High-dose Aprotinin Reduces Blood Loss in Patients Undergoing Total Hip Replacement Surgery

Marc Janssens, M.D.,* Jean Joris, M.D.,* Jean Louis David, M.D.,† Roger Lemaire, M.D.,‡ Maurice Lamy, M.D.§

Background: Aprotinin, a proteinase inhibitor, has been reported to reduce blood loss significantly during cardiac surgery. The mechanisms of this effect remain unclear. We studied the effect of aprotinin on blood loss and transfusion requirement during total hip replacement. Potential mechanisms of action and side effects were also investigated.

Methods: Forty patients scheduled for primary total hip replacement were randomized to receive, in double-blind fashion, either aprotinin given as a bolus of $2 \times 10^6$ kallikrein inactivator units (KIU) followed by an infusion of $5 \times 10^5$ KIU/h until the end of surgery or an equivalent volume of normal saline. Anesthesia and surgical techniques were standardized and systematic deep venous thrombosis prophylaxis was used. Peri- and postoperative blood loss and transfusion were measured. Fibrinolysis, coagulation pathways, and platelet function were assessed. Renal and hepatic function as well as the incidence of deep venous thrombosis were also assessed.

Results: Aprotinin reduced total blood loss from 1,943 ± 700 ml to 1,446 ± 514 ml ($P < 0.05$). This reduction of blood loss occurred during surgery ($P < 0.05$) and postoperatively ($P < 0.001$). Total amounts of blood transfused were 3.4 ± 1.3 units/patient in the control group and 1.8 ± 1.2 units/patient in the aprotinin group ($P < 0.001$). The activated partial thromboplastin time was significantly prolonged by aprotinin immediately after surgery, at 50.6 ± 12.4 seconds versus 32.3 ± 4.6 seconds in control patients ($P < 0.001$), but results of the other coagulation tests were not different between the two groups. No side effects were observed in the aprotinin group. The incidence of deep venous thrombosis in the two groups was not significantly different.

Conclusions: The use of high-dose aprotinin during total hip replacement results in a reduction in both blood loss and the amount of blood transfused. Aprotinin’s mode of action, however, remains to be elucidated. (Key words: Coagulation: aprotinin. Surgery, orthopedic: total hip replacement.)

ORTHOPEDIC surgery of the hip may be associated with substantial blood loss requiring transfusion of several units of blood. Even by combining several blood conservation techniques (predonation, normovolemic hemodilution, and peri- and postoperative shed blood recovery) or anesthetic techniques (regional anesthesia, controlled hypotension), it may be difficult to avoid transfusion. The use of high-dose aprotinin in cardiac surgery has been reported to reduce blood loss significantly.1–7 Although the full range of aprotinin’s effects has yet to be elucidated, several mechanisms have been proposed.8 First, high-dose aprotinin inhibits fibrinolytic activity both by direct inhibition of plasmin9 and by inhibition of the kinin–kallikrein system.4 Decreased production of bradykinin reduces the release of tissue plasminogen activator, resulting in decreased formation of plasmin.10 Second, high-dose aprotinin may partially inhibit the intrinsic coagulation pathway while leaving the extrinsic pathway intact.11–13 Finally, a protective effect of aprotinin on platelet function has been suggested.3,6,14–16 A reduction of blood loss by aprotinin also has been reported in patients undergoing total hip replacement surgery.14 Using the same doses as those used in cardiac surgery, we undertook a controlled, randomized, double-blind study of high-dose aprotinin for total hip replacement surgery to confirm the beneficial effects of aprotinin on blood loss and on the use of blood products. We also attempted to elucidate the mechanisms of action of aprotinin in this type of surgery and to investigate possible side effects of aprotinin on renal and hepatic function. The incidence of deep venous thrombosis (DVT), which conceivably could increase because of the potential hemostatic properties of aprotinin, was also evaluated.

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Materials and Methods

Patients

After our institution’s Ethics Committee had approved the study, forty patients scheduled for primary elective total hip replacement gave informed consent for enrollment. Exclusion criteria were known allergy to aprotinin; preoperative renal or hepatic failure; uncontrolled hypertension (i.e., diastolic blood pressure ≥100 mmHg); clinical cardiac or pulmonary failure; and preoperative coagulopathy suspected by clinical history or preoperative blood coagulation tests (platelet count, prothrombin time, and activated partial thromboplastin time [aPTT]).

After induction of anesthesia, patients were randomly allocated to receive either preservative-free aprotinin (10,000 kallikrein inactivator units [KIU/ml]) given as a bolus injection of 2 × 10^6 KIU over 30 min followed by an infusion of 5 × 10^5 KIU/h until the end of surgery, with a maximum dose of 3.5 × 10^6 KIU (group A, n = 20) or the same volume of normal saline according to the same protocol (group P, n = 20).

Anesthesia Management

Oral hydroxyzine 1 mg/kg was given 90 min before surgery, and midazolam 5 mg and atropine 0.5 mg were injected intramuscularly 30 min later. Anesthesia was induced with intravenous sufentanil 0.1 μg/kg and thiopental 4–5 mg/kg. Tracheal intubation was facilitated with intravenous pancuronium 0.1 mg/kg. Anesthesia was maintained with 40% O_2:N_2O and halothane (maximum 1.5%) as required to keep systolic blood pressure less than 140 mmHg. If necessary, sufentanil 0.05 μg/kg or labetalol 10 mg was injected. Controlled hypotensive anesthesia was not used in these patients.

Intravenous infusion of lactated Ringer’s (200 ml/h) was started on induction of anesthesia. Intra- and postoperative losses were replaced with gelatin solution (Haemaccel, Hoechst, Belgium) to maintain normovolemia. During surgery, blood samples were collected to measure hematocrit by microcentrifugation as soon as estimated blood loss exceeded 500 ml. The anesthesiologist estimated intraoperative blood loss by measuring the volume in the suction bottles and counting sponges (±5 ml/sponge). Hematocrit level also was determined at the time of arrival in the postanesthesia care unit (PACU), at discharge from the PACU 5 h later, and on postoperative days 1, 4, and 7. Packed red blood cells were transfused to maintain a hematocrit of 30%. (One unit is estimated to increase hematocrit by about 3%). No fresh frozen plasma or other blood components were transfused. Except for predonation in 17 patients in group P and 14 patients in group A, no special blood-saving techniques (such as intra- or postoperative shed blood recovery or intentional preoperative normovolemic hemodilution) were used. Finally, 6% hydroxyethyl starch (200,000 D, HAES-Steril, Codali) was infused as a complement to DVT prophylaxis: 500 ml during surgery, 500 ml in the PACU, and 500 ml over postoperative day 1.

Primary DVT prophylaxis was based on the use of low-molecular-weight heparin (CY 216, Fraxiparine, Sanofi-Pharma): 100 Choay U anti-Xa/kg were injected subcutaneously 12 h before surgery, 12 h after surgery, and once per day thereafter. This dose was increased to 150 Choay U anti-Xa/kg on the 4th postoperative day. Antistasis stockings were applied preoperatively to the leg that was not to receive surgery and as soon as possible to the other leg. Mobilization was routinely started on the first postoperative day.

Surgical and anesthesia techniques were standardized; the same surgeon (RL) performed all surgery, and the same anesthesiologist (MJ) was responsible for peri- and postoperative care and follow-up. Both the surgeon and the anesthesiologist were unaware as to whether patients were receiving aprotinin or placebo.

Blood Sampling and Data Collection

At the end of surgery, the surgeon evaluated bleeding on a four-point rating scale as slight, moderate, heavy, or very heavy. Postoperative blood loss also was measured from the surgical drains over the first 5 h, from the 5th to the 24th h, and on the 2nd postoperative day. After the first 5 h, hematocrit of the drainage fluid was measured. The drains were removed after 48 h. All transfusion of packed red cells was noted.

Blood samples were drawn on the day before surgery, on arrival in the PACU, on discharge from the PACU 5 h later, and on postoperative days 1, 4, and 7. To elucidate the potential hemostatic effect of aprotinin, the three putative mechanisms of action were explored. First, the effect on fibrinolysis was assessed by measuring the appearance of D dimers in patient’s blood. Second, prothrombin time and aPTT were measured to assess the extrinsic and the intrinsic coagulation pathways, respectively, while activation of the coagulation system was estimated by thrombin–antithrombin com-

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# 1 IU = 2.44 U Choay anti-Xa.
plexes and fibrinopeptide A. Finally, platelet function was explored: platelet counts and plasma levels of β-thromboglobulin, which reflects in vitro platelet activation, were measured; adenosine diphosphate and collagen-induced aggregation were used to assess in vitro aggregability. Bleeding time by the Ivy method (Simplate I, Organon Teknika) was measured on the day before surgery, at the time of arrival in the PACU, and on postoperative day 7.

Because of economic and laboratory constraints (technician availability), measurements of thrombin–antithrombin complexes, fibrinopeptide A, and β-thromboglobulin, as well as of adenosine diphosphate and collagen-induced aggregation, were carried out on only 18 patients (10 in group A and 8 in group P) on the day before surgery, in the PACU, and on day 7.

Serum concentrations of SGOT (serum glutamic oxaloacetic transaminase), SGPT (serum glutamic pyruvic transaminase), and total bilirubin were measured to assess liver function, and urea and creatinine to assess renal function.

Finally, all patients were examined daily for signs of DVT in the lower limbs. Any clinical sign (swelling or increase in the diameter of the calf, pain on palpation, or localized redness) called for venography.

**Statistical Analysis**

Results are expressed as the mean ± standard deviation. To compare groups, Student’s t test was used for continuous data and the chi-square test for discrete variables (bleeding intensity score, D dimers, and incidence of DVT). When the number of observations was too small, Fisher’s exact test was used. The Mann-Whitney test was used to compare the number of units of packed red cells transfused during and after surgery. The time courses of biochemical parameters in the two groups were compared using Zerbe’s method. This technique allows one to test the hypothesis of the equality of response curves for two or more groups at multiple time points or during any given time interval. Its criterion is distributed as a Snedecor F test whose degrees of freedom depend not only on the group sample size but also on the time period chosen.

**Results**

The two groups were comparable in demographic characteristics (age, weight, height, and sex), operative time, and hemorrhagic risk (history of excessive bleeding during previous operations or use of nonsteroidal anti-inflammatory drugs) (table 1). The hospital stay was not altered by the treatment.

Total blood loss (peri- and postoperative) was reduced by 26% in group A (P < 0.05) (table 2). This reduction in bleeding occurred both during (P < 0.05) and after surgery (P < 0.001). Subsequent losses were comparable in the two groups. This reduction in blood loss was clinically evident: the bleeding intensity score given by the surgeon was significantly less for the operations in the presence of aprotinin (P < 0.01) (table 3). In addition, the hematocrit of the drainage fluid

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 20)</th>
<th>Group P (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>64.9 ± 13.2</td>
<td>65.3 ± 15.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72.8 ± 15.2</td>
<td>65.7 ± 11.7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166 ± 9.3</td>
<td>163 ± 9.2</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>10/10</td>
<td>6/14</td>
</tr>
<tr>
<td>History of excessive bleeding during previous operation</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Use of nonsteroidal antinflammatory drugs</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Operative time (min)</td>
<td>169 ± 27</td>
<td>176 ± 32</td>
</tr>
<tr>
<td>Length of hospitalization (days)</td>
<td>13.9 ± 5</td>
<td>13.2 ± 2.3</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

A = aprotinin; P = placebo.

### Table 2. Perioperative Blood Loss (ml)

<table>
<thead>
<tr>
<th></th>
<th>Intraoperative</th>
<th>Postoperative (Drains)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Suction</td>
<td>Sponges</td>
</tr>
<tr>
<td>Group A (n = 20)</td>
<td>588 ± 273</td>
<td>205 ± 77</td>
</tr>
<tr>
<td>Group P (n = 20)</td>
<td>833 ± 422</td>
<td>280 ± 100</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

A = aprotinin; P = placebo; NS = not significant.

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was significantly lower \((P < 0.05)\) in group A (18 ± 7%) than in group P (23 ± 6%).

Aprotinin treatment resulted in a significant reduction in blood transfusion, which for group A was 1.8 ± 1.2 units/patient and for group P 3.4 ± 1.3 units/patient \((P < 0.001)\) (table 4). This reduction occurred not only perioperatively (from the day before surgery to postoperative day 1) \((P < 0.05)\) but also in the postoperative period (days 1–7) \((P < 0.05)\). Significantly fewer patients in the treated group required more than 3 units of red blood cells; two in group A versus nine in group P \((P < 0.05)\). Four patients in group A did not require any transfusion (no significant statistical difference). No statistical differences between the hematocrit of the two groups were observed except on postoperative day 1, when the hematocrit of the placebo group was lower \((P < 0.01)\) (fig. 1).

Postoperatively, fewer patients in group A had increases in D dimers, but this was not statistically significant (table 5). Whereas the extrinsic coagulation pathway (prothrombin time) was not affected by treatment, the intrinsic pathway (aPTT) was significantly inhibited by aprotinin during the early postoperative period (3 and 8 h) \((P < 0.001)\) (fig. 2). Similar activation of the coagulation system was observed in both groups. Plasma levels of thrombin–antithrombin complexes and fibrinopeptide A increased after surgery and returned to normal by 1 week after surgery (table 6). The platelet count and the bleeding time, similar in both groups, did not change significantly. No evidence of platelet activation was found: β-thromboglobulin remained normal throughout the study. No significant changes in \textit{in vitro} platelet aggregability were observed in either group.

The incidence of clinical DVT in the two groups was not significantly different. In group P, four clinically suspected cases of DVT, one in the deep femoral vein and three below the poplitical fossa, were confirmed with venography. In group A, only one patient had clinical signs of DVT, which was ruled out by venography (no significant statistical difference). No clinically evident pulmonary emboli were diagnosed.

### Table 3. Bleeding Intensity Scores

<table>
<thead>
<tr>
<th></th>
<th>Slight</th>
<th>Moderate</th>
<th>Heavy</th>
<th>Very Heavy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>9</td>
<td>6</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Group P</td>
<td>1</td>
<td>4</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

\(A = \text{aprotinin}; P = \text{placebo.}\)

Difference between groups A and P, \(P < 0.01\) (chi-square analysis).

### Table 4. Units of Packed Red Cells Transfused

<table>
<thead>
<tr>
<th></th>
<th>Perioperative (from D0 to D1)</th>
<th>Postoperative (from D1 to D7)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>Mean ± SD (1.1 ± 0.97)</td>
<td>Median (range) 1 (0–3)</td>
<td>0.7 ± 0.98</td>
</tr>
<tr>
<td>Group P</td>
<td>Mean ± SD (1.95 ± 1.28)</td>
<td>Median (range) 2 (0–5)</td>
<td>1.45 ± 1.10</td>
</tr>
<tr>
<td>(P)</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\(D0 = \text{day before surgery}; D1 = \text{1 day after surgery}; D7 = \text{7 days after surgery}; A = \text{aprotinin}; P = \text{placebo.}\)

### Table 5. Number of Patients with D Dimers Greater than Normal (≥0.5 μg/ml)

<table>
<thead>
<tr>
<th></th>
<th>PACU</th>
<th>Postoperative Day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preoperative</td>
<td>Arrival</td>
</tr>
<tr>
<td>Group A ((n = 20))</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Group P ((n = 20))</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>

\(A = \text{aprotinin}; P = \text{placebo.}\)

No significant statistical differences.
side effects were observed with the use of aprotinin; more specifically, neither allergic reactions nor hypotension (diastolic blood pressure \( \leq 55 \text{ mmHg} \)) during the loading dose were noted. Renal (urea and creatinine) and hepatic (SGOT, SGPT, and bilirubin) function remained normal in all patients throughout the study.

Discussion

We have shown that, in patients undergoing total hip replacement, aprotinin in doses recommended for cardiac surgery (2 \( \times 10^6 \) KIU followed by an infusion of 5 \( \times 10^5 \) KIU/h) resulted in a 26% decrease in external blood loss, allowing a 47% reduction in transfusion.

The apparent discrepancy between the reduction in transfusion of packed red blood cells (47%) and amount of bleeding (26%) can be explained in part by the different hematocrits in the drainage fluid. Like Wollinsky,\(^4\) we noted a lower hematocrit in the drainage fluid from group A. Accordingly, the surgeon routinely reported less oozing in the surgical field in group A (table 3). Moreover, we assessed postoperative bleeding only by measuring drainage fluid. All blood losses are not, however, recovered in the surgical drains. Like the external blood loss, the occult undrained blood loss, which was not objectively evaluated in this study, also might have been reduced in group A. Indeed, the hematocrit of group P, similar to group A on discharge from the PACU, was significantly lower than that of group A on postoperative day 1 despite similar external blood loss (table 2 and fig. 1) and transfusion protocol.

Any technique or treatment that allows a reduction in the number of units of packed red cells transfused is a potentially useful adjunct to other strategies for reducing transfusion-related risks. This study indicates that aprotinin treatment alone is not sufficient to avoid transfusion in most patients undergoing total hip replacement in our institution. However, 90% of the patients in group A received fewer than 4 units of packed red blood cells. Therefore, the association of the hemostatic effect of aprotinin and of predonation of 3 units of packed red blood cells, a goal achievable by most patients, would allow 90% of patients to have surgery without any homologous blood transfusion. Combination of aprotinin with other blood conservation or anesthetic techniques may further reduce the need for homologous blood transfusion. Although aprotinin is expensive (in Belgium, about $25 for 3.5 \( \times 10^6 \) KIU), the economic benefit of reducing the requirement for blood transfusion may justify the cost.

Three different mechanisms proposed to explain the hemostatic effect of aprotinin were investigated. An antifibrinolytic effect of aprotinin, a serine proteinase inhibitor, has been described and correlated with an anticoagulant effect originating at the activation phase of the contact system\(^5,19,20\) and at the initial phase of the intrinsic pathway,\(^21\) both of which involve serine proteinases. Dimer formation, however, was not different between the two groups, and the antifibrinolytic effect of aprotinin was not evident. Activation of the coagulation system is the second mechanism by which aprotinin might reduce blood loss and this was evaluated by thrombin–antithrombin and fibrinopeptide A. Thrombin–antithrombin complexes and, to a lesser extent, fibrinopeptide A, increased similarly in both groups during the early postoperative period, reflecting \textit{in vivo} formation of thrombin and fibrin, respectively. Despite this activation of coagulation, we observed a significant prolongation of the aPTT in group A, suggesting an anticoagulant effect of aprotinin. This apparent discrepancy might be due to the removal of platelets from blood before the aPTT test. \textit{In vitro}, the anticoagulant property of aprotinin might be masked by the procoagulant activity of platelets and

other blood cells as well as by the release of tissue thromboplastin from the surgical field. This hypothesis, which needs further investigation, may explain why aprotinin can reduce bleeding despite moderate anticoagulant activity. Finally, we observed no significant changes in platelet count or release of \( \beta \)-thromboglobulin. Effects of aprotinin on platelets therefore appear unlikely.

These data do not allow us to elucidate or confirm the mechanisms of action proposed for aprotinin in cardiac surgery patients, with the exception of the inhibition of the intrinsic coagulation pathway. During cardiac surgery, extracorporeal circulation activates several biochemical systems involved in coagulation and alters platelet receptors.\(^{22-25}\) This results in significant changes in coagulation tests and platelet function, which may facilitate detection of an effect of aprotinin on these systems. The differences in the perturbations of coagulation occurring during cardiac surgery and total hip replacement surgery might explain why we cannot confirm aprotinin’s mechanisms of action as reported after cardiac surgery.

The hemostatic effect of aprotinin reported in cardiac surgery,\(^1,7\) liver transplantation,\(^{26}\) and abdominal aortic surgery\(^{27}\) might facilitate the development of undesirable thromboembolic phenomena. Böhmer et al. reported early formation of thrombi on pulmonary artery catheters when aprotinin was used in cardiac surgery.\(^{28}\) The risk of graft occlusion after coronary artery bypass, however, does not seem to be increased by aprotinin.\(^{28}\) This potential problem cannot be neglected in hip surgery, which is associated with a high incidence of DVT.\(^{29}\) In our study, the incidence of DVT was not increased by aprotinin treatment. Instead, a trend toward reduction of DVT was observed (\( P = 0.10 \)). No DVT was diagnosed in group A, whereas we found a 20% incidence of DVT (5% proximal and 15% distal) in group P. This incidence is consistent with data in the literature.\(^{15,50}\) The anticoagulant effect of aprotinin (increased aPTT) might explain why we did not observe an increase in the incidence of DVT. Aprotinin partially inhibits the thromboembolic phenomena induced by intravenous injection of thromboplastin in the dog.\(^{31,52}\) It reduces the effects of disseminated intravascular coagulation induced by injection of sodium polyethanol sulfonate (Liquoid, Hoffman-La Roche, Basel, Switzerland), leading to decreased tissue damage and improved survival.\(^{53}\)

We conclude that during hip replacement surgery, high-dose aprotinin reduces both bleeding and the amount of blood transfused. No adverse effects due to aprotinin were seen; hepatic and renal function were not altered by the treatment, and the incidence of clinically suspected DVT was not increased in the treated group. Further research, however, is necessary to elucidate the mechanism of aprotinin’s hemostatic activity and to determine the optimal dosing regimen.

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### Table 6. Biochemical Parameters

<table>
<thead>
<tr>
<th>Group</th>
<th>D0</th>
<th>T1</th>
<th>T2</th>
<th>D1</th>
<th>D4</th>
<th>D7</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>279 ± 61</td>
<td>232 ± 48</td>
<td>212 ± 51</td>
<td>186 ± 39</td>
<td>228 ± 57</td>
<td>369 ± 79</td>
</tr>
<tr>
<td>A</td>
<td>261 ± 53</td>
<td>226 ± 49</td>
<td>206 ± 51</td>
<td>175 ± 55</td>
<td>221 ± 55</td>
<td>341 ± 106</td>
</tr>
<tr>
<td>TAT (ng/ml)</td>
<td>P 9.17 ± 10.7</td>
<td>40 ± 22.1*</td>
<td>—</td>
<td>—</td>
<td>15 ± 13</td>
<td></td>
</tr>
<tr>
<td>A 8.73 ± 14.9</td>
<td>42.7 ± 37.3*</td>
<td>—</td>
<td>—</td>
<td>14.6 ± 26.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPA (ng/ml)</td>
<td>P 4.29 ± 4.6</td>
<td>6.03 ± 6.5†</td>
<td>—</td>
<td>—</td>
<td>1.69 ± 1.1</td>
<td></td>
</tr>
<tr>
<td>A 2.29 ± 2</td>
<td>7.49 ± 10.5†</td>
<td>—</td>
<td>—</td>
<td>3.83 ± 5.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \beta )-Thromboglobulin (ng/ml)</td>
<td>P 42 ± 31</td>
<td>38.4 ± 17.7</td>
<td>—</td>
<td>—</td>
<td>35.4 ± 23</td>
<td></td>
</tr>
<tr>
<td>A 32.1 ± 22</td>
<td>32.1 ± 21</td>
<td>—</td>
<td>—</td>
<td>33 ± 27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding Time (s)</td>
<td>P 314 ± 100</td>
<td>311 ± 78</td>
<td>—</td>
<td>—</td>
<td>315 ± 83</td>
<td></td>
</tr>
<tr>
<td>A 321 ± 138</td>
<td>339 ± 116</td>
<td>—</td>
<td>—</td>
<td>302 ± 94</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SD.

D0 = day before surgery; T1 = arrival in the postanesthesia care unit; T2 = discharge from the postanesthesia care unit; D1 = 1 day after surgery; D4 = 4 days after surgery; D7 = 7 days after surgery; P = placebo; A = aprotinin; TAT = thrombin–antithrombin; FPA = fibrinopeptide A.

* \( P < 0.05 \) compared with D0.

† \( P = 0.07 \) compared with D0.
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References


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