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The Efficacy of Epsilon-aminocaproic Acid and its Timing in Reducing Blood Loss in Major Cardiac Coronary Bypass Surgery: A Randomized Double-blinded Placebo-controlled Study

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Abstract: It has been shown that in patients undergoing primary minor Coronary Artery Bypass Graft surgery (CABG), epsilon-aminocaproic acid (epsilon-ACA) produces a reduction in chest tube drainage and this effect was similar whether the drug is given prior to incision or following anticoagulation. The aim of this study was to investigate the efficacy of epsilon-ACA and its timing in reducing blood loss in major CABG. In a randomized double-blind study, 60 adult patients undergoing primary CABG requiring equal or more than 4 grafts with extracorporeal circulation were allocated to receive epsilon-ACA either prior to skin incision (bolus 150 mg kg^{-1}, followed by an infusion at 15 mg kg^{-1} h^{-1}), either prior to skin incision or after heparin, or placebo. All infusions were terminated at the end of cardiopulmonary bypass. Postoperative chest tube drainages (at 6, 12 h and at chest tube removal) were compared. The control group had significantly greater chest tube drainage than either of the two epsilon-ACA groups, at 6 h and chest tube removal times ($p<0.05$). Also there was a significant difference in postoperative chest tube drainages pattern between control and either of the two epsilon-ACA groups ($p<0.05$) but not between two epsilon-ACA groups. Epsilon-ACA effectively reduces blood loss through chest tubes in patients undergoing major CABG and its administration timing has no effects. Considering comparable hemostatic efficacy, it is recommended administering epsilon-ACA next to anticoagulation.

Key words: Blood loss, epsilon-aminocaproic acid, major cardiac coronary bypass surgery, timing

INTRODUCTION

One of the concerns for cardiac anesthesiologists and surgeons is bleeding after cardiac operations and the subsequent complication[1,2].The risk of resternotomy for hemorrhage following coronary artery bypass graft surgery (CABG), with its associated increase in mortality, has been estimated at 3-5%. 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[3].

Fibrinolysis and platelet dysfunction both have been implicated as most important causes of nonsurgical bleeding[4,5]. Several strategies, including the prophylactic administration of antifibrinolytic agents, are advocated to affect fibrinolysis and platelet function to reduce post bypass bleeding and transfusion requirements[1,2].

There is a concern over the time of its administration and its efficacy or potential to induce thrombosis complications. It has been shown that administration of ε-ACA prior to triggers of fibrinolysis during CABG such as skin incision, sternotomy, pericardiotomy, enhance its effects. By the administration of ε-ACA after skin incision (e.g., after heparinization), a reduction in the overall effectiveness of ε-ACA may be anticipated because inhibition of fibrinolytic activation associated with this event would not occur[2].

In a randomized, double-blind and placebo-controlled trial showed that anticoagulation effects of ε-ACA are similar whether the drug is given prior to incision or

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following anticoagulation[3]. But these results may not be applicable to more complex CABG surgeries, in which greater blood loss and transfusion rates are the normal[3]. Also it can be assumed that the anticoagulation effects of ε-ACA would be prominent in more complex surgeries with greater hemorrhage[6,7]. This randomized, double-blind protocol was applied to assess the efficacy of ε-ACA and its timing in reducing blood loss in major CABG.

MATERIALS AND METHODS

After approval by our research and human rights committee and written informed consent, 60 adult patients undergoing primary CABG elective requiring equal or more than 4 grafts with extracorporeal circulation were prospectively randomized into three groups using random number tables: placebo, ε-ACA post Heparin and ε-ACA preincision.

Patients were excluded for age greater than 80 years, hepatic or renal dysfunction (creatinine level>1.5 mg dL^{-1}), emergency surgery, unstable angina, preexisting bleeding diathesis, and preoperative anticoagulant medication.

All patients received four IV injections, in four synchronized times including preincision as bolus, postincision as infusion, post heparin (Heparin, B|Braun Inc.) as bolus and three minutes following heparin to the end of CPB as infusion respectively.

The placebo group received normal saline in all boluses and infusions. The ε-ACA Post-Heparin group received normal saline in preincision and postincision and ε-ACA (Amicar®; Lederle Laboratories) comprising 150 mg kg^{-1} over 10 minutes after heparin injection followed by 15 mg kg^{-1} h^{-1} ε-ACA from three minutes following heparin injection to the end of CPB.

The ε-ACA Pre-Incision group received 150 mg kg^{-1} ε-ACA over 10 minutes as preincision bolus, followed by 15 mg kg^{-1} h^{-1} ε-ACA as postincision infusion and normal saline for post heparin and 15 mg kg^{-1} h^{-1} ε-ACA as 3 min following heparin to the end of CPB infusion.

All surgeries were performed by unique anesthesia and surgical team supervising by a attending anesthesiologist and cardiac surgeon via an median sternotomy with CPB using a semiocclusive roller pump and membrane oxygenator (Affinity® NT, Trillium ™; Medtronic, Inc.). The pump circuit was primed with 2l of crystalloid prime (including 30 mmol $NaHCO_3$ and 10,000 U of heparin). Pump flows were pulsatile and maintained at 2.0–2.4 l min^{-1} m^{-2}. Intermittent anterograde and retrograde cardioplegia was used. The temperature during CPB was 30-33°C.

Heparin w as administered in an initial dose of 300 U kg^{-1}, prior to the initiation of CPB with subsequent doses given to maintain an activated clotting time of greater than 400 s. All patients have left internal mammary graft. At the end of CPB, residual heparinization was reversed with protamine sulfate (Leo®, Leo Pharmaceutical Ltd. A/S) 3 mg kg^{-1}, plus 0.5 mg kg^{-1} following the return of residual pump blood.

Pericardial and mediastinal drains were inserted in all patients and connected to continuous low-level suction (approximately 20 cm H_2O). Chest Tube Drainage (CTD) was recorded at 6 and 12 h and on removal at the judgment of the surgeon in the postoperative period as the primary outcome variables.

Continuous data were analyzed using analysis of variance for parametric data and Kruskal-Wallis or Mann-Whitney U tests for nonparametric data. Mean Chest Tube Drainage (CTD) levels versus time patterns between groups were analyzed utilizing general linear model repeated measures. Nominal and ordinal data were analyzed using Chi-square tests. These tests were performed using SPSS® Version 12.0 software. A $p<0.05$ was considered statistically significant.

RESULTS

The demographics and pre-bypass laboratory studies were similar between groups (Table 1).

There were no significant differences between the groups with respect to duration of aortic cross-clamping, CPB duration, minimal CPB temperature, duration of operation, total heparin and protamine doses. A statistically significant difference existed in number of coronary grafts and as expected, the Pre-Incision group had a significantly higher total dose of ε-ACA than the Post-Heparin group (Table 2).

General linear model repeated measures test showed that there is a significant difference in postoperative chest tube drainage pattern between control and groups received ε-ACA (either Pre-Incision or Post-Heparin) ($p<0.05$) but not between either of the two ε-ACA groups

Table 1: Demographics and pre-bypass laboratory data. Values are expressed as mean±SD or median (range) or numbers

Variables	Control (n=20)	Pre-incision (n=20)	Post-heparin (n=20)
Age (year)	59.00±8.56	60.60±8.61	58.10±8.42
Sex (M/F)	14/6	13/7	16/4
BMI	25.75±1.63	26.35±2.03	26.79±1.54
Preoperative platelet (10^6 mL^{-1})	206(37)	197(33)	194(26)

Table 2: Operative data. Values are expressed as mean±SD or numbers

Variables	Control (n=20)	Pre-Incision (n=20)	Post-Heparin (n=20)
4, 5 and 6 Grafts, 4/5/6 (no)**	10/8/2	9/10/1	1/17/2
Duration of aortic cross-clamping (min)	63.65±15.8	61.95±11.66	6.10±13.8
Duration of CPB (min)	119.60±19.1	113.20±15.9	121.55±18.3
Minimal CPB temperature (°C)	30.40±0.8	30.60±1.0	30.60±1.0
Duration of operation (min)	276.40±24.2	263.05±22.0	271.95±26.6
Total heparin dose (U kg^{-1})	516.40±43.7	511.30±37.9	490.90±40.5
Total protamine dose (mg kg^{-1})	4.03±0.4	4.0±0.5	3.91±0.4
Total ε-ACA dose (mg kg^{-1})*	0.00	202.95±6.2	181.80±5.9

*: $p<0.05$, ANOVA tukey,**:$p<0.05$, Chi-square test.

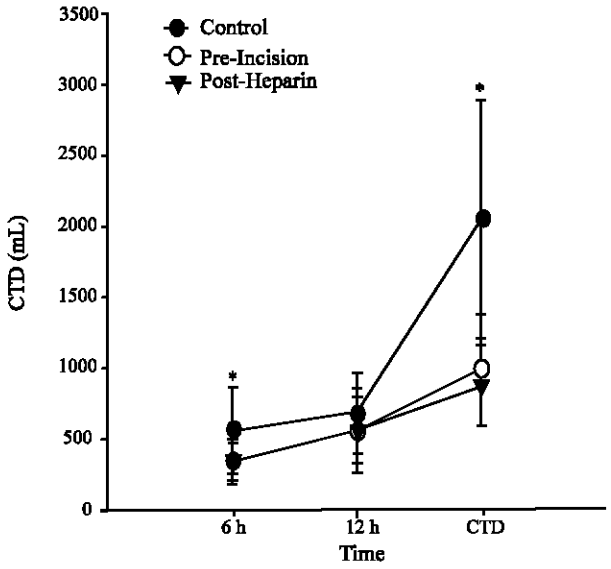

Fig. 1: Mean Chest Tube Drainage (CTD) levels versus time. General linear model repeated measures shows that there is a significant difference in postoperative Chest Tube Drainage pattern between control and Pre-Incision and Post-Heparin groups ($p<0.05$) but not between either of the two ε-ACA groups ($p>0.05$). *: $p<0.05$ Kruskal-Wallis and Mann-Whitney U tests (significant difference between Control vs. Pre-Incision and Control vs. Post-Heparin)

($p>0.05$). Also groups received ε-ACA (either Pre-Incision or Post-Heparin) had less mediastinal blood loss than the control group in chest tube removal ($p<0.05$ and Fig. 1). All the patients experience an uneventful recovery and postoperative period.

DISCUSSION

The results of this study demonstrated less bleeding in the ε-ACA groups after surgery which confirms the previously reported efficacy of ε-ACA in reducing bleeding following CABG. However a minimal benefit of ε-ACA during the first 12 h after major CABG, but the significant reduction in the amount of postbypass mediastinal bleeding was evident during the chest tube removal.

At present, three antifibrinolytic agents-two synthetic (ε-aminocaproic acid and tranexamic acid [TA]) and one natural (aprotinin), are available for clinical use[1].

ε-ACA, a synthetic lysine analog[3]. by competitively preventing the binding of plasminogen and plasmin to fibrin and the breakdown of crosslinked fibrin (fibrinolysis), substantially decreases the rate of plasmin formation as well as the plasmin-mediated degradation of fibrin and fibrinogen. It probably also has a platelet-sparing effect by reducing plasmin-mediated platelet damage[8]. While some investigators showed prophylactic administration of ε-ACA is of minimal benefit for reducing postoperative blood loss in patients undergoing primary CABG[2], antifibrinolytic medications such as ε-ACA are thought to improve coagulation after cardiac surgery and several studies have reported a beneficial effect of ε-ACA to treat or to prevent postoperative bleeding[1,3,9-15] and transfusion requirements[14,15].

This study confirms the previously reported efficacy of timing of ε-ACA in reducing bleeding by Kluger *et al.*[3]. Like in minor CABG (less than 3 grafts), the results of this randomized, double-blind and placebo-controlled study demonstrated that the efficacy of ε-ACA administration is similar irrespective of whether the drug is administered prior to incision or following anticoagulation in patients undergoing major CABG.

Serial measurements of markers of fibrinolysis such as tissue plasminogen activator suggest that CPB is the predominant stimulus of fibrinolysis during CABG[16,17]. Furthermore, the marked increase in tissue plasminogen activator seen in CABG is not present in patients undergoing thoracotomies for noncardiac surgery[18]. Then the significantly greater fibrinolytic activation occurring with initiation of cardiopulmonary bypass would be inhibited by ε-ACA[2]. Since fibrinolysis due to CPB is much greater than earlier stimuli, it is possible that

the Pre-Incision ε-ACA to be as effective as Post-Heparin in reducing blood loss. Then delayed administration of ε-ACA until after anticoagulation would not decrease its hemostatic efficacy[3].

Similar results with greater extent in this study may be resulted from the effects of ε-ACA on the all of bleeding beds with same proportion. Then the surgery extent (e.g., number of grafts) may not influence CTD but it needs further investigations comparing bleeding between less than 3 or more grafts.

Theoretically there are some concerns about prothrombotic potential resulting from inhibition of fibrinolysis by ε-ACA without suppressing thrombin generation, which have not been supported by any controlled trials, and it restricted to case reports[3]. There was no complication in this study. Larger trials are needed to specifically address these important issues.

Because of different transfusion criteria utilized in our service, transfusion requirements could not be assessed in this study. It is recommended to measure this in future studies with determined transfusion criteria as the retrospective or noncontrolled comparative studies suggested that ε-ACA reduce postoperative bleeding, but don't reduce transfusion of allogeneic blood products[19,20].

In summary, ε-ACA effectively reduces blood loss through CTs in patients undergoing primary major elective CABG and its administration timing has no effects. Considering comparable hemostatic efficacy and the theoretical potential for thrombotic complications, we recommend administering epsilon-ACA next to anticoagulation.

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