

## ***The Effect of Prophylactic $\epsilon$ -Aminocaproic Acid on Bleeding, Transfusions, Platelet Function, and Fibrinolysis during Coronary Artery Bypass Grafting***

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**Background:** Antifibrinolytic medications administered before skin incision decrease bleeding after cardiac surgery. Numerous case reports indicate thrombus formation with administration of  $\epsilon$ -aminocaproic acid ( $\epsilon$ -ACA). The purpose of this study was to examine the efficacy of  $\epsilon$ -ACA administered after heparinization but before cardiopulmonary bypass in reducing bleeding and transfusion requirements after primary coronary artery bypass surgery.

**Methods:** Seventy-four adult patients undergoing primary coronary artery bypass surgery were randomized to receive 125 mg/kg  $\epsilon$ -ACA followed by an infusion of 12.5 mg · kg<sup>-1</sup> · h<sup>-1</sup> or

an equivalent volume of saline. Coagulation studies, thromboelastography, and platelet aggregation tests were performed preoperatively, after bypass, and on the first postoperative day. Mediastinal drainage was recorded during the 24 h after surgery. Homologous blood transfusion triggers were predefined and transfusion amounts were recorded.

**Results:** One patient was excluded for surgical bleeding and five patients were excluded for transfusion against predefined criteria. One patient died from a dysrhythmia 2 h postoperatively. Among the remaining 67, the  $\epsilon$ -ACA group had less mediastinal blood loss during the 24 h after surgery, 529 ± 241 ml versus 691 ± 286 ml (mean ± SD),  $P < 0.05$ , despite longer cardiopulmonary bypass times and lower platelet counts,  $P < 0.05$ . Platelet aggregation was reduced in both groups following cardiopulmonary bypass but did not differ between groups. Homologous blood transfusion was similar between both groups.

**Conclusions:** Prophylactic administration of  $\epsilon$ -ACA after heparinization but before cardiopulmonary bypass is of minimal benefit for reducing blood loss postoperatively in patients undergoing primary coronary artery bypass grafting. (Key words:  $\epsilon$ -Aminocaproic acid; antifibrinolytic; blood loss; coronary bypass surgery.)

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Received from the Departments of Anesthesiology and Cardiovascular Surgery, The Mercy Hospital of Pittsburgh, and The Department of Mathematics, Duquesne University, Pittsburgh, Pennsylvania. Submitted for publication May 19, 1998. Accepted for publication April 6, 1999. Supported in part by grants from Pittsburgh Mercy Foundation (grant #7183), Mercy Heart Institute, and Pittsburgh Anesthesia Associates (research assistant services), Pittsburgh, Pennsylvania. Presented in part at the annual meetings of the Society of Cardiovascular Anesthesiologists, Philadelphia, Pennsylvania, May 9, 1995, and Salt Lake City, Utah, May 6, 1996.

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BLEEDING after cardiopulmonary bypass continues to be a problem for cardiac surgical patients. Both fibrinolysis and platelet dysfunction have been implicated as leading causes of nonsurgical bleeding.<sup>1,2</sup> Medications that affect fibrinolysis and platelet function have been used in an attempt to reduce postbypass bleeding and transfusion requirements. A recent metaanalysis found a paucity of data on the use of  $\epsilon$ -aminocaproic acid ( $\epsilon$ -ACA) during cardiac surgery based upon only three eligible studies, totaling 118 patients.<sup>3</sup> Antifibrinolytic medications such as  $\epsilon$ -ACA are thought to improve coagulation after cardiac surgery by preventing the breakdown of crosslinked fibrin. A platelet-sparing effect may play a role by inhibiting plasmin, thus reducing platelet mediator release and platelet activation.

Previous studies involved the administration of  $\epsilon$ -ACA before incision and heparinization, after bypass or using

smaller doses. There is a concern over the potential to induce thrombosis because of a number of case reports that implicated  $\epsilon$ -ACA as the cause for thrombotic complications.<sup>4-11</sup>  $\epsilon$ -ACA suppresses fibrinolysis in the absence of concomitant reductions in thrombin generation, creating a potentially hypercoagulable prethrombotic state.<sup>12</sup> Because of this concern, we administered  $\epsilon$ -ACA to cardiac surgical patients after systemic heparinization but before cardiopulmonary bypass. A reduction in the overall effectiveness of  $\epsilon$ -ACA may be anticipated because inhibition of fibrinolytic activation associated with skin incision would not occur. However, the significantly greater fibrinolytic activation occurring with initiation of cardiopulmonary bypass would be inhibited by  $\epsilon$ -ACA. This study was designed to evaluate the effectiveness of  $\epsilon$ -ACA while minimizing its potential risk. A randomized, double-blind protocol was applied to examine the effects of prophylactic  $\epsilon$ -ACA on bleeding, transfusion requirements, fibrinolysis, and platelet aggregation using this treatment strategy.

## Materials and Methods

After approval by our research and human rights committee and written informed consent, 104 adult patients undergoing cardiac surgery with extracorporeal circulation were prospectively randomized. Patients were excluded for age greater than 80 years, hepatic or renal dysfunction (creatinine level  $> 1.5$  mg/dl), and tissue plasminogen activator therapy within 36 h of surgery. Patients with preexisting coagulopathy were excluded with the exception of patients receiving intravenous or subcutaneous heparin preoperatively. Use of heparin preoperatively was noted but was not a reason for exclusion. Because previous studies demonstrated differences in outcome based on the type of surgery, this study was limited to patients undergoing primary coronary artery bypass surgery.

Seventy-four patients undergoing primary coronary artery bypass surgery were randomized in a double-blinded, placebo-controlled protocol. A bolus of either  $\epsilon$ -ACA or saline was administered in a dose of 0.5 ml/kg immediately after systemic heparinization (300 U/kg). An infusion was begun at a rate of  $0.05 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ . These volumes provided a 125 mg/kg bolus and an infusion of  $12.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  to the  $\epsilon$ -ACA group. The infusion was begun after the contents of the bolus syringe were administered and continued throughout the bypass period. This infusion was terminated after the

administration of protamine and before the patient left the operating room. Activated clotting time was measured in a preheated celite-activated tube using a HemoChron coagulation monitor (International Technidyne Corporation, Edison, NJ) and maintained in excess of 400 s during cardiopulmonary bypass.

Asanguinous solution, 2.5 l, containing 5,000 U heparin was used to prime the cardiopulmonary bypass circuit, which included a membrane oxygenator and non-pulsatile flow at a rate of  $2.0$  to  $2.4 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ . Crystalloid and colloid solutions were administered to maintain adequate left-ventricular filling before and after bypass, and adequate reservoir volume during bypass. Six percent hetastarch in 0.9% sodium chloride administration was limited to less than 15 ml/kg. Fluid remaining in the bypass circuit was spun, washed, and returned to the patient as concentrated erythrocytes. Protamine 3 mg/kg was administered after bypass. An additional 1 mg/kg protamine was administered if necessary to lower the activated clotting time to normal.

Homologous packed erythrocytes were administered during bypass if the hemoglobin value was less than 7.0 g/dl and the mixed venous oxygen saturation was less than 60%. After bypass, erythrocytes were administered if the hemoglobin value was less than 8.0 g/dl after the washed autologous erythrocytes were reinfused. Pericardial and mediastinal drains were inserted before mediastinal closure and were connected to low continuous suction. Blood accumulation was recorded hourly for 24 h. Platelets, fresh frozen plasma, or cryoprecipitate was administered on the basis of a laboratory-proven hemostatic defect (platelet count  $< 100,000/\mu\text{l}$ , prothrombin time  $> 18$  s, fibrinogen  $< 150$  mg/dl, respectively). Coagulation products were administered for chest-tube drainage greater than 200 ml/h for 2 consecutive h, regardless of the specific coagulation defect. Laboratory coagulation studies were performed preoperatively, after protamine, and on the first postoperative day. These studies included routine studies (platelet count, prothrombin time, partial thromboplastin time, fibrinogen level, fibrin split products), thromboelastography (TEG), and platelet aggregation. TEG data included reaction time, coagulation time, angle, maximum amplitude, and percent lysis at 30 and 60 min. Platelet aggregation was determined by turbidimetric Bio-Data platelet aggregation profiles (Bio-Data Corporation, Hatboro, PA) using adenosine diphosphate and collagen for stimulation of aggregation. Blood for platelet aggregation was added to 3.8% sodium citrate, nine parts to one part, and centrifuged for 10 min. A specimen of platelet-rich

**Table 1. Demographics and Preoperative Laboratory Values**

	Saline	$\epsilon$ -ACA	P
Number of patients	36	38	—
Age (yr)	65 $\pm$ 9	66 $\pm$ 9	NS
Weight (kg)	83 $\pm$ 16	84 $\pm$ 17	NS
Height (cm)	170 $\pm$ 13	169 $\pm$ 13	NS
Gender (M/F)	24/12	27/11	NS
Prothrombin time (s)	12.7 $\pm$ 1.4	12.3 $\pm$ 2.8	NS
Partial thromboplastin time (s)	39 $\pm$ 14	36 $\pm$ 15	NS
Hemoglobin (g/dl)	13.4 $\pm$ 1.7	13.4 $\pm$ 1.9	NS
Fibrinogen (mg/dl)	312 $\pm$ 91	282 $\pm$ 109	NS

Values are mean  $\pm$  SD.

$\epsilon$ -ACA = epsilon aminocaproic acid; NS = not significant.

plasma was obtained and a platelet count obtained. If the platelet count was greater than 250,000/ $\mu$ l, sufficient platelet-poor plasma was added to obtain a count of 250,000/ $\mu$ l. Stimulating reagents were added to samples of platelet-rich plasma and inserted into the aggregometer.

#### Statistical Analysis

Initially, two sample *t* tests (adjusted for inequality of variances) were used to compare the means between the  $\epsilon$ -ACA and the saline groups for the continuous variables (age, weight, height, prothrombin time, hemoglobin values, fibrinogen values, and duration of cardiopulmonary bypass). The Mann-Whitney U test was used to test the differences between groups in median levels for the ordinal variables (fibrin split products). The chi-square test was used to compare the difference in gender between the groups. Repeated-measures analysis of variance was performed to compare the differences between the groups across the three time points for blood loss, platelet aggregation, platelet count, TEG data, and hemoglobin values. Within the repeated-measures analyses of variance, Fisher's least significant difference was used as a *post hoc* test to compare the difference from the second 8-h period to the first period and the third 8-h period to the first period. Analysis of covariance was used to test the difference in the total blood loss, with the duration of CPB used as the covariate in the analysis. All analysis was performed using SAS software (SAS Institute, Cary, NC). A *P* value of less than 0.05 was considered significant.

## Results

The demographics and prebypass laboratory studies were similar between groups (table 1). Duration of car-

**Table 2. Blood Loss (ml)**

Period	Saline (n = 33)	$\epsilon$ -ACA (n = 34)	P
1st 8 h	380 $\pm$ 200	266 $\pm$ 148	0.008
2nd 8 h	185 $\pm$ 97	174 $\pm$ 95	NS
3rd 8 h	118 $\pm$ 124	88 $\pm$ 95	NS
Total	691 $\pm$ 286	529 $\pm$ 241	0.003*

Values are mean  $\pm$  SD.

$\epsilon$ -ACA = epsilon aminocaproic acid; NS = not significant.

\* Analysis included adjusting for duration of cardiopulmonary bypass time for total blood loss.

diopulmonary bypass was longer for the  $\epsilon$ -ACA group (111  $\pm$  39 min  $\pm$  SD vs. 88  $\pm$  24 min  $\pm$  SD; *P* < 0.01). Thirty-six patients were randomized to the saline group, and 38 patients were randomized to the  $\epsilon$ -ACA group. The data of seven patients (three randomized to saline and four randomized to  $\epsilon$ -ACA) were not included in the final data analysis. One patient had a surgical cause for postbypass bleeding, five patients received transfusions against study criteria, and one patient died 2 h postoperatively secondary to a dysrhythmia. The  $\epsilon$ -ACA group had less mediastinal blood loss than the saline group during the first 8 and 24 h postoperatively (*P* < 0.05; table 2).

Platelet aggregation was reduced for both groups after cardiopulmonary bypass but returned to baseline on the first postoperative day. There were no statistical differences in aggregation, fibrin split products, or TEG data between groups. Platelet counts (in 10<sup>3</sup> per microliter) were lower in the  $\epsilon$ -ACA-treated patients after cardiopulmonary bypass (132  $\pm$  41 vs. 173  $\pm$  71; *P* < 0.05) and on the first postoperative day (148  $\pm$  42 vs. 179  $\pm$  53; *P* < 0.05). Hemoglobin levels were similar between groups during bypass: 9.6  $\pm$  1.7 g/dl for the control group and 9.3  $\pm$  2.0 g/dl for the  $\epsilon$ -ACA group. Minimum hemoglobin level was 6.4 g/dl.

**Table 3. Twenty-four-hour Post-Cardiopulmonary Bypass Transfusions**

Product	Saline (n = 33)	$\epsilon$ -ACA (n = 34)	P*
RBC	6 (10)	7 (11)	NS
Platelets	6 (90)	2 (30)	NS
FFP	2 (4)	1 (2)	NS
CRYO	1 (6)	1 (6)	NS
Any product	9 (110)	8 (49)	NS

Values indicate number of patients; values in parentheses indicate the number of units transfused (donor exposure).

$\epsilon$ -ACA = epsilon aminocaproic acid; NS = not significant; RBC = packed red blood cells; FFP = fresh frozen plasma; CRYO = cryoprecipitate.

\* *P* values calculated using Fisher exact test (2-tailed).

ε-ACA AFTER HEPARINIZATION DURING CABG SURGERY

Table 4. Previous ε-ACA Studies during Cardiac Surgery

Study	Prospective	Double Blinded	Randomization	ε-ACA Dose	Time of Administration	Reduction in Blood Loss	Reduction in Transfusion	Surgical Procedures	Patient Population
Sterns <i>et al.</i> <sup>13</sup>	No	No	No	1-21 g 5 g to adults routinely 37.5 mg/kg, then 28 mg · kg <sup>-1</sup> · h <sup>-1</sup>	After CPB	7.6 ml/kg/12 h	NR	Congenital and valve	Pediatric and adult
Gomes <i>et al.</i> <sup>14</sup>	No	No	No	No	At sternotomy	NS	NR	Congenital and valve	Pediatric and adult
Montesano <i>et al.</i> <sup>15</sup>	No	No	No	5 g	Initiation of CPB	415 ml/24 h	1.7 units RBC	CABG	Adults
Vander Salm <i>et al.</i> <sup>16</sup>	Yes	Yes	Yes	5 g then 1 g/h	After CPB	59.5 ml/12 h	NR	CABG	Adults
Midell <i>et al.</i> <sup>17</sup>	Yes	No	No*	125 mg/kg	Immediately prior to CPB	785 ml	NR	Valvular or ascending aorta/congenital	Pediatric and adult
DelRossi <i>et al.</i> <sup>18</sup>	Yes	No	Yes	5 g then 1 g/h	Prior to skin incision	311 ml	1.4 units RBC	CABG valves	Adult
Arom <i>et al.</i> <sup>19</sup>	Yes	No	Not optimal†	5 g with DDAVP 0.03 μg/kg in all patients	Before CPB	266 ml	FFP, platelets, cryoprecipitate	CABG	Adult
Jordan <i>et al.</i> <sup>20</sup>	Yes	No	No	10 gm	After heparin and before CPB	NR	NS for RBC	CABG or valvular	Adult
McClure <i>et al.</i> <sup>21</sup>	Yes	Yes	Yes	75 mg/kg then 15 mg · kg <sup>-1</sup> · h <sup>-1</sup>	Sternotomy	26.4 ml/kg/NS	NR	Congenital cyanotic/congenital acyanotic	Pediatric
Daily <i>et al.</i> <sup>22</sup>	Yes	Yes	Yes	30 g	10 g before incision 10 g in CPB prime 10 g after protamine	222 ml	4.76% vs. 26.3%	CABG	Adult
Vander Salm <i>et al.</i> <sup>23</sup>	Yes	Yes	Yes	30 g	10 g before incision 10 g after heparin	192 ml/24 h	NS	CABG valves	Adult
Menichetti <i>et al.</i> <sup>24</sup>	Yes	NR	Yes	160 mg/kg and 30 mg · kg <sup>-1</sup> · h <sup>-1</sup>	10 g after CPB incision 80 mg/kg in CPB prime	299 ml	16% vs. 75%	CABG	Adult
Penta dePeppo <i>et al.</i> <sup>25</sup>	Yes	NR	Yes	10 g, then 2 g/h	induction of anesthesia	215 ml	NS	CABG valves	Adult

\* First 48 patients, every other; last 25 patients, all ε-ACA.

† Consecutive patients received ε-ACA.

RBC = packed red blood cells; NS = not significant; NR = not reported; CABG = coronary artery bypass grafting; ε-ACA = epsilon aminocaproic acid.

The incidence and amount of postoperative homologous blood transfusion were similar between the saline and  $\epsilon$ -ACA groups (table 3).

## Discussion

Previous studies examining the effect of  $\epsilon$ -ACA during cardiac surgery involved protocols that were retrospective and unblinded,<sup>13-15</sup> administered  $\epsilon$ -ACA after cardiopulmonary bypass,<sup>15,16</sup> or were prospective but not blinded or randomized (table 4).<sup>17-20</sup> The majority of previous studies demonstrated reduced blood loss with  $\epsilon$ -ACA.<sup>15-25</sup> Many investigators administered  $\epsilon$ -ACA before the activation of fibrinolysis initiated by skin incision.<sup>18,22-25</sup> Dentz<sup>4</sup> administered 10 g  $\epsilon$ -ACA before skin incision and noted the formation of thrombus before cardiopulmonary bypass in two patients. Gralnick and Greip<sup>5</sup> reported thrombus formation in a cardiac surgical patient in the postoperative period. Numerous other case reports in the literature raise a concern for thrombus formation associated with administration of  $\epsilon$ -ACA.<sup>4-11</sup> The present study was designed to investigate whether  $\epsilon$ -ACA administered after systemic heparinization but before cardiopulmonary bypass would be effective in decreasing postbypass bleeding and transfusions in a prospective, randomized, double-blinded, placebo-controlled protocol.

A minimal benefit of  $\epsilon$ -ACA was demonstrated in our study during the first 8 h after primary coronary artery bypass surgery. The only significant reduction in the amount of postbypass mediastinal bleeding was evident during the first 8 h after surgery. There was less bleeding in the  $\epsilon$ -ACA group after surgery despite a lower platelet count, attributed to the longer bypass time for the  $\epsilon$ -ACA group. This suggests that either a preservation of platelet function, decreased fibrinolysis, or another cause was operative in reducing blood loss. The determinants of platelet function and fibrinolysis used in this study did not reveal any difference between groups.

The effectiveness of prophylactic  $\epsilon$ -ACA after heparinization in reducing blood loss was minimal. Consequently, our study did not show a difference in transfusion between groups. Either the difference in blood loss was too small to account for a difference in transfusion rates, or other factors played a role in the need for transfusion. Transfused patients who received saline were exposed to 12.2 donors on average, compared with the transfused patients in the  $\epsilon$ -ACA group, who were exposed to 6.1 donors on average (table 3). Previous studies that included only coronary artery bypass

patients demonstrated reductions in blood loss ranging from 192 ml to 415 ml (table 4). The reduction in blood loss of 162 ml demonstrated in this study was less. It is not reasonable to attribute this reduced effect to the timing of  $\epsilon$ -ACA administration alone because of other differences in study protocol, including the dose of  $\epsilon$ -ACA, predefined transfusion triggers, and surgeons and surgical techniques. A limitation of our study was the lack of an additional group of patients receiving  $\epsilon$ -ACA before skin incision. Without this group, we cannot make comments regarding optimal administration time for efficacy of treatment.

A recent metaanalysis examined the efficacy and safety of aprotinin, desmopressin, tranexamic acid, and  $\epsilon$ -ACA acid in cardiac surgery.<sup>3</sup> The authors used perioperative blood transfusion as the outcome. Only randomized, prospective clinical studies that reported the proportion of patients receiving at least 1 U allogenic erythrocytes were included. The authors discovered only three eligible studies of  $\epsilon$ -ACA, with a total of 118 patients.<sup>22,24,25</sup> They found no statistically significant effect of  $\epsilon$ -ACA on the proportion of patients transfused with allogenic blood ( $P = 0.07$ ), although the odds ratio was considerably less than 1.0 (odds ratio, 0.20; 95% confidence interval, 0.04-1.12).<sup>3</sup> The problem with combining patients from different studies in a metaanalysis is the lack of uniform transfusion triggers. Transfusion criteria were followed in 69 of the 74 patients enrolled in our study. The importance of adhering to transfusion criteria is readily apparent. One must question the outcome of studies that do not use transfusion criteria or only use criteria for erythrocytes and not for coagulation components. Administration of coagulation components may decrease blood loss and the need for erythrocytes more significantly than antifibrinolytic therapy. We eliminated patients from analysis if they were transfused against our predefined criteria. This was an important distinction from other studies.

Previous studies demonstrating either a reduction in blood loss or a reduction in transfusions have led to the widespread use of antifibrinolytics in a variety of cardiac surgical settings. Our study demonstrates a minimal reduction in overall 24-h blood loss (162 ml) if  $\epsilon$ -ACA is administered after heparinization during coronary artery bypass surgery. This small reduction in blood loss was not accompanied by a decrease in the transfusion rate suggesting a minimal benefit.

The authors thank Peggy Flynn for her secretarial assistance and Lynne Rafalowski for her assistance with references.

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