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Epsilon-aminocaproic Acid in Coronary Artery Bypass Graft Surgery

Preincision or Postheparin?

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Background: **Epsilon-aminocaproic acid (ε-ACA), an antifibrinolytic agent, is used in cardiac surgery to decrease postoperative bleeding. Theoretical concerns exist about the potential for ε-ACA to contribute to thrombotic complications. For this reason ε-ACA administration is sometimes delayed until after heparinization. This study investigated the impact of the timing of ε-ACA administration on its efficacy.**

Methods: **In this double-blind study, 90 patients undergoing primary coronary artery bypass graft surgery were prospectively randomized to receive either ε-ACA commencing prior to skin incision (bolus 150 mg/kg, followed by an infusion at 15 mg · kg^{-1} · hr^{-1}), ε-ACA commencing after heparin (same doses), or placebo. All infusions were terminated at the end of cardiopulmonary bypass. Criteria for the transfusion of blood products were standardized. Postoperative chest tube drainage (at 6 h, 12 h, and at chest tube removal) and blood transfusion requirements of the three groups were compared.**

Results: **At all time intervals, the placebo group had significantly greater chest tube drainage than either of the two ε-ACA groups ($P < 0.005$). At no time did a significant difference exist between the two ε-ACA groups. A trend existed for the placebo group to require more blood products than either ε-ACA group.**

Conclusions: **ε-ACA produces a reduction in chest tube drainage in patients undergoing primary coronary artery bypass graft surgery. This effect is similar whether the drug is given prior to incision or following anticoagulation. Given the similar hemostatic efficacy and the theoretical potential for thrombotic complications, it may be prudent to administer ε-ACA following anticoagulation.**

DESPITE improvements in the outcome from cardiac surgery, excessive postoperative bleeding remains an important complication. The risk of resternotomy for hemorrhage following coronary artery bypass graft surgery (CABG), with its associated increase in mortality,[1] has been estimated at 3–5%.[2] Lesser degrees of bleeding frequently necessitate blood transfusion, with its associated risks such as transmission of viral pathogens. Blood loss may also expose patients to the risks of hemodynamic instability, hypothermia, and dilutional coagulopathies.

The etiology of bleeding following cardiac surgery is multifactorial; however, hyperfibrinolysis and platelet dysfunction are significant contributors.[3–6] For this reason, many cardiac anesthetists administer drugs, such as epsilon-aminocaproic acid (ε-ACA), prophylactically to inhibit fibrinolysis.

ε-ACA, a synthetic lysine analog, has been used in cardiac surgery since the 1960s to decrease postoperative bleeding.[7] ε-ACA acts by competitively inhibiting the binding of plasminogen and plasmin to fibrin. By blocking access to the fibrin template, it substantially decreases the rate of plasmin formation as well as the plasmin-mediated degradation of fibrin and fibrinogen.[8] It probably also has a platelet-sparing effect by reducing plasmin-mediated platelet damage.[8] ε-ACA has been shown to decrease both postoperative bleeding and transfusion requirements.[9–11]

ε-ACA inhibits fibrinolysis without suppressing thrombin generation[8] raising concerns regarding a prothrombotic potential. Although these theoretical concerns have not been supported by the results of any controlled trials, case reports have described excessive thrombus formation on pulmonary artery catheters in unheparinized patients receiving ε-ACA.[12] In addition, electrocardiographic ST segment changes have been described following the administration of aprotinin, another antifibrinolytic agent.[13] The risk of intracoronary thrombosis may be especially high in patients with unstable clinical syndromes because such syndromes are often associated with thrombosis on damaged coronary atherosclerotic plaques.

Triggers to fibrinolysis during CABG include skin incision, sternotomy, pericardiotomy, and cardiopulmonary bypass (CPB).[5] The administration of ε-ACA after heparinization will attenuate the fibrinolysis due to CPB but not that due to earlier stimuli and, hence, may not be as effective in reducing blood loss and transfusion requirements.

This prospective, double-blind, placebo-controlled study was designed to assess whether delaying administration of ε-ACA until after anticoagulation would decrease its hemostatic efficacy. It was not designed to answer the important questions of whether ε-ACA does indeed increase the incidence of thrombotic complications, or whether delaying administration of ε-ACA until after anticoagulation could offset any such increase. Very large-scale studies would be required to address these questions. For example, to detect an increase in incidence of thrombotic complications from 5% to 10% would require almost 500 patients in each group.

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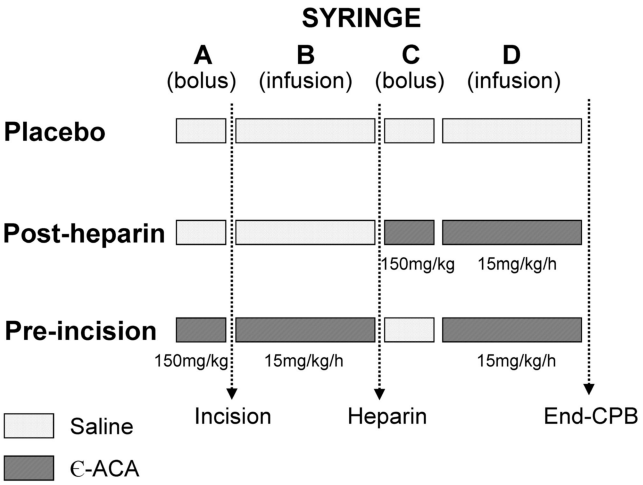

Fig. 1. Drug regimens.

In most previous randomized trials demonstrating the efficacy of ϵ-ACA, the drug was administered prior to skin incision.[3,5,6,8,14–16] No published randomized trial has compared the efficacy of ϵ-ACA administered prior to skin incision to that administered after heparinization.

The aims of our study were to assess the efficacy of ϵ-ACA in reducing blood loss in our practice of cardiac surgery, and to determine whether administration of ϵ-ACA only after heparin is as effective as administration prior to skin incision.

Materials and Methods

After institutional ethics committee approval, 90 patients undergoing primary CABG consented to participate in the trial. Exclusion criteria were emergency surgery, unstable angina, preexisting bleeding diathesis, preoperative anticoagulant medication, renal failure, hepatic failure, or symptomatic cerebrovascular disease. Aspirin use was noted but did not constitute grounds for exclusion. Patients underwent permuted block randomization using random number tables into three groups: placebo, ϵ-ACA postheparin, and ϵ-ACA preincision.

Drug Regimen

The study was placebo-controlled and double-blinded (patients, clinicians, and investigators were all blinded to group allocation). All patients received four syringes, labeled *A, B, C,* and *D*, as shown in figure 1. The preincision group received a bolus of ϵ-ACA (Amicar®; Lederle Laboratories, Baulkham Hills, New South Wales, Australia) comprising 150 mg/kg over 10 minutes after induction of anesthesia but before skin incision. This was followed by an infusion of 15 $mg \cdot kg^{-1} \cdot hr^{-1}$. Three minutes after heparin administration, to maintain blinding, this group received a bolus of normal saline over 10 min, followed by a resumption of the ϵ-ACA infusion until the termination of CPB. The postheparin group received an initial bolus of normal saline prior to skin incision, followed by a normal saline infusion. Three minutes after heparin administration, they received a bolus and then infusion of ϵ-ACA in the same doses as the preincision group. The placebo group received normal saline boluses and infusions throughout.

Surgical, CPB and Intensive Care Unit Management

All surgery was performed *via* a median sternotomy with CPB using a semiocclusive roller pump and membrane oxygenator (Optima® XP™; Cobe® Cardiovascular, Arvada, CO). The pump circuit was primed with 2 l of asanguinous crystalloid prime (including 30 mmol $NaHCO_3$ and 10,000 U of bovine heparin). Pump flows were nonpulsatile and maintained at $2.0–2.4\ l \cdot min^{-1} \cdot m^{-2}$. Intermittent anterograde and retrograde cardioplegia was used. The temperature during CPB was 30–33°C.

Prior to heparinization, isovolemic intraoperative hemodilution using crystalloid was used at the discretion of the attending anesthetist. Whole blood was collected into citrate bags (CPD Bags for Hemodilution, Baxter Fenwal®, Old Toongabby, New South Wales, Australia) for transfusion immediately after protamine administration. Prior to the initiation of CPB, bovine heparin was administered in an initial dose of 300 U/kg, with subsequent doses given to maintain an activated clotting time of greater than 400 s (kaolin-activated cartridges, HemoTec Inc., Englewood, CO). At the end of CPB, residual heparinization was reversed with protamine sulfate 3 mg/kg, plus 0.5 mg/kg following the return of residual pump blood, which was not concentrated by centrifugation.

Pericardial and mediastinal drains were inserted in all patients and connected to continuous low-level suction (approximately 20 cmH_2O). Drainage was recorded at hourly intervals in the postoperative period and was stored on a CareVue (Philips Medical Systems, Andover, MA) automated patient record system, as was the transfusion of any blood products. The timing of chest tube removal was at the discretion of the surgeon. Shed mediastinal blood was not retransfused. Hemoglobin and platelet levels were measured in all patients preoperatively, on postoperative day 1, and on postoperative day 5.

Transfusion Criteria

Criteria for the transfusion of packed red blood cells were hemoglobin levels below 60 g/l during CPB, below 70 g/l at the end of CPB, and below 80 g/l in the postoperative period. Criteria for the transfusion of platelets were excessive bleeding in the presence of normal prothrombin time, activated partial thromboplastin time, and fibrinogen levels. Criteria for transfusion of fresh frozen plasma were excessive bleeding in the presence of a prothrombin time $> 1.5 \times$ normal, but a normal ACT and activated partial thromboplastin time.

Table 1. Demographics and Baseline Hematologic Variables

	Placebo (n = 30)		Postheparin (n = 30)		Preincision (n = 28)	
Group	Mean	SD	Mean	SD	Mean	SD
Age (yr)	67	6.5	65	8.1	66	8.1
Weight (kg)	78	14.3	80	12.5	78	10.7
Height (cm)	167	8.8	165	7.9	168	6.6
Gender (M/F)	22/8		24/6		23/5	
Preoperative hemoglobin (g/l)	140	12.9	148	11.1	145	10.6
Preoperative hemoglobin mass (g)*	667	138	703	116	697	121
Preoperative platelets ($\times 10^9$/l)	216	45	226	49	253	55
Aspirin within 7 days (no. of patients)	12		13		16	

Values are expressed as mean ± SD unless otherwise stated. There were no differences between the groups.

* Hemoglobin mass = preoperative Hb × estimated blood volume (EBV). EBV = 0.3669 height^3 + 0.03219 weight + 0.6041 (male), or 0.3561 height^3 + 0.03308 weight + 0.1833 (female).[17]

Extra protamine was administered in the intensive care unit for excessive bleeding in the presence of a prolonged ACT.

Statistical Analysis

Sample size analysis was performed using Stata®7 software (Stata Corporation, College Station, TX). Assuming a standard deviation of 325 ml in postoperative chest tube drainage (CTD) (data from our intensive care unit) and a clinically relevant difference of 250 ml, we required a sample size of 27 in each group to achieve 80% power to detect a difference at the 0.05 level of significance (two-sided). Therefore, we planned to randomize a total of 90 patients.

Primary outcome variables were CTD at 6 h and 12 h and on removal, and on exposure to blood products. Continuous data were analyzed using analysis of variance for parametric data and Kruskal-Wallis or Mann–Whitney U tests for nonparametric data. Nominal data were analyzed using chi-square tests. These tests were performed using Statview® Version 4.5 software (Abacus Concepts, Berkeley, CA). Nonparametric confidence intervals were calculated using Confidence Interval Analysis® software (BMJ Books, London, United Kingdom). Regression (using Stata®7 software) was used to determine variables associated with CTD at removal (linear regression) and exposure to blood products (logistic regression). Variables analyzed were group (placebo, preincision, or postheparin), age, preoperative hemoglobin mass (hemoglobin concentration × estimated blood volume[17]), duration of CPB, minimum temperature during CPB, number of internal mammary artery grafts, preoperative aspirin use, total heparin dose/kg, total protamine dose/kg and volume of autologous blood collected for hemodilution. A *P* value of less than 0.05 was considered statistically significant.

Results

Ninety patients consented to the trial. Two patients, both from the preincision group, were withdrawn for protocol violations. Both received an inadvertent 5-g bolus of ε-ACA in the CPB pump prime in addition to the study drug. Demographics were similar between groups, as were baseline hematologic variables (table 1). No patients were taking clopidogrel, ticlopidine, or abciximab.

Operative details are shown in table 2. There were no differences between the groups with respect to volume

Table 2. Operative Details

Group	Placebo (n = 30)	Postheparin (n = 30)	Preincision (n = 28)
Autologous blood collected (ml), median (range)	490 (0–1,200)	550 (0–1,100)	500 (0–1,150)
No. of grafts, median	3	3	3
No. of patients with 0,1, or 2 internal mammary artery grafts, 0/1/2	0/19/11	3/18/9	2/13/13
Minimum temperature, °C	31.1 (1.9)	31.9 (1.8)	31.7 (1.5)
Total heparin dose, including CPB circuit prime (U/kg)	516 (85)	472 (81)	481 (67)
Total protamine dose (mg/kg)	3.4 (0.3)	3.6 (0.7)	3.4 (0.3)
CPB duration (min)	99 (31)	100 (29)	102 (23)
Surgery duration (min)	240 (62)	235 (41)	236 (50)
End CPB to skin closure (min)*	53 (17)	49 (11)	43 (15)
ε-ACA: infusion duration (min)*	0	127 (30)	212 (47)
ε-ACA: total dose (mg/kg)*	0	182 (7.5)	203 (11.8)

Values are expressed as mean ± SD unless otherwise stated.

* $P < 0.05$ (ANOVA).

CPB = cardiopulmonary bypass, ε-ACA = epsilon-aminocaproic acid.

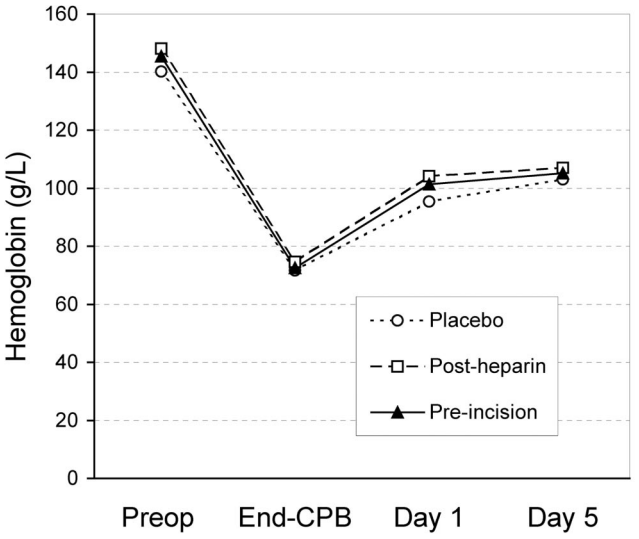

Fig. 2. Mean hemoglobin levels *versus* time.

of autologous blood collected, number of coronary grafts, number of internal mammary artery grafts, minimum temperature during CPB, heparin and protamine doses, duration of CPB, or duration of surgery. A statistically significant difference did exist in the time taken from termination of CPB to skin closure. As expected, the preincision group had a significantly longer duration and a higher total dose of ϵ-ACA than the postheparin group. There were no differences in hemoglobin levels between the groups at any time (fig. 2).

Figure 3 depicts the chest tube drainage (CTD) of the three groups at 6 and 12 h postoperatively and at the time of drain removal. The placebo group had significantly greater CTD than both ϵ-ACA groups at all time intervals, but there were no differences at any time between the two ϵ-ACA groups (median values in milliliters: placebo 495 *vs.* postheparin 320 *vs.* preincision 300 at 6 h; 655 *vs.* 485 *vs.* 475, respectively, at 12 hours; 1330 *vs.* 1060 *vs.* 900, respectively, at the time of chest tube removal).

Figure 4 shows the confidence intervals for differences in median chest tube drainage between the groups. This confirms the significant difference between the placebo and ϵ-ACA groups and the lack of a difference between the two ϵ-ACA groups.

Blood transfusion exposures until discharge from hospital are shown in table 3. Fifty percent of patients in the placebo group were exposed to blood products compared to 23% in the postheparin group and 32% in the preincision group. These differences did not reach statistical significance.

The results of our multivariate analysis are shown in tables 4 and 5. Variables associated with CTD at removal were ϵ-ACA use (but not timing of administration), number of internal mammary arteries harvested, and minimum temperature during CPB. Variables associated with exposure to blood products were preoperative red blood cell volume, duration of CPB, and the use of ϵ-ACA (postheparin group *vs.* placebo only).

Two patients underwent resternotomy for bleeding: one (placebo group) before skin closure and one (postheparin group) 4 h postoperatively. In both cases, the surgeons determined a surgical cause for the bleeding. These patients were still included in the analysis. An analysis excluding these two patients did not result in a significant change in our findings or conclusions.

Four patients suffered complications following their surgery. One patient (preincision group) died from intractable cardiogenic shock 90 min after a very difficult and unsatisfactory revascularization. The patient required high doses of inotrope and an intraaortic balloon pump to separate from CPB. Another patient (preincision group) suffered a myocardial infarct causing a ruptured right ventricle and death on the third postoperative day. Two patients (both preincision group) experienced cerebrovascular accidents, resulting in right arm weakness in one patient and visual symptoms in another.

Discussion

This study confirms the previously reported efficacy of ϵ-ACA in reducing bleeding and blood product requirements following CABG. Furthermore, it is the only published study demonstrating that this efficacy is similar irrespective of whether the drug is administered prior to incision or following anticoagulation.

Unlike many of the studies of ϵ-ACA for cardiac surgery, this study was randomized, double-blind, and placebo-controlled. Uniform transfusion criteria were used and hemoglobin levels on discharge were documented. These hemoglobin levels were similar in the three groups. Furthermore, there was no significant difference in hemoglobin levels on discharge between transfused (mean hemoglobin concentration = 103 g/l) and nontransfused (mean hemoglobin concentration = 106 g/l) patients.

We analyzed the blood loss data with nonparametric methods because it was not normally distributed—all groups were skewed with some outliers with high CTD. The fact that all groups appeared to have a similar distribution of CTD justified the calculation of nonparametric confidence intervals for the differences in median CTD between the groups. Such intervals give a more robust estimate of the precision of our data than the use of parametric confidence intervals for the difference in means.

Although there were no significant differences between the groups in a number of variables that could influence CTD and blood exposure (tables 1 and 2), we performed a multivariate analysis to formally assess the

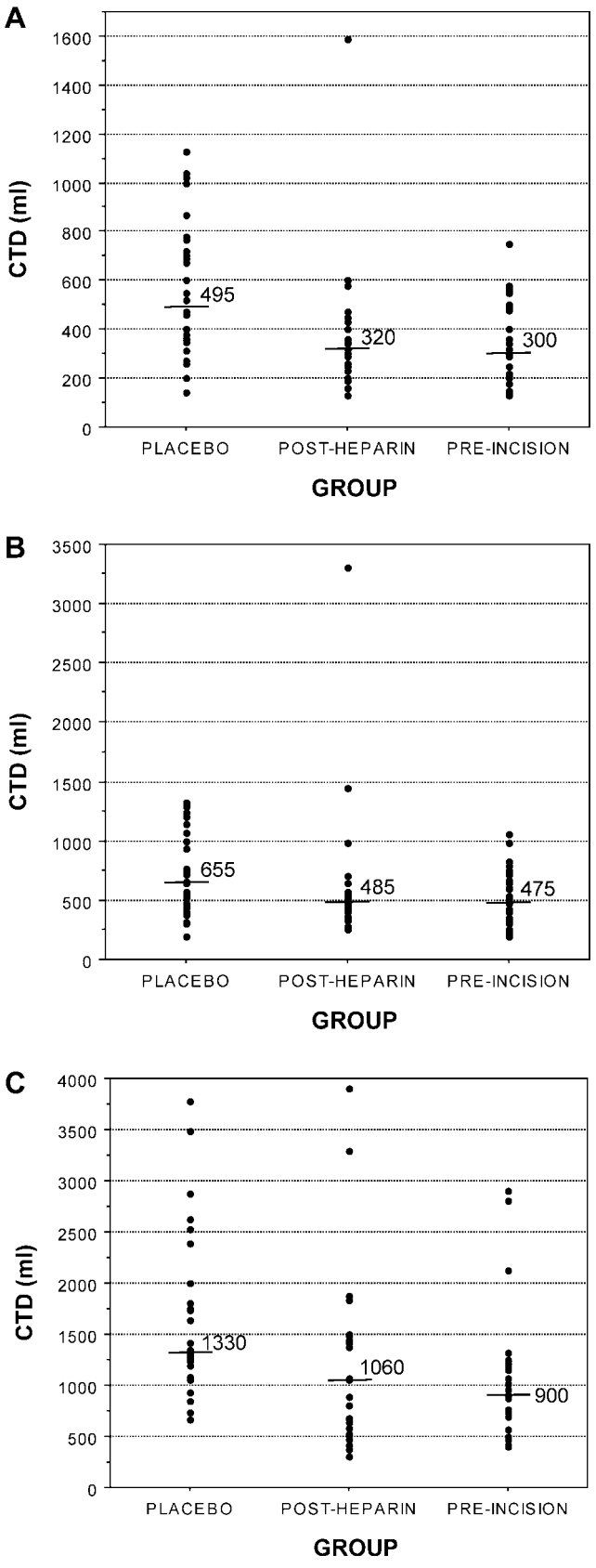

Fig. 3. Chest tube drainage (CTD) in milliliters *versus* group: (*A*) 6 h postoperatively, (*B*) 12 h postoperatively, and (*C*) at time of chest tube removal. Each *point* represents a patient, and the *numbers* and *cross lines* indicate median values. (The outlier in the postheparin group was a patient who underwent resternotomy 4 h postoperatively because of excessive CTD.) At all time intervals a significant difference was found between the groups (Kruskal-Wallis test $P < 0.005$) at 6 h, $P < 0.05$ at 12 h, $P < 0.005$ at chest tube removal. A significant difference was found between both ε-ACA groups and the placebo group, but no difference was found between the two ε-ACA groups (Mann–Whitney U test with Bonferroni correction).

effect of these potentially confounding variables on our results. The multivariate regression confirmed the beneficial effect of ε-ACA on CTD and the lack of a significant difference between the two ε-ACA groups. The main predictors of transfusion requirements were preoperative hemoglobin mass and duration of CPB. A trend existed for the ε-ACA groups to require less transfusion, but in the multivariate analysis, only the postheparin group *versus* placebo was statistically significant. Studies larger than this would be required to definitively assess the impact of ε-ACA use on transfusion requirements.

The 95% confidence intervals for the difference in CTD between the two ε-ACA groups straddle zero (postheparin–preincision: −140 ml to +110 ml at 12 h, and −230 ml to +350 ml at the time of chest tube removal). This indicates that either group may have some hemostatic advantage over the other; however, the magnitude of any such difference is likely to be low and hence unlikely to result in hemodynamic instability or altered transfusion requirements.

Most previous related reports describe the administration of ε-ACA prior to skin incision. Troianos *et al.*[18] compared ε-ACA after heparinization to placebo and found a statistically significant but clinically modest re-

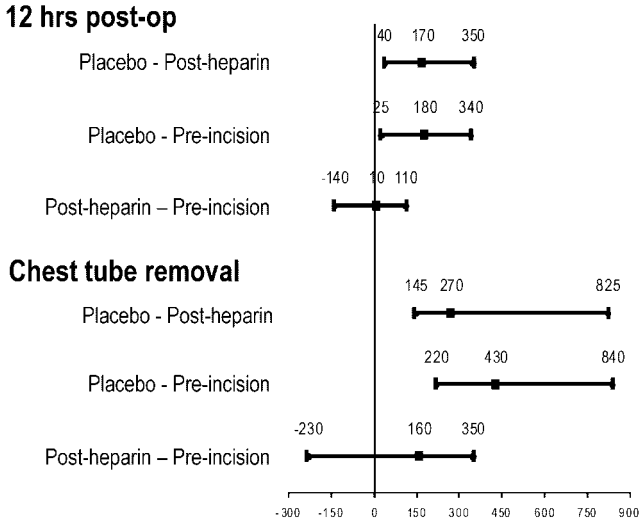

Fig. 4. Chest tube drainage confidence intervals. The *lines* represent nonparametric 95% CIs for the difference in median chest tube drainage (in milliliters) between the specified groups.

Table 3. Blood Product Exposure

Group	Placebo (n = 30)	Postheparin (n = 30)	Preincision (n = 28)	*P* Value (chi-squared)
Red blood cells	14 (2)	7 (2)	9 (2)	0.16
Platelets	4 (5)	2 (12)	2 (5)	0.61
Fresh frozen plasma	1 (3)	1 (4)	0	0.62
Any blood product	15 (3)	7 (2)	9 (2)	0.09
% exposed	50.0	23.3	32.1	0.09

The first four rows show the number of patients in each group exposed to blood products, with the median number of units transfused to each patient in parentheses. The bottom row shows the percentage of patients in each group exposed to any blood product. No patient received cryoprecipitate.

duction in mediastinal blood loss in the study group, concluding that ". . .ϵ-ACA after heparinization. . .is of minimal benefit." However, as the authors acknowledged, this study did not include a group receiving ϵ-ACA before skin incision and thus did not directly assess the effect of the timing of ϵ-ACA administration on its efficacy. The significant variability in blood loss and transfusion practice following cardiac surgery in different units[19,20] hampers comparison of hemostatic interventions between institutions. Indeed, the relatively low blood loss in all groups, including the placebo group, in Troianos *et al.*'s study limited the potential benefit of ϵ-ACA in absolute terms. In percentage terms, however, the decrease in CTD in Troianos *et al.*'s study was approximately 23%, which is similar to our data. Furthermore, the ϵ-ACA group had a significantly longer CPB duration in their study, which may have masked the hemostatic efficacy of ϵ-ACA.

Our result, that ϵ-ACA seems effective when given before CPB but after skin incision and sternotomy, is consistent with studies that have investigated the effects of surgery on fibrinolysis. Serial measurements of markers of fibrinolysis such as tissue plasminogen activator suggest that CPB is the predominant stimulus to fibrinolysis during CABG.[21,22] Furthermore, the marked increase in tissue plasminogen activator seen in CABG is not present in patients undergoing thoracotomies for noncardiac surgery.[23]

There was a statistically significant difference in closure times between groups, but in the context of the total duration of these operations, the magnitude of this difference (up to 10 min) was not thought to be clinically significant.

Table 4. Variables Associated with CTD at Time of Removal (Stepwise Linear Regression)

Predictor Variable	*P* Value
Placebo *vs.* preincision group	0.001
Placebo *vs.* postheparin group	0.003
Preincision *vs.* postheparin group	0.55*
No. of IMAs harvested	0.001
Minimum temperature on CPB	0.03

* Stepwise regression with forced inclusion of preincision group.

CPB = cardiopulmonary bypass; IMA = internal mammary artery grafts.

Study Limitations

These results may not be applicable to units in which techniques differ to our own (*e.g.*, warmer or colder surgery), or to repeat CABG or more complex surgery, in which greater blood loss and transfusion rates are the norm. It also remains unclear whether our results can be extrapolated to other commonly used hemostatic agents such as tranexamic acid and, especially, aprotinin, with its more complex and extensive pharmacologic effects.

As discussed in the introduction, our sample size was far too small to meaningfully address the incidence of complications associated with ϵ-ACA or whether the timing of ϵ-ACA administration affects this incidence. The two cardiac and two cerebrovascular complications occurred in the preincision group. If these different complications were combined, then this is significantly ($P < 0.05$, Fisher exact test) higher than each of the other groups. However, as the study was not designed to address this issue, important predictors of such complications (*e.g.*, poor left ventricular function, atrial fibrillation, respiratory comorbidities, diabetes) were not considered in the randomization process and may not have been spread evenly between the groups. There is no evidence from other studies regarding the hemostatic efficacy of ϵ-ACA, including two recent meta-analyses,[10,11] that ϵ-ACA is associated with an increased incidence of cardiac and cerebrovascular complications. Clearly, larger trials are needed to specifically address these important issues.

In conclusion, ϵ-ACA produces a reduction in CTD in patients undergoing primary CABG. This effect is similar whether the drug is given prior to incision or following anticoagulation. Given the similar hemostatic efficacy

Table 5. Variables Associated with Exposure to Blood Products (Stepwise Logistic Regression)

Predictor Variable	OR	95% CI	*P* Value
Preoperative hemoglobin mass	0.48	0.30–0.77*	0.002
CPB duration	1.32	1.08–1.62†	0.006
Placebo *vs.* preincision group	2.9	0.82–10.3	0.09
Placebo *vs.* postheparin group	4.05	1.07–15.4	0.04
Preincision *vs.* postheparin group	1.39	0.36–5.4	0.64‡

* Odds ratio (OR) per 100-g increase in hemoglobin mass; †OR per 10-min increase in CPB duration; ‡stepwise logistic regression with forced inclusion of preincision group.

CPB = cardiopulmonary bypass.

and the theoretical potential for thrombotic complications, it may be prudent to administer ϵ-ACA following anticoagulation. Larger studies are needed to address this issue conclusively.

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