Is epsilon-aminocaproic acid as effective as aprotinin in reducing bleeding with cardiac surgery: a meta-analysis

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Authors' objectives
To compare the relative effectiveness and adverse-effect profile of epsilon-aminocaproic acid with aprotinin against placebo in patients undergoing cardiac surgery.

Searching
MEDLINE was searched using the keywords: aprotinin, epsilon-aminocaproic acid, cardiac surgery and randomized. Bibliographies of published review articles were inspected and a search made using the SCI-EXPANDED database of the Web-based ISI Citation Database. Searches were conducted between 1985 and 1998 for studies published in the English language.

Study selection

Study designs of evaluations included in the review
Randomised controlled trials (RCTs).

Specific interventions included in the review
Treatment regimes included conventional high-dose aprotinin (mainly 6 million kallikrein inhibiting units); low dose aprotinin (doses ranging from 1 to 3 million kallikrein inhibiting units) and epsilon-aminocaproic acid (doses ranging from 7 to 30 g); and placebo.

Participants included in the review
Patients undergoing the following types of routine cardiac surgery were included: primary and redo valve replacement or repair; primary and redo coronary artery bypass graft (CABG); and both.

Outcomes assessed in the review
The following outcomes were assessed: % of patients transfused; amount of packed red blood cells transfused (pRBC); total blood loss (intra and post operative) incidence of re-exploration regardless of indication; mortality; stroke, myocardial infarction, renal impairment; and allergic reactions as defined in the individual trials.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
Validity assessment included random allocation to placebo-control and double-blindedness. The authors do not state how the papers were assessed for validity, or how many of the authors performed the validity assessment.

Data extraction
The following data were extracted: author; date of publication; surgical procedure; drug regime; drug group; validity assessment criteria; trial multicentre or not; and outcomes reported. No details were given of methods used to extract data. Clarification of any ambiguous data were sought from the authors. Transfusion requirements recorded in millilitres were transformed to packed red blood cells by a conversion factor of 350 mL/ U. For dichotomous outcomes the total number of patient outcomes in the drug and treatment group was recorded in 2 x 2 tables.
Methods of synthesis

How were the studies combined?
The Peto odds ratio (OR) was calculated for dichotomous outcomes using the methods described by Yusuf et al (see Other Publications of Related Interest). Random-effects models were used for continuous and dichotomous summary estimates of effect.

How were differences between studies investigated?
Stratified analysis was performed to determine the influence of the following factors on effect size: trials restricted to primary CABG vs trials including patients undergoing mixed procedures; and study design criteria such as whether trials were placebo controlled or double-blinded. No details were given of statistical tests used to assess heterogeneity.

Results of the review

Fifty-two RCTs, including 37 trials of high-dose aprotinin, 17 trials of low dose aprotinin, and 9 trials of epsilon-aminocaproic acid were studied. Total number of patients was not stated.

71% of trials were double-blind; 71% were placebo controlled and 8% multicentre.

Crude event rates for drug group vs placebo group and ORs were reported as follows:

Transfusion of pRBC: high-dose aprotinin (32 studies, 2605 patients) 45.5% vs 70.1%; low dose aprotinin (13 studies, 1176 patients) 45.0% vs 67.7%; and epsilon-aminocaproic acid (5 studies, 302 patients) 24.5% vs 47%; P = 0.005. The OR for any pRBC transfusion for epsilon-aminocaproic acid: 0.32 (95%CI: 0.15, 0.69; P = 0.004).

Re-exploration: high-dose aprotinin (27 studies, 2154 patients) 1.1% vs 4.2%; P < 0.001; low dose aprotinin (13 studies, 1042 patients) 1.7% vs 3.7%; P = 0.048; and epsilon-aminocaproic acid (7 studies, 747 patients) 1.1% vs 2.6%; P = 0.127. Only significant for high-dose aprotinin. OR for high-dose aprotinin 0.39 (95%CI: 0.24, 0.61; P = 0.001). OR for low-dose aprotinin 0.56 (95%CI: 0.29, 1.08; P = 0.085). OR for epsilon-aminocaproic acid 0.54 (95%CI: 0.22, 1.33; P = 0.179).

Stroke: high-dose aprotinin (15 studies, 1341 patients) 0.6% vs 1.7%; P = 0.066; low dose aprotinin (9 studies, 973 patients) 0.4% vs 1.4%; P = 0.091; and epsilon-aminocaproic acid (7 studies, 775 patients) 0.0% vs 1.0%; P = 0.049. OR for high-dose aprotinin 0.56 (95%CI: 0.26, 1.21; P = 0.14). OR for low-dose aprotinin 0.54 (95%CI: 0.2, 1.45; P = 0.22). OR for epsilon-aminocaproic acid 0.47 (95%CI: 0.15, 1.56; P = 0.22). No significant differences found.

Myocardial infarction: high-dose aprotinin (17 studies, 1710 patients) 6.0% vs 4.9%; P = 0.316; low dose aprotinin (10 studies, 1125 patients) 4.1% vs 5.0%; P = 0.470; and epsilon-aminocaproic acid (6 studies, 735 patients) 3.9% vs 3.8%; P = 0.949. No significant differences found.

Mortality: high-dose aprotinin (25 studies, 4015 patients) 2.7% vs 3.1%; P = 0.468; low dose aprotinin (11 studies, 1165 patients) 3.3% vs 2.2%; P = 0.280; and epsilon-aminocaproic acid (5 studies, 677 patients) 1.8% vs 1.4%; P = 0.710. No significant differences found.

Renal dysfunction: insufficient data to evaluate effects of epsilon-aminocaproic acid. High dose aprotinin OR = 1.46 (95%CI: 0.92, 2.33; P = 0.11); low dose aprotinin OR = 1.01 (95%CI: 0.65, 1.57; P = 0.96). No significant differences found.

Allergic reactions: insufficient data to evaluate effects of epsilon-aminocaproic acid. High dose aprotinin OR = 1.58 (95%CI: 0.59, 4.23; P = 0.36). No significant differences found.

Stratified analysis: no important interactions between transfusion requirements and characteristics of trial (placebo-controlled or double blinding) or between trials restricted to patient undergoing primary CABG and those studying mixed populations. It was not possible to assess the effect on other outcomes due to sample size limitations.
Cost information
Estimates of drug costs given as follows: aprotinin $1000 for the conventional high dose regime, $500 for the low dose aprotinin regime; and $40 per average dose for epsilon-aminocaproic acid.

Authors' conclusions
Since aprotinin and epsilon-aminocaproic acid appear to have similar efficacies, the considerably less expensive epsilon-aminocaproic acid may be preferred over aprotinin for reducing haemorrhage with cardiac surgery.

CRD commentary
The aims and inclusion criteria were clearly stated. The influence of some aspects of validity on effect size was assessed. Some relevant details from the individual studies were presented. Results were presented graphically. The discussion includes consideration of the following limitations: impossibility of excluding publication bias; lack of sufficient power to detect clinically important effects on relatively infrequent outcomes; inability to exclude clinically meaningful effects of epsilon-aminocaproic acid on risks of myocardial infarction and mortality; variability in drug dosing, administration protocols, and in definitions of outcomes across trials.

By limiting primary studies to articles published in the English language some relevant studies may have been omitted. No details were given of methods used to select primary studies or extract data. Heterogeneity among trials was not discussed. Costs are quoted per regime for aprotinin but given per dose for epsilon-aminocaproic acid. Thus, costs quoted do not appear to be comparable.

The strength of evidence favouring epsilon-aminocaproic acid would be increased by considering results from randomised controlled trials that directly compared the two drugs.

Implications of the review for practice and research
Practice: Prophylactic antifibrinolytic therapy should be considered for routine use in patients undergoing cardiac surgery.

Research: The authors do not state any implications for research.

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Other publications of related interest

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MeSH
Aminocaproic Acid/adverse effects/therapeutic use; Antifibrinolytic Agents/adverse effects/therapeutic use; Aprotinin/adverse effects/therapeutic use; Dose-Response Relationship, Drug; Humans; Postoperative Hemorrhage
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.