The Effect of Three Different Doses of Tranexamic Acid on Blood Loss After Cardiac Surgery With Mild Systemic Hypothermia (32°C)

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Objective: **Prophylactic administration of tranexamic acid (TA), an antifibrinolytic agent, decreases bleeding after cardiac surgery with systemic hypothermia (25°C to 29°C). Warmer systemic temperatures during cardiopulmonary bypass (CPB) may reduce bleeding and thus alter the requirement for TA. The effect of three different doses of TA on bleeding after cardiac surgery with mild systemic hypothermia (32°C) is evaluated.**

Design: **Double-blind, prospective, randomized study.**

Setting: **University hospital.**

Participants: **One hundred fifty adult patients undergoing aortocoronary bypass or valvular cardiac surgery.**

Interventions: **Patients received TA, 50 (n = 50), 100 (n = 50), or 150 (n = 50) mg/kg intravenously before CPB with mild systemic hypothermia.**

Measurements and Main Results: **Blood loss through chest drains over 6, 12, and 24 hours after surgery and total hemoglobin loss were measured. Autotransfused blood, transfused banked blood and blood products, and coagulation profiles were measured. Analysis of variance on log-transformed data for blood loss and confidence intervals (CIs) of 0.95 were calculated and transformed to milliliters of blood. No patient was re-explored for bleeding. Blood loss at 6 hours was statistically greater in the 50-mg/kg group compared with the other two groups ($p = 0.03$; $p = 0.02$). Total hemoglobin loss was statistically greater in the 50-mg/kg group compared with the 150-mg/kg group ($p = 0.04$). There was no statistical difference in blood transfusion rate or coagulation profiles among the three groups. However, preoperative hemoglobin level was statistically lower in the 150-mg/kg group compared with the other two groups ($p = 0.01$).**

Conclusion: **Of the three doses of TA studied, the most efficacious and cost-effective dose to reduce bleeding after cardiac surgery with mild hypothermic systemic perfusion is 100 mg/kg.**

KEY WORDS: cardiac surgery, tranexamic acid, bleeding complications, temperature, mild systemic hypothermia

BLEEDING AFTER cardiac surgery performed with cardiopulmonary bypass (CPB) is a major complication that affects 18% of all patients undergoing cardiac surgery.[1] Subsequent transfusion of blood and blood products puts the patient at risk for transfusion-acquired infection and transfusion reactions.[2] The mechanism of bleeding is subclinical induction of fibrinolysis and platelet-receptor damage.[3-7] These changes are induced by the activation of coagulation factor XII caused by contact with the CPB circuit, initiating a systemic inflammatory response involving the coagulation cascade, fibrinolysis, and complement activation.[8] Also, hypothermia during CPB causes reversible platelet membrane dysfunction, inhibition of coagulation factors, and disordered fibrinolysis.[9]

The antifibrinolytic agent tranexamic acid (TA) administered before CPB reduces postoperative bleeding.[1,10,11] This effect was shown in the setting of CPB with systemic hypothermia (systemic temperatures actively cooled to 25°C to 29°C). Recently, normothermic or mild hypothermic systemic perfusion, compared with the conventional hypothermic regimens, has been proposed as a more physiologic means of maintaining the body's homeostatic functions during CPB.[12] The incidence of post-CPB coagulopathy and bleeding may be reduced when normothermic or mild hypothermic systemic perfusion is used during CPB.[9,13,14] This may alter the dose requirement for TA.

At this institution, systemic hypothermia (systemic temperatures actively cooled to 28°C to 30°C) during CPB is no longer used, but systemic temperature is allowed to drift to 32°C (mild hypothermic systemic perfusion). This study evaluated three different doses of TA (50, 100, and 150 mg/kg of body weight) to define the optimal dose of TA necessary to control blood loss after CPB with mild hypothermic systemic perfusion.

METHODS

The study was a prospective, double-blind, randomized trial (randomization was performed with computer-generated randomized numbers by the Research Division of Pharmacy at The Toronto Hospital, Canada). Approval was received from the institution's ethics review board and informed consent was obtained from all patients.

One hundred fifty patients aged 21 to 80 years undergoing first-time aortocoronary bypass and valvular heart surgery were entered into the study. All patients underwent surgery at the same center over an 18-month period. Patients were excluded from the study if they had significant renal dysfunction (serum creatinine level >150μmol/L), a clinical history of abnormal bleeding, coumadin use within the previous 7 days, or a known allergy to TA. Enrolled patients were randomly distributed to one of three groups. Fifty patients received TA, 50 mg/kg of bodyweight (TA-50); 50 patients received TA, 100 mg/kg (TA-100); and 50 patients received TA, 150 mg/kg (TA-150), intravenously over 20 minutes after induction and before CPB. No placebo group was included because it has already been proven that bleeding and the red blood cell (RBC) transfusion rate are significantly reduced with TA compared with placebo and, therefore, it becomes unethical to place patients into a placebo group.[1]

Anesthesia was induced with fentanyl, 10 to 15 μg/kg, with or without thiopental, 50 to 200 mg, and maintained with midazolam, 0.1 mg/kg, plus inhalation agents before CPB and with a propofol infusion during CPB. Neuromuscular blockade was facilitated by pancuronium, 0.15 mg/kg. Anticoagulation for CPB was provided by heparin, 300 U/kg intravenously. An activated coagulation time (ACT) of more than 400 seconds was achieved before CPB and this was maintained with additional heparin as indicated by the ACT during CPB. After CPB, the effect of heparin was neutralized with protamine sulfate, 1 mg/100 U of

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heparin, to achieve an ACT within 10% of baseline values. Protamine sulfate, 50 to 100 mg, was administered after admission to the intensive care unit if the ACT was more than 10% greater than baseline values.

The CPB circuit was primed with 2 L of Ringer's lactate, 100 mL of 25% albumin, 50 mEq of sodium bicarbonate, and 100 mL of mannitol. Roller pumps and membrane oxygenators (Maxima; Medtronic Inc, Minneapolis, MN) were used in all cases. Cardiac protection was provided with cold blood cardioplegia. Mild hypothermic systemic perfusion (systemic temperature was allowed to drift to 32°C) was used during CPB.

The blood from the CPB circuit was salvaged and transfused to the patient after sternal closure. The transfusion regimen was developed in this center in collaboration with cardiac surgeons and hematologists and was based on research performed over a 10-year period on postoperative bleeding in cardiac surgery. Postoperatively, mediastinal and pleural drains were connected to a citrated sterile cardiotomy reservoir. When drainage of shed blood exceeded 150 mL in the first 6 hours, it was autotransfused to the patient. Autotransfusion continued for 6 hours postoperatively. No attempt was made to measure blood loss during surgery. Blood loss through the chest drains was measured at 6, 12, and 24 hours postoperatively. Total hemoglobin loss was calculated by multiplying the total volume of blood in the chest drains by the hematocrit of the shed blood multiplied by 0.3. Homologous blood and blood products administered during surgery and up to 48 hours after surgery were recorded. Coagulation profiles (prothrombin time, partial thromboplastin time, bleeding time) were measured preoperatively and at 2 and 24 hours after arrival in the intensive care unit.

Blood was transfused during CPB if the hematocrit was 19% or less. Blood was transfused in the intensive care unit after surgery if the hematocrit was less than 20% on two consecutive measurements. Postoperatively, patients who lost more than 200 mL of blood per hour in two consecutive hours or 400 mL in 1 hour were treated with additional TA, 50 mg/kg, over 1 hour. If bleeding continued, desmopressin, 0.3 μg/kg in 50 mL of normal saline, was infused intravenously over 20 minutes. Platelet concentrate, fresh frozen plasma, and cryoprecipitate were administered at the discretion of one hematologist. Platelets were administered only if the platelet count was less than 50×10^9/L. Cryoprecipitate and fresh frozen plasma were administered to patients if the prothrombin time was greater than 1.5 times the reference or normal value.

Sample size calculation was performed for a mean value difference among the group with 200 mL of blood loss and standard deviation of 200 mL with an α error of 0.05 and a β error of 80%. Blood loss volumes (milliliters) at 6, 12, and 24 hours and hemoglobin loss did not distribute normally and were logarithmically transformed. Mean values of the three groups were compared using one-way and two-way analysis of variance. When p equaled 0.05, multiple post hoc comparisons were performed (Tukey tests). Confidence intervals (CI) at 95% were calculated on logarithmically transformed values and antilog transformed to milliliters and grams of hemoglobin. Blood and blood products transfused were analyzed as the proportion of patients per group receiving a transfusion. Chi-squared tests were used to compare frequencies. CIs at 95% were calculated for proportions. Continuous measurements were compared with analysis of variance within and between group effects. Demographic values are expressed as means ± standard error of the mean (SEM). Statistical analysis was performed using SYSTAT version 5.0 (Systat Inc, Evanston, IL).

RESULTS

Demographic variables and surgical characteristics for all patients are listed in Table 1. None of these data differed statistically among the groups with the exception of preoperative hemoglobin level, which was significantly lower in the 150-mg/kg group compared with the remaining two groups ($p = 0.01$). Preoperative aspirin use was similar in the three groups, as were the mean ± SEM number of days off aspirin therapy (8.4 ± 0.8, 11.5 ± 3.2, and 10.4 ± 2.0 days in the 50-mg/kg, 100-mg/kg, and 150-mg/kg groups, respectively). Coagulation profiles measured preoperatively at 2 and 24 hours after arrival in the intensive care unit did not show any difference among the three groups.

Table 1. Patient Demographics

Parameters	TA-50 (n = 50)	TA-100 (n = 50)	TA-150 (n = 50)
Age (yr)	59.1 ± 1.5	59.4 ± 1.5	61.5 ± 1.5
Sex (men/women)	39/11	43/7	37/13
Weight (kg)	84.0 ± 1.9	80.3 ± 1.9	78.8 ± 1.9
Preoperative hemoglobin (g/L)	147.9 ± 1.6	147.2 ± 1.67	141.3 ± 1.6*
Preoperative hematocrit	0.43 ± 0.004	0.43 ± 0.005	0.41 ± 0.005
Preoperative platelets	248.6 ± 7.7	234.2 ± 7.8	255.1 ± 7.7
Preoperative PT	10.1 ± 0.09	10.2 ± 0.09	10.1 ± 0.09
Preoperative PTT	29.5 ± 1.7	30.5 ± 1.7	30.2 ± 1.7
Bypass time (min)	86.7 ± 3.6	82.8 ± 3.6	82.4 ± 3.5
Aortic cross-clamp time (min)	62.8 ± 2.5	59.9 ± 2.6	61.8 ± 2.5
Surgery time (min)	171.8 ± 5.8	169.1 ± 5.8	170.7 ± 5.7
Lowest CPB temperature (°C)	32.2 ± 0.2	32.5 ± 0.2	32.2 ± 0.2
Valve operations (No.)	7	7	8
Bypass operations (No.)	43	43	42
Patients with LITA (No.)	40	38	42

NOTE. Data are expressed as mean ± SEM. No statistical difference was found among the groups in any of the variables except preoperative hemoglobin level.

Abbreviations: LITA, left internal thoracic artery; CPB, cardiopulmonary bypass; PT, prothrombin time; PTT, partial thromboplastin time.

*$p = 0.01$.

Blood loss in the first 6 hours after surgery was greatest in the 50-mg/kg group compared with the 100-mg/kg group ($p = 0.03$) and the 150-mg/kg group ($p = 0.02$; Fig 1). There was no predisposing factor for bleeding in the patients in the 50-mg/kg group. Blood loss at 24 hours after surgery showed no statistical difference among the three groups. Total hemoglobin loss was greatest in the 50-mg/kg group (67 g) compared with the 100-mg/kg group (50 g) and the 150-mg/kg group (39 g); this latter difference attained statistical significance ($p = 0.04$). Only one patient in each group bled excessively (>760 mL in the first 6 hours). No study patient required surgical reexploration for bleeding.

Autotransfusion was performed if the patient had greater than 150 mL of blood loss in the first 6 hours. Ten patients (20%) in the 50-mg/kg group, six patients (12%) in the 100-mg/kg group, and five patients (10%) in the 150-mg/kg group underwent autotransfusion. The mean volume of blood autotransfused was low in all three groups (280 mL in the TA-50 group, 267 mL in the TA-100 group, and 401 mL in the TA-150 group). There was no statistical difference in the volume of blood autotransfused among the three groups (Fig 2). Additional pharmacologic therapy for excessive bleeding was required in the postoperative period in five patients (10%) in the 50-mg/kg group, two

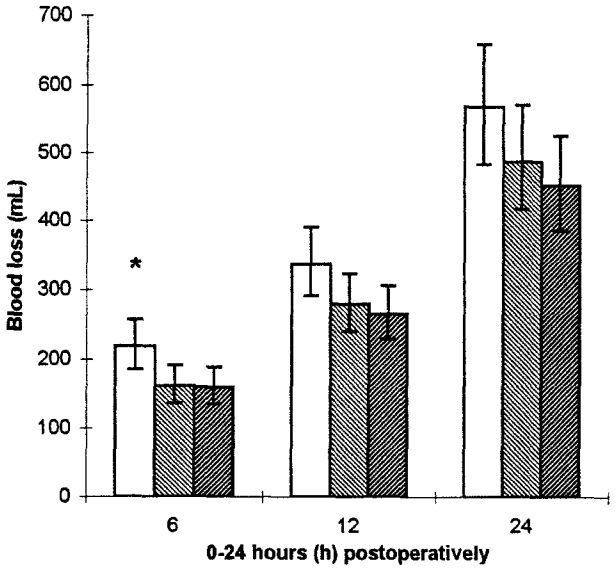

Fig 1. Blood loss during the period from 0 to 6 (6h), 6 to 12 (12h), and 0 to 24 hours (24h) after surgery. Data are presented as mean values with 95% CIs. (□) TA-50; (▧) TA-100; (▨) TA-150. *Blood loss was significantly greater in the first 6 hours in the TA-50 group compared with the TA-100 group (p = 0.03) and the TA-150 group (p = 0.024). There was no significant difference in blood loss between the TA-100 and TA-150 groups during the first 6 hours.

patients (4%) in the 100-mg/kg group, and two patients (4%) in the 150-mg/kg group. There was no statistically significant difference in the use of additional pharmacologic therapy among the groups.

Seven patients in the 50-mg/kg group, 4 patients in the 100-mg/kg group, and 11 patients in the 150-mg/kg group received blood transfusions (Table 2). There was no statistically significant difference in this RBC transfusion rate or in the median number of units of RBCs transfused per patient among the three groups. Nine of the 11 patients who received

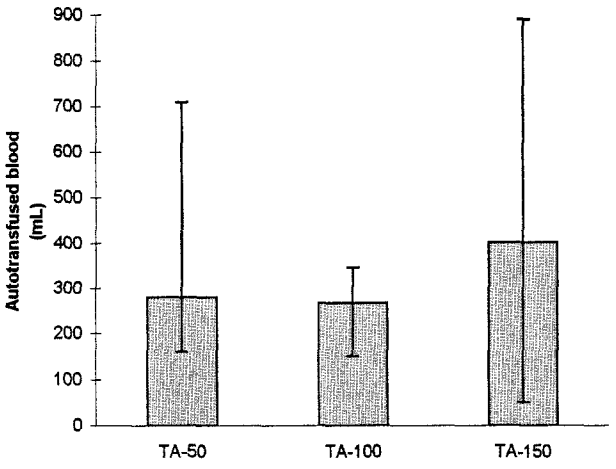

Fig 2. Autotransfused blood volumes in TA-50, TA-100, and TA-150 groups. Blood was autotransfused for up to 6 hours postoperatively when drainage exceeded 150 mL. Data are presented as mean values with 95% CIs.

Table 2. Units of RBCs Transfused

	TA-50 (n = 50)	TA-100 (n = 50)	TA-150 (n = 50)
Units RBCs during bypass (No.)	2	2	9*
Units RBCs postoperatively (No.)	5	2	2
Total units RBCs in 48 hours (No.)	7	4	11
RBC units per patient†	1.0 (1-5)	2.0 (1-3)	2.0 (1-4)

*RBC transfusion during CPB was significantly greater in the TA-150 group compared with the other two groups ($p = 0.012$).

†Median (range) of red blood cell units transfused (patients receiving transfusion only).

transfusions in the 150-mg/kg group underwent transfusion during CPB. This resulted in a significantly greater ($p = 0.012$) RBC transfusion rate during CPB in the 150-mg/kg group compared with the other two groups. However, the 150-mg/kg group had a significantly lower preoperative hemoglobin level compared with the other two groups ($p = 0.01$).

No patient received a transfusion of platelets, fresh frozen plasma, or cryoprecipitate perioperatively. Logistic regression analysis identified preoperative hemoglobin level as the strongest predictor of the need for blood transfusion postoperatively ($p = 0.001$). Women were also associated with an increased rate of intraoperative transfusion ($p = 0.01$).

No patient was re-explored for bleeding. No patient had a perioperative myocardial infarction as indicated by electrocardiographic changes and plasma concentrations of cardiac enzymes measured at 8, 16, and 24 hours postoperatively.

DISCUSSION

The most significant finding in this study is that blood loss was statistically greater in the 50-mg/kg group compared with the 100-mg/kg group ($p = 0.03$) and the 150-mg/kg group ($p = 0.02$) at 6 hours postoperatively. Total hemoglobin loss postoperatively was greater in the 50-mg/kg group compared with the 100-mg/kg and the 150-mg/kg group, the latter attaining statistical significance ($p = 0.04$). There was no statistically significant difference in the RBC transfusion rate among the three groups.

These findings have a significant impact on cost savings. It was calculated that the reduction of the TA dose from 150 mg/kg to 100 mg/kg will save CAN$72.00 for an average 70-kg patient (cost of a 10-mL vial = CAN$20.55) undergoing cardiac surgery. Because approximately 2,500 patients undergo CPB annually at this institution, this would represent an approximate annual saving of CAN$180,000. It is concluded that the most efficacious and cost-effective dose of TA, of the three doses studied, for reduction of bleeding after CPB with mild hypothermic systemic perfusion (systemic temperature drifting to 32°C) is 100 mg/kg. The nonsignificant differences in blood loss and RBC transfusion rate between the 100-mg/kg and the 150-mg/kg groups show that it is permissible to reduce the dose of TA administered in the preoperative period to 100 mg/kg without adversely affecting bleeding after CPB with mild hypothermic systemic perfusion.

A low dose of TA, 10 mg/kg followed by an infusion at 1 mg/kg/hr for 12 hours, has previously been shown to be better than placebo and equally efficacious to higher doses of TA at

reducing bleeding, but not transfusion rate, after CPB with systemic hypothermia to 27°C.[15] Other studies have failed to show equal efficacy of low-dose versus high-dose TA and have shown increased efficacy from larger doses of TA (10 g and 5 g).[10,16] For this reason, and because there is a theoretic risk that a prolonged infusion of antifibrinolytic agents may induce a hypercoagulable state,[17] this low dose of TA was not tested in the current study.

The authors' previous published studies indicated that a higher dose of TA (mean dose of 127 mg/kg) was required to reduce excessive blood loss after cardiac surgery with systemic hypothermia to 25°C to 29°C.[10] Comparing the results of the current study with these previous results, bearing in mind the limitations when comparing results of different studies, mild systemic hypothermia versus systemic hypothermia to 25°C appears to have reduced the dose requirement for TA. This decreased requirement for TA may be explained by the multiple complex changes in the hemostatic mechanism induced by hypothermia during CPB.

Concomitant increases in fibrinolysis[4-7] and platelet activation occur during CPB.[9,18,19] Plasmin generated from fibrinolysis activates platelets, and this effect appears to be enhanced at lower temperatures.[20] In vitro studies have shown that at 37°C, plasmin activates platelets at high plasmin concentrations (>1.5 caseinolytic unit [CU]), but inhibits platelet activation at lower concentrations (0.1 to 1.0 CU); whereas at 22°C, plasmin fully activates platelets at low concentrations (<0.1 CU).[20] Thus, temperatures of 28°C during CPB increase plasmin activation of platelets. These activated platelets are quickly eliminated from the blood stream, leading to thrombocytopenia and postoperative bleeding. Hypothermia also alters platelet function during CPB by reducing thromboxane production. Production of thromboxane B_2, the breakdown product of thromboxane A_2 (a potent platelet-aggregating agent and vasoconstricting substance), is inhibited by hypothermia (27°C).[21] This reduction in thromboxane production by platelets at lower temperatures causes a prolongation of the bleeding time in vitro and contributes to bleeding after CPB.

The significant effect of hypothermia on the hemostatic mechanism during CPB has been shown clinically in a prospective study that showed that normothermic systemic perfusion (35°C to 37°C) compared with moderate systemic perfusion (25°C to 29°C) preserved platelet function and reduced postoperative blood loss.[14]

Whereas blood loss was significantly reduced with the higher doses of TA in this study, blood transfusion requirements were no different among the three groups. This may be related to the use of autotransfusion or the criteria used for transfusion of banked blood, which was a hematocrit of 19% or less during CPB and a hematocrit of 20% or less on two consecutive measurements while in the intensive care unit. These criteria allowed for significant hemodilution before blood was transfused. Although more patients were transfused in the 150-mg/kg group than in the other two groups, this was not statistically significant and the majority (9/11 patients) were transfused during CPB. The 150-mg/kg group had a significantly lower preoperative hemoglobin level compared with the other groups ($p = 0.01$), indicating that the main reason for transfusion in this group was hemodilution during CPB, rather than postoperative blood loss. Preoperative hemoglobin was the strongest predictor of the need for postoperative RBC transfusion using logistic regression analysis ($p = 0.001$).

In conclusion, of the doses of TA studied, 100 mg/kg is the optimal and most cost-effective dose of TA for reducing blood loss after cardiac surgery with moderate hypothermic systemic perfusion. The problem of preoperatively identifying patients who will bleed after cardiac surgery must be addressed.

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