Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints
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Authors' objectives
Authors conducted a meta-analysis of all randomised, controlled trials of the three most frequently used pharmacological strategies to decrease perioperative blood loss (aprotinin, lysine analogues (aminocaproic acid and tranexamic acid), and desmopressin). A separate meta-analysis was done for studies concerning complicated cardiac surgery.

Searching
MEDLINE and EMBASE were searched between 1966 and December 1998. Terms used were both MESH terms and (part of) the textwords "heart surgery", "heart valve prosthesis", "myocardial revascularization", "coronary artery bypass", or "heart bypass", in combination with "hemostatics", "antifibrinolytic agents", "aprotinin", "trasylol", "tranexamic acid", "cyklokapron", "aminocaproic acid", "caprolest", "desmopressin", or "DDAVP". The search results were limited to "humans" and "clinical trials". References in all reports were cross-checked for other potentially relevant studies and the manufacturers of the pharmacological agents were asked to indicate missing trials or unpublished data. Studies were included irrespective of the type of publication or the language used.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs). Studies not truly randomised and double publications were excluded.

Specific interventions included in the review
Aprotinin (3x281 mg and 1x70 mg to 3x140 mg), lysine analogues (aminocaproic acid 10-30 g and tranexamic acid 3-10g), and desmopressin (0.3-0.6 micrograms) versus placebo.

Participants included in the review
People with perioperative bleeding. Trials that included children were excluded.

Outcomes assessed in the review
Studies were included if they reported at least one of the following clinically relevant outcomes; mortality, rethoracotomy, proportion of patients receiving a transfusion, and/or the occurrence of adverse affects (in particular perioperative myocardial infarction) in addition to perioperative blood loss.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

Assessment of study quality
The following criteria were considered: correct randomisation procedure, inclusion of consecutive patients, double-blind study design, similar baseline characteristics among study groups, similar treatment of groups (aside from the intervention), adequate assessment of end points, and statement of the fate of all patients who entered the trial. For fulfilment of each of these criteria, a score of 1 point was given (maximum score 7) to each article. Two independent investigators assessed the methodological quality of selected studies.

Data extraction
Data from the study reports were independently recorded by two investigators and entered into separate databases. The
results were compared and any disagreements resolved by consensus. Investigators were contacted for incomplete data or clarification, if necessary.

**Methods of synthesis**

How were the studies combined?

Data were analysed with RevMan version 3.1, and odds ratios with 95% CI for dichotomous data were calculated according to the fixed-effect model of Peto and Mantel-Haenszel, and the random-effects model of DerSimonian and Laird. Data presented are derived from the fixed-effect model. Continuous data were analysed by the weighted-mean-difference method. A separate analysis was performed to assess the effect of a lower dose of aprotinin compared to the conventional dose. A direct comparison between the various treatment strategies was conducted if sufficient trials were available. Studies concerning complicated cardiac surgery were analysed separately. Outcome measures were separately analysed for studies with the highest methodological score (7 points).

How were differences between studies investigated?

Tests for heterogeneity were done with each meta-analysis.

**Results of the review**

Seventy-two RCTs considering 8409 patients were included. 45 trials compared aprotinin with placebo; 16 trials compared lysine analogues and placebo; and 16 trials compared desmopressin and placebo. In addition, 12 studies compared treatment with conventional dose of aprotinin with lower doses of aprotinin. Lastly, in 8 trials, a direct comparison was made between treatment with aprotinin and lysine analogues. There was only one trial directly comparing desmopressin with aprotinin, and one trial directly comparing desmopressin with lysine analogues.

Treatment with aprotinin decreased mortality almost two-fold OR=0.55 95% CI 0.34-0.90 compared with placebo (26 studies). Treatment with aprotinin and with lysine analogues decreased the frequency of surgical re-exploration OR=0.37 95% CI 0.25-0.55 (26 RCTs), and OR=0.44 95% CI 0.22-0.90 (11 RCTs), respectively. These two treatments also significantly decreased the proportion of patients receiving any allogeneic blood transfusion. By contrast, the use of desmopressin resulted in a small decrease in perioperative blood loss, but was not associated with a beneficial effect on other clinical outcomes. Aprotinin and lysine analogues did not increase the risk of perioperative myocardial infarction; however, desmopressin was associated with a 2.4-fold increase in the risk of this complication. Results for other outcome measures were not found to be statistically significant.

Studies of patients undergoing complicated cardiac surgery showed similar results.

Tests for heterogeneity were not significant.

**Authors' conclusions**

Pharmacological strategies that decrease perioperative blood loss in cardiac surgery, in particular aprotinin and lysine analogues, also decrease mortality, the need for rethoracotomy, and the proportion of patients receiving a blood transfusion.

**CRD commentary**

The authors of this review attempt to answer a well defined question in a comprehensive manner. They state clear objectives and inclusion/exclusion criteria. The search for relevant studies was thorough and details of the search strategy were presented. The search was not restricted by language of publication and attempts were made to search for unpublished literature.

Relevant studies were subject to a comprehensive quality assessment procedure. Two independent reviewers both assessed trial quality and extracted data from included studies. Information presented on primary studies was limited. Details of analyses conducted were well presented. The authors conclusions that the results of this review should be interpreted with caution as a result of insufficient data are supported by the data presented.
Implications of the review for practice and research

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

Research: Further RCTs are required to confirm that treatment with aprotinin results in better clinical outcome than lysine analogues.

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