Intraoperative Antifibrinolysis and Blood-Saving Techniques in Cardiac Surgery

Prospective Trial of 3 Antifibrinolytic Drugs

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Sixty consecutive patients undergoing elective open-heart surgery were prospectively enrolled in a study to compare the efficacy of 3 different antifibrinolytic drugs to reduce postoperative bleeding and to reduce homologous blood requirements in combination with blood-saving techniques and restrictive indications for blood transfusion. The patients were randomized to 1 of 4 intraoperative treatment regimens: 1) control (no antifibrinolytic therapy); 2) ε-aminocaproic acid (10 g IV at induction of anesthesia, followed by infusion of 2 g/h for 5 hours); 3) tranexamic acid (10 mg/kg IV within 30 minutes after induction of anesthesia, followed by infusion of 1 mg/kg per hour for 10 hours); or 4) high-dose aprotinin (2 million KIU IV at induction of anesthesia and 2 million KIU added to the extracorporeal circuit, followed by infusion of 500 thousand KIU/h during surgery). Hemoconcentration and reinfusion of blood drained from the operative field and the extracorporeal circuit after operation were used in all patients. Indications for blood transfusion were hypotension, tachycardia, or both, with hemoglobin values <8.5 g/dL; or severe anemia with hemoglobin values <7 g/dL.

Compared with the blood loss in the control group, patients receiving aprotinin and ε-aminocaproic acid showed significantly less postoperative blood loss at 1 hour (control, 128 ± 94 mL; aprotinin, 54 ± 47 mL, p=0.01; and ε-aminocaproic acid, 69 ± 35 mL, p=0.03); this trend continued at 24 hours after operation (control, 724 ± 280 mL; aprotinin, 344 ± 106 mL, p <0.0001; and ε-aminocaproic acid, 509 ± 148 mL, p=0.01). Aprotinin was significantly more efficient than ε-aminocaproic acid (p=0.002). Tranexamic acid did not have a statistically significant effect on blood loss. Homologous blood requirements were not significantly different among the groups; postoperative hematologic values and coagulation times were also comparable.

Despite the efficacy of aprotinin and ε-aminocaproic acid shown in the present study, the blood requirements were not significantly different from those that are found when transfusions are restricted, autotransfusions are used, and blood from the operative field and extracorporeal circuit is concentrated and reinfused. Therefore, intraoperative antifibrinolysis may not be indicated in routine cardiac surgery when other blood-saving techniques are adopted. ***(Tex Heart Inst J 1995;22:231-6)***

Key words: *Aminocaproic acids; antifibrinolytic agents; aprotinin; blood loss, surgical/prevention & control; blood transfusion; cardiopulmonary bypass; heart surgery; hemostasis, surgical; tranexamic acid*

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Blood-saving techniques are of great interest to cardiac surgeons, due to a shortage of blood donors and the risk of allergic reactions and transmission of viral infections. Recently, intraoperative antifibrinolytic therapy has been reported as an effective means of reducing postoperative bleeding after the use of extracorporeal circulation.[1-9] However, adoption of a restrictive policy for homologous blood transfusion, along with the use of blood-saving techniques, may be equally or more effective than intraoperative antifibrinolytic therapy in limiting blood requirements.[10-15] Hemoconcentration and transfusion of blood drained from the operative field and from the extracorporeal circuit at the end of the operation, intraoperative autotransfusion, and autotransfusion of shed blood from the chest drains during the 1st few hours after surgery are used currently, with good results.[11,12]

In this prospective study, we compared the efficacy of 3 currently used antifibrinolytic drugs—ε-aminocaproic acid, tranexamic acid, and aprotinin—to reduce bleeding and to reduce blood requirements after open-heart surgery in combination with blood-saving techniques.

Patients and Methods

Sixty consecutive adult patients undergoing elective open-heart surgery were prospectively randomized into 4 groups: 1) control group, no antifibrinolytic therapy; 2) ε-aminocaproic acid group, 10 g intravenously (IV) at the induction of anesthesia followed by infusion of 2 g/h for 5 hours; 3) tranexamic acid group, 10 mg/kg IV within 30 minutes after the induction of anesthesia, followed by infusion of 1 mg/kg per hour for 10 hours; or 4) high-dose aprotinin group, 2 million kallikrein inhibiting units (KIU) IV at the time of anesthetic induction and 2 million KIU added to the extracorporeal circuit, followed by infusion of 500 thousand KIU/h during surgery. Each group comprised 15 patients. Administration of nonsteroidal anti-inflammatory drugs was discontinued at least 24 hours before surgery; patients with a history of gastrointestinal bleeding were excluded from the study.

Patients ranged in age from 30 to 76 years (mean, 62 ± 9 years), and the male–female ratio was 5:1. The randomized groups were comparable in age and sex (Table I), type of operation, cardiopulmonary bypass time, and aortic cross-clamp time (Table II).

After premedication with diazepam (0.1 mg/kg orally), morphine (0.14 mg/kg intramuscularly [IM]), and scopolamine (0.003 mg/kg IM), anesthesia was induced with fentanyl (50 μg/kg IV), diazepam (0.1 mg/kg IV), and pancuronium (0.1 mg/kg IV).

The extracorporeal circulation circuit was primed with 1800 cc of Ringer's lactate solution and 100 mL of 20% human albumin. A capillary membrane oxygenator (Monolyth, Sorin Biomedica; Saluggia, Italy), an arterial line filter, polyvinyl chloride tubing, and silicon rubber tubing for the pump were used in all patients.

Heparin (3 mg/kg) was given for anticoagulation, repeated if necessary to maintain the activated clotting time at 3 times the control value, and neutralized with protamine chlorhydrate (1.3 mg protamine per 1 mg heparin). Blood from the operative field and from the extracorporeal circuit at the end of the operation was drained and hemoconcentrated by the Cell Saver® system (Haemonetics Corporation; Braintree, MA) and reinfused to the patient. Chest drains were connected to a cardiotomy/autotransfusion reservoir (CATR® 3500, Baxter Healthcare Corporation, Bentley Division; Irvine, CA), and shed blood was reinfused within the first 4 hours in the intensive care unit if volume loss was significant (over 150 mL) and there were signs of hypovolemia.

Homologous blood was transfused when hemoglobin values dropped below 8.5 g/dL in monitored patients who showed hypotension with low central venous and pulmonary artery pressures, in mobilized patients who showed hypotension and tachycardia, and in those who showed signs of severe anemia (hemoglobin values <7 g/dL).

The amount of blood drained intraoperatively by the Cell Saver system and postoperatively through the chest drains was recorded before reinfusion to the patient, as was the total blood loss both 1 hour and 24 hours after surgery. The number of homologous blood units (300 mL/Unit) transfused during and after surgery was recorded.

The hemoglobin, hematocrit, and fibrinogen values, red blood cell and platelet counts, prothrombin time (PT) as patient-to-normal ratio, and activated partial thromboplastin time (PTT) were recorded preoperatively and at hospital discharge (5 to 8 days postoperatively).

Values are presented as mean ± standard deviation; using the Student's *t*-test for independent data, p values <0.05 were considered significant.

TABLE I. Clinical Characteristics

Group	Mean Age (yr)	Age Range (yr)	Sex (M/F)
Control (n=15)	63 ± 7	50-73	13/2
ε-Aminocaproic Acid (n=15)	62 ± 7	50-74	13/2
Tranexamic Acid (n=15)	60 ± 12	30-74	12/3
Aprotinin (n=15)	64 ± 10	34-76	12/3

p-values not significant

Results

The preoperative hematologic mean values and coagulation times were similar in all groups (Table III). Hemoglobin mean values were significantly higher in the control group (14.5 g/dL) compared with the values in the tranexamic acid group (13.45 g/dL, p=0.008) and in the aprotinin group (13.5 g/dL, p=0.04). The mean platelet count was significantly lower in the aprotinin group compared with the tranexamic acid group (174 × 10^9/L vs 212 × 10^9/L, p=0.03).

The amount of blood drained by the intraoperative Cell Saver system and reinfused to the patients was similar in all groups (Table IV). Autotransfusion of shed blood in the intensive care unit was used only in a few patients and differences were not statistically significant among the groups. As shown in Table V, the postoperative blood loss at 1 hour was 128 ± 94 mL in the control group and was significantly lower both in the ε-aminocaproic group (69 ±

35 mL, p=0.03) and in the aprotinin group (54 ± 47 mL, p=0.01). One-hour blood loss in the aprotinin group was also significantly lower than that in the tranexamic acid group (125 ± 110 mL, p=0.02). The total postoperative blood loss measured at 24 hours was 724 ± 280 mL in the control group. In comparison, the total blood loss was significantly lower in both the ε-aminocaproic acid group (509 ± 148 mL, p=0.01) and the aprotinin group (344 ± 106 mL, p <0.0001). The total blood loss in the aprotinin group was also significantly lower compared with that in the tranexamic acid group (534 ± 288 mL, p=0.023) and with that in the ε-aminocaproic group (509 ± 148 mL, p=0.002). The postoperative blood loss in the tranexamic acid group was not significantly different from that in the control group at 1 or 24 hours.

The numbers of patients requiring blood transfusions were not statistically different among the 4 groups (Table VI). The postoperative red blood cell counts, platelet counts, fibrinogen values, and coagulation times were also comparable in all groups (Table VII). The aprotinin group showed significantly higher postoperative hematocrit values than those in the tranexamic acid group only (0.30 ± 0.04 vs 0.26 ± 0.06, respectively; p=0.05).

TABLE II. Operative Techniques

Surgical Treatment	Control (n=15)	ε-Aminocaproic Acid (n=15)	Tranexamic Acid (n=15)	Aprotinin (n=15)
Coronary artery bypass	14	14	12	9
Mitral valve replacement	-	1	1	-
Aortic valve replacement	-	-	2	4
Coronary artery bypass + mitral commissurotomy	1	-	-	-
Coronary artery bypass + aortic valve replacement	-	-	-	1
Coronary artery bypass + carotid endarterectomy	-	-	-	1
Cardiopulmonary bypass time (min)	115 ± 28	118 ± 35	111 ± 34	120 ± 32
Aortic cross-clamp time (min)	64 ± 21	63 ± 20	63 ± 22	69 ± 27

p-values not significant

TABLE III. Preoperative Hematologic Values and Coagulation Times

Hematologic Variable	Control (n=15)	ε-Aminocaproic Acid (n=15)	Tranexamic Acid (n=15)	Aprotinin (n=15)
RBC × 10^{12}/L	4.74 ± 0.46	4.67 ± 0.44	4.47 ± 0.33	4.66 ± 0.59
Hemoglobin (g/dL)	14.5 ± 1	14 ± 1	13.45 ± 1[a]	13.5 ± 1.5[b]
Hematocrit	0.42 ± 0.04	0.41 ± 0.04	0.40 ± 0.04	0.41 ± 0.05
PT	0.93 ± 0.29	0.95 ± 0.22	0.98 ± 0.18	0.92 ± 0.19
PTT (sec)	31 ± 5	31.7 ± 6.3	30.6 ± 4.1	32.4 ± 5
Fibrinogen (g/L)	3.80 ± 0.92	3.99 ± 1.01	3.84 ± 0.72	4.03 ± 0.94
Platelets × 10^9/L	213 ± 63	198 ± 45	212 ± 43	174 ± 50[c]

PT = prothrombin time; PTT = activated partial thromboplastin time; RBC = red blood cells

[a]Tranexamic acid vs control, p = 0.008;
[b]Aprotinin vs control, p = 0.04;
[c]Aprotinin vs tranexamic acid, p = 0.034

TABLE IV. Amount (mL) of Shed Blood Reinfused to Patients

Group	Intraoperative	Postoperative
Control (n=15)	447 ± 330	56 ± 163
ε-Aminocaproic Acid (n=15)	463 ± 326	0
Tranexamic Acid (n=15)	410 ± 315	0
Aprotinin (n=15)	553 ± 181	10 ± 39

p-values not significant

TABLE V. Postoperative Blood Loss (mL)

Group	Blood Loss at 1 Hour	Blood Loss at 24 Hours
Control (n=15)	128 ± 94	724 ± 280
ε-Aminocaproic Acid (n=15)	69 ± 35[a]	509 ± 148[b]
Tranexamic Acid (n=15)	125 ± 110	534 ± 288
Aprotinin (n=15)	54 ± 47[c]	344 ± 106[d]

[a]ε-Aminocaproic acid vs control, p = 0.031
[b]ε-Aminocaproic acid vs control, p = 0.01
[c]Aprotinin vs control, p = 0.01;
aprotinin vs tranexamic acid, p = 0.02
[d]Aprotinin vs control, p <0.0001;
aprotinin vs ε-aminocaproic acid, p = 0.002;
aprotinin vs tranexamic acid, p = 0.023

TABLE VI. Homologous Blood Requirements

Group	Pts. Requiring Transfusion	No. of Units
Control (n=15)	3	6
ε-Aminocaproic Acid (n=15)	3	8
Tranexamic Acid (n=15)	1	1
Aprotinin (n=15)	0	0

p-values not significant

One patient in the tranexamic acid group was returned to surgery for bleeding during the 1st postoperative hour. Clots were removed, but no surgical bleeder was detected; blood loss thereafter was consistently less. When we excluded this patient from the tranexamic group and repeated the analysis of data, we found no significant change in the results and p values.

Discussion

Antifibrinolytic drugs prevent fibrinolysis and platelet activation from occurring during cardiopulmonary bypass:[16-18] tranexamic acid preserves platelet function and blocks the action of plasmin on fibrin,[19] ε-aminocaproic acid prevents activation of plasminogen,[20] and aprotinin blocks both kallikrein and plasmin and preserves platelet function.[21-23] Several studies[1-9] have shown these drugs to be effective in reducing blood loss after cardiopulmonary bypass.

We used high-dose aprotinin therapy, because the efficacy of low-dose aprotinin is still controversial.[24,25] Our study confirms that aprotinin and ε-aminocaproic acid, but not tranexamic acid, significantly reduce blood loss after open-heart surgery. Furthermore, aprotinin appears to be the most efficient drug for reducing postoperative blood loss within 24 hours.

In accordance with most studies,[3,6,7-11] we decided that patients undergoing valve replacement, coronary revascularization, or both, would be eligible for this study, since all would undergo cardiopulmonary bypass and thus would be representative of the daily surgical patients.

In the patient in the tranexamic acid group who required reoperation to establish hemostasis, no surgical bleeding was found and only clots were removed. He was, therefore, not excluded from the study. In addition, we found that his inclusion in the study did not change the results of the study.

Although the only patients who did not require postoperative blood transfusion were those in the aprotinin group, differences between the groups were not statistically significant (Table VI). These results may have been slightly influenced by the higher preoperative hemoglobin values in the control group compared with the aprotinin and tranexamic acid groups. A lower blood requirement might have been predictable in control patients, thus favoring a lack of statistical significance. However, it is noteworthy that blood requirements were low in all groups, presumably due to the restrictive indications for postoperative blood transfusions established by the study protocol.

We recently reported a lower blood requirement per patient (0.7 units vs 1.4 units)[13] after using a series of blood-saving techniques. We limited homologous blood transfusions to patients with evidence of hypovolemia in the intensive care unit and with hemoglobin values less than 8.5 g/dL, to patients

TABLE VII. Postoperative Hematologic Values and Coagulation Times

Hematologic Variable	Control (n=15)	ε-Aminocaproic Acid (n=15)	Tranexamic Acid (n=15)	Aprotinin (n=15)
RBC × 10^{12}/L	3.07 ± 0.57	3.17 ± 0.38	2.99 ± 0.71	3.43 ± 0.47
Hemoglobin (g/dL)	9.5 ± 1.4	9.8 ± 1.4	9.0 ± 2	10.0 ± 1.4
Hematocrit	0.28 ± 0.06	0.27 ± 0.03	0.26 ± 0.06	0.30 ± 0.04[a]
PT	0.88 ± 0.20	0.87 ± 0.15	0.91 ± 0.25	0.65 ± 0.26
PTT (sec)	35 ± 14	32 ± 7	34 ± 13	34 ± 7
Fibrinogen (g/L)	4.78 ± 1.23	3.87 ± 1.43	4.56 ± 1.39	5.04 ± 0.65
Platelets × 10^9/L	178 ± 61	167 ± 44	205 ± 49	151 ± 50

PT = prothrombin time; PTT = activated partial thromboplastin time; RBC = red blood cells

[a]Aprotinin vs tranexamic acid, p = 0.05

with asthenia and tachycardia after mobilization in the ward, or to patients with severe anemia (hemoglobin <7 g/dL). In addition, we instituted hemoconcentration and postoperative reinfusion of blood drained from the operative field and the extracorporeal circuit.

Comparison of those results[13] with the findings of the present study provide some indication that antifibrinolytic drugs may be of limited value in further reducing blood requirement in elective cardiac surgery.

Although the efficacy of intraoperative aprotinin in reducing postoperative bleeding seems confirmed by our results, its safety is still under investigation. The use of aprotinin has been linked with a higher incidence of both perioperative myocardial infarction and early vein graft closure.[26,27] Therefore, due to the cost, possible side effects, and the limited saving of homologous blood, intraoperative antifibrinolytic therapy may not be indicated in routine cardiac surgery. We recommend that the use of such therapy be reserved for patients at high risk of postoperative bleeding, such as those undergoing redo operations or those recently weaned from fibrinolytic therapy.[28,29]

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