The effect of aprotinin, tranexamic acid, and aminocaproic acid on blood loss and use of blood products in major pediatric surgery: a meta-analysis

Schouten ES, van de Pol AC, Schouten AN, Turner NM, Jansen NJ, Bollen CW

CRD summary
This review found no evidence to suggest that alternative fibrinolytics (like tranexamic acid) were less effective in reducing blood loss in major surgery in children than aprotinin. Although this appeared to be a generally well-conducted review, the possibility of publication and language bias and unclear reporting of some review processes mean the reliability of the authors' conclusion is unclear.

Authors' objectives
To compare the relative effectiveness of aprotinin, tranexamic acid and aminocaproic acid for reducing blood loss in children undergoing cardiac or scoliosis surgery.

Searching
PubMed, EMBASE and the Cochrane Library were searched from August 2006 to October 2006 for studies published in English, German, Dutch and Spanish. Search terms were reported. Reference lists were also scanned for additional studies.

Study selection
Randomised controlled trials (RCTs) of administration of aprotinin and/or tranexamic acid and/or aminocaproic acid to children (aged 0 to 18 years) undergoing cardiac or scoliosis surgery were eligible for inclusion in the review. Eligible trials were required to evaluate blood loss, transfusion of packed red cells, plasma or thrombocytes.

The included trials compared aprotinin (doses ranged from 2.1 to 153.4mg/kg), tranexamic acid (30 to 300mg/kg) or aminocaproic acid (300mg/kg) with saline or no treatment. The age of the participants ranged from 0.4 to 14.4 years, where reported. In the cardiac studies, cardiopulmonary bypass time ranged from 55 to 152 minutes and closure ranged from 19 to 76 minutes, where reported. The duration of scoliosis surgery ranged from 242 to 417 minutes.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
Methodological quality was assessed by two reviewers in terms of quality of randomisation, blinding and percentage follow-up and a score greater than four was deemed "good". Disagreements were resolved through discussion.

Data extraction
Mean differences (MDs) and 95% confidence intervals (CIs) were calculated for differences in volume of blood loss, volume of transfused packed red cells, plasma and thrombocytes with the antifibrinolytic drug compared with placebo. The cumulative doses were standardised by conversion to mg/kg/day; if the duration of surgery was not known, this was estimated at 1.5 times cardiopulmonary bypass time. The volume of blood loss and blood product use was also standardised to mL/kg/24 hours. It appeared that data were extracted on an intention-to-treat basis. Authors of primary studies were contacted for missing data or to clarify uncertainties.

The authors did not state how many reviewers extracted the data.

Methods of synthesis
Weighted mean differences (WMDs) and 95% confidence intervals were pooled for homogeneously distributed outcomes using Mantel-Haenszel meta-analyses. Heterogeneity was assessed using the I² statistic; if I² was greater than 50%, the trials were considered too heterogeneous to be pooled. Publication bias was assessed using funnel plots. Meta-regression analyses were used to test equivalence of the drugs and to explore possible relationships between outcome measures and baseline features. Type of drug and other explanatory variables were put into a multivariable model in order to explore differences in outcome between trials.
Results of the review
Twenty-eight RCTs were included in the review; 23 cardiac RCTs (n=1,893 children) and five scoliosis RCTs (n=207 children). The methodological quality of the cardiac studies was considered poor as only eight out of 23 RCTs scored more than 4 points. All of the scoliosis RCTs scored at least 4 points.

Cardiac RCTs:
Tranexamic acid was associated with a significantly reduced blood loss (WMD -11mL/kg, 95% CI -13 to -8; n=542 children) compared with placebo; it was also associated with reduced packed red cell transfusion (WMD -7, 95% CI -10 to -5; n=460 children), reduced plasma transfusion (WMD -7mL/kg, 95% CI -9 to -4; n=419 children) and reduced thrombocyte transfusion (WMD -5mL/kg, 95% CI -7 to -3; n=370 children) compared with placebo.

Aprotinin was associated with reduced packed red cell transfusion (WMD -4mL/kg, 95% CI -7 to -2; n=250 children) and reduced plasma transfusion (WMD -5mL/kg, 95% CI -8 to -2; n= 228 children) compared with placebo.

Aminocaproic acid was associated with reduced plasma transfusion compared with placebo (WMD -3mL/kg, 95% CI -5 to -1; n=410 children).

Meta-regression analyses suggested that age (p=0.002) and weight (p=0.007) could account for variation in the amount of blood loss between trials, but the type of antifibrinolytic did not significantly influence differences in outcomes.

Scoliosis RCTs:
Aprotinin (WMD -385mL, 95% CI -727 to -42; n=44 children) and tranexamic acid (WMD -682mL, 95% CI -1,149 to -214; n=84 children) were associated with reduced blood loss compared with placebo.

Tranexamic acid was also associated with reduced packed red cell transfusion compared with placebo (WMD -349mL, 95% CI -620 to -77; n=84 children) and a non significant reduction in plasma transfusion.

Aminocaproic acid was associated with a non significant reduction in blood loss compared with placebo.

Authors’ conclusions
There was no evidence to suggest that alternative fibrinolytics, such as tranexamic acid, were less effective in reducing blood loss in major paediatric surgery compared with aprotinin.

CRD commentary
The research question was well defined. Several relevant databases were searched. However, as searches were restricted to certain languages and no searches for unpublished studies were reported, language and publication bias could not be ruled out. Validity assessment was performed in duplicate, reducing the possibility of reviewer error and bias, but it was not clear whether similar precautions were taken for study selection and data extraction.

Study quality was assessed using appropriate criteria. Pooling appeared to be appropriate and sources of heterogeneity were investigated.

Although this appeared to be a generally well-conducted review, the possibility of publication and language bias and unclear reporting of some review processes mean that the reliability of the authors’ conclusions is unclear.

Implications of the review for practice and research
Practice: The authors stated that, bearing in mind the potential side effects of aprotinin and the higher costs, tranexamic acid should be the antifibrinolytic of choice in major surgery in children.

Research: The authors stated that a multicentred RCT in a number of paediatric intensive care units comparing tranexamic acid and/or aminocaproic acid with placebo in major paediatric surgery is warranted. The trial should be double-blinded and powered for clinically relevant outcomes including mortality, use of blood products, and reoperations and side-effects.
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