Cost-benefit and efficacy of aprotinin compared with epsilon-aminocaproic acid in patients having repeated cardiac operations: a randomized, blinded clinical trial


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
The use of aprotinin (6 x 10^6 kallikrein inactivator units) for the reduction of bleeding in patients undergoing repeated cardiac surgery.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
Patients undergoing repeated cardiac surgery.

Setting
The practice setting was the hospital. The economic study was carried out in the USA and in Argentina.

Dates to which data relate
Effectiveness and resource use data related to the period from October 1994 to May 1996. 1996 drug prices were used. Certain categories of cost were taken from previously published estimates, including one relating to 1991/2 costs.

Source of effectiveness data
Evidence for final outcomes was derived from a single study.

Link between effectiveness and cost data
Costing was undertaken prospectively on the same patient sample as that used in the effectiveness study.

Study sample
204 patients, who were eligible and consented, were randomly allocated to receive aprotinin (99) or EACA (105). The mean age of the aprotinin group was 62 (+/- 14) years, the mean weight was 76 (+/- 14) kg and 67 (68%) of the patients were male. The mean age of the EACA group was 63 (+/- 12) years, the mean weight was 75 (+/- 14) kg and 65 (62%) of the patients were male. The number of patients who refused to participate, or who were excluded from the trial, was not stated. Power calculations were used to determine sample size. A sample of 200 was estimated to have at least 90% power at the 5% level to detect a difference of 250 ml in 24 hour thoracic drainage (assuming SD 200 ml). This sample size also had 90% power at the same significance level to detect a difference of 1 unit in allogeneic erythrocyte transfusions (assuming SD of 2 units).
Study design
The study was a randomised controlled trial, based at 3 centres: Durham, North Carolina, USA, Michigan, USA and Buenos Aires, Argentina. Randomisation was carried out using a computer-generated schedule and stratified according to surgeon to ensure an even distribution of groups among surgeons. All clinicians and investigators were blinded to treatment allocation, with drugs administered in equal volumes. Patients received a 1 mg blinded test dose of the study drug before surgery to check for allergy. Blinding was broken in 4 patients, 2 in each group, during surgery because of clinicians' concerns over level of bleeding. These were included in final analysis, but did not affect the statistical significance of results. Duration of follow up was not specified.

Analysis of effectiveness
The analysis was based on intention to treat. The primary health outcome was the 24 hour postoperative volume of thoracic drainage. The number of allogeneic blood product transfusions, the number of donor exposures, duration of chest closure, and the surgical assessment of "dryness" of surgical field, were also estimated. Groups were demonstrated to be comparable in terms of demographic factors, preoperative medical condition and intra-operative characteristics.

Effectiveness results
Results are expressed as medians, with the 25th and 75th percentiles given in brackets. The 24 hour postoperative volume of thoracic drainage (unit of measurement not specified) was 511 (383 - 805) in the aprotinin group and 655 (464 - 1045) in the EACA group, (p=0.016). The only statistically significant difference detected between the number of allogeneic blood product transfusions received by the two groups, was that the aprotinin group received significantly fewer platelets (p=0.036). The number of donor exposures was 2 (0 - 7) in the aprotinin group and 3 (1 - 13) in the EACA group, (p=0.084). The duration of chest closure was 50 minutes (40 - 69) in the aprotinin group and 54 minutes (42 - 67) in the EACA group, (p=0.439). The surgeon considered the field "dry" in 44% of cases in the aprotinin group and 26% in the EACA group, (p=0.012).

Clinical conclusions
Aprotinin therapy was more effective than EACA therapy at reducing bleeding associated with repeated cardiac surgery.

Measure of benefits used in the economic analysis
The number of donor exposures was the measure of benefit the authors considered relevant for the economic study and, because the differences were insignificant, the economic analysis was based on costs only.

Direct costs
Costs were analysed from the perspective of the hospital and included the cost of bleeding-related events during repeat cardiac surgery. Resource use and prices were reported separately. 1996 drug prices were used. The cost of a unit of allogeneic erythrocytes included the costs of overheads and infectious complications. The estimate, taken from a previous study, was dated 1991/2. The authors took previous estimates for platelets, fresh frozen plasma and cryoprecipitate and, to these, added a charge for each donor exposure to account for infectious complications. A cost per minute was estimated for operating room time, reference again being made to a previous study.

Statistical analysis of costs
Costs were analysed using a two-way analysis of variance.

Indirect Costs
Indirect costs were not included in the analysis.
Currency
US dollars ($).

Sensitivity analysis
A two-way, simple sensitivity analysis was performed to test the effect of changes in the cost of blood products and in operating room times on the cost-effectiveness of EACA. A one-way simple sensitivity analysis was performed to test the effect of changes in the cost of aprotinin therapy on the cost-effectiveness of EACA.

Estimated benefits used in the economic analysis
Not applicable.

Cost results
Costs were reported in terms of the median and 25th and 75th percentiles. The median bleeding-related per-patient cost in the aprotinin group was $1,813 ($1,476 - $2,605) compared with $1,088 ($511 - $2,057) in the EACA group. The difference ($725) was significant at the 5% level, (p=0.0001); this was found to be insensitive to a 100% increase in both the estimated cost of blood products and in operating time, (p=0.02). EACA was found to be less costly to a threshold value of $486 for the cost of aprotinin therapy. Consequently, even if the dose of aprotinin were halved, EACA therapy was still less costly (p=0.022).

Synthesis of costs and benefits
A synthesis of costs and benefits was not performed.

Authors’ conclusions
Epsilon-aminocaproic acid was more cost-effective than aprotinin over a broad range of cost estimates.

CRD COMMENTARY - Selection of comparators
The reason for the choice of comparator is clear. You, the user of this database, should decide if this is a widely used health technology in your own setting.

Validity of estimate of measure of benefit
The measures of effectiveness were based on a randomised controlled trial, powered to detect differences in clinical outcomes. Although some significant differences between groups were detected, these were not converted to a summary measure of health benefit. The duration of follow up was not specified and the longer term impact of the intervention and comparator drugs on clinical outcomes was not investigated.

Validity of estimate of costs
Prices and cost estimates were combined from several sources with different dates. Some of the prices used predated 1996, but it is unclear whether these prices were reflated. Costs and quantities were reported separately and the methods used to estimate costs were adequately reported, facilitating the generalisability of the results to other settings. Costs were investigated by both sensitivity and statistical analyses.

Other issues
The central result of the study was that aprotinin is both more effective and more costly than EACA. However, the authors did not combine costs and effects, arguing that none of the measures of effectiveness could be converted to a measure of health benefit (such as the quality-adjusted life year). This study therefore failed to justify the authors’ conclusion regarding the cost-effectiveness of aprotinin, relative to EACA.

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