Is blood superior to crystalloid cardioplegia: a meta-analysis of randomized clinical trials

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CRD summary
The authors concluded that adults having cardiac surgery and receiving blood cardioplegia are at a moderately reduced risk of post-operative low output syndrome compared with those receiving crystalloid cardioplegia, though no difference in myocardial infarction or in-hospital death rates was evident. Despite some limitations of the search, the review was well-conducted overall and these conclusions are likely to be reliable.

Authors' objectives
To compare the effects of blood and crystalloid cardioplegia for improving outcomes after cardiac surgery.

Searching
MEDLINE (1966 to July 2005), PubMed, EMBASE and the Cochrane CENTRAL Register were searched for peer-reviewed articles published in English. Articles appearing only in abstract form were excluded.

Study selection
Randomised controlled trials (RCTs) comparing blood and crystalloid cardioplegia were eligible for inclusion. The primary review outcomes were low output syndrome (LOS), including use of inotropic agents and/or intra-aortic balloon pump (IABP) support; myocardial infarction (MI), either electrocardiogram (ECG) and/or enzyme-defined; and death in hospital. A secondary (surrogate) outcome in the review was creatinine kinase-MB fraction (CKMB) at 7, 24 and 48 hours post-operatively.

Blood cardioplegia was delivered at a range of temperatures in the included studies, while crystalloid cardioplegia was always cold. Most studies delivered cardioplegia intermittently by the antegrade route, but some studies also utilised retrograde and/or continuous/semicontinuous delivery. The overall mean pump time ranged from 49 to 146 minutes and mean aortic cross-clamp time ranged from 32 to 102 minutes. In most cases (where reported), the included studies defined LOS in terms of unusual requirement for inotropes or IABP for maintenance of blood-pressure: thresholds for hypotension, inotrope dose and duration of support varied. Where reported, definitions of MI generally included criteria relating to both ECG and enzyme changes. Most of the participants in the included studies were at low risk of adverse outcomes. Nearly all studies enrolled patients undergoing coronary artery bypass graft surgery, either elective or with a degree of clinical urgency. The other studies included patients undergoing valve procedures.

Two blinded reviewers assessed studies for inclusion.

Assessment of study quality
No systematic validity assessment was described. However, the following aspects of study validity were considered in the text: randomisation procedures, blinding of the patients and/or outcome assessors, sample size and number of study centres.

It appears that two blinded reviewers assessed the studies. If necessary, additional information on study methodology was requested from study authors.

Data extraction
Odds ratios (ORs) were calculated for dichotomous outcomes and mean differences for continuous outcomes, along with 95% confidence intervals (CIs) in both cases.

Two reviewers extracted the data and, if necessary, additional information was requested from study authors.

Methods of synthesis
The studies were combined in meta-analyses using random-effects models to calculate pooled ORs and weighted mean differences (WMDs), along with 95% CIs. Meta-regression analysis was conducted to examine the effect of temperature and delivery route on estimates of effect for MI and death. Statistical heterogeneity was assessed using the $\chi^2$ and $I^2$ statistics. Sources of clinical and methodological heterogeneity were discussed in the text. Publication bias was assessed using a funnel plot.

**Results of the review**

Thirty-four RCTs (n=5,044) were included.

Most of the studies reported few details about randomisation procedures or about the blinding of patients and outcome assessors. The majority of studies were small (n<100) and underpowered for clinical end points. All were conducted in single centres.

**Post-operative LOS, MI and death.**

When 10 RCTs (n=879) were pooled, the risk of post-operative LOS was significantly lower in the blood cardioplegia group (OR 0.54, 95% CI: 0.34, 0.84, p=0.006). However, when relevant studies were pooled, there was no significant difference between the two groups in the risk of MI (OR 0.78, 95% CI: 0.54, 1.13; 23 RCTs n=4,317) or death (0.80, 95% CI: 0.46, 1.40;17 RCTs n=4,022). There was no evidence of statistical heterogeneity in any of these analyses.

**Post-operative CKMB release (10 RCTs).**

The group receiving blood cardioplegia had significantly lower CKMB release than the crystalloid group at 7 and 24 hours after surgery: WMD -7.09 (95% CI: -12.92, -1.26) and WMD -5.91 (95% CI: -10.21, -1.62, p=0.007), respectively. There was no significant difference between the groups for this outcome at 1 or 48 hours.

The meta-regression found no statistically significant association between MI or death and the temperature (cold versus warm) or route of delivery (antegrade versus retrograde) of cardioplegia.

A funnel plot for the largest patient comparison (MI) showed no evidence of publication bias.

**Authors' conclusions**

It is fairly clear that adult patients having cardiac surgery who receive blood cardioplegia are at a moderately decreased risk of post-operative LOS and early CKMB release, compared with those who receive crystalloid cardioplegia. No significant difference between the groups in rates of MI or in-hospital death was evident.

**CRD commentary**

The review question and inclusion criteria were clear and relevant sources were searched for studies. The limitation to studies published in English introduces the possibility of language and publication biases; however, no evidence of publication bias was found upon investigation. Steps were apparently taken to minimise the risk of error and bias in the review process by having more than one reviewer make decisions about the study selection, validity assessment and data extraction. Relevant quality criteria were considered, but no details about the quality of the individual studies were presented. However, detailed information was provided about other characteristics of the primary studies. Appropriate statistical methods were used to pool the studies and to assess statistical heterogeneity and publication bias, and potential sources of clinical and methodological heterogeneity were well-addressed in the text. Despite some limitations of the search and a lack of detail in the reporting of study quality, the review was well-conducted overall and the authors' conclusions are likely to be reliable.

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

Practice: The authors stated that although the evidence is somewhat limited, it supports the use of blood in preference to crystalloid cardioplegia for coronary surgery.

Research: The authors did not state any implications for further research.
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