Effect of prophylactic epsilon-aminocaproic acid on blood loss and transfusion requirements in patients undergoing first-time coronary artery bypass grafting

A randomized, prospective, double-blind study

The prophylactic use of aprotinin has recently been reported to be associated with a significant decrease in blood loss in patients undergoing cardiopulmonary bypass procedures. One of the primary effects of aprotinin is prevention of plasmin degradation of platelet function. Because aprotinin is commercially unavailable in the United States at this time, we evaluated epsilon-aminocaproic acid with respect to decreased perioperative blood loss. We prospectively randomized 40 patients undergoing first-time coronary artery bypass grafting without prior sternotomy into two groups: one group ($n = 21$) received prophylactic and preincision epsilon-aminocaproic acid and the other ($n = 19$) received a placebo. No significant differences existed between patient groups with respect to age, body surface area, cardiopulmonary bypass time, and aortic crossclamp time. Cumulative blood loss at 4, 8, 12, and 24 hours after chest closure was significantly less in the epsilon-aminocaproic acid group (426 ± 242 ml versus 634 ± 224 ml, $p = 0.002$, at 12 hours). Only one patient receiving epsilon-aminocaproic acid was given blood or blood components compared to five patients in the placebo group ($p < 0.02$). D-dimers and fibrin split products were significantly less prevalent in the epsilon-aminocaproic acid group (at 4 hours: 0/20 versus 7/16, $p < 0.002$ and 5/20 versus 12/19, $p < 0.05$, respectively). None of the patients had a perioperative myocardial infarction or cerebrovascular accident. The prophylactic administration of epsilon-aminocaproic acid results in a significant decrease in blood loss in patients undergoing first-time coronary artery bypass grafting, and blood transfusion requirements are significantly less. It may be important to administer epsilon-aminocaproic acid before skin incision to be optimally effective. (J THORAC CARDIOVASC SURG 1994;108:99-108)

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In a number of recent reports,¹⁻⁹ the prophylactic administration of aprotinin has been associated with a decrease in blood loss and the need for blood or blood component replacement in patients undergoing cardiopulmonary bypass (CPB) procedures. The mechanism of action of aprotinin has not been fully elucidated. Previously, platelet dysfunction, not fibrinolysis, was thought to be

Table I. Preoperative patient descriptors

	EACA (n = 21)	Placebo (n = 19)	p Value (if <0.2)
Male, No. (%)	14 (67%)	18 (95%)	0.05
Age (yr)	63 ± 9	67 ± 10	0.11
BSA (m ²)	1.89 ± 0.19	2.00 ± 0.25	0.15
Urgency of surgery operation			
Elective, No. (%)	13 (62%)	9 (47%)	
Urgent, No. (%)	7 (33%)	9 (47%)	
Emergency, No. (%)	1 (5%)	1 (6%)	
Aspirin in last week, No. (%)	11 (52%)	9 (47%)	
CPB ACT (sec)			
Low	474 ± 102	478 ± 61	
High	658 ± 157	659 ± 140	
Hematologic and coagulation studies			
HCT (%)	39.9 ± 4.6	40.1 ± 5.2	
PLT (x × 1000)	237 ± 45	217 ± 62	
PT (sec)	12.6 ± 1.2	12.0 ± 0.7	
PTT (sec)	43.1 ± 22.1	41.7 ± 19.1	
Fibrinogen (mg/dl)	432 ± 158	388 ± 122	
BT (min)	5.2 ± 3.4	4.8 ± 1.6	
TT (sec)	17.9 ± 9.6	19.9 ± 17.5	
D-dimer % positive	0	1 (5%)	
FSP % positive (1:12)	5 (24%)	6 (32%)	

BSA, Body surface area; CPB ACT, cardiopulmonary activation time; HCT, hematocrit; PLT, platelets; PT, prothrombin time; PTT, partial thrombin time; BT, bleeding time; TT, thromboplastin time; FSP, fibrin split products. Values are mean ± standard deviation.

sible for compromised coagulation.¹⁰⁻¹³ More recently, Marx and associates⁷ attributed the platelet preservation characteristics of aprotinin to its antifibrinolytic effects. Specifically, aprotinin is said to preserve platelet function by preventing plasmin from adversely affecting the platelet membrane by blocking plasmin at the glycoprotein Ib platelet membrane site.¹⁴

Aprotinin is not available commercially in the United States at this time. Consequently, after an initial experience with the prophylactic use of epsilon-aminocaproic acid (EACA), we evaluated its efficacy with respect to decreased perioperative blood loss and associated decreased need for blood or blood component replacement in patients undergoing first-time coronary artery bypass grafting (CABG). In this study EACA administered before the skin incision is compared with a placebo.

Methods

Patients. After approval by the Sharp Memorial Hospital Investigational Review Committee, informed consent, and reading of the patient's bill of rights, 40 patients were prospectively randomized into two groups. The first group (n = 21) received EACA and the second group (n = 19) received a placebo, saline. The placebo and EACA were delivered to the operating room in numbered, but otherwise identical, vials labeled "study drug." Consequently, the study was double blind.

Table II. Operative patient descriptors

	EACA (n = 21)	Placebo (n = 19)	p Value (if <0.2)
Grafts, No. (%)			
2	3 (14%)	3 (16%)	0.17
3	2 (10%)	3 (16%)	
4	6 (29%)	8 (42%)	
5	7 (33%)	1 (5%)	
6+	3 (14%)	4 (11%)	
Total	91	79	
Grafts per patient (all)	4.33 ± 1.39	4.16 ± 1.66	
Grafts per patient (3VD)	4.72 ± 1.10	4.56 ± 1.50	
Arrest, No. (%)			
AOXC	20 (95%)	19 (100%)	
Fibrillatory	9 (43%)	8 (42%)	
Conduit, No. (%)			
SVG	100%	100%	
LITA	18 (86%)	14 (74%)	
RITA	1 (5%)	2 (10%)	
CPB time (min)	57 ± 17	68 ± 19	0.07
AOXC time (min)	27 ± 17	30 ± 9	
Closure time (min)	62.2 ± 30.8	74.1 ± 28.0	0.21

3VD, Three-vessel disease; AOXc, aortic crossclamp; SVG, saphenous vein graft; LITA, left internal thoracic artery; RITA, right internal thoracic artery; CPB, cardiopulmonary bypass. Values are mean ± standard deviation.

Both EACA (10 gm of EACA plus saline to equal 40 ml of solution) and placebo (40 ml of saline) were given after induction of anesthesia but before the skin incision. Another 40 ml was given after heparin administration in the pump, and a third 40 ml dose was given after administration of protamine. Criteria for inclusion in the study included the presence of multivessel coronary disease, age less than 80 years, ejection fraction 30% or more, no thrombolytic therapy within the previous 48 hours, no preoperative donation of autologous blood, hematocrit value of 36% or more, normal renal function, and asanguineous pump prime. Also, patients with preoperative abnormal clotting studies were rejected from the study.

Before the operation, immediately after the operation, and then at 4, 8, 12, and 24 hours after chest closure, a number of hematologic and coagulation studies were performed. These included complete blood count, platelet count, prothrombin time, activated partial thromboplastin time, fibrinogen level, bleeding time, thrombin time, fibrin split products analysis, and D-dimer determination.

Operative considerations. After induction of anesthesia with fentanyl and routine instrumentation including radial artery and Swan-Ganz pressure lines (Baxter Healthcare Corp., Edwards Div., Irvine, Calif.), the patients underwent median sternotomy and harvesting of a sufficient length of saphenous vein and either or both internal thoracic arteries. A Medtronic Maxima membrane oxygenator (Medtronic, Inc., Minneapolis, Minn.) was used in all cases. After the pump had been primed with 1200 ml of electrolyte solution (Plasma-Lyte) 10,000 IU of heparin, 100 ml of albumin, 100 ml of mannitol, and 50 ml of sodium bicarbonate, the oxygenator prime was circulated and then 500 to 750 ml was removed before the pump tubing was connected to the arterial and venous cannulas. Cardiopulmonary bypass was instituted with bicaval cannulation through the right atrium and direct cannulation of the ascending aorta. A

sump tube in the pulmonary artery was routinely used. All distal grafts were performed during intermittent aortic cross-clamping or fibrillatory arrest with control of the grafted coronary artery by silicone elastomer tapes.¹⁵

The time required for chest closure was recorded from the completion of administration of protamine to completion of skin closure of the sternotomy incision. Starting at the latter time point, blood loss was recorded at hourly intervals for the next 24 hours. The administration of blood or blood products was determined by a hematocrit value of 21%, or less, or by the clinical condition of the patient as judged by the operating surgeon. Cell Saver devices (Haemonetics Corporation, Natick, Mass.) were used intraoperatively in all patients.

In the postoperative period, shed mediastinal blood was infused in some patients. For the number of patients and amounts, see Table III ($p = \text{NS}$).

Statistical methods. The main outcome variable was the cumulative blood loss from the time of sternal closure through the first 12 hours. The trial was designed to detect a 50% reduction in blood loss for the EACA group compared with the placebo group with 95% power and a one-tailed significance level of 0.05. Data for estimating the expected magnitude of blood loss and its standard deviation were obtained from prior studies. For sample size determination and analysis, the log transform of blood loss was used to make the group variances more homogeneous. Furthermore, it was planned to sequentially analyze the data each time approximately 10 patients were entered into each study group. To guard against falsely terminating the trial early, we required a smaller significance level (approximately 0.005) for the intermediate analyses according to the procedure outlined by Haybittle.¹⁶

Although a strong trend to reduced blood loss was observed in the group receiving EACA compared with the placebo group at the first analysis, statistical significance was not reached at the required level and the trial was continued. The results reported are based on the second analysis. In three patients the randomization code was broken during the operation at the request of the physician; all three were from the placebo group and were given EACA in the intensive care unit. However, these patients were analyzed as part of the placebo group.

Baseline characteristics and data from the operation and recovery period for the EACA and placebo groups were compared by an unpaired t test for continuous variables and Fisher's exact test for categorical variables. Log cumulative blood loss was analyzed with an unpaired t test. In addition, the proportion of patients requiring blood products was compared between the groups by means of Fisher's exact test.

Results

Baseline characteristics. Table I presents the characteristics of the two patient groups at baseline. The EACA group tended to have fewer men ($p = 0.05$) and consequently a slightly lower mean body surface area than the placebo group ($p = 0.15$). Also a trend toward lower mean age was observed in the EACA group ($p = 0.11$).

Only one patient in each group had an emergency operation, and even though it appears that a somewhat higher percentage of the EACA group had elective pro-

cedures, the overall distribution of cases by surgical urgency was not statistically different.

None of the blood chemistry parameters measured showed even borderline statistical differences at baseline. In particular, no patient in the EACA group and only one patient in the placebo group had a positive D-dimer at baseline, and five patients (24%) from the EACA group compared with six (32%) from the placebo group showed positive fibrin split products at 1:12 dilution.

Operative variables. Characteristics of the surgical procedure are presented in Table II for the two patient groups. Most of these factors were similar for the placebo and EACA groups.

The mean total CPB time tended to be shorter in the EACA group than in the placebo group (57 versus 68 minutes, $p = 0.07$). However, aortic crossclamp times were similar. The mean time from protamine completion to completion of skin closure was 62 minutes for the EACA group and 74 minutes for the placebo group ($p = 0.21$).

Outcome. Table III compares the patient groups with respect to cumulative blood shed and transfusion requirements. The main outcome measure, the mean cumulative amount of blood shed to 12 hours, was 428 ml in the EACA group versus 634 ml in the placebo group. The statistical test on the logs of cumulative shed blood demonstrated a significant difference ($p < 0.0017$). Significant differences were also observed at 6 hours and at 24 hours. The variability in patient response increased with time so that the magnitude of the p value increased (was less significant). Because more women, with smaller body size, were randomized to the EACA group, we also analyzed the log of the cumulative shed blood per square meter of body surface area. The results of this analysis were essentially the same.

Only one patient in the EACA group required transfusion (8 units) within the first 24 hours compared with five (for a total of 17 units) in the placebo group ($p < 0.02$). There was no difference in the percentage of patients in the two groups receiving shed mediastinal blood, nor was the amount transfused in those individuals different. For specific amounts, see Table III. Furthermore, there were no significant differences in perfusion times or aortic crossclamp times in the 34 patients not receiving blood or blood products (60.9 ± 20.4 minutes and 27.3 ± 11.4 minutes, respectively) as compared with the six patients who received a transfusion (68.7 ± 13.4 minutes and 32.7 ± 5.6 minutes, respectively).

Four hours after the operation in patients with a test for the presence of D-dimer, 0 of 20 patients in the EACA group and 7 of 16 patients in the placebo group had positive results ($p < 0.002$). Also, fibrin split products were

*NS = Not significant.

Table III. Outcomes

	EACA (n = 21)	Placebo (n = 19)	p Value (if <0.2)
Cumulative shed blood (ml)			
To 6 hr	272 ± 190	487 ± 197	<0.001*
To 12 hr	426 ± 242	634 ± 224	0.0017*
To 24 hr	623 ± 380	845 ± 339	0.012*
Use of banked blood products			
No. of patients requiring blood/blood products	1 (4.76%)	5 (26.3%)	<0.02
No. of Units			
1	0	0	
2	0	3	
3	0	1	
4+	1†	1	
Total	8	17	
Use of shed blood (%)	7 (33%)	8 (42%)	
Amount used (ml)	436 ± 259	572 ± 189	
Hematocrit at 24 hr (%)	29.0 ± 4.3	29.1 ± 4.6	

Values are mean ± standard deviation.

*p Values are from analysis of log blood loss. Note that the standard deviation increases over time, so that even though the difference at 6, 12, and 24 hours is nearly identical, statistical significance diminishes.

†This person required 8 units of blood and blood products (4 units of packed red blood cells, 2 units of platelets, and 2 units of fresh frozen plasma).

evident at 4 hours in 5 of 20 patients in the EACA group compared with 12 of 19 patients in the placebo group ($p < 0.05$). None of the other laboratory factors listed in Table I showed differences during the postoperative course. None of the patients had perioperative myocardial infarction or cerebrovascular accident.

Discussion

Rationale for selection of the patient study group and closure time. Redo CABG procedures are associated with the frequent need for extensive dissection of vascular adhesions and increased CPB times, both of which may contribute to increased perioperative bleeding. Also, in patients with valvular lesions, modifications in platelet function and other variations in clotting factors may occur. For multiple valve replacements and combined valve/CABG procedures, CPB times are often longer than for CABG.

We selected patients undergoing first-time CABG because in this group these and other factors frequently related to increased perioperative bleeding would be minimized. Therefore, this group of patients would represent a more stringent test of the potential efficacy of EACA. Also, patients with single vessel disease were eliminated because they represent a vanishing cohort and are associated with shorter CPB times and, potentially, less perioperative bleeding. To eliminate a potential difference in intraoperative hemostasis, we compared the closure

times. Although not significantly different ($p = 0.21$), the closure times in the placebo group were longer (74.1 ± 28.0 versus 62.2 ± 30.8 minutes) than in the EACA group. This suggests that more meticulous hemostasis in the EACA group did not account for the lower blood loss and that a tendency for more intraoperative bleeding occurred in the placebo group.

Fibrinolysis and platelet dysfunction related to perioperative bleeding and the effect of aprotinin.

Although perioperative bleeding associated with CPB is multifactorial,^{17,18} platelet dysfunction and fibrinolysis have been described as the most common causes. Considerable controversy has arisen as to which is the more significant. Clearly, CPB is associated with the activation of fibrinolysis.¹⁹⁻²⁶

After Alkjaersig, Fletcher, and Sherry²⁷ described EACA as an inhibitor of plasminogen activation and plasmin, Gans,²⁸ in 1962, reported the cessation of postoperative bleeding in a patient undergoing aortic valve replacement with administration of EACA. In 1965 Gans²⁹ noted that once a significant bleeding tendency had developed, results with EACA were unpredictable. This was related to the fact that the breakdown of fibrin resulted in the release of fibrinopeptides, which, in turn, interfered with the polymerization of fibrin and functioned as an anticoagulant. Furthermore, it was emphasized that the activity of this anticoagulant was resistant to any known form of therapy. Therefore, to be optimally effective, EACA should be given before significant fibrinolysis occurs. However, other authors reported a decrease in blood loss if EACA was administered at the end of CPB.³⁰⁻³²

Despite these earlier experiences with EACA and apparent diminution in perioperative bleeding, only the 1979 report of Lambert and colleagues³³ appeared until the 1988 publications of Vander Salm and coworkers³⁴ and Marengo-Rowe and Leveson.³⁵ Perhaps during this time period this was because platelet dysfunction was considered to be the primary cause of CPB-related bleeding. Harker and associates¹⁰ stated that the severity of postoperative bleeding was probably due to defective platelet plug formation. The degree of impairment was related to CPB time and probably to the level of hypothermia. More recently, Harker,¹¹ and Woodman and Harker¹² in 1986 and 1990 reaffirmed this opinion. Similarly, Campbell and Addonizio¹³ described platelet dysfunction as the most significant cause of CPB-related bleeding.

However, in a controlled trial of the routine administration of platelets immediately after CPB, Simon, Akl, and Murphy³⁶ found that 4 units of platelet concentrates

did not prevent prolongation of the bleeding time nor decrease chest tube blood loss and, therefore, transfusion requirements. They concluded that "prophylactic use of this blood component in the surgical setting of bypass is not indicated." Consequently, it is difficult to reconcile this observation that platelet transfusion did *not* decrease blood loss and blood transfusion requirements with the contention that CPB-related platelet dysfunction is the *primary* cause of perioperative bleeding.¹⁰⁻¹³

The importance of platelet dysfunction was further emphasized by Royston and associates¹ in 1987. High-dose aprotinin (280 mg) was given before skin incision followed by a continuous infusion of 70 mg/hr until skin closure. Also, an additional 280 mg was added to the oxygenator prime. Postoperative blood loss in the aprotinin group was 286 ± 48 ml (standard error of the mean) compared with 1509 ± 388 ml. The authors concluded that because a membrane oxygenator was used, fibrinolysis was unlikely to have been the principal mode of action. They stated: "A more probable explanation lies in its platelet-sparing action—the platelet count fell less in the aprotinin treated group during the period of by-pass." Other authors^{2,3} evaluating the efficacy of aprotinin with respect to decreasing perioperative blood loss have concurred with Royston's group¹ in that aprotinin acts primarily by virtue of preservation of platelet function. More specific delineation of the mechanism of aprotinin with respect to platelet function was provided by Lavee and coworkers³⁷ in 1993. By means of scanning electron microscopy, platelet aggregation was found to be normal in aprotinin-treated patients but was severely disturbed in patients receiving placebo. They concluded "that improved postoperative hemostasis is directly related to the complete preservation of platelet function achieved by the protective properties of aprotinin."

The opposing viewpoint of aprotinin functioning primarily as an antifibrinolytic, rather than protecting platelets by some other mechanism, was advocated by Dietrich and coworkers.⁴ Higher fibrinolytic activity was found in the control group but platelet function was not evaluated. Blauhut and associates⁶ in 1991 determined that in control patients, fibrinogen degradation products doubled and α_2 -antiplasmin was halved. A similar conclusion regarding the significance of fibrinolysis was reached by Havel and colleagues⁵ in 1991. Finally, Marx and coworkers⁷ in 1991 were *unable* to demonstrate a significant postoperative effect of aprotinin with regard to platelets. They did find, however, that aprotinin almost completely inhibited the formation of fibrin and fibrinogen degradation products. van Oeveren and colleagues,³⁸ in 1988, made the observation that aprotinin inhibits the

plasmin-related degradation of the glycoprotein Ib receptor in platelets. Consequently, it appears that although aprotinin minimizes degradation of platelet function, the mechanism of action is the antiplasmin and antifibrinolytic effect of aprotinin.

Rationale for the use of EACA in lieu of aprotinin. In 1992 Blauhut¹⁴ unified the seemingly mutually exclusive theories of preservation of platelet protection by aprotinin versus antifibrinolysis. First, platelet adhesion is dependent on glycoprotein Ib, which is rapidly altered by plasmin, thus causing a progressive loss of von Willebrand factor-associated ristocetin-induced aggregation. Consequently, aprotinin, by rapid inactivation of plasmin, protects the functionally important platelet surface glycoproteins and preserves platelet function. Second, aprotinin may inhibit the activation of prekallikrein, which, in turn, may attenuate the generation of bradykinin, which is known to stimulate the release of tissue plasminogen activator from its sources. Third, aprotinin minimizes systemic lysis of fibrin and fibrinogen by enhancing the natural plasmin inhibitor α_2 -antiplasmin.

The relative roles of plasmin causing platelet dysfunction and fibrinolysis of in situ thrombosis in causing perioperative bleeding have not been determined. Also, it is not known if antifibrinolytics also have a direct antiplasmin effect as well as antifibrinolysis. Therefore, because aprotinin is not currently commercially available in the United States and EACA is much less expensive than aprotinin, we decided to evaluate the efficacy of EACA in decreasing perioperative bleeding, assuming that EACA, like aprotinin, may also decrease perioperative blood loss by preventing the plasmin degradation of platelet glycoprotein Ib, thus preserving platelet function. Our early experience was reported at the 1992 meeting of The Western Thoracic Surgical Association in discussion of a presentation by Schaff and associates (unpublished data). Before the use of EACA, in a series of 64 consecutive patients, there was a per-patient average of 0.81 units of blood, 0.55 units of single donor platelets, and 0.75 units of fresh frozen plasma. With the prophylactic administration of EACA in 85 consecutive patients, the units were 0.33, 0.32, and 0, respectively ($p < 0.05$). Since that time, all patients under our care having CPB procedures have received prophylactic EACA except the placebo group in this study and patients undergoing pulmonary thromboendarterectomy for chronic pulmonary embolism.³⁹ In the group of patients having pulmonary thromboendarterectomy, EACA was not used because many of these patients have proven hypercoagulable tendencies.⁴⁰

Rationale for EACA timing of administration and

dose. The initiation of fibrinolysis has been shown to be associated with skin incision,⁴¹ sternotomy,⁴² pericardiotomy,^{23, 43} and initiation of CPB.^{19, 20, 22, 30} Thus it seemed logical to begin EACA administration before skin incision. This was the same rationale used by Gans²⁸ in 1962 and Del Rossi and coworkers.⁴⁴ Furthermore, in most cases aprotinin has been administered in similar fashion.¹⁻⁹

Lambert and colleagues³³ determined that once significant fibrinolysis developed, up to 60 gm of EACA in 1 hour was required to reverse it. Even so, no thrombotic complications were encountered. Because we administered the first dose of EACA before skin incision (before fibrinolytic activity), we halved the total dose of 60 gm of EACA used by Lambert's group.³³ Another 10 gm of EACA was given in the pump prime and a third dose of 10 gm after protamine administration. The effectiveness of this regimen in minimizing fibrinolytic activity is evidenced by the fact that in the EACA group 4 hours after skin closure, none of the 21 patients had positive D-dimer results.

Experience with tranexamic acid. Tranexamic acid is said to have greater efficacy, longer half-life, and stronger plasminogen binding than EACA.⁴⁵ Horrow and associates⁴⁶ found that tranexamic acid after induction of anesthesia decreased blood loss in patients undergoing CABG or valve replacement. No thrombotic complications were encountered. In a subsequent study in 1991, Horrow and coworkers⁴⁷ found that whereas desmopressin exerted no hemostatic effect, tranexamic acid decreased blood loss and the percentage of patients receiving homologous blood by 30%. Øvrum and associates⁴⁸ in 1993 determined by a nonrandomized study that blood loss was less with tranexamic acid than without ($p = 0.02$).

In a study by Yau and colleagues⁴⁹ in 1992, tranexamic acid was compared with EACA in patients undergoing normothermic perfusion (35° to 37° C) and moderately hypothermic perfusion (25° to 29° C) for isolated primary CABG. Blood loss was less in patients receiving EACA or tranexamic acid regardless of perfusion temperature. No significant difference between EACA and tranexamic acid was observed. Platelets were better preserved in patients with warm perfusion, EACA, and tranexamic acid than in control patients subjected to cold perfusion.

Consequently, it appears that tranexamic acid is as effective as EACA, if not more effective. An obvious trial would be comparison of the effectiveness of EACA and tranexamic acid to aprotinin.

Hypercoagulation associated with antifibrinolysis.

The question of an increased incidence of thrombotic problems associated with antifibrinolysis has been raised.⁵⁰⁻⁵³ However, in the majority of reported studies with EACA,^{30, 32-34, 44} tranexamic acid,^{46, 47} and aprotinin,^{8, 9, 54} no such increase has been observed. One possible explanation is that heparin minimizes the prevalence of this complication.⁵⁵

Inferences. In this study it has been demonstrated that EACA, started before skin incision, resulted in a significant decrease in blood loss and, therefore, the need for blood replacement. The fact that statistical significance with respect to blood loss and the number of patients requiring transfusion was reached with a relatively low number of patients receiving EACA ($n = 21$) (compared with the placebo [$n = 19$]) while having first-time CABG with relatively shorter CPB times (as opposed to redo or valvular procedures) suggests that EACA is, indeed, clinically useful. Conceivably, EACA would be even more effective in decreasing perioperative blood loss in patients undergoing more extensive or redo procedures. The question remains as to the relative effectiveness of EACA, tranexamic acid, and aprotinin. Because of the potentially relatively small differences among the three drugs, a multicenter trial would probably be required to resolve the differences, if any. This could be of significance because the cost differential of EACA and tranexamic acid compared with aprotinin, when approved commercially in the United States, will likely be considerable. For example, the cost of 30 gm of EACA is less than \$10.00 compared with \$1000.00 for the usual dose of aprotinin.

Plasmin leading to platelet dysfunction accounts for a significant amount of perioperative bleeding. The relative importance of bleeding related to fibrinolysis of fibrin or platelet plugs is unknown. Many other coagulation defects can and do occur. Consequently, these defects must be specifically defined by an array of coagulation tests and treated specifically to minimize perioperative bleeding.

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Discussion

Dr. Mark T. Metzdorff (*Portland, Ore.*). Excessive postoperative bleeding remains the bane of cardiothoracic surgeons. The problem seems especially bad in the current era when aspirin usage is widespread and as surgeons strive to maximize arterial grafts. It is therefore appropriate to revisit the antifibrinolytic drug, EACA, as we await the approval of a potentially even more effective drug in the United States. Aprotinin is widely used in Europe and currently the focus of a multicenter study in the United States, in which our group is participating. After operating on a number of study patients, I have no doubt that aprotinin will play an important role in our practices in the near future. However, it is very expensive and in the meantime we have an approved and perhaps neglected antifibrinolytic drug that we may study anew. In fact, the price differential between EACA and aprotinin raises the specter of a potential battle somewhat akin to the ongoing war between streptokinase and tissue-type plasminogen activator. I trust that as sensible surgeons we will arrive at a solution in a much more dispassionate and cost-effective manner.

In the present study, the authors use the appropriate prospective, randomized, double-blind approach that is ideally suited for such investigation. The study group selected was relatively homogeneous: patients having first-time CABG, relatively young, without abnormal coagulation studies or severe ventricular dysfunction. Such patients might be expected to have less of a tendency toward postoperative bleeding for a variety of reasons and one might therefore anticipate difficulty in demonstrating improvement with a specific therapy.

Nevertheless, in this study of limited sample size, the authors have demonstrated a small but statistically significant difference in postoperative chest tube drainage in patients receiving EACA versus placebo. The results of their analysis of blood samples for products of fibrin degradation imply that the difference in bleeding between the groups might be the result of the study drug's antifibrinolytic action. However, the limited sample size calls into question the statistical power of this analysis. I am concerned that the authors may have biased their results in favor of the hypothesis by terminating the study at the earliest achievement of statistically significant difference but before enough patients were enrolled to eliminate the possibility of chance associations. For example, one might just as easily conclude from the data that men are more likely to be randomized to the placebo group or that placebo patients are more likely to have a longer CPB time, both associations which were significant in their analysis. A swing of one or two patients in the transfusion data might have negated the conclusion that blood transfusion requirements are significantly less with EACA.

These criticisms could easily be remedied by increasing the sample size.

Furthermore, although the authors present some arguments regarding the timing of EACA dosage in the discussion, the study does not really address the question of when EACA should be given to be optimally effective. In fact, in two previous randomized, double-blind studies, both larger than the present study, patients receiving EACA showed similar mild reduction in postoperative chest tube drainage. In one study, the drug was given preoperatively and in the other it was given after bypass.

To a discussion of ways to reduce postoperative bleeding and the need for homologous blood transfusion, I would like to add a personal bias. I think that within the context of cardiac surgery in 1993, where our patients are older, sicker, and treated preoperatively with a host of anticoagulants, thrombolytics, and other poisons, that patients place disproportionate emphasis on the risk of homologous transfusion and that we as surgeons to a large extent buy into this fear and help perpetuate it. The current risk of transmission of human immunodeficiency virus by transfusion is literally one in a million. At this rate it is unlikely that any of us will see a case in our careers from this day. The risk of other transfusion-related complications in the average cardiac surgical case is much less than any one of half a dozen other morbidities that we see in our practices every month. The fact is that none of us can do our job without the support of safe, effective blood banks, and they in turn deserve our support and credit in the face of an onslaught by the media and by litigators.

That having been said, it nevertheless obviously behooves us to continue to strive to improve our care, which includes efforts to minimize the need for homologous transfusion. Studies such as the present one are important contributors to this end, and I believe this study confirms and builds on previous work.

I have three questions for the authors. The table in the manuscript I reviewed reported three patients in EACA group receiving transfusion for a total of 12 donor exposures, whereas one patient with eight exposures was reported today. Could you comment on this discrepancy?

Dr. Daily. The three patients that started out in the placebo group remained in the placebo group. They received EACA at the discretion of their physicians because they were having significant postoperative fibrinolysis.

Dr. Metzdorff. There is some evidence in the literature that EACA may have a salutary effect on platelet function as well. Can you comment based on your measurements and experience on this possibility?

Dr. Daily. The general theory in giving an antifibrinolytic to decrease perioperative blood loss is essentially because the antifibrinolytic action prevents the action of plasmin on the platelet surface membrane glycoprotein 1B. Theoretically, then, any antifibrinolytic, whether or not it is aprotinin or EACA or tranexamic acid, should be effective. In fact, I think what we really need is a much larger study, as you have suggested, certainly a multicenter study, looking at all three of these drugs. That is important, because cost will be a major consideration, and certainly the cost of EACA and tranexamic acid is a lot lower than aprotinin or will be if and when aprotinin is available.

Dr. Metzdorff. That leads nicely into my third question, which is that although EACA is relatively inexpensive, adding any new modality to routine use in all cardiac surgical patients nationwide would add tremendous cost to our overburdened health care system. Do you think there might be a role for the

selective use of this drug either preoperatively or postoperatively in the high-risk patient on the basis of clinical evidence of fibrinolytic bleeding?

Dr. Daily. What is not apparent from this study is that this is probably the lowest risk group in terms of the patient cohorts that we work with. There is potentially a greater saving in blood and blood products in patients having repeat valve operations combined with CABG. But, even in this group of first-time sternotomy patients undergoing reasonably straight-forward bypass procedures, there was a little more than a 50% decrease in the amount of blood and blood products used. Even that is skewed in the direction of equality because only one patient required blood in the EACA group. That patient had a different kind of coagulopathy and required 8 units.

There is still some rationale for using an antifibrinolytic prophylactically in most patients undergoing at least complex CPB procedures until an unacceptably high incidence of thrombotic problems can be demonstrated.

Dr. James B. D. Mark (Stanford, Calif.). If the cost of the EACA isn't so great and it saves blood and blood transfusions, you are going to make up that money very quickly.

Dr. Daily. That's right, Jim. You should be doing this discussion instead of me.

Dr. Dan Ciaburri (Bridgeport, Conn.). We have been using EACA before CPB in approximately our last 450 to 500 cases routinely and have documented a significant decrease in postoperative blood transfusion and blood component requirements in our patients. We have had a few cases, however, of postoperative severe disseminated intravascular coagulopathy with small-vessel thrombosis that has been severe enough to cause necrosis of some distal digits. From what I understand in the product literature, EACA is contraindicated in a disseminated intravascular coagulopathy state.

I have two questions: How do you arrive at the dosages that you use? Have you seen any significant disseminated intravascular coagulopathy states such as the ones I have described?

Dr. Daily. The dosage was primarily related to the article by Lambert and associates³³ in 1979. They discovered that if the fibrinolytic state was fairly far advanced, it took up to 50 or even 60 gm of EACA to reverse it as assessed by euglobulin clot lysis times. That is the first part.

The second part is that a number of different authors have investigated when fibrinolysis begins in terms of the procedure. It has been reported even after heparin. It has been reported with the skin incision, with sternotomy, with pericardiotomy, and of course with onset of CPB. Given the fact that it may occur with skin incision and the fact that 50 or 60 gm EACA or more must be given once fibrinolysis is ongoing, then we arrived at the rationale of taking about half of that, namely about 30 gm, and distributing that at the three time points that were mentioned. That is why we do it that way.

We have not seen disseminated intravascular coagulopathy. Only very occasionally, maybe 1 in 500 or 1 in 1000 patients with bypass procedures, do we see disseminated intravascular coagulopathy. In the past this has been in patients receiving no antifibrinolytic agents.

Dr. Steven R. Gundry (Loma Linda, Calif.). In November of last year, we began giving 10 gm of EACA immediately on weaning the patient from the pump because with warm blood cardioplegia we were having to return to the pump to control

bleeding usually two to three times per month. Since starting EACA we have not had to do so for bleeding. However, spurred by my colleagues' question of how costly this new therapy is, I checked with our pharmacy about prices. The members would like to know that 10 gm of EACA costs \$0.38, so I submit it is a very effective therapy at a cheap price.

Dr. Daily. The one thing I've discovered in our pharmacy is it may cost the pharmacy \$0.38 but the patients get charged \$38 for it.

Dr. D. Craig Miller: (*Stanford, Calif.*). Getting back to what Mark Metzdorff said, in Toronto surgeons were given the opportunity to use aprotinin. It is approved, but it costs \$1,200

Canadian per case. I learned from Tirone David and Dick Weisel that \$1,200 is a lot of money in the Canadian health care system; it is about what the surgeons get for doing the case. So, the health care authorities gave them a choice: You can use aprotinin or you can get paid, but not both. Guess what the surgeons chose? However, this prompted the Toronto group to do several randomized studies. These studies are not yet complete, but it has been hinted that 30 gm of EACA or 10 gm of tranexamic acid is essentially just as effective as aprotinin, but cheaper by a factor of 100.