Hemostatic effects of aprotinin, tranexamic acid and epsilon-aminocaproic acid in primary cardiac surgery

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Epsilon-aminocaproic acid (EACA) and tranexamic acid (TA), two synthetic antifibrinolytic drugs, in first-time elective cardiac surgery. The EACA patients received 5 g EACA during the 20 minutes after induction of anaesthesia, before sternotomy, followed by a constant infusion of 2 g/hour until the end of operation and 2.5 g added to priming. The TA patients received 1 g TA over 20 minutes before sternotomy, followed by a constant infusion of 400 mg/hour during operative period and 500 mg added to priming.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study investigated adult patients scheduled for first-time elective cardiac surgery requiring cardiopulmonary bypass (CPB). Exclusion criteria were: severe left ventricular dysfunction (EF less than 35%); impaired renal function (serum creatinine more than 2 mg/dL); active chronic hepatitis or cirrhosis; previous haematological disorders; and need for ventricular assist device for weaning from CPB. Preoperative treatment with aspirin or heparin was not a contraindication to enrollment in the trial.

Setting
The study setting was hospital. The economic analysis was carried out in Milan, Italy.

Dates to which data relate
No dates were reported.

Source of effectiveness data
The evidence for the final outcomes was based on a single study.

Link between effectiveness and cost data
Costing appears to have been conducted prospectively on the same patient sample as that used in the effectiveness analysis.

Study sample
Power calculations were not used to determine the sample size. A total of 210 patients (203 evaluable) were randomly
assigned to the EACA group (n=68; 66 after the exclusion of 2 patients) with a mean (SD) age of 58.7 (10) years, the TA group (n=72; 70 after the exclusion of two patients) with a mean (SD) age of 61.9 (9.6) years, or the AP group (n=70; 67 after the exclusion of three patients) with a mean (SD) age of 63.6 (9.6) years.

**Study design**
The study took the form of a randomised controlled trial carried out in a single centre. The duration of the follow-up appears to have been until two days after operation or until death. A total of 7 patients were withdrawn from the study. Consecutive first-time elective cardiac surgery patients were unblinded and randomly allocated to receive one of the three drugs. A standardised technique of balanced anaesthesia with propofol, fentanyl, pancuronium bromide, and isoflurane, as needed, was routinely used.

**Analysis of effectiveness**
The principle used in the analysis of effectiveness was treatment completers only; patients with a surgical cause of bleeding were excluded from statistical analysis. The health outcome measures were postoperative blood loss and homologous transfusions. Cases of perioperative acute myocardial infarction (AMI) (new Q-waves and Ckmb greater than 10%), postoperative renal insufficiency (creatinine twice the baseline), thrombotic complications and major focal neurological disfunction were recorded. Operative characteristics were also reported. The study groups were comparable in terms of baseline characteristics except for age. Analysis of covariance was used to investigate differences among the three groups after adjustment of the variables for age. Multiple regression was performed to investigate which variables were independently associated with bleeding at each considered time.

**Effectiveness results**
Bleeding, but not allogeneic transfusions, was significantly higher in the EACA group (467 +/- 234 versus TA group, 311 +/- 231 versus AP group, 283 +/- 233; p<0.001).

Total transfusion packed red blood cells (PRBC) was 0.78 +/- 1.2 in the EACA group, 0.47 +/- 0.9 in the TA group, and 0.54 +/- 1.02 in the AP group, p=0.46.

The groups were not significantly different in terms of operative characteristics.

The incidence of total adverse events was not different among the three groups.

**Clinical conclusions**
TA was equally effective to high-dose AP in reducing blood loss and transfusion requirements in first-time cardiac surgery. The lack of any statistically significant difference in the amount of homologous transfusions among the three groups was probably due to the inadequate number of patients enrolled. No clear conclusion can be made regarding the safety of these agents based on the lack of enrollment of an appropriate number of patients.

**Measure of benefits used in the economic analysis**
No summary benefit measure was identified in the economic analysis, and only individual clinical outcomes were reported.

**Direct costs**
Costs were not discounted due to the short time frame of the cost analysis. Quantities were reported separately from the costs and cost items were reported separately. The cost analysis covered the costs of antifibrinolytic treatment and allogeneic products transfused. The perspective adopted in the cost analysis was that of the hospital. The price year was not given.
Statistical analysis of costs
The Mann-Whitney test was used to compare the groups in terms of costs.

Indirect Costs
Indirect costs were not considered.

Currency
US dollars ($). The conversion rate from Italian currency to US dollars was not given.

Sensitivity analysis
No sensitivity analysis was carried out.

Estimated benefits used in the economic analysis
See effectiveness results reported above.

Cost results
Costs of pharmacological and transfusional treatment were significantly lower in the TA group ($58.10 +/- $105.10) versus the EACA group ($100.70 +/- $158.60), and versus the AP group ($432.60 +/- $118.70) (p<0.0001).

Synthesis of costs and benefits
Costs and benefits were not combined. The use of TA appears to be the dominant strategy (at least weakly).

Authors' conclusions
Compared to AP, TA has the same effects on bleeding and transfusions, but with a significant reduction of costs. The patients treated with EACA showed a significantly higher postoperative bleeding with an increased trend of transfusion requirement.

CRD COMMENTARY - Selection of comparators
A justification was given for the choice of the comparator; it was reported that the previous studies had demonstrated the efficacy of high-dose AP, in reducing blood loss and homologous blood requirements, particularly in high-risk patients. You, as a database user, should consider which strategy is a widely used health technology in your own setting.

Validity of estimate of measure of effectiveness
The internal validity of the effectiveness results is likely to be high due to the randomised nature of the study design, and the comparability of the study groups in all baseline variables except age (and adjustment was made in the analysis for the effect of age). However, the lack of power analysis in the determination of the sample size (as acknowledged by the authors), and the fact that the effectiveness analysis was based on treatment completers only may weaken the validity of the study results. The details of the randomisation process and the dates during which the effectiveness data were collected were not reported.

Validity of estimate of measure of benefit
The authors did not derive a summary measure of health benefit. The analysis was therefore of cost-consequences design.
Validity of estimate of costs
The validity of the cost analysis was weakened by the following features of the analysis: the price year and conversion rate were not reported; it is not clear whether the cost data were based on charges or true costs; due to lack of sufficient information, it is not entirely clear whether any important direct cost components were omitted from the analysis; the effects of alternative treatment strategies on indirect costs were not addressed. These features tend to limit the generalisability of the cost results outside the study setting. However, the strengths of the cost analysis were that some details of methods of cost estimation were given; the perspective adopted in the cost analysis was reported; and statistical analyses were performed on resource use and cost data.

Other issues
The authors’ conclusions appear to be justified given the uncertainties in the data. The issue of generalisability to other settings or countries was not addressed, although appropriate comparisons were made with other studies. The degree to which the study sample was representative of the study population was addressed in the authors comments; although not in a systematic fashion.

Implications of the study
A fully-powered randomised study is required to rectify some of the limitations of this study regarding the safety of the alternative agents.

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