Avoiding transfusions in children undergoing cardiac surgery: a meta-analysis of randomized trials of aprotinin

CRD summary
This review investigated aprotinin for children undergoing cardiac surgery. The authors concluded that aprotinin reduces the proportion of children transfused, but has no significant effect on the volume of blood transfused or chest tube drainage. Further research is needed before aprotinin can be routinely recommended in this population. Given the poor quality of the included studies, the authors' cautious conclusions seem appropriate.

Authors' objectives
To determine the effects of intravenous aprotinin, given peri-operatively to children undergoing cardiac surgery with cardiopulmonary bypass, on the proportion of children needing allogeneic red blood cell or whole blood transfusions, the volume of blood transfused, and the amount of chest tube drainage in the immediate post-operative period.

Searching
MEDLINE (1966 to November 2004), EMBASE (1980 to 2005) and the Cochrane Register of Controlled Trials were searched; the search terms were stated. In addition, the 'related article' search feature of PubMed was used and bibliographies of identified papers and reviews were checked for further relevant studies. Abstracts and proceedings were identified using PapersFirst and ProceedingsFirst. Only studies written in English were included.

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

Specific interventions included in the review
Trials that compared pre-operative or intra-operative administration of intravenous aprotinin in any dose with placebo, no aprotinin, or other antifibrinolytic drugs, were eligible for inclusion. In the included trials, aprotinin was compared with placebo, no treatment, E-aminocaproic acid (EACA), or aprotinin plus EACA. Details of the aprotinin dose used in each of the individual studies were provided in the paper.

Participants included in the review
Trials of children (younger than 18 years) undergoing primary or redo open-heart corrective or palliative surgery with cardiopulmonary bypass were eligible for inclusion. Where reported, the mean age ranged from 9.1 to 77 months across the included studies and the mean weight from 6.0 to 16.4 kg. The surgical procedures used in the included studies were Tetralogy of Fallot repair; atrial septal defect and/or ventricular septal defect repair including complete atrio-ventricular septal defects; repair of transposition of the great arteries; repair of hypoplastic left heart syndrome including Fontan and modified Fontan procedures; and valvular replacement or repairs.

Outcomes assessed in the review
The outcomes eligible for inclusion were the proportion of children requiring blood transfusion (in excess of pump prime), the amount of blood transfused and/or the amount of chest tube drainage. Red blood cell or whole blood transfusions were counted as the outcome unless the type of blood transfusion was not specified.

How were decisions on the relevance of primary studies made?
Two independent reviewers selected studies for inclusion; any disagreements were resolved by consensus.

Assessment of study quality

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Validity was assessed using the Jadad criteria, which assess randomisation and treatment allocation, blinding, and withdrawals and drop-outs. An overall score of 2 or lower (out of a maximum of 5) was considered poor methodological quality. In addition, reviewers judged the adequacy of the method of allocation concealment and the use of an objective, predefined transfusion protocol. Two independent reviewers, who were blind to authors, affiliated institutions, sponsors, journal name, date of publication and study results, assessed validity. Any disagreements were resolved by third-party adjudication.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Where possible, study authors were contacted for missing information. Where measures of variance were not available, they were imputed. Reported volumes of blood transfused and chest tube drainage were converted, where necessary, to mL/kg using the mean body weight or average body surface area of the study population. For studies that compared different doses of aprotinin, the proportion of children transfused was calculated by dividing the total number of cases in all aprotinin arms by the total number of children; the amount of blood transfused and chest tube drainage were estimated by calculating the mean of all aprotinin arms.

Methods of synthesis
How were the studies combined?
For dichotomous data, relative risks (RRs) were pooled using the random-effects model of DerSimonian and Laird; for continuous data, a weighted mean difference was calculated. Both were weighted by the inverse of the variance. Publication bias was assessed using funnel plots.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the I-squared (I²) statistic. Heterogeneity was classified as low (I²=25%), moderate (I²=50%) and high (I²=75%). Study quality, type of procedure (primary or redo sternotomies), age or weight criteria, cyanotic morphologies and aprotinin dose were identified a priori as possible sources of heterogeneity, and were investigated in subgroups analyses where possible.

Results of the review
Twelve RCTs (n=626) were included in the review.

Four studies were rated as good methodological quality (score 3 out of 5), while the rest were classified as poor.

Based on 6 studies, aprotinin produced a statistically significant reduction in the proportion of children transfused relative to control (RR 0.67, 95% confidence interval, CI: 0.51, 0.89). Heterogeneity was low (I²=15%). The result remained statistically significant in favour of aprotinin when only studies of good methodological quality were pooled; when only studies that used an objective transfusion protocol were pooled; when only studies that enrolled patients undergoing sternotomy alone were pooled; when the average weight of children was more than 10 kg; and in the single trial which only enrolled children weighing less than 10 kg.

There was no statistically significant difference between the aprotinin and the control groups in volume of blood transfused (7 studies) or volume of chest tube drainage (10 studies). Heterogeneity was high for both analyses (I²=96% and I²=77%, respectively).

Cost information
The average cost of aprotinin for a 10-kg child undergoing a 3-hour procedure using the large-dose regimen described in the Boldt et al. study (see Other Publications of Related Interest) would be approximately US$470.
Authors' conclusions
Aprotinin reduced the proportion of patients requiring transfusion during cardiac surgery with cardiopulmonary bypass, but had no significant effect on the volume of blood transfused or amount of test tube drainage. Before the routine use of aprotinin in children undergoing cardiac surgery can be recommended, further independent RCTs examining bleeding, reoperation rates and death, as well as peri-operative transfusion, are needed.

CRD commentary
The authors set out a clear objective and the inclusion criteria were defined clearly in terms of the participants, interventions, outcomes and study design. Relevant sources were searched. However, the included studies were limited to those published in English, which increases the likelihood of language bias, and relevant studies might have been missed. The authors stated that publication bias was assessed, but no results were reported. Methods were used to reduce the risk of error and bias in the study selection and validity assessment processes, but it was unclear whether similar methods were used for the data extraction. Validity was assessed using appropriate criteria.

Details of the individual studies were presented. The methods used to statistically combine the studies seem appropriate, and statistical heterogeneity was assessed and potential causes investigated for one of the outcomes. Given the poor quality of the included studies, the authors’ cautious conclusions seem appropriate.

Implications of the review for practice and research
Practice: The authors stated that any effect of aprotinin in reducing the proportion of children requiring transfusion should be weighed against its associated complications and cost. Further research is required before aprotinin can be recommended for routine use in children undergoing cardiac surgery.

Research: The authors stated that further independent RCTs, which examine clinically important outcomes such as bleeding, reoperation rates and death, as well as peri-operative transfusion, are required. Further, there is a need for consistency in the reporting of dosing regimens and transfusion requirements using objective transfusion protocols.

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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.