Anesthesiology
2000; 92:674–82

Comparison of Blood-conservation Strategies in Cardiac Surgery Patients at High Risk for Bleeding

Gregory A. Nuttall, M.D., William C. Oliver, Jr., M.D.,* Mark H. Ereth, M.D.,* Paula J. Santrach, M.D.,† Sandra C. Bryant, M.S.,‡ Thomas A. Orszulak, M.D.,§ Hartzell V. Schaff, M.D.§*

Background: **Aprotinin and tranexamic acid are routinely used to reduce bleeding in cardiac surgery. There is a large difference in agent price and perhaps in efficacy.**

Methods: **In a prospective, randomized, partially blinded study, 168 cardiac surgery patients at high risk for bleeding received either a full-dose aprotinin infusion, tranexamic acid (10-mg/kg load, 1-mg · kg^{-1} · h^{-1} infusion), tranexamic acid with pre–cardiopulmonary bypass autologous whole-blood collection (12.5% blood volume) and reinfusion after cardiopulmonary bypass (combined therapy), or saline infusion (placebo group).**

Results: **There were complete data in 160 patients. The aprotinin (n = 40) and combined therapy (n = 32) groups (data are median [range]) had similar reductions in blood loss in the first 4 h in the intensive care unit (225 [40–761] and 163 [25–760] ml, respectively; *P* = 0.014), erythrocyte transfusion requirements in the first 24 h in the intensive care unit (0 [0–3] and 0 [0–3] U, respectively; *P* = 0.004), and durations of time from end of cardiopulmonary bypass to discharge from the operating room (92 [57–215] and 94 [37, 186] min, respectively; *P* = 0.01) compared with the placebo group (n = 43). Ten patients in the combined therapy group (30.3%) required transfusion of the autologous blood during cardiopulmonary bypass for anemia.**

Conclusions: **The combination therapy of tranexamic acid and intraoperative autologous blood collection provided similar reduction in blood loss and transfusion requirements as aprotinin. Cost analyses revealed that combined therapy and tranexamic acid therapy were the least costly therapies. (Key words: Aprotinin; cardiopulmonary bypass; cost; intraoperative autologous blood; combined therapy; tranexamic acid; transfusion.)**

EXCESSIVE bleeding requiring transfusion of blood components after cardiopulmonary bypass (CPB) is one of the most common complications of cardiac surgery, and it has important health and economic consequences.[1,2] Prophylactic administration of aprotinin has been shown to decrease blood loss and blood transfusion requirements in cardiac surgery patients.[3–7] The proposed mechanisms by which aprotinin decreases bleeding are decreases in contact phase activation of coagulation, "platelet sparing" through attenuation of plasmin-mediated glycoprotein Ib platelet receptor dysfunction, preservation of glycoprotein IIb/IIIa receptor populations, and reduction in fibrinolysis.[8–12]

Tranexamic acid has been found to be effective in reducing bleeding and blood transfusions associated with cardiac surgery, but there have been few comparisons between tranexamic acid and aprotinin.[6–8,13–15] Further, aprotinin has both antifibrinolytic and platelet-sparing effects, but there have been no prospective blinded studies comparing aprotinin with the combined therapy of tranexamic acid and a platelet-sparing maneuver. Withdrawal and careful storage of fresh autologous whole blood before CPB with reinfusion after CPB has been shown to be effective in reducing bleeding and transfusion requirements in cardiac surgery patients; this is thought to be a platelet-sparing maneuver.[16,17] Other studies have had mixed results.[18–26]

In this prospective, randomized, double-blind study, we determined the effectiveness of aprotinin, tranexamic acid, tranexamic acid, and intraoperative autologous blood collection (combined therapy) compared with placebo for reduction of bleeding, transfusion requirements, and transfusion-related costs associated with cardiac surgical procedures placing patients at high risk for bleeding.

* Assistant Professor of Anesthesiology, Mayo Graduate School of Medicine.

† Assistant Professor of Laboratory Medicine and Pathology, Mayo Graduate School of Medicine.

‡ Statistician, Biostatistics, Mayo Clinic, Rochester, Minnesota.

§ Professor of Surgery, Mayo Graduate School of Medicine.

Received from the Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota. Submitted for publication January 27, 1999. Accepted for publication October 7, 1999. Supported by a Bayer Corporation 1995 Research Grant and the Mayo Foundation for Medical Education and Research, Rochester, Minnesota. Presented at the annual meeting of the Society of Cardiovascular Anesthesiologists, Seattle, Washington, April 25, 1998.

Address reprints requests to Dr. Nuttall: Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota 55905. Address electronic mail to: nuttall.gregory@mayo.edu

Materials and Methods

Patients

After institutional review board approval and written informed patient consent were obtained, 168 patients scheduled for elective revision sternotomy for coronary artery bypass grafting, or cardiac valve surgery, or a combination of the two were enrolled. Patients were excluded if they had histories of bleeding or a platelet disorder, prothrombin time (PT) $>$ 15.0 s, blood urea nitrogen level greater than 100 mg/dl, or a recent history of thrombolytic, warfarin, or heparin therapy. Patients were excluded if they were taking $\geq$325 mg of aspirin a day, had a bleeding time $>$ 8.0 min, or had congenital heart disease. Because one of the four study arms required a 12.5% blood volume isovolemic autologous blood draw, patients were excluded if their weight was less than 45 kg, or if they had a preoperative hemoglobin level $<$ 12.5 g/dl.

The participants were randomly assigned by a computer-generated random number sequence in a blinded fashion to receive one of four treatment regiments. The aprotinin group received an aprotinin infusion: a test dose of 1 ml (1.4 mg) followed by a loading dose of 200 ml (280 mg) over 20–30 min, a continuous infusion of 50 ml/h (70 mg/h), and a "CPB circuit prime" of 200 ml (280 mg).[3] The placebo group received a normal saline infusion. The tranexamic acid group received a tranexamic acid infusion (10-mg/kg load, and 1-mg $\cdot$ kg^{-1} $\cdot$ h^{-1} infusion).[13] The combined therapy group received a tranexamic acid infusion (10-mg/kg load and 1-mg $\cdot$ kg^{-1} $\cdot$ h^{-1} infusion) and intraoperative autologous blood collection, an intentional presumptive platelet-sparing maneuver. The drug and placebo infusions were started 30 min after central venous cannulation was completed, and the infusions were continued 2 h into treatment in the intensive care unit (ICU). In the intraoperative autologous blood collection, 12.5% of the patient's calculated whole-blood volume was withdrawn, before CPB and within 10 min after central venous cannulation, by gravity through an internal jugular 8-French catheter into blood collection bags containing citrate phosphate dextrose anticoagulant. The whole-blood units were kept at room temperature in the operating room (OR) and reinfused after CPB and protamine administration.[16]

Blinding Procedure

The anesthesiologist and surgeon were blinded to the drug therapy; the blood draw or sham blood draw was also performed in a blinded fashion. The drug and placebo therapies were devised so that each of them appeared to be an aprotinin infusion: test dose, load, infusion, and CPB circuit-prime dose. Because aprotinin combined with heparin can cause a greater prolongation of the celite activated clotting time (ACT), the kaolin-based ACT and heparin concentrations (Hepcon HMS, Medtronic HemoTec, Englewood, CO) guided heparin therapy. Aprotinin does not affect the kaolin-based ACT. All patients had either a sham blood draw (aprotinin, tranexamic acid infusion, and placebo groups) or the normovolemic autologous whole-blood withdrawal (combined therapy group) performed under a blind. The anesthesia care team was replaced by an investigator anesthesiologist during the normovolemic autologous whole-blood withdrawal or the sham blood draw. The aprotinin, tranexamic acid infusion, and placebo groups for which the sham blood draw was performed had the blood collection bags filled with albumin by a person under the blind. Both the autologous whole blood and the albumin in the blood collection bags were stored in a covered container at room temperature in the OR. All patients had a blinded infusion of either the autologous whole-blood or the albumin *via* the 8-French catheter after protamine administration. An opaque sleeve was placed over the entire collection bag and tubing.

Intraoperative Management

All patients received a moderate-dosage opioid-based anesthetic technique, supplemented with benzodiazepines, muscle relaxants, and inhalational anesthetic agents. CPB was conducted with a Univox membrane oxygenator (Bentley, Irvine, CA) and a Sarns 9000 CPB machine (Sarns, Ann Arbor, MI) at a flow of 2.4 l $\cdot$ min^{-1} $\cdot$ m^{-2}. The CPB circuit was primed with 1.5 l plasmalyte, 10 mEq sodium bicarbonate, and 12.5 g mannitol. Porcine heparin was administered to patients as follows: An initial dose was given consisting of a bolus of 300 U/kg and an oxygenator-priming dose of 10,000 U. Additional heparin (5,000 U) was administered if the kaolin ACT was less than 450 s or the heparin concentration was less than 2.5 mg/kg. After discontinuation of CPB, the initial protamine sulfate dose was 0.013 mg/U heparin administered. Heparin neutralization was regarded as adequate if the postprotamine ACT value was within 10% of the preheparin ACT value. Additional protamine (20–50 mg) was added at the discretion of the attending anesthesiologist if the ACT did not returned to this range. Intraoperative blood salvage and reinfusion of shed mediastinal blood was used in all cases.

Allogeneic erythrocytes were transfused when the he-

moglobin concentration was < 8 g/dl after discontinuation of CPB and < 7 g/dl during CPB. Allogeneic erythrocyte transfusions were allowed in patients who were rapidly bleeding or if there were signs of ischemia. Transfusion of allogeneic fresh-frozen plasma, platelets, or cryoprecipitate was based on clinical evidence of bleeding and supporting laboratory studies (thromboelastography, platelet count, PT, activated partial thromboplastin time [aPTT], and fibrinogen level). The general criteria for "coagulation blood product" transfusion at our institution are (1) transfusion of platelets with evidence of platelet dysfunction or thrombocytopenia (a platelet count less than 50×10^9/l) in a bleeding patient, (2) transfusion of fresh-frozen plasma with evidence of coagulation-factor deficiencies (PT or aPTT > 1.5 times upper limits of normal), and (3) transfusion of cryoprecipitate for suspected clotting-factor deficiency (elevated bleeding time or fibrinogen level < 100 mg/dl).

If the patient's hemoglobin concentration was less than 7 g/dl during CPB, the primary investigator was contacted, and it was determined whether the patient had intraoperative autologous blood available (combined therapy group). If intraoperative autologous blood was available, this was given to the patient rather than allogeneic erythrocyte units.

Clinical Outcomes

The primary efficacy outcome was the number of allogeneic blood transfusions in the OR and in the first 24 h in the ICU. Other measures of efficacy were the volume of intraoperative and ICU blood loss over the first 24 h, and duration of time between the end of CPB and OR discharge. Thromboelastography and measurement of PT, aPTT, platelet count, and mean platelet volume were performed before heparin administration, 10 min after reversal of heparin with protamine, 90 min after reversal of heparin with protamine, and 24 h after reversal of heparin with protamine. The bleeding time was performed before the patients entered the OR and 90 min after reversal of heparin with protamine.

Statistical Analysis

Based upon data from a previous study,[27] *a priori* power analysis determined we could detect ($\alpha = 0.05$ and 80% power) a change on the geometric scale from 8.6 units of blood components transfused to 4.7 units with 45 patients in each group. This analysis assumed that the mean and SD of the blood components transfused on the natural log scale were 2.15 and 1.13, respectively. The Kruskal-Wallis test was used to test for differences among the for groups. Statistical significance was defined as $P \leq 0.05$. The rank-sum test was then used to assess pairwise differences for any variables with significant differences among the groups. Using a Bonferroni *P*-value adjustment for multiple comparisons, significance of the pairwise comparisons was defined as $P \leq 0.008$. The laboratory data measured preoperatively, 10 min after protamine neutralization of heparin, 90 min after protamine neutralization of heparin, and 24 h after protamine neutralization of heparin were examined using a repeated-measures analysis of variance.

Results

Eight patients were excluded from analysis, two patients died within 24 h of surgery of causes unrelated to bleeding or transfusion (both in the placebo group), and six patients had surgical reexploration of their mediastinum for bleeding and a surgical source of bleeding found (five patients in the aprotinin group, one patient in the combined therapy group). Ten patients in the combined therapy group (30.3%) required transfusion of the platelet-sparing blood during the CPB period for treatment of anemia secondary to dilution. Patient enrollment in this group was terminated prematurely secondary to the high rate of early autologous blood reinfusion (before completion of CPB). This was done without prior knowledge of the study outcome.

There were 160 patients remaining in the study, 43 patients in the placebo group, 45 patients in the tranexamic acid group, 32 patients in the combined therapy group, and 40 patients in the aprotinin group. There were no differences between the groups in demographic or surgical variables (CPB duration, cross-clamp duration, and heparin concentrations) (table 1). There was a significant reduction ($P = 0.01$) in the median (range) duration from end of CPB to OR discharge for the aprotinin group (92 [57–215] min) and the combined therapy group (94 [37–186] min) compared with the placebo group (114 [78–176] min).

The combination of tranexamic acid with intraoperative autologous blood collection (combined therapy group) resulted in similar reduction in the median (interquartile range) transfusion requirements of erythrocytes in the ICU (0 [0–0] U) and aprotinin groups (0 [0–0] U) compared with the placebo group (0 [0–2] U) ($P = 0.004$; table 2). None of the patients had preoperatively donated autologous blood available. The median

Table 1. Demographic and Surgical Variables

Variable	Placebo (n = 43)	TA (n = 45)	Combined (n = 32)	Aprotinin (n = 40)	*P* Value
Height (cm)					0.329
Median	171	175	173	170	
Range	117.8–186	115–190	157–191	155–188	
Weight (kg)					0.187
Median	79.6	86.2	85.9	78.3	
Range	55.7–136	44.8–138	58.5–118	52.9–121.2	
Age (yrs)					0.116
Median	63	71	67.5	70.5	
Range	29–83	43–83	42–91	45–86	
BSA (m^2)					0.270
Median	1.99	2.04	2.06	1.95	
Range	1.59–2.76	1.19–2.69	1.69–2.48	1.53–2.4	
CPB time (min)					0.734
Median	107	106	109	116	
Range	47–207	40–352	48–210	33–236	
X-clamp time (min)					0.816
Median	69	66	57	67	
Range	17–156	21–173	26–128	17–183	
Post CPB–out of OR time (min)					0.010*
Median	114	104	92	94	
Range	78–176	48–212	57–215	37–186	
ICU time (h)					0.389
Median	26.5	45.5	30	45.5	
Range	13–212	18–280	17–183	17–141	
ICU intubation duration (h)					0.338
Median	13	15	14	17	
Range	4–159	4–161	4–134	2–48	
Male					0.167
No.	35	31	28	28	
%	81.4	68.9	87.5	70.0	
Revision sternotomy					0.178
No.	10	11	13	16	
%	23.3	24.4	40.6	40.0	

TA = tranexamic acid; Combined = combined therapy; BSA = body surface area; X-clamp = cross clamp; CPB = cardiopulmonary bypass; OR = operating room; ICU = intensive care unit.

* $P < 0.05$, Kruskal-Wallis test for difference.

amount of blood loss in the OR after protamine administration was 75 ml for the aprotinin group, 88 ml for the combined group, 150 ml for the tranexamic acid group, and 125 ml for the placebo group ($P = 0.52$). The placebo group had greater median (range) blood loss in the first 4 h in the ICU (320 [80–1,550] ml) than the tranexamic acid group (195 [30–1,190] ml), the combined therapy group (225 [40–761] ml), and the aprotinin group (163 [25–760] ml) ($P = 0.014$). The placebo group also had greater amounts of bleeding in the first 12 h in the ICU than the aprotinin group and greater amounts of bleeding in the first 24 h in the ICU than the tranexamic acid and aprotinin groups (fig. 1). Three patients had surgical reexploration of their mediastinum for bleeding in which no surgical source was found, one in the placebo group, one in the combined therapy group, and one in the aprotinin group.

There also were no significant differences found in hemoglobin concentration, hematocrit level, mean platelet volume, PT, international normalization ratio, aPTT, bleeding time, thromboelastography variables (reaction time + bikoatugulerung time, α-angle, maximum amplitude, and maximum amplitude + 30),[28] or heparin concentration among groups at different time points. The combined therapy group had a lower median platelet count at 10 min after protamine neutralization of heparin before the reinfusion of the autologous blood. The platelet count was the same as the other groups at the other time intervals. The median thromboelastography R in all groups were in the normal range at all times, but the placebo

Table 2. Allogeneic Blood Transfusions in the Operating Room and Intensive Care Unit

	Placebo (n = 43)	TA (n = 45)	Combined (n = 32)	Aprotinin (n = 40)	Time group *P* value
PRBC in OR					
Median (25%, 75%)	0 (0, 1)	0 (0, 2)	0 (0, 0)	0 (0, 1)	0.21
% not transfused	67	58	84	60	
Platelet in OR					
Median (25%, 75%)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.21
% not transfused	79	84	94	85	
FFP in OR					
Median (25%, 75%)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.51
% not transfused	79	87	91	88	
Cryo in OR					
Median (25%, 75%)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.65
% not transfused	98	98	100	100	
Total in OR					
Median (25%, 75%)	0 (0, 4)	0 (0, 2)	0 (0, 0)	0 (0, 1)	0.08
% not transfused	56	51	81	60	
PRBC in ICU					
Median (25%, 75%)	0 (0, 2)	0 (0, 1)	0 (0, 0)	0 (0, 0)	0.004*
% not transfused	52	67	81	85	
Platelets in ICU					
Median (25%, 75%)	0 (0, 6)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.41
% not transfused	71	82	84	85	
FFP in ICU					
Median (25%, 75%)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.37
% not transfused	76	80	88	87	
Cryo in ICU					
Median (25%, 75%)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.37
% not transfused	98	93	97	100	
Total in ICU					
Median (25%, 75%)	0 (0, 8)	0 (0, 2)	0 (0, 1)	0 (0, 2)	0.17
% not transfused	52	64	72	69	

Values in parentheses are interquartile ranges.

OR = operating room; PRBC = packed red blood cells; FFP = fresh-frozen plasma; Cryo = cryoprecipitate; ICU = intensive care unit.

* $P < 0.05$, Kruskal-Wallis test for differences.

group and combined therapy groups had a marginally longer R at 24 h after protamine neutralization of heparin.

Discussion

The combination therapy of tranexamic acid and intraoperative autologous blood collection (combined therapy group) provided a reduction in blood loss and packed erythrocyte ICU transfusion requirements similar to that provided by aprotinin. Excessive bleeding requiring transfusion of blood components after CPB is one of the most common complications of cardiac surgery.[1] This increases morbidity and mortality rates secondary to surgical reexploration for bleeding and transfusion complications.[29,30] Bleeding also increases hospital costs.[2]

Aprotinin has been shown to be very effective in reducing bleeding and transfusion requirements associated with cardiac surgery with CPB.[3,4] Aprotinin has antifibrinolytic and platelet-sparing effects.[3,8–12] Because aprotinin is an expensive drug ($500–1,000 per patient), and it may sensitize patients, which can result in allergic reactions on reexposure,[31] interest in cheaper lysine-analog antifibrinolytic drugs (tranexamic acid and ε-aminocaproic acid) has increased.[6–8,14,15,32–34] There have been few studies directly comparing aprotinin with tranexamic acid treatment for reduction of bleeding and transfusion requirements.[6–8,14,15] Many of these studies are limited by small sample size, lack of blinding, and lack of revision cardiac procedures. Patients undergoing revision cardiac procedures make up the patient population for which aprotinin is primarily indicated. In this investigation of revision sternotomy or combination cardiac surgery patients, we found aprotinin, combined therapy, and tranexamic acid to be effective in reducing

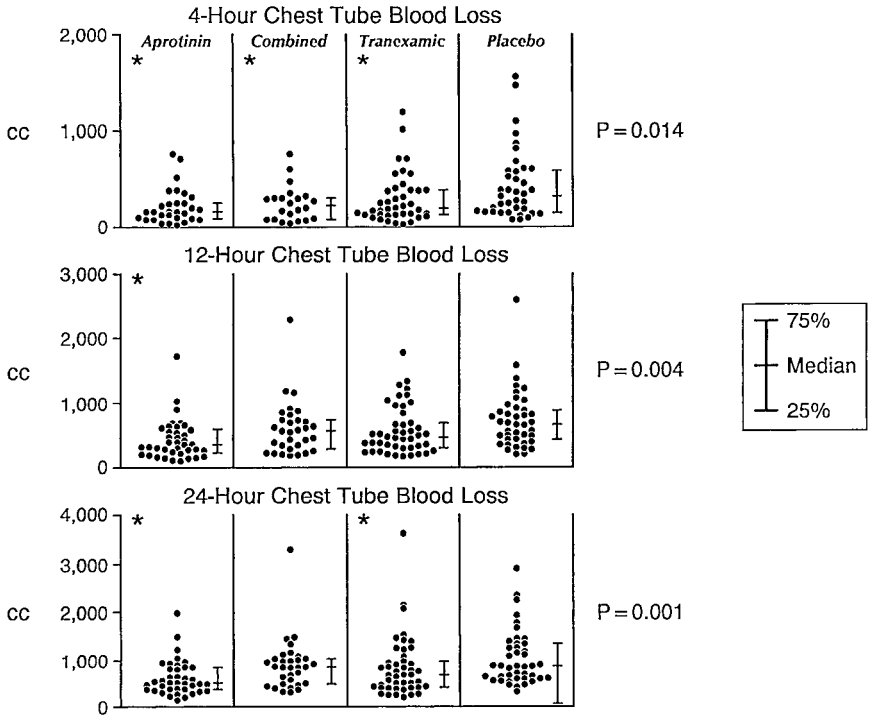

Fig. 1. Chest-tube (mediastinal) blood loss in the intensive care unit from intensive care unit entry until 4, 12, and 24 h after cardiac surgery. TA, tranexamic acid; Combined, combined therapy. *$P < 0.05$ by the rank-sum test for a difference between these groups and the control group.

blood loss in the ICU. Our results are consistent with previous comparisons between aprotinin and tranexamic acid.[6–8,14,15]

No studies have compared combined tranexamic acid and autologous fresh whole-blood collection as a presumptive platelet-sparing maneuver with aprotinin therapy in a blinded prospective fashion. We found that aprotinin and combined therapy had similar reductions of packed erythrocyte transfusion requirements in the ICU and duration of time from end of CPB to leaving the OR. The combined therapy was designed to be a "poor man's" aprotinin, combining antifibrinolysis with autologous whole blood as a presumptive platelet-sparing maneuver. The autologous blood collection was designed to maximally preserve the platelets that were removed, stored, and reinfused. A large 8-French catheter was used along with gravity drainage to reduce shear effects on the platelets during withdrawal of blood before CPB and reinfusion after CPB. The blood was stored at room temperature in a standard blood collection bag containing citrate phosphate dextrose anticoagulant. Previous studies using intraoperative autologous blood withdrawal as a platelet-sparing maneuver have had mixed results.[18–26] The technique used for the autologous blood collection and reinfusion is very important. One study found the use of autologous blood as a platelet-sparing maneuver to be effective, and we used a very similar low-shear technique.[16]

Pressure to reduce healthcare costs and public concern over the risks of blood transfusion[35] have generated considerable interest in determining the cost-effectiveness of different therapies to reduce bleeding after CPB. Very few cost–benefit studies of aprotinin compared with the lysine-analog antifibrinolytics for prevention of bleeding after CPB have been performed.[33,36,37] We performed a cost-comparison model analysis to evaluate the relative bleeding and transfusion-related costs associated with the therapies in question. Costs to the hospital in constant 1997 dollars, in contrast to charges to patients, were evaluated. The institutional costs of aprotinin and tranexamic acid along with the pharmacist costs and mixing costs were used. Personnel already trained and available to perform the intraoperative blood collection were used in this study, and the cost of the salary and benefits for the technician performing the intraoperative blood collection was used. The cost of the anesthesiologist's time for placing the 8-French catheter was also determined. No attempt was made to determine the cost of possible complications from the 8-French catheter. The disposable costs for the intraoperative blood collection were determined. The institutional costs for erythrocytes, platelets, fresh-frozen plasma, and cryoprecipi-

tate included the cost of procurement and indirect costs as well as the cost of transfusion tubing, filters, and blood-warming coils; a previously reported cost of $3.45 for each donor exposure was also added to account for the hospital cost of infectious complications.[38] Our institutional costs for blood transfusions are consistent with those previously published.[39] The duration of OR time from the end of CPB until OR discharge was incorporated in the analysis. The cost of OR time for cardiac surgery was estimated and included the salaries and benefits of the OR nurses, certified surgical technicians, and support personnel, the cost of medical supplies, and the costs of OR equipment and space use (*i.e.*, light, heat, electricity). The cost of OR time for cardiac surgery was found to be several times higher than the previously reported $4.70 per minute for laparoscopic cholecystectomy.[40] There were statistically significant differences in overall median bleeding-related costs between the groups. Aprotinin group had the highest median (range) bleeding-related costs of $3,210 ($2,586–5,893). The placebo group had a median cost of $2,537.00 ($1,507–6,005). The tranexamic acid group had median cost of $2,168.00 ($1,318–5,049). The lowest median bleeding-related costs were $1,916.00 [$1,170–4,388] in the combined therapy group. The combined therapy was less costly than aprotinin and achieved a comparable benefit. Our cost-comparison model results are very similar to those previously published comparing aprotinin with ϵ-aminocaproic acid in revision cardiac procedure patients.[33]

There are potential problems with this study. The combined therapy group was discontinued prematurely for clinical reasons. When this study was begun, we did not know whether the intraoperative fresh autologous blood would be effective in reducing transfusion requirements. We therefore decided that for those patients in whom the hemoglobin level was lower than 7 g/dl during CPB, we would determine if there were intraoperative autologous blood units available to reinfuse into the patient, thus preventing an allogeneic erythrocyte transfusion. We noted a high rate of early reinfusion of the autologous blood during CPB (30.3%) in the combined therapy group. Because reinfusion during CPB of this fresh intraoperative autologous blood theoretically negated the platelet-sparing effect of this blood in those patients, we discontinued this group prematurely. This was done without knowledge of the blood loss or transfusion results of the study groups. Therefore, the combined therapy group was underpowered. Further, the high rate of early autologous blood reinfusion (30.3%) with the combined therapy limits the utility of this approach. The limitation to the combined therapy is that it can only be used in patients with high preoperative hemoglobin levels, because the intraoperative blood collection before CPB lowers the patient's hemoglobin concentration. This reduction in hemoglobin concentration increases the need for transfusion of the autologous blood or erythrocytes during CPB for anemia. We found that if our patients' hemoglobin levels were greater than 13.6 g/dl, they did not need early reinfusion of their autologous blood unless there was surgical bleeding before CPB. Patients with high hemoglobin levels before cardiac surgery are relatively rare. Another problem with the combined therapy group is that the volume of autologous blood removed was a rather modest 12.5% of whole-blood volume. This would contain a rather small percentage of the patients' platelets. This is the greatest volume we felt we could safely take from the patient, and it did result in a significant reduction in packed erythrocyte transfusions and ICU bleeding. Finally, the unmasking of the combined therapy group causes significant problems with the blinding of this study. The personnel monitoring the blood loss and making transfusion decisions in the ICU were still blinded as to group identities, but there clearly was a loss of blinding for these patients in the OR. Another limitation of our study is that we excluded patients with known coagulopathies, patients on preoperative anticoagulant medications, and uremic patients. This limits the broad applicability of our study. Our study did not employ a dose-response design. The dose of tranexamic acid used in our study was based on a dose-response study performed by Horrow *et al.*[13] Other studies have used up to 10 times the dose of tranexamic acid than we used in our study.[32] A half-dose of aprotinin has been shown to be effective in reducing bleeding and transfusion requirements and could be more cost-effective. Finally, our cost-comparison model analysis only incorporated the cost associated with the drugs and maneuvers used in the study, along with the costs associated with those variables that were different among the groups. This analysis is limited and not a true cost–benefit analysis.

Though aprotinin is an effective drug for reducing bleeding and prevention of blood transfusions, tranexamic acid and especially tranexamic acid combined with a presumptive platelet-sparing maneuver, such as intraoperative autologous whole-blood collection, were essentially equally efficacious and much less costly therapies. Our study was powered to detect a difference in the total number of different allogeneic blood compo-

nents transfused in the ICU, but we were only able to demonstrate a significant reduction in blood loss and packed erythrocyte units transfused in the ICU. A larger study would have to be performed to determine whether combined therapy or tranexamic acid alone could produce the same reduction in the total number of different allogeneic blood components transfused in the ICU as aprotinin.

References

1. Munoz J, Birkmeyer N, Birkmeyer J, O'Connor G, Dacey L: Is ε-aminocaproic acid as effective as aprotinin in reducing bleeding with cardiac surgery? A meta-analysis. Circulation 1999; 99:81–89

2. Goodnough LT, Soegiarso W, Birlmeier JD, Welch HG: The economic impact of inappropriate blood transfusion in coronary artery bypass graft surgery. Am J Med 1993; 94:509–14

3. Royston D: Aprotinin prevents bleeding and has effects on platelets and fibrinolysis. J Cardiothor Vasc Anesth 1991; 5:18–23

4. Davis R, Whittington R: Aprotinin: A review of its pharmacology and therapeutic efficacy in reducing blood loss associated with cardiac surgery. Drugs 1995; 49:954–83

5. Lemmer JH Jr, Dilling EW, Morton JR, Rich JB, Robicsek F, Bricker DL, Hantler CB, Copeland JG III, Ochsner JL, Daily PO, Whitten CW, Noon GP, Maddi R: Aprotinin for primary coronary artery bypass grafting: a multicenter trial of three dose regimens. Ann Thorac Surg 1996; 62:1659–67

6. Menichetti A, Tritapepe L, Ruvolo G, Speziale G, Cogliati A, Di Giovanni C, Pacilli M, Criniti A: Changes in coagulation patterns, blood loss and blood use after cardiopulmonary bypass: Aprotinin vs tranexamic acid vs epsilon aminocaproic acid. J Cardiovasc Surg 1996; 37: 401–7

7. Pugh SC, Wielogorski AK: A comparison of the effects of tranexamic acid and low-dose aprotinin on blood loss and homologous blood usage in patients undergoing cardiac surgery. J Cardiothor Vasc Anesth 1995; 9:240–44

8. Blauhut B, Harringer W, Bettelheim P, Doran JE, Spath P, Lundsgaard-Hansen P: Comparison of the effects of aprotinin and tranexamic acid on blood loss and related variables after cardiopulmonary bypass. J Thorac Cardiovasc Surg 1994; 108:1083–91

9. Lu H, Du Buit C, Soria J, Touchot B, Chollet B, Commin PL, Conseiller C, Echter E, Soria C: Postoperative hemostasis and fibrinolysis in patients undergoing cardiopulmonary bypass with or without aprotinin therapy. Thromb Haemost 1994; 72:438–43

10. Van Oeveren W, Harder MP, Roozendaal KJ, Eijsman L, Wildevuur CR: Aprotinin protects platelets against the initial effects of cardiopulmonary bypass. J Thorac Cardiovasc Surg 1990; 99:788–96

11. Huang H, Ding W, Su Z, Zhang W: Mechanism of the preservation effect of aprotinin on platelet function and its use in cardiac surgery. J Thorac Cardiovasc Surg 1996; 106:11–8

12. Shigeta O, Kojima H, Jikuya T, Terada Y, Atsumi N, Sakakibara Y, Nagasawa T, Mitsui T: Aprotinin inhibits plasmin-induced platelet activation during cardiopulmonary bypass. Circulation 1997; 96:569–74

13. Horrow JC, Van Riper DF, Strong MD, Grunewald KE, Parmet JL: The dose-response relationship of tranexamic acid. ANESTHESIOLOGY 1995; 82:383–392

14. Speekenbrink RG, Vonk AB, Wildevuur CR, Eijsman L: Hemostatic efficacy of dipyridamole, tranexamic acid, and aprotinin in coronary bypass grafting. Ann Thorac Surg 1995; 59:438–42

15. Mongan PD, Brown RS, Thwaites BK: Tranexamic acid and aprotinin reduce postoperative bleeding and transfusions during primary coronary revascularization. Anesth Analg 1998; 87:258–65

16. Rosengart TK, Helm RE, DeBois WJ, Garcia N, Krieger KH, Isom OW: Open heart operations without transfusion using a multimodality blood conservation strategy in 50 Jehovah's witness patients: Implications for a "bloodless" surgical technique. J Am Coll Surg 1997; 184: 618–29

17. Parolari A, Antona C, Rona P, Gerometta P, Huang F, Alamanni F, Arena V, Biglioli P: The effects of multiple blood conservation techniques on donor blood exposures in adult coronary and valve surgery performed with a membrane oxygenator: A multivariate analysis on 1310 patients. J Card Surg 1995; 10:227–35

18. Hallowell P, Bland JH, Buckley MJ, Lowenstein E: Transfusion of fresh autologous blood in open-heart surgery: A method for reducing bank blood requirements. J Thorac Cardiovasc Surg 1972; 64:941–48

19. Hardesty RL, Bayer WL, Bahnson HT: A technique for the use of autologous fresh whole blood during open-heart surgery. J Thorac Cardiovasc Surg 1968; 56:683–88

20. Vedrinne C, Girard C, Jegaden O, Blanc P, Bouvier H, Ffench P, Mikaeloff P, Estanova S: Reduction in blood loss and blood use after cardiopulmonary bypass with high-dose aprotinin versus autologous fresh whole blood transfusion. J Cardiothorac Vasc Anesth 1992; 6:319–323

21. Pliam MB, McGoon DC, Tarhan S: Failure of transfusion of autologous whole blood to reduce bank-blood requirements in open-heart surgical patients. J Thorac Cardiovasc Surg 1975; 70:338–43

22. Wagstaffe JG, Clarke AD, Jackson PW: Reduction of blood loss by restoration of platelet levels using fresh autologous blood after cardiopulmonary bypass. Thorax 1972; 27:410–14

23. Sherman MM, Dobnik DB, Dennis RC, Berger RL: Autologous blood transfusion during cardiopulmonary bypass. Chest 1976; 70: 592–95

24. Kaplan JA, Cannarella C, Jones EL, Kutner MH, Hatcher CR, Dunbar RW: Autologous blood transfusion during cardiac surgery: A re-evaluation of three methods. J Thorac Cardiovasc Surg 1977; 74: 4–10

25. Szecsi J, Batonyi E, Liptay P, Orosi P, Medgyessy I, Petterffy A: Early clinical experience with a simple method for autotransfusion in cardiac surgery. Scand J Thor Cardiovasc Surg 1989; 23:51–56

26. Mohr R, Goor DA, Yellin A, Moshkovitz Y, Shinfeld A, Martinowitz U: Fresh blood units contain large potent platelets that improve hemostasis after open heart operations. Ann Thorac Surg 1992; 53: 650–4

27. Ereth MH, Oliver WC Jr, Beynen FM, Mullany CJ, Orszulak TA, Santrach PJ, Ilstrup DM, Weaver AL, Williamson KR: Autologous platelet-rich plasma does not reduce transfusion of homologous blood products in patients undergoing repeat valvular surgery. ANESTHESIOLOGY 1993; 79:540–7

28. Speiss BD, Tuman KJ, McCarthy RJ, DeLaria GA, Schillo R, Ivankovich AD: Thromboelastography as an indicator of post-cardiopulmonary bypass coagulopathies. J Clin Monit 1987; 2:25–30

29. Unsworth-White MJ, Herriot A, Valencia O, Poloniecki J, Smith EE, Murday AJ, Parker DJ Treasure T: Resternotomy for bleeding after cardiac operation: A marker for increased morbidity and mortality. Ann Thorac Surg 1995; 59:664–7

30. Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ: The risk of transfusion-transmitted viral infections. NEJM: 1996; 334:1685–90

31. Dietrich W, Spath P, Ebell A, Richter JA: Prevalence of anaphylactic reactions to aprotinin: analysis of two hundred forty-eight reexposures to aprotinin in heart operations. J Thorac Cardiovasc Surg 1997; 113:194–201

32. Karski JM, Teasdale SJ, Norman PH, Carroll JA, Weisel RD, Glynn MFX: Prevention of postbypass bleeding with tranexamic acid and ε-aminocaproic acid. J Cardiothor Vasc Anesth 1993; 17:431–435

33. Bennett-Guerrero E, Sorohan JG, Gurevich ML, Kazanjian PE, Levy RR, Barbera AV, White WD, Slaughter TF, Sladen RN, Smith PK, Newman MF: Cost-benefit and efficacy of aprotinin compared with ε-aminocaproic acid in patients having repeated cardiac operations: A randomized, blinded clinical trial. ANESTHESIOLOGY 1997; 87:1373–80

34. Penta de Peppo A, Pierri MD, Scafuri A, De Paulis R, Colantuono G, Caprara E, Tomai F, Chiariello L: Intraoperative antifibrinolysis and blood-saving techniques in cardiac surgery, prospective trial of 3 antifibrinolytic drugs. Tex Heart Inst J 1995; 22:231–6

35. Newman RJ, Podolsky D, Loeb P: Bad blood. U.S. News and World Report 1994; (June 27):68–78

36. Harmon DE: Cost/benefit analysis of pharmacologic hemostasis. Ann Thorac Surg 1996; 61:S21–5

37. Yost CS: Clinical utility and cost effectiveness of aprotinin to reduce operative bleeding: Comparison with other antifibrinolytics. Am J Anesthesiol 1996; 23:233–41

38. Lubarsky DA, Hahn C, Bennett DH, Smith LR, Bredehoeft SJ, Klein HG, Reves JG: The hospital cost (fiscal year 1991/1992) of a simple perioperative allogeneic red blood cell transfusion during elective surgery at Duke University. Anesth Analg 1994; 79:629–37

39. Gan TJ, Lubarsky D, Robertson K, Bennett D, Parrillo S, Sanderson I, Jhaveri R: The hospital cost of perioperative transfusion of a unit of red blood cells and other products. Anesth Analg 1996; 82:S123

40. Traverso LW, Hargrave K: A prospective cost analysis of laparoscopic cholecystectomy. Am J Surg 1995; 169:503–6