

Aprotinin in Major Orthopedic Surgery: A Systematic Review of Randomized Controlled Trials

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Aprotinin therapy is a promising strategy for reducing blood loss and blood transfusion requirements. The efficacy and safety of aprotinin in orthopedic surgery, however, remain controversial. We searched electronic databases for randomized controlled trials on the efficacy and safety of the use of aprotinin in orthopedic surgery. Thirteen trials that included a total of 506 patients who underwent major orthopedic surgery were analyzed. The pooled intraoperative and perioperative blood loss was significantly less in the aprotinin-treated patients than in the control patients (weighted mean difference [WMD] for intraoperative blood loss = -229 mL, 95% confidence interval [CI] = -367 to -91 mL, $P = 0.0011$; WMD for perioperative blood loss = -557 mL; 95% CI = -860 to -254 mL; $P < 0.0001$). The pooled amounts of red

blood cell (RBC) units (U) transfused intraoperatively and perioperatively were significantly less in the aprotinin-treated patients than in the control patients (WMD for intraoperative RBC U = -1.1 U; 95% CI = -1.7 to -0.4 U; $P = 0.0001$; WMD for perioperative RBC U = -1.1 U; 95% CI = -1.7 to -0.5 U; $P < 0.0001$). Aprotinin was not associated with an increased incidence of deep vein thrombosis (odds ratio = 0.39; 95% CI = 0.14 to 1.05, $P = 0.061$). The authors conclude that aprotinin reduces the intraoperative and perioperative blood loss and allogeneic blood transfusion requirement and may not be associated with increased risk of deep vein thrombosis in the presence of pharmacological or mechanical prophylaxis in patients undergoing major orthopedic surgery.

(Anesth Analg 2005;101:1602-7)

Major orthopedic surgery is associated with significant blood loss, frequently requiring allogeneic transfusions of blood and other blood products. Allogeneic blood transfusion carries risks for transmission of known or unknown viruses, immunosuppression, transfusion-related acute lung injury, and graft-versus-host disease or an unidentified reaction (1). In addition, the cost of supplying blood has increased over the past decade, mainly as a result of new tests and processes aimed at reducing the risk of infection (2). Therefore, methods for reducing blood transfusion have attracted recent attention (2).

Antifibrinolytic therapy is a promising strategy to reduce blood loss and blood transfusion requirements. Aprotinin, a serine protease inhibitor, is already used in cardiac surgery, and its efficacy in reducing blood

loss and transfusion requirements is widely recognized (3-5). Aprotinin reduces the risk of stroke in patients undergoing coronary artery bypass surgery (4) and decreases (3) or does not affect (4) mortality associated with cardiac surgery. However, its efficacy and safety in patients undergoing noncardiac surgery remain controversial, and conflicting results have been published even recently (5-8). In orthopedic surgery, such as hip or knee replacement when patients are at the most intense risk of venous thromboembolism, the safety of using aprotinin is debatable; it may predispose the patient to a procoagulable state and result in an adverse event such as myocardial infarction, stroke, or atrial fibrillation (5-8). Furthermore, aprotinin is not currently approved for orthopedic surgery by the United States Food and Drug Administration or in most other developed countries. This may explain orthopedists' reluctance to use aprotinin. Therefore, we performed a meta-analysis of randomized controlled trials on the efficacy and safety of aprotinin in patients undergoing major orthopedic surgery. We focused on blood loss and the transfusion requirement as primary end-points to clarify the efficacy of aprotinin and on the incidence of deep vein

Accepted for publication July 15, 2005.

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DOI: 10.1213/01.ANE.0000180767.50529.45

thrombosis (DVT) as a secondary end-point to clarify the safety of aprotinin.

Methods

This systematic review was performed according to recommendations of the Quality of Reporting of Meta-analyses statement (9). We searched the literature for all reports of randomized controlled trials that tested the effect of aprotinin versus no aprotinin on blood loss and the transfusion requirement during orthopedic surgery. Trials were identified from MEDLINE (1980 through October 2004), EMBASE (1980 through October 2004), and the Cochrane Central Register of Controlled Trials (Issue 3, 2004). Only English language literature was included. The initial search terms were "aprotinin," "orthopedic surgery," "hip surgery," "knee surgery," and "spine surgery," and various combinations of these words were used. A manual search of references listed in reports and reviews was also performed. Our inclusion criteria were as follows: 1) prospective, randomized, single-blind or double-blind trial, 2) use of aprotinin alone as treatment, 3) presence of a control group (placebo or routine care), 4) available data to calculate weighted mean difference (WMD) or dichotomous outcome, 5) a single, fixed dose of aprotinin. We did not include studies with insufficient data, studies without a control group or randomization, nonblinded studies, retrospective studies, dose-range studies, or studies of aprotinin combined with other compounds.

Assessment of the methodological quality of the included studies was performed by two independent investigators (TS and ZW). Disagreements were resolved by consensus. Each study was assessed according to the 5-point scale introduced by Jadad et al. (10), which scores randomization, double-blinding, withdrawals, and dropouts. Briefly, if the study was described as randomized, 1 point was assigned. If the randomization process was appropriate, an additional point was assigned. If the randomization was inappropriate (e.g., allocation by date of birth), the original point was lost. One point was assigned if a study was described as blinded. If the blinding method was appropriate, an additional point was assigned. Finally, 1 point was assigned if the number of and reasons for withdrawals and dropouts were described. The maximum possible score was 5.

The information extracted included the following: patient characteristics, type of surgery, dose of aprotinin, blood infusion criteria, intraoperative and perioperative (intraoperative + postoperative) blood loss, and red blood cell (RBC) requirements, incidence of DVT, method of DVT diagnosis, use or nonuse of DVT prophylaxis. Data were extracted by two independent investigators (TS and ZW). Disagreements or uncertainties were resolved by consensus. When results

were not presented in the original paper in a usable form, attempts were made to obtain additional data from the authors. Where these data were not forthcoming, the trial was excluded from the meta-analysis.

Treatment effects for dichotomous and continuous outcomes were expressed as odds ratios and WMDs. The effect sizes were calculated with the use of a random-effects model (11). When zero outcome occurred in one or both groups, 0.5 was added to each cell of the respective contingency table. Homogeneity of effect size across trials was tested by the Cochran Q statistic.

To assess the potential for publication bias, a funnel plot was constructed in which log-relative risks were plotted against associated standard errors. In addition, rank correlation of the association between standardized log-relative risks and associated standard errors was determined by the Kendall correlation coefficient. The correlation between sample size and relative risk would be high if small studies with null results were less likely to be published (12). A significant correlation between sample size and relative risk would not exist in the absence of publication bias. Statistical significance for treatment effects was defined by $P < 0.05$, for heterogeneity was defined by $P < 0.1$, and for publication bias was defined by $P < 0.1$. Analyses were performed with NCSS 2004 statistical software (NCSS, Kaysville, UT).

Results

After excluding 53 abstracts from the screening, we identified 18 trials for review (Fig. 1). Five failed to meet our criteria and were excluded: one was retrospective (13), two had insufficient data (14,15), and two included groups with different aprotinin doses (16,17). Thus, 13 randomized controlled trials (18-30) were included in our analysis. Details of the selected trials are shown in the Table. The median Jadad score was 4 (range, 1-5).

Ten trials (18,20,23-29) evaluated the use of aprotinin for reduction of intraoperative blood loss, with 214 aprotinin-treated patients and 213 control patients. The pooled intraoperative blood loss was significantly less in the aprotinin-treated patients than in the control patients (WMD = -228.9 mL, 95% confidence interval [CI] = -366.8 to -91.0 mL; $P = 0.0011$, with significant heterogeneity among trials ($P < 0.0001$) (Fig. 2A). Eight trials (18,20,24-29) with 163 aprotinin-treated patients and 160 control patients evaluated the use of aprotinin for reduction of perioperative blood loss. The pooled perioperative blood loss was significantly less in the aprotinin-treated patients than in the control patients (WMD = -556.8 mL, 95% CI = -860.1 to -253.5 mL; $P < 0.0001$), with significant heterogeneity among trials ($P < 0.0001$) (Fig. 2B).

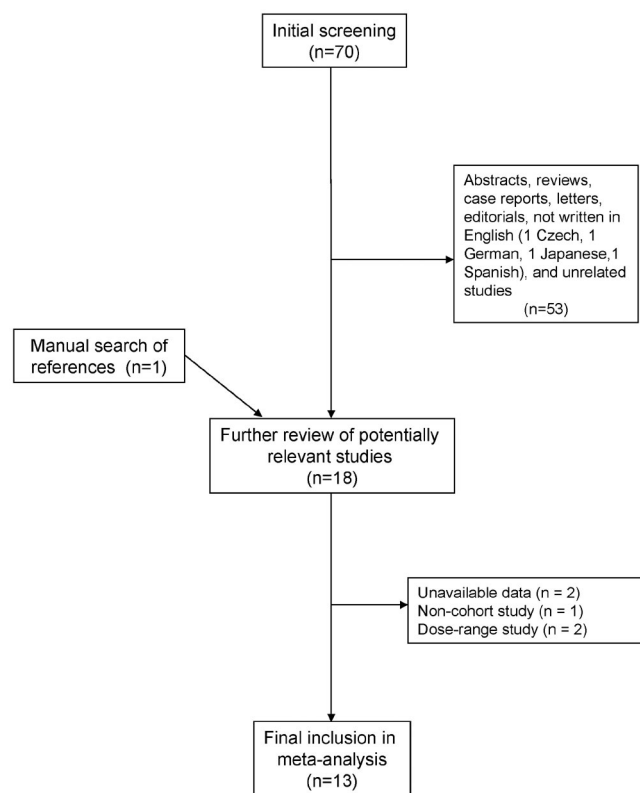


Figure 1. Meta-analysis flow chart.

Six trials (18–20,24,26,29) evaluated the use of aprotinin for reduction of the amount of blood transfused intraoperatively, with 100 aprotinin-treated patients and 102 control patients. The pooled number of intraoperatively transfused RBC units (U) was significantly less in the aprotinin-treated patients than in the control patients (WMD = -1.1 U, 95% CI = -1.7 to -0.4 U; $P = 0.0001$), with no heterogeneity among trials ($P = 0.11$) (Fig. 3A). Nine trials (18,20–22,24,26–29) evaluated the use of aprotinin for reduction of perioperative blood transfusion, with 160 patients in the treatment group and 153 patients in the control group. The pooled number of perioperatively transfused RBC U was significantly less in the aprotinin-treated patients than in the control patients (WMD = -1.1 U, 95% CI = -1.74 to -0.45 U; $P < 0.0001$), with significant heterogeneity among trials ($P < 0.0001$) (Fig. 3B).

In 4 studies, all patients underwent routine ultrasonography (18,26,28) or venography (27). In 3 studies (21,25,29), routine clinical examinations were performed in all patients, and then, if positive, further venography was performed. Some studies (19,20,24,30) did not clarify whether examinations were performed for all or specific patients. For the remaining 128 patients (22–24), the diagnostic method was not specified. In 364 patients (18,20,21,24–30), DVT prophylaxis was performed by means of heparin (25,26,28,30), low-molecular weight heparin (20,21,24,27,29), warfarin (28), or a mechanical

device (18,27,29). For the remaining 142 patients (19,22,23), the method of prophylaxis was not specified. Diagnosis of DVT was confirmed by clinical signs (18,21,25), ultrasonography (18,19,26,28), or venography (21,25,27,29,30). DVT occurred in 1 patient and arteriovenous thrombosis occurred in 1 of 204 aprotinin-treated patients, and DVT occurred in 15 of 204 control patients. Aprotinin did not significantly affect the incidence of thrombotic events (odds ratio = 0.38; 95% CI = 0.14 to 1.05; $P = 0.061$), with no heterogeneity among trials ($P = 0.75$) (Fig. 4). The D-dimer test for the diagnosis of DVT, the length of hospital stay, and the incidence of pulmonary embolism were reported in only 2 (18,21), 3 (18,19,29) and 2 trials (18,29), respectively. We, therefore, did not include these data in the analysis.

During consecutive recruitment of patients in all trials, the investigators excluded patients with suspected or known allergy to aprotinin or with previous exposure to aprotinin. There were no reported anaphylactic or anaphylactoid reactions to aprotinin.

There was marked asymmetry of the funnel plot, confirmed by a significant Kendall correlation coefficient for intraoperative blood loss of -0.42 ($P = 0.09$), for intraoperative transfusion of -0.60 ($P = 0.09$), and for incidence of DVT of 0.60 ($P = 0.01$); this suggests a publication bias for these outcomes. The Kendall correlation coefficients for total blood loss and total transfusion were -0.36 ($P = 0.22$) and -0.39 ($P = 0.14$), respectively, indicating no publication bias in the analyses of total blood loss and transfusion.

Discussion

Our meta-analysis showed that aprotinin used in patients undergoing major orthopedic surgery reduces intraoperative blood loss by a mean of 229 mL, perioperative blood loss by a mean of 557 mL, intraoperative RBC requirement by a mean of 1.1 U, and perioperative transfusion requirement by a mean of 1.1 U. Aprotinin is not associated with an increased risk of DVT in the presence of pharmacologic or nonpharmacologic prophylaxis.

This is the first systematic review of the efficacy of aprotinin in patients undergoing major orthopedic surgery. Another pharmacologic strategy, use of tranexamic acid, a lysine analog, has already been shown in the meta-analysis by Ho and Ismail (31) to be safe and effective for reducing blood loss and the transfusion requirement in patients undergoing orthopedic surgery. Their results are comparable to ours: tranexamic acid reduces perioperative blood loss by 460 mL (mean) and the transfusion requirement by 0.85 U (mean). Ho and Ismail did not focus on the incidence of DVT but rather on the overall risk/incidence of thromboembolic complications, which do not increase with hip and knee arthroplasty. Like tranexamic acid,

Table. Summary of Randomized Placebo-Controlled Trials Meeting Inclusion Criteria

Authors	Year	Jadad Score	N	Treatment group		Placebo group	Regimen of aprotinin administration	Type of surgery	Criteria for initiation of blood transfusion	Method of DVT diagnosis	Incidence of DVT		DVT prophylaxis
				Mean age (yr)	N	Mean age (yr)					Treatment group	Placebo group	
Amar et al. (18)	2003	5	23	48.0	24	55.0	2×10^6 KIU followed by 500 000 KIU/hr until end of surgery	Malignancy for pelvic, extremity or spine surgery	Hb < 8.0 g/dL or Hct < 24%	Clinical examination and Doppler ultrasonography	0	3	Compression/decompression boots
Cole et al. (19)	2003	4	21	13.0	23	12.2	1.7×10^6 KIU followed by 0.4×10^6 mg/m ² /h continuing 4 h after surgery	Posterior spinal fusion	Hemodynamic instability, Hb < 8.5 g/dL, or Hct < 27%	Ultrasound study	0	3	NS
Jeserscheck et al. (20)	2003	3	9	67.0	9	73.0	1×10^6 KIU followed by 500 000 KIU/hr	Revision of arthroplasty of the hip or knee, or for resection of a soft-tissue sarcoma	Decision by anesthesiologists	Clinical signs	0	0	5000U of low molecular weight heparin
Engel et al. (21)	2001	1	12	68.0	12	66.0	1×10^6 KIU followed by 500 000 KIU/hr for 4 h	Total knee arthroplasty	Hb < 10.0 g/dL	Clinical signs, and venography if positive	1	0	Low molecular weight heparin
Urban et al. (22)	2001	4	20	NS	18	NS	1×10^6 KIU followed by 250 000 KIU/hr	Antero-posterior spinal fusion	Hb $\leq$ 8.0 g/dL	NS	NS	NS	NS
Langdown et al. (23)	2000	4	30	70.0	30	72.8	1.5×10^6 KIU at the time of anesthesia	Primary total hip surgery	NS	NS	NS	NS	NS
D'Ambrosio et al. (24)	1999	3	15	66.6	15	60.5	0.5×10^6 KIU followed by 500 000 KIU/hr until skin was sutured	Primary total hip arthroplasty	NS	NS	0	0	Low molecular weight heparin (nadroparin)
Lentschener et al. (25)	1999	4	35	46.0	37	51.0	2×10^6 KIU followed by 500 000 KIU/hr until skin closure	Lumbar spinal fusion	Maintaining Hct $\geq$ 26%	Clinical signs, and venography if positive	0	0	Subcutaneous heparin
Capdevila et al. (26)	1998	4	12	NS	11	NS	1×10^6 KIU followed by 500 000 KIU/hr for the duration of surgery	Surgery of the hip, femur, or pelvis for sepsis, or malignant tumor	Maintaining intraoperative Hct > 25%, and postoperative Hct $\geq$ 28%	Ultrasound study	0	1	Heparin (150 U/kg for 24h) and maintained for 7 days
Hayes et al. (27)	1996	2	20	70.0	20	72.9	2×10^6 KIU as a single dose	Total hip replacement	When blood loss is more than the calculated maximum allowable blood loss	Venography	0	1	Enoxaparin and graduated compression stockings
Murkin et al. (28)	1995	5	29	66.9	24	65.5	3.8×10^6 KIU total	Bilateral or revision total hip surgery	Intraoperative blood loss exceeding 15% of blood volume of body, and postoperative Hb < 8.0 g/dL	Ultrasound study	0	3	Oral warfarin 7.5–10 mg, or subcutaneous heparin 5000U
Janssens et al. (29)	1994	3	20	65	20	65	2×10^6 KIU followed by 500 000 KIU/hr until the end of surgery	Total hip replacement	Maintaining Hct $\geq$ 30%	Venography	0	4	Low molecular weight heparin and Antistasis Stocking
Thorpe et al. (30)	1994	3	8	NS	9	NS	1×10^6 KIU followed by 500 000 KIU/hr over the next 2 h	Total knee replacement	Decision by surgical team with clinical signs	Angiography	1	0	Small dose heparin

DVT = deep vein thrombosis, KIU = Kallikrein inhibitor units, NS = not specified, Hb = hemoglobin, Hct = hematocrit.

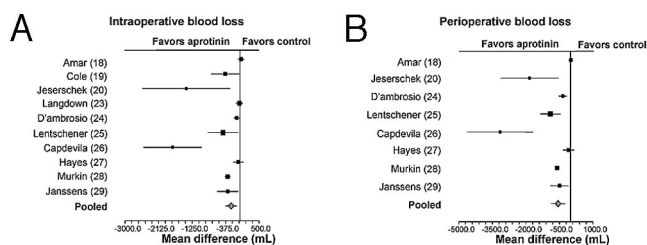


Figure 2. Forest plots for the efficacy of aprotinin on the weighted mean differences for intraoperative (A) and perioperative blood loss (B). Diamond indicates pooled weighted mean differences. Horizontal line for each trial denotes 95% confidence interval. Squares represent point estimates. The area of each square is proportional to the sample size.

aprotinin moderately decreases blood loss and the allogeneic blood transfusion requirement. It may be argued that if the efficacy of both drugs in reducing blood loss and the transfusion requirement is similar, tranexamic acid is advantageous over aprotinin because of its lack of anaphylactic effects and its lower cost (aprotinin costs approximately \$1000 per patient). However, Ho and Ismail did not clarify the presence or absence of pharmacologic DVT prophylaxis, which may have strongly influenced outcomes. Thus, we

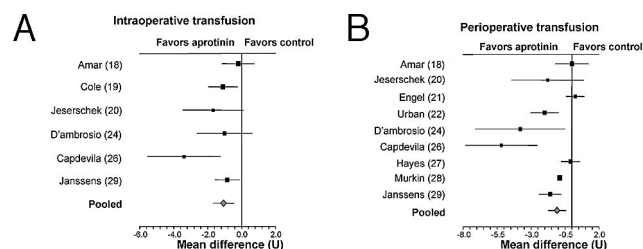


Figure 3. Forest plots for the efficacy of aprotinin on the weighted mean differences for intraoperative (A) and perioperative (B) allogeneic blood transfusion requirements. Diamond indicates pooled weighted mean differences. Horizontal line for each trial denotes 95% confidence interval. Squares represent point estimates. The area of each square is proportional to the sample size.

cannot directly compare the efficacies of the two drugs.

The effective dosage of aprotinin remains inconclusive. There are two basic regimens: full dose (≥ 2 million KIU [kallikrein inhibitor units] as an initial dose) and half doses (32). In most of the trials included in our analysis, an initial dose of 1–2 million KIU was administered. We did not analyze the relation between dose and the amount of blood loss because of

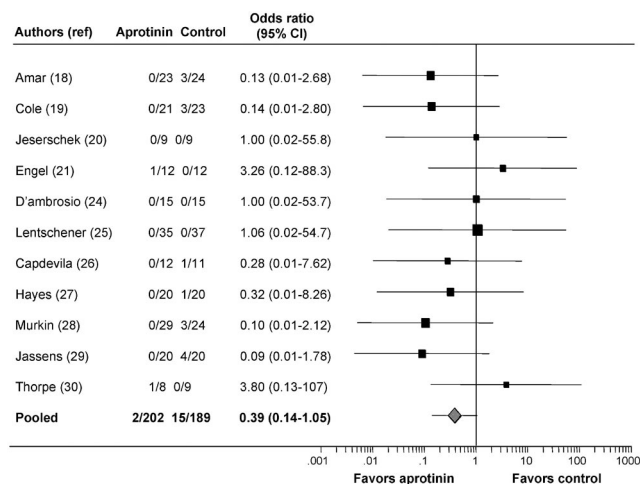


Figure 4. Forest plot of odds ratios for the effect of aprotinin on incidence of deep vein thrombosis. Diamond indicates the pooled odds ratio. Horizontal line for each trial denotes 95% confidence intervals. Squares represent point estimates. The area of each square is proportional to the sample size. CI = confidence interval.

the small number of trials. Nevertheless, a dose-related reduction in blood loss has been suggested in some studies and reviews (16,17,32). Further large randomized trials are needed.

Without thromboprophylaxis, DVT occurs in 50% to 80% of patients after total hip or knee replacement or after surgery for hip fracture (33), and in 1% to 13% of these cases, it may lead to fatal pulmonary embolism (34). In the trials included in our analysis, nearly 90% of patients received antithrombotic or mechanical prophylaxis for DVT; therefore, the incidence of DVT was infrequent at 7.4% among control patients. It is controversial whether aprotinin may produce a procoagulable state resulting in increased risk of DVT. Our results suggest that aprotinin has no effect on the incidence of DVT in patients who receive thromboprophylaxis. Although statistically not significant, there was a trend toward fewer episodes of DVT in aprotinin-treated patients. It is unlikely that aprotinin has a direct antithrombotic effect. Instead, given the fact that transfusion itself poses a risk of hypercoagulability (35), we hypothesize that the decrease in transfusion resulting from aprotinin could reduce the occurrence of thromboembolism. One aprotinin-treated patient developed serious arteriovenous thrombosis requiring knee amputation, so the trial was discontinued. The use of aprotinin was not necessarily a cause of the complication in this case.

Several issues remain to be addressed. First, no anaphylactic reactions were reported in patients in the included trials, probably because of the strict exclusion of patients at risk for anaphylaxis and its infrequent incidence (<0.1%) (32). However, the risk of anaphylaxis increases by approximately 5% when re-exposure occurs within a few weeks (32,36). Levy (5)

recommends avoiding re-exposure to aprotinin within 6 months after an initial exposure. Thus, despite the notable efficacy of aprotinin, routine clinical use in patients undergoing major orthopedic surgery cannot be recommended. Its use is particularly contraindicated when subsequent surgery is planned within several months (e.g., revision surgery). Patient eligibility must be carefully determined. Nevertheless, enthusiasm for use of aprotinin in noncardiac surgery is growing because the wide variety of complications of blood transfusion and increasing conservation costs are now better understood (2). Second, aprotinin is metabolized in the kidneys and is potentially nephrotoxic at large concentrations (37). Although clinical trials did not show that its use was significantly associated with serious renal dysfunction (37,38), aprotinin may have limited indications in patients with existing renal insufficiency or in combination with drugs such as certain antibiotics (e.g., gentamicin) that have potential detrimental effects on the kidneys (39). Third, there was heterogeneity in the results of our meta-analysis. This could be attributable to differences in the types of surgery, the backgrounds of patients, the criteria for blood transfusion, and other unidentified factors. Last, the possible publication bias suggests that small trials with negative results might not have been reported.

In summary, results of our meta-analysis indicate that aprotinin reduces intraoperative and perioperative blood loss and allogeneic blood transfusion requirements. Aprotinin may not be associated with an increased risk of DVT in the presence of pharmacologic or nonpharmacologic prophylaxis; however, definitive conclusions are precluded as the result of several study limitations.

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