Are antifibrinolytic drugs equivalent in reducing blood loss and transfusion in cardiac surgery: a meta-analysis of randomized head-to-head trials

Carless P A, Moxey A J, Stokes B J, Henry D A

CRD summary
This review assessed the use of tranexamic acid and epsilon aminocaproic acid, compared with aprotinin, to reduce peri-operative blood loss in cardiac surgery. The authors concluded that there was insufficient evidence to suggest that aprotinin could be replaced with either drug. The review methods were appropriate and the cautious conclusions reflect the limitations of the evidence.

Authors' objectives
To assess whether tranexamic acid (TXA) and epsilon aminocaproic acid (EACA) are as effective as aprotinin for reducing peri-operative blood loss during cardiac surgery.

Searching
MEDLINE (1966 to September 2003), EMBASE (1980 to September 2003), Current Contents (1993 to week 34, 2003) and the Cochrane CENTRAL Register (Issue 2, 2003) were searched; the search terms were reported. In addition, experts were contacted and the bibliographies of identified papers were checked. Studies in any language were sought.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) of parallel design were eligible for inclusion.

Specific interventions included in the review
Studies that assessed the prophylactic use of intravenous TXA or EACA given pre- or intra-operatively in comparison with aprotinin, were eligible for inclusion. Studies of post-operative administration were excluded. In some of the included studies cell salvage and reinfusion of shed mediastinal blood were used. The majority of studies excluded people who had been taking either aspirin or dipyridamole before surgery. Full details of the drug regimens were given.

Participants included in the review
Studies on adults (18 years or older) undergoing elective cardiac surgery were eligible for inclusion. In the majority of included studies the surgery was coronary artery bypass graft, with some including additional valve surgery or atrial septal defect repair. The mean ages of the participants ranged from 60.5 to 62.4 years and 77 to 79% were men.

Outcomes assessed in the review
Studies that reported on the number of individuals who received allergenic red blood cell (RBC) transfusions, or the volume of RBCs received, were eligible for inclusion. Other reported outcomes were blood loss, reoperation rates (because of blood loss) and clinical outcomes (mortality, myocardial infarction, thrombosis and stroke).

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed studies for inclusion in the review.

Assessment of study quality
Two reviewers independently assessed studies for quality. Any disagreements were resolved by consensus. The criteria used in the assessment related to double-blinding, allocation concealment, participant inclusion and exclusion, and methods of randomisation.
Data extraction
Two reviewers extracted the data; the data were checked for accuracy and consistency. Trials were excluded if the available data were presented in a form not useable in the analysis. Blood transfusion data expressed in millilitres was converted to units by dividing by 300.

Methods of synthesis
How were the studies combined?
Pooled relative risks (RRs) or weighted mean differences (WMDs), together with 95% confidence intervals (CIs), were calculated using a random-effects model. A Bayesian analysis was also performed to estimate the probability of TXA and EACA being non-inferior to aprotinin. The Bayesian mean RR was calculated using a random-effects model; a uniform (0,1) prior for risk of RBC transfusion with aprotinin was used, whilst the prior for reoperation rates with aprotinin was calculated from the results of a published systematic review. The non-inferiority limit for reoperations was taken to be 20%; for RBC transfusions, non-inferiority was concluded if the upper limit of the pooled RR was 1.2 or below. The non-inferiority limits were varied in the sensitivity analyses.

How were differences between studies investigated?
Heterogeneity was assessed using the Q statistic. To investigate heterogeneity one or more studies were removed from the analysis.

Results of the review
Twenty RCTs (2,430 participants) were included.

Generally the methodological quality of the included studies was poor. Only 42% reported double-blinding, 21% had adequate allocation concealment, 21% reported the randomisation method and 26% had complete follow-up.

TXA versus aprotinin (10 trials).
TXA was inferior to aprotinin for reducing 24-hour blood loss (WMD 106 mL, 95% CI: 37, 176; 10 trials). However, there was no difference between TXA and aprotinin in the number of units of blood transfused (WMD 0.06 units, 95% CI: -0.18, 0.31; 5 trials). There was no difference in the number of people requiring transfusion using conventional meta-analysis (RR 1.08, 95% CI: 0.88, 1.32; 9 trials) or Bayesian methods (RR 1.11, 95% Bayesian CI: 0.92, 1.45), nor was there evidence of a difference between treatments for reoperation for bleeding using either conventional or Bayesian methods. For RBC transfusion, the estimated probability that TXA was non-inferior to aprotinin was 0.82 when using an RR threshold of 1.2 and 0.57 when using an RR threshold of 1.1. For reoperation the probabilities of non-inferiority were 0.92 and 0.90 when using non-inferiority limits of 20% and 10% respectively.

EACA versus aprotinin (6 trials).
EACA was inferior to aprotinin for reducing 24-hour blood loss (WMD 185 mL, 95% CI: 134, 235; 4 trials). However, there was no difference in the number of units of blood transfused (WMD -0.22 units, 95% CI: -0.52, 0.09). There was also no difference between treatments in transfusion rates using conventional meta-analysis (RR 1.14, 95% CI: 0.84, 1.55) or Bayesian meta-analysis (RR 1.08, 95% Bayesian CI: 0.73, 1.52). For RBC transfusion, the estimated probability that EACA was non-inferior to aprotinin was 0.76 when using an RR threshold of 1.2 and 0.54 when using an RR threshold of 1.1.

Data for the clinical outcomes were sparse, but the authors reported that there were no trends favouring any of the treatments.

Authors’ conclusions
The available data provide insufficient evidence to suggest that aprotinin could be replaced by TXA or EACA in cardiac surgery. The trials were small and of poor quality, and did not evaluate clinically meaningful end points.
CRD commentary
The aims and inclusion criteria for this review were clearly stated. The authors searched a number of relevant databases and studies in any language were sought. Although they did not investigate publication bias, it was unlikely that relevant studies would have been missed. The methods of the review (study selection, data extraction and quality assessment) were appropriate for minimising the introduction of bias at these stages. Study quality was assessed and the authors discussed the implications of this in the results.

The authors stated that the trials were heterogeneous in terms of drug dose and treatment regimen and, although most outcomes did not show significant statistical heterogeneity, it was unclear how clinically relevant it was to pool the data. Bayesian methods were used to assess whether TXA and EACA were no worse than (non-inferior to) aprotinin, but no justification for the choice of non-inferiority margin was provided and the results were shown to be sensitive to the values chosen. Based on the limitations of the data, the authors' cautious conclusions appear reasonable.

Implications of the review for practice and research
Practice: The authors stated that the evidence was uncertain for replacing aprotinin with TXA or EACA in clinical practice.

Research: The authors stated that larger comparative trials using clinically important end points are necessary.

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**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.