10 RCTs).

Warm cardioplegia was associated with improved postoperative cardiac index (WMD 0.28, 95% CI 0.26 to 0.31), lower peak cardiac troponin concentrations (WMD -1.45, 95% CI -2.47 to -0.42), and reduced CK-MB release after surgery (WMD -8.03, 95% CI -13.08 to -2.97).

There was no evidence of statistical heterogeneity or publication bias.

Sensitivity analysis did not significantly alter results. In subgroup analysis the risk of stroke was increased with warm blood cardioplegia compared to cold crystalloid cardioplegia (RR 2.44, 95% CI 1.07 to 5.59; three trials); there was no difference between warm blood and cold blood cardioplegia (seven trials) or any significant difference in other subgroup analyses. Metaregression did not reveal any significant interactions between variables and the main outcomes.

Authors' conclusions
Compared to cold cardioplegia, use of warm cardioplegia for myocardial protection during cardiac surgery resulted in similar incidences of clinical events, significant improvement in postoperative cardiac index and reduction in postoperative enzyme release.

CRD commentary
The aims of the review were clearly stated in terms of participants, intervention and study design. The search covered several relevant sources. The limitation to English-language studies meant it is possible that language bias affected the review. The review methods were not well described and it was unclear whether these were aimed at reducing reviewer error and bias. Study quality was assessed. Methods of synthesis appeared appropriate. Differences between studies were investigated and no statistical heterogeneity was evident. However, the authors said that surgical and anaesthetic techniques used in the trials varied considerably and that, although they investigated this, it was not entirely clear whether this may have had any effect on results. Many of the included studies were small, of lower quality and overall covered the period 1992 to 2005. As the authors commented, techniques changed over time and some of the studies may not have related to contemporary practice. Longer-term results were not available. Full details of data for clinical outcomes were presented, but detail of the analyses for cardiac index and enzyme release outcomes were not presented. In particular, there was no information about how many studies (participants) contributed to these
results and it was difficult to assess the validity of this data.

The authors' conclusions appeared to reflect the evidence, but given the potential for bias in the review and limitations of the included studies the conclusions should be treated with caution.

**Implications of the review for practice and research**
The authors did not state any implications for practice or research.

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