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The Dose-Response Relationship of Tranexamic Acid

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Background: **Prophylactic administration of the antifibrinolytic drug tranexamic acid decreases bleeding and transfusions after cardiac operations. However, the best dose of tranexamic acid for this purpose remains unknown. This study explored the dose-response relationship of tranexamic acid for hemostatic efficacy after cardiac operation.**

Methods: **In prospective, randomized, double-blinded fashion, 148 patients undergoing cardiac operation with extracorporeal circulation were divided into six groups: a placebo group and five groups receiving tranexamic acid in loading doses before incision (range 2.5 to 40 mg · kg^{-1}) and one-tenth the loading dose hourly for 12 h. The mass of blood collected by chest tubes over 12 h represented blood loss. Allogeneic transfusions within 12 h and within 5 d of surgery were tallied.**

Results: **The six groups presented similar demographics. Patients receiving placebo had increased postoperative D-dimer concentration compared to groups receiving tranexamic acid. Patients receiving at least 10 mg · kg^{-1} tranexamic acid followed by 1 mg · kg^{-1} · h^{-1} bled significantly less (365, 344, and 369 g · 12 h^{-1}, respectively, for those three groups) compared with patients who received placebo (552 g, $P < 0.05$). Tranexamic dose did not affect transfusions. Only initial hematocrit affected whether a patient received an allogeneic transfusion within 5 days of operation (odds ratio 2.08 for each 3% absolute decrease in hematocrit).**

Conclusions: **Prophylactic tranexamic acid, 10 mg · kg^{-1} followed by 1 mg · kg^{-1} · h^{-1}, decreases bleeding after extracorporeal circulation. Larger doses do not provide additional hemostatic benefit. (Key words: Extracorporeal circulation. Blood: antifibrinolytics; tranexamic acid. Hemorrhage.)**

CONCERNS of transfusion-acquired infection have revived interest in hemostatic pharmaceuticals, including desmopressin,[1–5] aminocaproic acid,[6–8] tranexamic acid,[5,6,9–12] and aprotinin.[12–19] Most applications focus on patients undergoing extracorporeal circulation (ECC), perhaps owing to the frequency and severity of postoperative hemorrhage after ECC[20] and the known hemostatic defects engendered by ECC.[21–24] Aprotinin administered in small doses provides little hemostatic efficacy,[25] whereas much larger doses decrease bleeding and transfusion requirements after ECC.[19] The synthetic antifibrinolytic agent tranexamic acid (TA) decreases blood loss and transfusion requirement in patients undergoing ECC[5,9,26] when administered in doses previously determined to inhibit plasma fibrinolytic activity.[27,28] A few investigators have administered TA in doses exceeding 20 mg · kg^{-1}, in some cases giving as much as 20 g.[6,10–12] But the dose-response relationship for TA to decrease bleeding after ECC remains unexplored. Might TA, like aprotinin, exhibit greater efficacy at increased dosage? Perhaps less drug would provide an equally efficacious, and thus less costly, hemostatic effect. This study elucidates the optimum dose of TA, defined as the minimum amount yielding the greatest hemostatic effect on a heterogeneous group of patients undergoing ECC.

Methods

Patients aged 21–80 yr for elective cardiac operation performed by either of two surgeons (M.D.S. or K.E.G.) gave informed consent after institutional review board approval. Patients excluded from participation took warfarin or estrogens within 7 days of surgery, had active hematuria or a serum creatinine concentration of 2.0 mg · dl^{-1} or more, had a personal or family history of abnormal bleeding, weighed more than 100 kg, or underwent intraaortic balloon counterpulsation before surgery. Patients receiving aspirin within 7 days of operation, heparin infusion within 8 h, or nonsteroidal antiinflammatory medication within 3 days participated. Inclusion of these patients permits application of the study results to a representative population of

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elective surgical patients. Enrolled patients underwent coronary revascularization, valve replacement, both procedures combined, or repair of atrial septal defect.

Group Assignment

A table of random numbers determined patient allocation initially to one of five groups. The placebo group (P) received saline infusions. Four other groups received tranexamic acid beginning after induction of anesthesia but before skin incision as a loading dose over 30 min followed by a 12-h constant infusion. Table 1 displays the different doses of tranexamic acid, which initially ranged from one-quarter (2.5 $mg \cdot kg^{-1}$ loading followed by 0.25 $mg \cdot kg^{-1} \cdot h^{-1}$ infusion) to twice (20 $mg \cdot kg^{-1}$ loading followed by 2.0 $mg \cdot kg^{-1} \cdot h^{-1}$) the recommended doses.[28] After enrollment of 60 patients without perioperative stroke or clinically evident deep vein thrombosis, a sixth group of patients receiving fourfold the recommended dose (40 $mg \cdot kg^{-1}$ loading followed by 4.0 $mg \cdot kg^{-1} \cdot h^{-1}$) was added to the randomization scheme in such a way that each group would contain approximately equal numbers after a target enrollment of 155 patients. Power analysis predicted the need for approximately 25 patients per group to demonstrate a difference of at least 150 g chest tube drainage after operation between the placebo group and the group receiving the standard, recommended dose (10 $mg \cdot kg^{-1}$ followed by 1.0 $mg \cdot kg^{-1} \cdot h^{-1}$). Coded infusion bags for both loading and infusion doses and sealed envelopes prepared by a pharmacist provided double-blinded conditions.

Anticoagulation

Beef lung heparin (Organon, West Orange, NJ), 400 units $\cdot kg^{-1}$, provided anticoagulation for ECC. Automated celite activated coagulation time (Hemochron, International Technidyne, Edison, NJ) greater than 480 s, determined in duplicate every 30 min, ensured continued anticoagulation. ECC employed nonocclusive roller pumps, membrane oxygenators (Maxima, Medtronic Cardiopulmonary, Anaheim, CA), cold sanguinous cardioplegic arrest, and systemic hypothermia to 25°C. The ECC circuit initially contained 5,000 U of beef lung heparin in 2 L of clear fluid prime (Plasmalyte A solution, Baxter Healthcare, Deerfield, IL). Termination of ECC required a distal esophageal temperature of 37°C or greater and urinary catheter temperature of 34°C or greater. Protamine (4 $mg \cdot kg^{-1}$) neutralized heparin to obtain an activated coagulation time within 15 s of baseline.[29] Infusion of residual blood from the extracorporeal circuit followed approximation of the sternal wound edges. A subsequent additional protamine infusion (30% of the initial dose) neutralized heparin in the pump blood and protected against heparin rebound,[30] as confirmed by repeat activated coagulation time measured 2 h after sternal closure.

Table 1. Study Groups According to Dose of Tranexamic Acid

Group	Loading Dose ($mg \cdot kg^{-1}$)	Infusion dose ($mg \cdot kg^{-1} \cdot h^{-1}$)
Placebo (P)	0	0
Quarter (Q)	2.5	0.25
Half (H)	5.0	0.50
Whole (W)	10	1.0
Double (D)	20	2.0
Fourfold (F)	40	4.0

Blood Loss

The mass of blood collected *via* mediastinal and pleural drains for a period beginning with chest closure and lasting 12 h represented blood loss. No attempt was made to estimate blood loss before or during ECC or before insertion of mediastinal drainage tubes. The study ignored estimates of irrigation fluid, sponge and suction container losses, and soaking of linens; all of these measures of operative blood loss lack accuracy. All mediastinal blood lost after initial heparin administration until termination of ECC eventually was returned to the patient. After ECC, a citrated autotransfusion drainage system (Pleur-evac, Deknatel, Queens Village, NY) permitted return of shed blood to those patients experiencing initial rapid blood loss.

Transfusion

Transfusion of packed erythrocytes in the first 12 h after surgery required one or more of the following: hematocrit less than 21% measured at least 1 h after surgery, chest tube drainage of at least 250 $ml \cdot h^{-1}$, or a hematocrit less than 24% associated with hemodynamic signs of hypovolemia, defined as both heart rate greater than 110 beats/min and pulmonary arterial diastolic pressure less than 10 mmHg. Transfusions of fresh frozen plasma or platelets required a prolonged prothrombin time or thrombocytopenia respectively coupled with bleeding of 250 $ml \cdot h^{-1}$ or more. After 12 h, strict transfusion criteria no longer applied; clinician preference supervened. The number of units

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each of homologous blood, fresh frozen plasma, and platelets administered within 12 h and within 5 days of operation was recorded.

Coagulation Tests

Before induction of anesthesia and 2 h after completion of initial protamine infusion, coagulation assessment included measurement of activated partial thromboplastin time, platelet count, plasma fibrinogen, serum fibrin-fibrinogen-related antigen (latex agglutination, Thrombo-Wellco Test, Burroughs Wellcome, Research Triangle Park, NC), and latex agglutination D-dimer (D-di, American Bioproducts, Parsippany, NJ). D-dimer is a specific breakdown product of factor XIIIa-stabilized, cross-linked fibrin.

Data Analysis

Although blood loss did not distribute normally, its logarithmic transform did. Transformed blood loss data underwent analysis of variance followed by the Tukey HSD multiple comparison test. Back transformed mean and 95% confidence intervals provided summary statistics for blood loss.

Because most patients in the study did not receive a transfusion, traditional analytic techniques did not apply. A dichotomous variable, "occurrence of transfusion," described whether or not a patient received any banked blood product. Multinomial logistic regression determined the effects of patient grouping and demographic factors on the occurrence of transfusion. This technique uses a stepwise approach, Wald statistics, and the log-likelihood ratio test[31] to obtain the determinants of blood transfusion among selected variables.

Because analysis of the blood loss data must account for the multifactorial nature of bleeding after surgery, a stepwise multivariate linear regression technique sought those factors associated with bleeding. This method first uses univariate analysis of variance to identify potential contributors, then a stepwise multiple regression to include any of those potential contributors that provide further predictive information.

Analysis of variance compared group continuous demographic data, and contingency tables analyzed frequency data. Coagulation data underwent a two-way analysis of variance using as factors patient group, sample time (before operation or after operation), and their interaction. For any data not conforming to the normal distribution, nonparametric tests applied. All tests were two-tailed with $P < 0.05$ denoting significance.

Results

Of 155 patients enrolled, 7 did not complete the study. One patient did not undergo surgery. Another patient (group W) sustained a torn atrium during surgery accompanied by rapid blood loss, hypotension, and intraoperative myocardial infarction. A third patient (group Q) bled so much during surgery that the surgeon insisted antifibrinolytic therapy (epsilon aminocaproic acid) be administered at that time. A fourth patient (group P) developed cardiogenic shock after bypass for repeat sternotomy for coronary grafting and expired soon after operation. For one patient in group Q and two patients in group F, human error resulting in violations of the study protocol terminated study participation.

Demographic variables for the remaining 121 men and 27 women did not differ among groups. Table 2 displays these data by group, along with the duration of ECC, and the hematocrits measured before skin incision, after termination of ECC, and 2 h after arrival in the intensive care unit. None of these differed among groups with the exception of final hematocrit for the group that received one-fourth the usual dose of tranexamic acid. All aortocoronary bypass graft procedures except one each in groups P and F included an internal mammary artery graft.

Coagulation

Baseline coagulation studies did not differ among groups. Table 3 displays the aggregate data. Most patients for aortocoronary graft procedures received heparin infusions up to 4 h before surgery, resulting in prolonged aPTT results just before skin incision. This population of cardiac surgical patients, like other patients with cardiac disease,[5,32,33] displayed fibrin degradation products and increased D-dimer concentrations before surgery. The aggregate median FDP concentration was 0 $\mu g \cdot ml^{-1}$ for preoperative specimens and 10 $\mu g \cdot ml^{-1}$ for postoperative specimens. The aggregate median D-dimer concentration was 0.0 fibrinogen equivalency units (FEU, $\mu g \cdot ml^{-1}$) before operation and 0.25 FEU after operation. As expected, postoperative specimens demonstrated a decrease compared to the preoperative value in both platelet count (pooled values 158 ± 59 (SD) *vs.* 228 ± $76 \cdot 10^9 \cdot l^{-1}$, $P < 10^{-15}$) and fibrinogen concentration (217 ± 74 *vs.* 319 ± 103 mg · dl^{-1}, $P < 10^{-15}$). Groups differed with respect to postoperative D-dimer concentrations ($P = 10^{-5}$, table 3). The placebo group

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Table 2. Demographic and Other Descriptors of the Treatment Groups

	Placebo	Quarter	Half	Whole	Double	Fourfold
N	27	24	22	21	27	27
Age (yr)	63 ± 2	67 ± 2	61 ± 2	66 ± 2	63 ± 2	65 ± 2
Gender (M/F)	23/4	18/6	19/3	18/3	22/5	21/6
Weight (kg)	83 ± 3	79 ± 3	81 ± 3	79 ± 3	84 ± 3	80 ± 3
BSA (m^2)	2.0 ± 0.04	1.9 ± 0.04	1.9 ± 0.04	1.9 ± 0.04	2.0 ± 0.4	1.9 ± 0.04
Surgeon*	19/8	19/7	14/8	15/6	20/7	17/10
% Aspirin	52	52	41	38	52	59
% Heparin	31	46	41	24	33	19
%ACB†	85	71	86	71	74	89
% 2° operation‡	11	4.2	14	29	11	11
ECC (min)	77 ± 5.5	86 ± 5.9	93 ± 5.5	95 ± 6.3	97 ± 5.5	94 ± 5.5
Autoxfuse§	384 (15)	321 (14)	296 (5)	245 (5)	296 (9)	246 (11)
Hematocrits						
Initial	37 ± 1.0	34 ± 1.1	38 ± 1.1	37 ± 1.2	38 ± 1.0	37 ± 1.0
After ECC	26 ± 0.80	24 ± 0.85	27 ± 0.91	25 ± 0.96	26 ± 0.82	26 ± 0.80
In ICU	28 ± 0.81	25 ± 0.85¶	29 ± 0.89	27 ± 0.91	28 ± 0.81	28 ± 0.81

Values are mean ± SEM unless otherwise indicated.

BSA = body surface area; ACB = aortocoronary bypass; ECC = extracorporeal circulation; ICU = intensive care unit.

* Number of patients operated by M.D.S./number of patients operated by K.E.G.

† Percentage of procedures that were aortocoronary grafts. All other procedures were either valve replacement or combined aortocoronary grafts with valve replacement, with the exception of one atrial septal defect repair in group Q.

‡ Percentage of patients presenting for repeat sternotomy.

§ Shed blood returned (g) as median (number receiving shed blood). Other patients in each group did not receive shed blood. $P = 0.03$ for difference among groups in number of patients receiving shed blood. P = NS among groups for amount of shed blood returned to those patients who received it.

¶ Group Q < group H by the Tukey HSD comparison ($P < 0.018$). All other comparisons: P = NS

Table 3. Coagulation Data

	Placebo	Quarter	Half	Whole	Double	Fourfold
Preoperative specimen						
aPTT	15 ± 2.8	11 ± 3.1	14 ± 3.4	12 ± 3.4	11 ± 3.6	6.7 ± 3.8
Platelet count	220 ± 14	258 ± 14	228 ± 14	223 ± 15	230 ± 13	210 ± 13
Fibrinogen	300 ± 18	353 ± 19	322 ± 19	307 ± 20	301 ± 18	237 ± 17
FDP (%)	40	30	20	20	33	52
D-Dimer*	0.5	0.0	0.0	0.0	0.0	0.0
Range	0.0–4.0	0.0–8.0	0.0–2.0	0.0–2.0	0.0–8.0	0.0–0.25
Postoperative specimen						
aPTT	12 ± 2.8	8.6 ± 3.1	12 ± 2.8	8.0 ± 3.1	12 ± 2.9	5.7 ± 3.1
Platelet count	166 ± 14	175 ± 14	158 ± 14	158 ± 15	154 ± 13	135 ± 13
Fibrinogen	227 ± 18	226 ± 19	226 ± 19	217 ± 22	198 ± 17	209 ± 17
FDP (%)	76	43	38	50	57	63
D-Dimer*	1.0†	0.25	0.25	0.25	0.25	0.0
Range	0.25–8.0	0.0–4.0	0.0–2.0	0.0–2.0	0.0–2.0	0.0–0.25

Values are mean ± SEM for aPTT, activated partial thromboplastin time expressed as seconds above control; platelet count in $19^9 \cdot 1^{-1}$; fibrinogen as $mg \cdot dl^{-1}$; FDP, fibrin degradation products as percent of patients demonstrating $\geq 10\ \mu g \cdot ml^{-1}$.

* Values are median and range for D-dimer in fibrinogen equivalency units (FEU, $\mu g \cdot ml^{-1}$).

† $P < 10^{-5}$ for effect of group on D-dimer by Kruskal-Wallis analysis of variance.

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demonstrated statistically significantly increased D-dimer concentrations compared to every group receiving TA ($P \leq 0.022$). Furthermore, groups differed ($P = 0.043$) with respect to the change, postoperative minus preoperative, in D-dimer concentration. The largest median changes occurred in groups D (−0.5 FEU) and F (−0.125 FEU), whereas groups P, Q, and H exhibited no change in median D-dimer concentration.

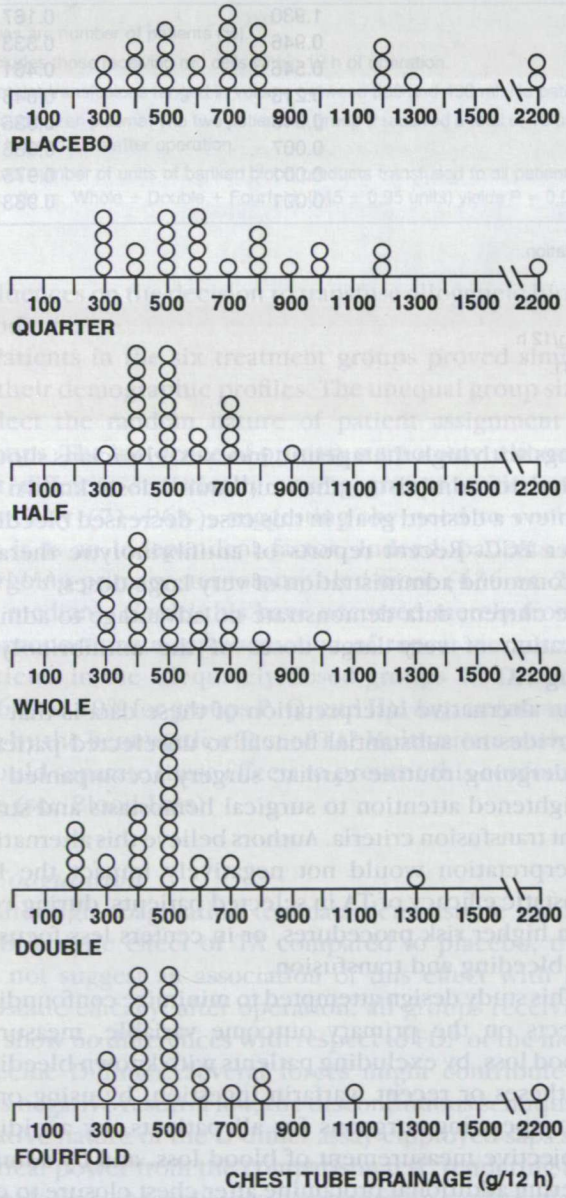

Fig. 1. Frequency distribution of 12 h blood loss *via* mediastinal drains for each group. Vertical axes represent number of patients. Horizontal axes represent grams of blood lost, rounded to the nearest 100 g.

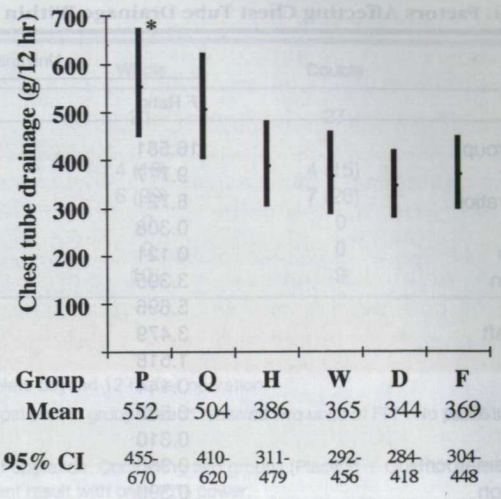

Fig. 2. Mean and 95% confidence intervals for blood loss in the first 12 h for the six groups. Group abbreviations as defined in table 1. *$P < 0.05$ for group P greater than each of groups W, D, and F.

Blood Loss and Transfusion

Figure 1 displays the blood loss data for the six groups. Figure 2 displays the associated back transformed mean and 95% confidence intervals for blood loss. Analysis of variance confirmed a dose-response relationship: patients in groups W, D, and F each bled significantly less than those in group P ($P = 0.042$, 0.005, and 0.030, respectively) but not less than those in group Q ($P = 0.233$, 0.062, and 0.210, respectively). As expected in a dose-response study, no group's blood loss differed from that of its immediate neighbor in dosing scale (*i.e.*, group P with group Q, group Q with group H, group H with group W). Groups Q, H, W, D, and F form a logarithmic sequence. Because group P received no drug, its logarithm is undefined, precluding a strict dose-response mathematical model of this relationship.

Stepwise multivariate linear regression identified four factors accounting for chest tube drainage within 12 h of operation. Table 4 lists the results of this analysis. Factors associated with decreased bleeding were drug treatment group, female gender, increased body weight, and repeat (rather than primary) sternotomy. Substitution of blood loss indexed by body weight or by body surface area did not eliminate the association of bleeding with drug treatment group.

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Table 4. Factors Affecting Chest Tube Drainage Within 12 Hours of Operation

	Univariate		Multivariate	
	F Ratio	*P* Value	*F* Ratio	*P* Value
Drug group	16.581	0.00008	18.407	0.00003*
Gender	9.777	0.002	18.400	0.00003†
2° operation	8.721	0.0037	14.691	0.0002‡
Weight	0.308	0.580	7.974	0.0057§
Heparin	0.121	0.729	3.245	0.074
Surgeon	3.395	0.068	2.055	0.154
Height	5.696	0.018	1.930	0.167
IMA graft	3.479	0.064	0.946	0.333
Age	1.518	0.220	0.546	0.461
BSA	0.144	0.705	0.213	0.645
ECC duration	0.580	0.448	0.043	0.835
Aspirin	0.310	0.579	0.007	0.936
Initial hematocrit	0.350	0.852	0.001	0.975
Operation	0.390	0.533	0.001	0.983

IMA = internal mammary artery; BSA = body surface area; ECC = extracorporeal circulation.

* See figure 2 for breakdown of blood loss by drug treatment group.

† Male: 441 (401–485), female: 314 (273–361) g per 12 h (median and range).

‡ Primary sternotomy, 436 (400–474) g/12 h *versus* repeat sternotomy, 297 (222–396) g/12 h.

§ Blood loss = 480 g · exp(−0.0018 · weight in kg), contribution to $r^2 = 0.042$, $P = 0.0041$.

In each of the six groups, similar numbers of patients received transfusion. Table 5 summarizes the transfusion requirements of study patients. Although blood loss differed between those patients in groups P, Q, and H and those in groups W, D, and F, transfusions given did not achieve a statistically significant difference ($P = 0.075$). Stepwise multinomial logistic regression examined drug treatment group, initial hematocrit, operating surgeon, patient weight, kind of operation, and sternotomy status (primary *vs.* repeat) as possible factors associated with administration of packed erythrocytes within 12 h of operation and within 5 days of operation. Only initial hematocrit predicted ($P < 0.00005$) whether a patient would receive a transfusion within 12 h of operation. Each 3% (absolute) decrease in initial hematocrit increased the likelihood of transfusion by a factor of 1.74 (95% confidence interval 1.33–2.27). For transfusions within 5 days of operation, initial hematocrit again emerged as the sole significant predictor ($P < 10^{-5}$), with each 3% (absolute) decrease in initial hematocrit increasing the likelihood of transfusion by a factor of 2.08 (95% confidence interval 1.57–2.76).

Discussion

Responsible medical practice includes consideration of the cost of pharmaceuticals prescribed. Even for drugs with high therapeutic indexes, clinicians should strive to administer the minimum dose known to achieve a desired goal, in this case, decreased bleeding after ECC. Recent reports of antifibrinolytic therapy recommend administration of very large doses.[6,11,12,19] The current data demonstrate no advantage to administration of very large doses of the antifibrinolytic drug TA.

An alternative interpretation of these data is that TA provides no substantial benefit to unselected patients undergoing routine cardiac surgery accompanied by heightened attention to surgical hemostasis and stringent transfusion criteria. Authors believe this alternative interpretation would not negatively impact the hemostatic efficacy of TA in selected patients, during certain higher risk procedures, or in centers less focused on bleeding and transfusion.

This study design attempted to minimize confounding effects on the primary outcome variable, measured blood loss, by excluding patients with known bleeding diatheses or recent warfarin ingestion, by using only two operating surgeons for all patients, by avoiding subjective measurement of blood loss, and by administering additional protamine after chest closure to obviate heparin rebound. Measurement of blood loss by weight instead of volume improves its precision. Specific criteria for blood transfusion minimized subjective

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Table 5. Transfusions Given to Study Patients

	Placebo	Quarter	Half	Whole	Double	Fourfold
N	24	24	22	21	27	27
Red cells						
12 h	4 (15)	5 (21)	3 (14)	4 (19)	4 (15)	4 (15)
5 days*	7 (26)	9 (38)	8 (36)	6 (29)	7 (26)	7 (26)
Platelets†	1 (3.7)	2 (8.3)	0	0	0	0
FFP‡	2 (7.4)	3 (13)	0	0	0	0
All products§	19	33	13	10	9	14.5

Values are number of patients (%).

* Includes those receiving red cells within 12 h of operation.

† Platelet transfusions ranged in volume between 360 and 430 ml. No patient received platelets beyond 12 h after operation.

‡ Fresh frozen plasma. The two patients in group P received a total of 10 units of FFP; three patients in group Q each received two units of FFP. No patient received FFP beyond 12 h after operation.

§ Total number of units of banked blood products transfused to all patients within 5 days of operation. Comparing two groups (Placebo + Quarter + Half, 0.89 ± 1.9 units *vs.* Whole + Double + Fourfold, 0.45 ± 0.95 units) yields $P = 0.075$, a nonsignificant result with only 46% power.

influences on the decision to transfuse allogeneic blood products.

Patients in the six treatment groups proved similar in their demographic profiles. The unequal group sizes reflect the random nature of patient assignment to groups. The incidence of primary sternotomy, although not different statistically among groups, varied substantially (71–96%), suggesting the need to control for it as an independent factor. Indeed, patients undergoing primary sternotomy bled more (436 *vs.* 297 ml median). Could this have occurred merely from a disproportionate representation of repeat sternotomy patients in the adequately dosed groups W, D, and F (16% *vs.* 10% for groups P, Q, and H), *i.e.*, a confounding by the hemostatic effect of TA? Multivariate analysis should separate these effects to prevent this confounding (see Blood Loss).

Coagulation

Although coagulation test data demonstrate the antifibrinolytic effect of TA compared to placebo, they do not suggest an association of this effect with hemostatic efficacy: after operation, all groups receiving TA show no differences with respect to FDP or the more specific D-dimer. Several forces might contribute to this negative result. First, the discontinuous semiquantitative nature of the D-dimer assay employed saps statistical power from the comparison test, rendering the sample sizes inadequate to demonstrate a modest effect. Second, the study design may have limited demonstration of such an effect: the fourfold dosed group's D-dimer summary statistics (0.0 median, 0.0–0.25 range) contrast with those of the smaller dosed groups. Perhaps an eightfold group would have revealed a progression of decreased D-dimer concentration with increasing TA dose. Third, ample evidence exists for a multifactorial mechanism of antifibrinolytic drugs on blood conservation. If these drugs also reduce bleeding by preserving platelet function[26,34,35] *via* plasmin and thrombin receptor blockade,[36,37] then the direct association of D-dimer and blood loss becomes diluted.

Blood Loss

Multivariate analysis identified drug treatment group as the most significant factor affecting blood loss, with higher dose groups displaying decreased bleeding. Of the other three significant predictors of decreased bleeding—increased body weight, female gender, and repeat sternotomy—female gender does not agree with a previously published series,[38] in which women more often bled excessively after primary coronary artery surgery. That study, however, used a retrospective design. Furthermore, female gender did not survive logistic regression analysis by those authors and thus did not form part of a nomogram developed to predict excessive blood use. In agreement with the current results, a report of 20,524 patients undergoing coronary artery surgery by Loop *et al.* documented the need to reoperate for bleeding in only 3.8% of women compared to 5.5% of men.[39] The lesser bleeding among female patients remains unexplained.

The current study comprised only 20 patients (13%) undergoing repeat sternotomy, a cohort too small to draw definitive conclusions regarding the decreased

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bleeding seen with repeat operation. Nevertheless, anecdotal reports of improved operating conditions owing to diminished capillary bleeding with antifibrinolytic administration for repeat sternotomy[19] agree with the current results, leading one to speculate some unknown interactive effect of antifibrinolytic with the thromboplastin-rich scar tissue encountered during repeat sternotomy. Patients also might have received additional attention to surgical hemostasis with repeat operation compared to primary operation. The effect of body weight on blood loss, while significant statistically, accounts for only 4.2% of the variance of the logarithm of blood loss, demonstrating minimal clinical significance. Indeed, the regression model predicts that a doubling of body weight reduces blood loss by only 9%.

Most patients bled little in this study (fig. 1). Minimal bleeding overall renders difficult the demonstration of hemostatic efficacy by pharmaceuticals. Does such success make any such demonstration moot? No, because adjunctive efforts may not always be available or provided. Despite surgical or design factors contriving to minimize overall blood loss, this study demonstrates that TA provides a small but measurable hemostatic efficacy in a heterogeneous population of patients undergoing ECC. Also, doses lower than those needed to affect antifibrinolytic activity *in vitro* (groups Q and H)[27,28] do not provide hemostatic benefit compared with the dose that does (group W). Furthermore, doses in excess of the effective dose (groups D and F) confer no additional benefit. Do these results disagree with those of aprotinin, in which higher doses demonstrated hemostatic efficacy[19] not seen earlier with modest doses?[25] Recent work with moderate doses of aprotinin suggest that these moderate doses demonstrate hemostatic efficacy.[10,12,40–45] Other factors, such as improved ECC equipment, changes in patient demographics, or surgical technique modifications render suspect comparisons of data from 25 yr ago[25] with more recent investigations. Both TA and aprotinin appear to provide hemostatic benefit in moderate doses.

Transfusion Requirement

These data do not demonstrate an effect of TA dose on blood transfused, despite an effect on blood lost. How can this be? First, the criteria require significant hemodilution to trigger a transfusion, thus providing an overall low incidence of transfusion (98.5 total units given to 44 out of 148 patients). Because mean postoperative hematocrits exceeded 25% for each group and transfusion criteria specify a hematocrit ≤21%, a group difference in transfusions would be unexpected. Blood loss, not transfusion requirement, was the primary outcome variable in this study. Studies that use more liberal transfusion criteria, such as a hematocrit less than 30% rather than 21%, and in which patients bleed more in general, *i.e.*, a placebo group 12 h loss ≈ 850 g instead of 552 g, can more easily demonstrate an effect of drug on transfusion requirement. As with blood loss, any potential effect of TA on blood transfused is not rendered moot by these factors; rather, a savings in blood transfused may attain clinical significance when other mitigating factors are absent or not effective. Likewise, routine administration of TA may be unwarranted when blood loss is minimal and transfusion criteria strict, *i.e.*, hematocrit < 25%.

Safety

Although none of the patients in this study suffered a detectable thrombotic event, the clinician should exercise caution in interpreting these limited results when considering the safety of TA. For this cohort of 148 patients with zero strokes, the 95% confidence interval for stroke incidence is 0–2.0%.[46] Thus, these data are consistent with a true rate of 2.0% or less. Although a larger cohort could yield stricter predictions of safety, 300 patients would be required to achieve a 95% confidence interval incidence of 1.0% or less, and 3,000 patients for less than 0.1%. This study's design did not attempt to yield safety statistics of that magnitude. On the other hand, prophylactic use of TA for hemostasis after ECC lasted only 12 h in the current study. Previously reported anecdotes of thrombotic complications of antifibrinolytic therapy in patients without malignancy all feature long-term (greater than several days') infusion of drug.

Because excretion of TA depends solely upon glomerular filtration, patients with serum creatinine concentrations above 2.0 $mg \cdot dl^{-1}$ did not participate. Although this study provides data on neither the efficacy nor safety of TA administration to patients with significant impairment of renal function, prudent clinicians should consider modifying TA dosages to such patients.

Based on the postoperative blood loss response of this heterogeneous cardiac surgical population to a 16-fold range of TA doses, we recommend a 10 $mg \cdot kg^{-1}$ intravenous loading dose followed by an infusion of 1.0 $mg \cdot kg^{-1} \cdot h^{-1}$ for prophylactic administration of TA. Larger doses provide no additional savings in blood

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loss, whereas smaller doses carry decreased hemostatic efficacy.

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