Economic evaluation of high-dose and low-dose aprotinin therapy during cardiopulmonary bypass


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 differing dosages of aprotinin treatment in surgery to reduce intraoperative and postoperative bleeding.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population consisted of patients undergoing cardiopulmonary bypass. Patients were excluded if they had previously received aprotinin therapy, were under 18, had abnormal preoperative blood coagulation for reasons other than anticoagulant therapy, or would not consent to blood transfusions.

Setting
The study setting was a hospital. The economic analysis was conducted in Brisbane, Queensland, Australia.

Dates to which data relate
The dates for data collection do not appear to have been stated. The base price year used in the analysis does not appear to be stated.

Source of effectiveness data
Effectiveness data were derived from a single study.

Link between effectiveness and cost data
Resource and costs data were collected prospectively, using the same patient sample as in the effectiveness analysis.

Study sample
Power calculations do not appear to have been used to determine sample size. 150 consecutive patients gave informed consent and met the study inclusion criteria, and were included in the study. The surgical procedures undergone by patients were thought by the authors to provide a homogenous group of patients that were likely to require blood transfusions. There were 50 patients in each of the three groups. No details of numbers, reason for refusal, or problems with clotting were provided. Baseline characteristics were also omitted. A comparison between the sample and the population is therefore not possible.
Study design
The study was a single centre randomised controlled trial. The duration of follow-up was until patients were discharged from hospital, and there was no loss to follow-up.

Analysis of effectiveness
The analysis of effectiveness was based on intention to treat. Primary health outcomes were observed but were not reported in this paper. Instead the clinical analysis concentrated on intermediate measures: the severity of intraoperative (minimal/mild/moderate/severe) and postoperative (g Haemoglobin (Hb)) blood loss, the need for intraoperative/postoperative blood transfusions and the need for additional surgery (referred to in the paper as 'reopens'). At baseline analysis all groups were stated to have had similar clinical and demographic characteristics.

Effectiveness results
There were no statistically significant differences in intraoperative blood loss rates between the three groups. Using a scale from 1 (minimal) through to 4 (severe), the mean (standard deviation) scores were 2.1 (0.7) for the high dose, 2.1 (0.9) for the low dose, and 2.3 (0.9) for the placebo groups. Equally there were no significant differences in the need for intraoperative blood transfusions between the three groups. Values were not reported and the results were presented in the form of a graph.

Cumulative postoperative blood loss was found to be significantly lower in the aprotinin groups than placebo at each four hour monitoring period in the first 24 hours following surgery, (p<0.0001). Values were not reported, and the results were presented in the form of a graph. After 24 hours, approximate median (25th, 75th percentiles) cumulative haemoglobin loss was 20g (15 - 35) in the placebo group compared with 10 (6 - 17) in the low dose and 6 (5 - 12) in the high dose aprotinin groups. Postoperative blood transfusions were also significantly lower in the aprotinin groups, with 9 (18%) in the high dose group, 15 (30%) in the low dose group, and 22 (44%) in the placebo group requiring transfusions, (p=0.005). Only five patients required reopens, all being in the placebo group: this was significant, (p=0.004).

Clinical conclusions
Aprotinin was an effective way of reducing postoperative bleeding, the need for transfusions and the need for additional surgery. High dose aprotinin was associated with the greatest clinical improvements, but low use aprotinin was still significantly superior to placebo.

Measure of benefits used in the economic analysis
The authors considered that this was a cost minimisation analysis, which assumes that the results showed equal effectiveness. However, the authors admitted that there was evidence of greater effectiveness for high, compared to low, dose aprotinin. They did refer to equality in terms of mortality and the incidence of cerebrovascular accidents, but data for this were not presented here. Since no summary measure of benefit was reported, this is considered to be a cost-consequences analysis (CCA).

Direct costs
The base price year used in the analysis was not stated. Costs were not discounted, which was appropriate given the short duration of the study. Prices (unit costs) were reported separately from resources used. Resources were aprotinin use, preoperative crossmatching, cell saver use, operating room time, reopens, number of blood transfusions and the length of stay both in intensive care and in the general ward. However, operating time and length of stay were not used to calculate final costs in the base case because the authors thought it unnecessary, given that there was no statistical difference between groups. Cell saver use was also not included, but no reason for this was given. Preoperative crossmatching was not included, but this probably had the same cost for each group. The price of transfusion, estimated from the Australian Red Cross, was given per unit, but the number of units per patient was not given. The median extra cost for the 5 patients requiring reopens was Aus$4,880, and multiplied by the risk of reopening in the placebo group (10%) the cost per patient was estimated to be Aus$488.
Statistical analysis of costs
Although no results were given, this was reported to have been carried out on the difference between times and costs by particular resource: "This study showed only two statistically significant sources of cost savings...". Alpha was set at 0.05.

Indirect Costs
Indirect costs were not reported.

Currency
Australian dollars (Aus$).

Sensitivity analysis
Sensitivity analyses were conducted to test the effect of including resource use where there was no statistically significant difference, i.e. operating and ward times, and not using cell saver in the aprotinin groups. The latter was based on lack of statistically significant effect on transfusions or bleeding of use of cell saver, although the cost of cell saver was still included in the placebo group. Finally, the reopen rate was varied between 1 and 3%, compared to the 10% observed in the study, assuming a higher cost per 5 reopens of $5,550. Why the 1-3% range was used is not clear, although going from 2 to 3% changes the use of low dose from cost increasing to cost saving in comparison to placebo.

Estimated benefits used in the economic analysis
Not applicable.

Cost results
The total cost per patient in the three groups were:

- high dose, Aus$662;
- low dose, Aus$362;
- and placebo, Aus$710.

As given, costs of Aus$348 would be avoided using low dosage aprotinin compared with placebo, and costs of Aus$48 would be saved using high dosage aprotinin compared with placebo.

Including median time savings increases the cost savings to $434 for high dose and $715 for low dose in comparison to placebo.

Excluding cell saver from the aprotinin groups only increases savings to $167 for high and $467 for low dose versus placebo.

At up to 3% reopens in the placebo group, high dose aprotinin costs at least $274 more than placebo. Low dose costs $196 more at 2% and $26 less at 3%.

Synthesis of costs and benefits
Not applicable.

Authors' conclusions
Low dosage aprotinin therapy, although less effective in reducing intra and post operative bleeding, produces greater
cost savings than high dosage aprotinin therapy compared with placebo therapy, whilst not impacting on health outcomes.

**CRD COMMENTARY - Selection of comparators**
A justification was provided by the authors for the comparators used: high dosage aprotinin is an effective means of reducing intra and postoperative bleeding. The placebo was used to identify the impact on costs if aprotinin therapy were to be removed entirely from treatment.

**Validity of estimate of measure of effectiveness**
Intermediate effectiveness data were obtained from a randomised controlled trial which was appropriate for the study question. However, details of exclusions and baseline characteristics were not provided in order to show that the study sample was representative of the population and that groups were comparable at baseline. A positive point was that the analysis was based on intention to treat with no loss to follow-up. Although prevention of blood loss and reopens is a reasonable measure of effectiveness, it is unfortunate that the authors neglected it in terms of measure of benefit, relying on the results in terms of mortality and incidence of cerebrovascular accidents from a previous study. For example, the extra surgery would carry some mortality risk. It would have been more useful to have reported all the results together. Also the measure of intraoperative loss by category was not supported by evidence of validity.

**Validity of estimate of measure of benefit**
Not applicable although the authors assumed a cost minimisation by evidence from a previous paper and contrary to the evidence on blood loss reported here.

**Validity of estimate of costs**
All cost categories relevant to the perspective adopted seem to have been included in the analysis. Only costs from resources that were statistically different were reported in the economic analysis, and some costs were therefore omitted, under the assumption of equivalence. However, this is not valid for two main reasons. Firstly, even though in isolation the difference might not reach significance, when combined, it could. Secondly, any test of significance is based on an arbitrary cut-off, for example the 5% used here. It is better to produce the total costs, with any statistical tests or sensitivity analysis required, so that the reader (decision maker) can judge the importance of the difference for themselves. In fact this was done later in the sensitivity analyses, but no explanation was given as to why two separate analyses were carried out or why the median rather than the mean was used. There was also no account of variability by range or standard deviation.

Prices and quantities were estimated separately, although not all prices were reported in the paper. The source of prices used in the analysis, and the dates during which the resource data were collected were not stated. Discounting was not conducted, which was appropriate given the short duration of the study. Finally, it is not appropriate to compare costs of both doses to placebo. The more expensive should be compared to the next most expensive, where effectiveness increases and therefore high dose should have been compared to low dose. This is because a decision maker needs to know how much more effectiveness/benefit can be gained by the increase in cost. In fact, both high and low dose dominated placebo, having higher effectiveness and lower costs. The main question would therefore be whether it is worth sacrificing some savings for the increase in benefit from reduced blood loss of high versus low dose treatment.

**Other issues**
The authors made appropriate comparison of their findings with those from other studies and the issue of generalisability to other settings was addressed, particularly with regard to the dependence of the cost savings on institutional resource costs (prices), i.e. aprotinin versus reopens. The authors do not appear to have presented the results of the study selectively, although the lack of data on health outcomes such as mortality is unfortunate. They also acknowledged that no account was taken of drug side effects such as hypersensitivity.
Implications of the study
It is clear from the study that the use of aprotinin prevents the need for reopens and, as such, also saves in terms of the cost of the extra surgery, net of the cost of the treatment. Whether there are any disadvantages, in terms of drug side effects, are not accounted for. The main decision would seem to be whether it is worth losing some savings in order to gain by reduced bleeding by using high instead of low dose therapy. However, the lack of other health outcome data, and sensitivity analysis by distribution of resources, significantly affects the generalisability of these results.

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