Aprotinin in major orthopedic surgery: a systematic review of randomized controlled trials

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CRD summary
The authors concluded that while aprotinin reduces intra-operative and peri-operative blood loss and does not appear to increase deep vein thrombosis, the conclusions are not definitive. These conclusions appear to be supported by the results presented. The authors’ caveat about the conclusions not being definitive seems appropriate given the incomplete reporting of review methods and study quality, and differences between the studies.

Authors' objectives
To evaluate the efficacy and safety of aprotinin in patients undergoing major orthopaedic surgery.

Searching
MEDLINE (1980 through October 2004), EMBASE (1980 through October 2004) and the Cochrane CENTRAL Register (Issue 3, 2004) were searched for studies published in the English language; the search terms were reported. Reference lists in reports and reviews were screened.

Study selection
Study designs of evaluations included in the review
Single- or double-blinded randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Studies that compared a single fixed-dose of aprotinin as the sole treatment with placebo or routine care were eligible for inclusion in the review; studies of aprotinin combined with other treatments were excluded. Most of the included studies evaluated aprotinin 0.5 to 2 million Kallikrein inhibitor units (KIU) followed by 500,000 KIU/hour for varying time periods. The majority of studies included a specific treatment for the prevention of deep venous thrombosis (DVT), such as heparin, low molecular weight heparin, warfarin or a mechanical device; other studies did not describe a method of DVT prophylaxis.

Participants included in the review
Studies of patients undergoing major orthopaedic surgery were eligible for inclusion. The patients in the included studies varied in age (mean values ranged from 13 to 71.5 years) and the type of surgery they were undergoing (spinal fusion, primary or revision arthroplasty of the hip or knee, or surgery for malignancy or sepsis). In their discussion, the authors stated that the included studies excluded patients at risk of aprotinin anaphylaxis.

Outcomes assessed in the review
Studies that assessed blood loss and transfusion requirements were eligible for inclusion. The studies had to present adequate data to enable the calculation of weighted mean differences (WMDs) or dichotomous outcomes. The review assessed intra-operative and peri-operative blood loss and the quantity of blood transfused intra-operatively and peri-operatively. The secondary review outcome was DVT or thrombotic events. In some of the included studies all patients underwent routine ultrasonography or venography, whilst in others venography was performed when findings on routine clinical examination were suggestive of DVT; some studies did not specify routines for the detection of DVT. In the included studies, DVT was confirmed by clinical signs, ultrasonography or venography.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Two reviewers independently assessed validity and resolved any disagreements by consensus. Validity was assessed
using the Jadad scale, which considers the reporting and handling of randomisation, blinding and withdrawals. The maximum possible score was 5 points.

**Data extraction**
Two reviewers independently extracted the data and resolved any disagreements through consensus. For each study, continuous and dichotomous data were extracted for the outcomes of interest. Where data were not presented in a usable format in the original publication, the authors were contacted. Odds ratios (ORs) were calculated.

**Methods of synthesis**
How were the studies combined?
Pooled ORs and 95% confidence intervals (CIs) were calculated using a random-effects model for dichotomous data, while pooled weighted mean differences (WMDs) and 95% CIs were calculated for continuous data. The possibility of publication bias was explored using funnel plots and tested using the Kendall correlation coefficient.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Cochran Q statistic. Potential reasons for differences between the studies were mentioned briefly.

**Results of the review**
Thirteen RCTs (n=506) were included in the review.

The Jadad scores ranged from 1 to 5 out of 5 (median 4).

The pooled intra-operative blood loss was significantly less in patients treated with aprotinin compared with control; the WMD was -228.9 mL (95% CI: -366.8, -91, p=0.0011), based on 10 RCTs with 427 patients. Significant heterogeneity was found (p<0.0001).

The pooled peri-operative blood loss was significantly less in patients treated with aprotinin compared with control; the WMD was -556.8 mL (95% CI: -860.1, -253.5, p<0.0001), based on 8 RCTs with 323 patients. Significant heterogeneity was found (p<0.0001).

The amount of blood transfused intra-operatively was significantly less in patients treated with aprotinin compared with control; the WMD was -1.1 red blood cell units (95% CI: -1.7, -0.4, p=0.0001), based on 6 RCTs with 202 patients. No significant heterogeneity was found (p=0.11).

The amount of blood transfused peri-operatively was significantly less in patients treated with aprotinin compared with control; the WMD was -1.1 red blood cell units (95% CI: -1.74, -0.45, p<0.0001), based on 9 RCTs with 313 patients. Significant heterogeneity was found (p<0.0001).

There was no significant difference between aprotinin and control in the incidence of thrombotic events, which was low: one DVT and one arteriovenous thrombosis among 204 patients treated with aprotinin versus 15 DVTs among 204 control patients; the OR was 0.38 (95% CI: 0.14, 1.05, p=0.061). No significant heterogeneity was found (p=0.75).

No anaphylactic or anaphylacoid reactions to aprotinin were reported.

There was marked asymmetry of the funnel plots and significant Kendall correlation coefficients, which suggested the presence of publication bias for intra-operative blood loss (p=0.09), intra-operative transfusion (p=0.09) and DVT (p=0.01).

**Cost information**
The authors stated that the cost of aprotinin was approximately $1,000 per patient.
Authors' conclusions
Aprotinin reduces intra-operative and peri-operative blood loss in patients undergoing major orthopaedic surgery and does not appear to increase the incidence of DVT where prophylactic treatment is also given. However, these conclusions are not definitive.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Limiting the search to studies published in English might have resulted in other relevant studies being missed. No specific attempts were made to locate unpublished studies, thereby raising the possibility of missing relevant data and publication bias. The potential for publication bias was assessed and some evidence suggesting its presence was found. Methods were used to minimise reviewer errors and bias in the assessment of validity and extraction of data, but it was unclear whether similar steps were taken at the study selection stage. Only RCTs with some level of blinding were included and study quality was assessed, although only the composite score was presented; this makes it difficult to independently comment on the reliability of the evidence presented.

Adequate information on the characteristics of the interventions and patients was provided. The studies were pooled using meta-analysis and statistical heterogeneity was assessed. Having found significant heterogeneity for some meta-analyses, the authors only briefly mentioned potential explanations for such differences between the studies. Although the forest plots showed similar direction of treatment effects for statistically heterogeneous studies, the presence of significant heterogeneity indicated that summary estimates of treatment effect may not be reliable. In their concluding sentence in the review text, the authors stated that study limitations preclude drawing definitive conclusions, but they did not explicitly state which study limitations this referred to. The conclusion appears to be supported by the results presented but, in view of evidence suggesting publication bias, their reliability is uncertain. The authors’ caveat about the conclusions not being definitive seems appropriate given these limitations.

Implications of the review for practice and research
Practice: The authors stated that although aprotinin is effective in patients undergoing major orthopaedic surgery, they cannot recommend its routine clinical use. They stated that aprotinin is contraindicated in patients who may have further surgery in the next few months and that patients for aprotinin treatment should carefully selected.

Research: The authors stated that additional large RCTs to determine the most effective regimen for aprotinin are required.

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