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Aprotinin Decreases Blood Loss and Homologous Transfusions in Patients Undergoing Major Orthopedic Surgery

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Background: **Major orthopedic surgery can be associated with dramatic blood loss, thereby requiring high-volume homologous transfusions in patients unable to benefit from blood salvage techniques. The effect of aprotinin on blood loss and transfusion requirements during orthopedic surgery for either the resection of malignancies of the removal of infected hardware was prospectively studied.**

Methods: **Twenty-three patients scheduled for orthopedic surgery of the hip, femur, or pelvis for sepsis or malignant tumors, all under general anesthesia, were randomly allocated to receive during operation, in a blinded manner, either aprotinin administered as a bolus of 1.10^6 kallikrein inactivation units (KIU) followed by an infusion of 5×10^5 KIU/h, or the equivalent volume of saline. The anesthesia and perioperative management, as well as the designated transfusion criteria, were standardized. The total blood loss of each patient was evaluated using intraoperative suction losses, sponge weights, and postoperative volumetric drainage. Homologous transfusion requirements were noted. Hemoglobin and hematocrit measures, as well as coagulation and fibrinolytic pathway explorations, were performed before and after surgery. Deep venous thrombosis prophylaxis was applied, and the incidence of this complication was assessed.**

Results: **Twelve patients received aprotinin. Aprotinin reduced the total blood loss from a median of 5,305 ml (range, 3,000–9,770 ml) to a median of 1,783 ml (range, 1,140–4,955 ml; $P < 0.05$). A blood loss reduction of 56% during surgery and 68% on discharge from the postanesthesia care unit was observed. Seven units (range, 4–16) of packed erythrocytes were transfused per patient in the placebo group, and 3 (range, 2–5) were transfused in the aprotinin group ($P < 0.05$). In the aprotinin group, platelet counts were higher, and postoperative prothrombin times and D. Dimer values were lower. The activated partial thromboplastin time values showed no significant difference between the two groups. No side effects were observed in the aprotinin group. A deep venous thrombosis developed in one patient in the placebo group.**

Conclusion: **Aprotinin treatment during major orthopedic surgery significantly reduces both blood loss and consequent homologous blood transfusion requirements. (Key words: Antifibrinolytic drugs; perioperative use; sepsis.)**

ORTHOPEDIC surgical procedures used to treat malignant tumors or infected hardware are associated with substantial blood loss. The resulting high transfusion requirements are often further complicated by complex acquired coagulopathies (during the intra- and postoperative periods). Furthermore, blood salvage techniques are contraindicated because of the risk related to dissemination of either tumor cells or the infection. Aprotinin treatment was first shown to decrease blood loss in patients undergoing repeated cardiac surgery,[1] primary coronary and valve replacement procedures,[2,3] and in patients with endocarditis. This benefit was then shown during procedures such as liver transplantation,[4] major vascular reconstruction,[5] and, more recently, orthopedic surgery.[6–8] Documenting the efficacy and inocuity of aprotinin use during orthopedic surgery has been delayed due to the high thromboembolic risk of these procedures.

Although the mechanism of action has not yet been clearly established, it appears that aprotinin has a protective effect on platelet function,[9] and antifibrinolytic activity *via* the direct inhibition of plasmin and the kinin-kallikrein system.[2,10] Aprotinin may also partially inhibit the intrinsic coagulation pathway.[2,10,11]

This study was undertaken to assess the efficacy of aprotinin in decreasing the blood loss and homologous blood transfusion requirements of patients undergoing major orthopedic surgery.

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Materials and Methods

Patients

Once approval from our Institutional Ethics Committee and written informed patient consent were obtained, 23 patients scheduled for major orthopedic surgery of the hip or pelvis for sepsis or malignant tumors were recruited for this study.

Patients presenting one or more of the following criteria were excluded from the study: known or suspected allergy to aprotinin, preoperative renal or hepatic failure, evolutive thromboembolic disease, preoperative congenital or acquired coagulopathy suspected by clinical history or preoperative coagulation tests (platelet count, prothrombin time [PT], and activated partial thromboplastin time [aPTT]).

Anesthesia Management

Induction was obtained using intravenous 5 mg/kg thiopental, 5 μg/kg fentanyl, and 0.1 mg/kg vecuronium, thereby facilitating tracheal intubation. General anesthesia was then maintained with 40% nitrous oxide in oxygen, 0.5% to 1.5% isoflurane, and 0.08 to 0.13 $\mu g \cdot kg^{-1} \cdot min^{-1}$ fentanyl, as required to keep the systolic blood pressure between 80 and 90 mmHg. The central venous blood pressure was maintained between 2 and 6 cmH_2O. All of the patients received mechanical volume-controlled ventilation.

After induction of anesthesia, the 12 patients in the aprotinin group received a bolus of 10^6 kallikrein inactivation units (KIU) of aprotinin during a 30-min injection period, followed by a continuous infusion of 5×10^5 KIU/h throughout the duration of surgery. The 11 patients in the control group received identical volumes of saline over the same time periods. Both the surgeon and the anesthesiologist were blinded to the choice of product. The administered fluids were prepared by the hospital's central pharmacy in identical 100-ml bottles. The syringe pumps used for the administrations were then prepared by nurses not included in the study protocol.

During surgery, the measured blood and insensible fluid ($4 \text{ ml} \cdot kg^{-1} \cdot h^{-1}$) losses were replaced with colloids (modified fluid gelatin and 6% hydroxyethyl starch solutions) and crystalloids (lactated Ringer's solution) at equal volumes until a maximal colloid dose was reached: gelatins, 2,000 ml and hydroxyethyl starch, 33 ml/kg. Any remaining losses were replaced with lactated Ringer's solution. The systolic and mean blood pressure, esophageal temperature, pulse oximetry, and end-tidal carbon dioxide level were monitored continuously.

Blood Samples and Data Collection

Blood samples were drawn on the day before surgery, every 2 h during surgery, on arrival in the postanesthesia care unit (PACU), and on postoperative days 1 and 2. The samples were used to determine the hematocrit, hemoglobin, erythrocyte and platelet counts, and the PT, aPTT, and fibrinogenemia values. The kaolin-aPTT was performed using a coagulation automate ST 888 (reagent and automate from Diagnostica Stago, Asnières, France). The kaolin-aPTT value of the pool was 34 s. The plasma D. Dimer levels were measured on arrival in the PACU and on day 1 using the D-DI test (Dianostica Stago), a quantitative, rapid, latex agglutination slide test. The results were expressed in initial fibrinogen equivalent units, and the retained positive cutoff value was 0.5 μg/ml. Bleeding time, evaluated by the Ivy method (Simplate I; Organon-Technica, Türnhout, Belgium), was measured on the day before surgery and on arrival in the PACU. Systematic lactate levels were measured in the PACU. Serum concentrations of sodium, potassium, urea, and creatinine were also measured before surgery, on arrival in the PACU, and on postoperative day 1.

The anesthesiologist estimated intraoperative blood loss by measuring the volumes in the suction bottles and by weighing the swabs. The transfusions performed during the study period were based only on objective blood losses, once confirmed by the laboratory set points. During the intraoperative period, systematic hourly hematocrit determinations where measured using a microcentrifugation method. The laboratory set points were determined when these rapidly determined values decreased to less than 25% and or when the anesthesiologist measured a considerable blood loss. On confirmation, one homologous packed red blood cell unit was transfused, and the laboratory set points were determined again. This process was repeated as necessary to maintain the laboratory-based hematocrit values at 25%. At the end of each surgical procedure, the surgeon gave a descriptive assessment of the intraoperative blood loss (weak, moderate, heavy, very heavy). The surgeon's subjective opinion concerning the blood loss could not, as such, influence the anesthesiologist's objective determination.

Postoperative blood loss was assessed during a 5-day

period by measuring the blood in the drain bottles (at discharge from the PACU, on postoperative days 1 and 2, and from days 3 to 5). Homologous transfusions were performed if the hematocrit concentration decreased to less than 28% in any of the postoperative measures. Throughout the study period, fibrinogen was administered as 1.5 g cryoprecipitate whenever the fibrinogemia level decreased to less than 1 g/l. Similarly, two units of fresh-frozen plasma were administered if the PT values increased to more than 49 s, and one platelet unit/10 kg body weight was administered if the platelet count decreased to less than 30,000 mm^3. This procedure was repeated as necessary to maintain the cited threshold values. No special blood salvage techniques were used, because they were contraindicated in this patient population. Primary deep venous thrombosis (DVT) prophylaxis was initiated 6 h after surgery using continuous intravenous infusions of heparin (150 U/kg for 24 h) and maintained from postoperative days 1–7. All of the patients were examined daily for signs of lower limb DVT and underwent a systematic doppler ultrasound on postoperative day 6. Any clinical sign of DVT (swelling or increase in the diameter of the calf, pain on palpation, or localized redness) resulted in a bilateral compression color doppler ultrasound, and any positive results of doppler ultrasound was further examined by venography.

Statistical Analysis

Randomization was performed using a random number list generated by computer program (VAX/VAS version V5.3; Digital Equipment Corp., California). A 10% beta risk was retained for an anticipated 30% intergroup difference concerning blood loss and transfusion requirements. Although the study was originally designed to include 30 patients, an interim analysis indicated a highly significant reduction of blood loss in the aprotinin group. Consequently, in compliance with the recommendations of our institution's ethics committee, the study was aborted after the twenty-third patient was tested. The beta risk remained at 10% after reduction of our patient population to 23 persons because of the significant intergroup differences found in the blood loss and transfusion requirements.

The quantitative variables were compared using the nonparametric Kruskall-Wallis test due to their non-normal distribution and the small patient groups. To provide better information on the distribution of certain parameters (blood loss, transfusion volumes), their values were reported on a patient-by-patient basis. Chi-squared or Fischer's exact tests were used to compare the qualitative variables. The temporal evolution of the biological parameters was evaluated using a variance analysis. If a total time effect was significant, the different times were successively compared with the preoperative value to isolate the difference. The Bonferroni correction was then applied to avoid the statistical error induced by the multiplication of the tests. If a time group interaction was significant, the temporal evolution of the two groups was studied separately. Results are expressed as means ± SD or medians (range). A significant threshold of $P < 0.05$ was retained.

Table 1. Patient Characteristics, Perioperative Mean Arterial Pressure Values, and Operative Times

	Aprotinin Group (n = 12)	Control Group (n = 11)
Age (yr)	48.6 ± 17.3	48.5 ± 16.3
Weight (kg)	61 ± 8	65 ± 8.6
Height (cm)	165 ± 6	170 ± 7
Sex (M/F)	7/5	6/5
Oncologic surgery	5	4
Septic revision THA	5	4
Acute osteitis of the femoral shaft	2	3
Intraoperative MAP (mmHg)	61.3 ± 13	64.7 ± 9.4
MAP in PACU (mmHg)	69.7 ± 21.2	71.4 ± 11.7
Operative time (min)	266 ± 120	311 ± 140

Values are mean ± SD.

THA = total hip arthroplasty; MAP = mean arterial pressure.

Results

The two groups were comparable regarding demographic characteristics (age, weight, height, and sex), operative time, type of surgery, and preoperative mean arterial pressure values. Table 1 reports these results.

Fourteen patients underwent orthopedic surgery to remove infected hardware. Nine revisions of total hip arthroplasties were performed as single procedures, with the acetabular and femoral components of the prostheses being replaced, and five cases of femoral osteomyelitis were treated by removing the appliance and autologous bone grafts. Seven of these patients received aprotinin. Nine patients underwent surgical procedures for the resection of femoral osteosarcomas and adenocarcinoma metastases. Five of these patients received aprotinin.

Table 2. Subanalysis of Perioperative Blood Loss and PRBC Transfusions Presented on a Patient-by-Patient Basis, Undergoing the Removal of Either Malignant Tumors or Infected Hardware

	Intraoperative Blood Loss (ml)		Total Blood Loss (ml)		Intraoperative PRBCs (units)		Total PRBCs (units)	
	Aprotinin Group	Control Group	Aprotinin Group	Control Group	Aprotinin Group	Control Group	Aprotinin Group	Control Group
Surgical removal of infected hardware	750	2,355	1,140	6,035	1	4	2	7
	1,140	5,400	2,520	9,770	2	12	4	16
	725	1,650	1,670	3,160	0	2	3	4
	1,270	2,940	1,855	5,620	2	4	3	7
	1,100	2,755	1,710	5,575	0	5	2	10
	1,580	2,870	2,860	4,005	2	3	5	7
	1,150	2,110	1,540	3,000	0	1	2	4
Median	950*	2,233	1,810*	5,475	0.5*	2.5	3*	8
Range	725–1,580	1,650–5,400	1,140–2,860	3,000–9,770	0–2	1–12	2–5	14–16
Surgical removal of malignant tumors	1,570	2,560	2,595	5,305	2	5	4	8
	610	2,400	1,430	3,815	1	2	2	5
	2,240	4,800	4,955	8,420	3	10	6	16
	1,664	2,540	2,185	3,540	2	3	3	8
	430		1,250		0		2	
Median	1,000*	2,550	2,185*	4,560	1*	4	3*	7
Range	430–2,240	2,400–4,800	1,256–4,955	3,540–5,305	0–3	2–10	2–6	5–16

PRBCs = packed red blood cells.

* $P < 0.05$ *versus* Control group.

The intraoperative fluid replacement consisted of 1,500 ml (range, 750-2,550 ml) colloids and 1,950 ml (range, 100-3,400 ml) crystalloids in the placebo group, and 850 ml (range, 500-1,550 ml) colloids and 1,110 ml (range, 750-2,040 ml) crystalloids in the aprotinin group ($P < 0.05$). In the PACU, 250 ml (range, 0-750 ml) colloids and 515 ml (range, 250-1,200 ml) crystalloids were administered in the placebo group, and 250 ml (range, 0-500 ml) colloids and 255 ml (range, 200-755 ml) crystalloids in the aprotinin group. Group A patients received a mean dose of $3.3 \times 10^6 \pm 1 \times 10^6$ UIK aprotinin per patient.

The total blood loss in the aprotinin patients was 65% lower than in controls: 5,305 ml (range, 3,000-9,770 ml) compared with 1,783 ml (range, 1,140-4,955 ml; $P < 0.05$). Intraoperative blood losses were reduced by 56% in the aprotinin group: 2,550 ml (range, 1,650-5,400) compared with 1,145 ml (range, 430-2,240 ml). Blood loss on discharge from the PACU was reduced by 68% in the aprotinin group: 870 ml (range, 355-2,210 ml) compared with 280 (range, 70-820 ml). Table 2 shows the transfusion volumes and blood losses during both the intraoperative and total study periods reported on a patient-by-patient basis. Table 2 also represents a subanalysis based on the total blood losses and the homologous transfusion requirements of the four patient subgroups: those undergoing surgery for either malignancies or infected hardware, and those receiving either aprotinin or a placebo. Although less total blood loss was noted in the subgroup including septic patients receiving aprotinin treatment, no differences were statistically significant.

The decreased blood losses of the aprotinin group seem to have been clinically evident, because the bleeding intensity scores subjectively evaluated by the surgeon correlate with the treatment groups (table 3).

All of the patients received blood transfusions. The aprotinin group had 67% lower intraoperative transfusion requirements than did the placebo group, and 58% less over the entire study period. The total number of packed erythrocytes transfused was 36 for the aprotinin

Table 3. Bleeding Intensity Scores

	Slight	Moderate	Heavy	Very Heavy
Aprotinin group (n = 12)	7*	5	0*	0*
Control group (n = 11)	0	4	5	2

* $P < 0.05$ *versus* Control group.

Table 4. Amount of Transfused Blood Products

	Aprotinin Group (n = 12)	Control Group (n = 11)	*P* Value
Intraoperative red cell units	1 (0–3)	3 (1–13)	<0.05
PACU red cell units	1 (0–2)	3 (1–4)	<0.05
Total red cell units	3 (2–5)	7 (4–16)	<0.01
Intraoperative FFP	0 (0–2)	0 (0–5)	NS
PACU FFP	0	0 (0–2)	NS
Total FFP	0 (0–2)	1 (0–6)	<0.05
Intraoperative PU	0	0	NS
PACU PU	0	0 (0–6)	NS
Total PU	0	0 (0–6)	NS
Intraoperative Fg (g)	0	0 (0–3)	NS
PACU Fg (g)	0	0 (0–1)	NS
Total Fg (g)	0	1 (0–3)	<0.05

Values are median (range).

FFP = fresh frozen plasma; PU = platelet unit; Fg = fibrinogen; PACU = postanesthesia care unit; NS = not significant.

group and 92 for the control group ($P < 0.01$). Table 4 shows the packed red cells, fresh frozen plasma, platelet units, and fibrinogen transfusions used. No difference existed between the groups concerning hematocrit and hemoglobin values at any time of the study (table 5).

When compared with the preoperative values, the average platelet count of the patients in the control group decreased on discharge from the PACU and on postoperative days 1 and 2, whereas those of the aprotinin group remained stable (table 5). There was a slight but nonsignificant preoperative intergroup difference in the values of aPTT. However, the postoperative aPTT values of both groups increase through the trial period with no significant intergroup differences. The postoperative fibrinogen values decreased with a statistically significant intergroup difference (table 5). The PT was lower in the aprotinin group than in the control group on discharge from the PACU and on postoperative day 1 (table 5). The aprotinin group presented significantly lower D. Dimer and bleeding time values and lower lactate levels (table 6).

No significant difference was noted between the two groups regarding the incidence of DVT. An ultrasound examination detected one DVT below the popliteal fossa in a patient in the placebo group, which was later confirmed by venography.

No side effects such as allergic reactions or hypotension were observed in association with aprotinin use. All patients presented stable renal function throughout the study (Na^+, K^+, urea, creatinine).

Discussion

In this randomized, double-blind clinical trial, aprotinin use resulted in a 65% decrease in blood loss, and in a 58% reduction in homologous transfusion require-

Table 5. Perioperative Values of Hemoglobin (Hb), Hematocrit (Hct), aPTT, PT, Platelet Count, and Fibrinogen (Fib) throughout the Study Period

	Hb (g/dl)	Hct (%)	aPTT (s)	PT (s)	Platelet Count ($\times 10^3$ platelets/dl)	Fib (g)
Aprotinin group						
Preoperative	10.6 (9.9–12.3)	32 (29–37)	32.1 (27–41)	15.2 (15–17.2)	355 (93–453)	4.5 (3–10)
PACU	8.5 (6.5–10)	27 (20–30)	42 (32–120)	17 (15.5–19.3)	310 (100–750)	4 (1.3–5.6)
D1	10 (7–11)	30 (22–33.5)	38 (32–120)	16.4 (15–22.3)	317 (75–847)	3.7 (1.3–8.6)
D2	10 (7.5–11)	30 (22–33)	40 (31–70)	15.7 (15–18)	302 (98–850)	5 (3–7.6)
D3	10 (9–11)	30 (28–33)	39 (28–47)	15.5 (15–18)	327 (101–740)	5.5 (4–7.6)
Control group						
Preoperative	10.5 (8.5–11.5)	32 (27–36)	35 (29.5–55)	15 (15–17)	287 (137–535)	4.3 (3–7)
PACU	9.1 (5–10)	27 (15–31)	43 (34–105)	21 (16–51)*	120 (30–540)*	1.9 (0.5–5.6)*
D1	9.7 (7.5–11)	28 (24–31.5)	39.5 (31–61)	19 (16.4–26.5)*	137 (75–347)*	3 (1–8.6)
D2	9.8 (7–10.5)	28 (20–31)	39 (30–61)	17 (16–18.7)	147 (101–476)*	3.5 (1.8–5.2)
D3	9.7 (8–10.6)	30 (24–33)	40 (32–55)	16.5 (15–18)	144 (100–500)*	4 (2–8.2)

Values are median (range).

D1, D2, D3 = postoperative days 1, 2, and 3, respectively; aPTT = activated partial thromboplastin time; PT = prothrombin time.

* $P < 0.05$ between groups.

Table 6. D. Dimer, Bleeding Time, and Systemic Lactate Levels

	D. Dimers (PACU) (μg/ml)	D. Dimers (day 1) (μg/ml)	Bleeding Time (PACU) (min)	Lactate (PACU) (mM)
Aprotinin group (n = 12)	2 (1–4)	2 (1–2)	7.5 (5–10)	2.2 (1.4–4.2)
Control group (n = 11)	8 (4–21)	2 (0.5–6)	9.5 (6–14)	3.4 (1.8–5.2)
P	<0.01	NS	<0.05	<0.05

Values are median (range).

PACU = postanesthesia care unit; NS = not significant.

ments in patients undergoing major orthopedic surgery. No differences in venous hematocrit and hemoglobin concentrations between the two groups were noted at any time of the study, as the intra- and postoperative transfusion criteria were the same in both groups. Further, other parameters affecting bleeding (*i.e.*, intra- and postoperative mean arterial pressure, intraoperative end-tidal carbon dioxide level, central venous pressure, mean airway pressures, body temperature, and length of surgery) were similar in the two groups. This confirms that the lower transfusion requirements of the aprotinin-treated cohort did not result in a more significant degree of anemia. These results are consistent with those of other studies concerning orthopedic surgery[6–8] in which the authors found a 25–45% decrease in blood loss and transfusion requirements, as well as during cardiac surgery[1,2,10] and orthotopic liver transplantation.[12] The plasma half-life of aprotinin is approximately 150 min.[13] Because the pharmacologic effect of a drug lasts longer than its half-life, it is reasonable to expect aprotinin's pharmacologic effects to persist 4–8 h after the end of the aprotinin infusion. For this reason, our patient's blood losses were mainly reduced during the intraoperative and early postoperative periods.

Although use of aprotinin has been evaluated in only a few studies involving orthopedic procedures, it has been shown to be effective. Our study population was of particular relevance in the evaluation of aprotinin use because no blood salvage techniques were applicable. Further, major orthopedic surgery is known to produce more blood loss than are other orthopedic procedures. Nevertheless, the mechanism underlying the beneficial effects of aprotinin has not yet been fully elucidated. There seems to be three possible sites of action. Septic state activation of coagulation primarily concerns the extrinsic pathway.[14,15] In addition, in the presence of cytokines and endotoxins known to increase capillary permeability, high quantities of tissue factor, originating from subendothelial sites, are released into the blood stream.[16,17] As such, aprotinin could play a protective role against disseminated intravascular coagulopathy *via* its anti-VIIa activity.[18] Complex acquired coagulopathy may occur in many surgical settings associated with infection and severe tissue damage.[19] It has also been reported in patients with metastatic bone cancer[20,21] and during major orthopedic procedures such as spinal surgery.[22] Because all of our patients had either malignant or septic conditions, the risk of disseminated intravascular coagulopathy was elevated. We cannot discount an initial preoperative intergroup difference with respect to disseminated intravascular coagulopathy, because the median preoperative value of aPTT was slightly increased in the placebo group. The control group's elevated postoperative aPTT values may translate a consumption of the coagulation factors (*i.e.*, dilution, transfusion), although no significant intergroup difference was noted. The elevated postoperative aPTT values of the aprotinin group would reflect the partial inhibition of the intrinsic coagulation pathway. Because kaolin was used as the aPTT activator, these findings are unlikely to be the result of an *in vitro* celite–aprotinin interaction, despite the postoperative heparin administration.[23] Murkin *et al.*[7] concluded similarly when they observed increased postoperative aPTT values in the aprotinin group, whereas the PT values of both groups were identical. The preserved PT values of the aprotinin group may be explained by the limitation of a complex acquired coagulopathy.[19] Furthermore, as reported by Dietrich *et al.*,[24] aprotinin might have reduced the consumption of thrombin-mediated coagulation factors. Finally, aprotinin has been shown to reduce bleeding related to the administration of heparin.[25] Although both groups received the same dose of heparin, the patients receiving aprotinin may have had less heparin-related bleeding.

In our study, it is unlikely that the *in vitro* concentra-

tions required to obtain effective antikallikrein activity were reached.[7] In contrast, the doses of aprotinin were probably sufficient to invoke antiplasmin activity.[26] By its circulating anti-plasmin effect, aprotinin could have inhibited plasmin formation. This inhibition would be due to the antifactor XII activity, and perhaps to some antikallikrein effect of aprotinin. Tumor necrosis factor-α, whose levels are probably high in our patient population, seems able to promote the release of tissue plasminogen activator from the endothelial cells.§ As such, the anti-tumor necrosis factor-α properties of aprotinin could have contributed to the antifibrinolytic effect. Tissue hypoxia and the resulting maintained local fibrinolysis[19] seem to have been limited in the aprotinin group, because plasma lactic acid levels sampled in the PACU were lower than those of the control group. An identical finding concerning hip surgery was reported by Haas *et al.*[27] In any case, the antifibrinolytic effect obtained as a significant difference was noted between the immediate postoperative plasma D. Dimer levels of the two groups. In contrast, Janssens *et al.*[6] found no significant differences between the aprotinin and control groups concerning the fibrinolysis markers, although the plasma D. Dimer levels tended to diminish in the treated group. These results probably can be explained by the different surgical procedures performed in the two studies.

Primary hemostasis is the third target whereby aprotinin might act. One hypothesis involves a direct platelet-preserving property.[9] Although the platelet function was not tested in our study, bleeding time values were higher in the placebo group. Hass *et al.*[27] found that collagen-induced platelet aggregability and glass-bead platelet retention, both measures of surgically induced platelet activation, were significantly decreased after aprotinin administration. Aprotinin may also inhibit the plasmin-induced cleavage of GpIb, or the translocation of GpIb from the plasma membrane into the canalicular system.[28,29] The preservation of the platelet count in the aprotinin group could be the illustration of these protective effects. However, the decreased platelet count of the placebo group patients can be explained by a dilutional thrombopenia and the high number of packed red blood cell transfusions. In contrast, neither Janssens *et al.*[6] nor Murkin *et al.*[7] found a difference between the groups' platelet counts. In addition, Janssens *et al.*[6] found no platelet activation, because β-thromboglobin levels and platelet aggregation tests were identical in the aprotinin and placebo groups.

No significant differences were noted between the two groups regarding either renal function or DVT formation. We used a combination of clinical follow-up and ultrasonography to detect relevant DVT. Although aprotinin may have anticoagulant properties,[24,30] it may lead to a hypercoagulable state due to the inhibition of plasmin and protein C.[31] Decreased graft patency[32,33] and thromboembolic complications[34] have been evoked in the literature. In contrast, other studies report no reduction in graft patency[35,36] and no thromboembolic complications associated with aprotinin use. Furthermore, the anticoagulant properties of aprotinin could account for the reduction in transfusion requirements[10] and stroke rate observed in clinical trials.[1] Studies concerning orthopedic surgery[6,7] do not demonstrate an increase in DVT rate, and even a trend toward a lower incidence of DVT in aprotinin-treated patients was reported by Murkin *et al.*[7] Only Thorpe *et al.*[8] described one patient in the aprotinin group in whom an arteriovenous thrombosis developed during knee replacement surgery, which required leg amputation. This elderly patient suffered from peripheral vascular disease, a condition that could account for the thrombosis.

We conclude that during major orthopedic surgery, aprotinin treatment dramatically reduces bleeding and subsequent blood transfusion requirements. The complex acquired coagulopathy frequently observed during these surgical procedures seems to be a privileged target of aprotinin. No adverse effects due to the use of aprotinin or increased incidence of DVT were observed.

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