

# Comparison of Effectiveness of Tranexamic Acid and Epsilon-amino-Caproic-Acid in Decreasing Postoperative Bleeding in Off-pump CABG Surgeries: A Prospective, Randomized, Double-blind Study

## Abstract

**Context:** Off-pump coronary artery bypass graft (CABG) surgeries have been shown to have increased fibrinolysis due to tissue plasminogen activator release. There are no trials comparing the two available antifibrinolytics (tranexamic acid and epsilon-amino-caproic acid) in off-pump CABG surgeries. **Aims:** The aim of the present study was to compare the effectiveness of tranexamic acid and epsilon-amino-caproic acid with respect to postoperative bleeding at 4 and 24 hours as the primary outcome, and rate of postoperative transfusion, re-operations, complication rate, serum fibrinogen, and D-dimer levels as secondary outcomes. **Settings and Design:** The study was carried out at a tertiary-level hospital between June 2017 and June 2018. It was a prospective, randomized, double-blind study. **Materials and Methods:** Eighty patients undergoing off-pump CABG, were randomly allocated to receive tranexamic acid or epsilon-amino-caproic acid. The patients were followed up in the postoperative period and were assessed for primary and secondary outcomes. **Statistical Analysis Used:** Statistical analysis was performed using SPSS software, version 19.0 (SPSS Inc., Chicago, IL). Nonparametric data were expressed as median with interquartile range and compared using Mann-Whitney U-test, parametric data was represented as mean with standard deviation and analyzed using Student's *t*-test. Nominal data were analyzed using Chi-square test. **Results:** Bleeding at 4 hours did not show significant difference between groups, 180 ml (80–250) vs 200 ml (100–310). Bleeding at 24 hours was significantly lesser in tranexamic acid group as compared to epsilon-amino-caproic acid group, 350 ml (130–520) vs 430 ml (160–730) ( $P = 0.0022$ ). The rate of transfusion, re-operations, seizures, renal dysfunction, fibrinogen levels, and D-dimer levels did not show significant difference between the groups. **Conclusions:** Tranexamic acid significantly reduced postoperative bleeding in off-pump CABG at 24 hours as compared to epsilon-amino-caproic-acid.

**Keywords:** Epsilon-amino-caproic acid, off-pump CABG, tranexamic acid

## Introduction

Perioperative bleeding has been the greatest complication in cardiac surgery for decades. The institution of cardiopulmonary bypass (CPB) has had the central role in complement activation, platelet activation, and hyperfibrinolysis that commonly contribute to bleeding in on-pump coronary artery bypass graft (CABG). Since its advent, off-pump CABG (OPCAB) has been shown to be devoid of CPB-induced coagulopathy. However, increased levels of biomarkers that are indicative of systemic activation of coagulation and fibrinolysis have been found that imply the association of some degree of defective haemostasis.<sup>[1-3]</sup>

Tranexemic acid (TA) is a synthetic antifibrinolytic that blocks lysine binding site on plasminogen molecule, thus inhibiting the interaction with plasmin and fibrin. It has been extensively evaluated for antifibrinolytic role in on-pump as well as off-pump CABGs. It has resulted in significant decrease in postsurgical bleeding in both scenarios.<sup>[4,5]</sup>

Epsilon-amino-caproic acid (EACA) is a synthetic lysine analog that works on the same mechanism as TA. It reduces the rate of plasmin formation and further decreases degradation of fibrin to fibrin degradation products.<sup>[6]</sup> It also exerts platelet sparing effect by inhibiting plasmin-mediated platelet injury.<sup>[7]</sup>

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**How to cite this article:** Verma S, Srinivas U, Sathpathy AK, Mittal P. Comparison of effectiveness of tranexamic acid and epsilon-amino-caproic-acid in decreasing postoperative bleeding in off-pump CABG surgeries: A prospective, randomized, double-blind study. *Ann Card Anaesth* 2020;23:65-9.

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Submitted: 18-Jul-2018  
Revised: 24-Nov-2018  
Accepted: 07-Jan-2019  
Published: 07-Jan-2020

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### Access this article online

Website: www.annals.in

DOI: 10.4103/aca.ACA\_142\_18

### Quick Response Code:



OPCAB surgery may result in lesser rate of complications and postsurgical bleeding,<sup>[8]</sup> nevertheless there are concerns that it results in increased fibrinolysis as a result of release of tissue plasminogen activator from damaged endothelium.<sup>[9]</sup> Hence, antifibrinolytics have a significant role in minimizing postoperative bleeding in OPCAB.

Since the safety concerns and massive cost burden of aprotinin have appeared in the BART trial,<sup>[10,11]</sup> there has been an increased interest in the use of antifibrinolytics in cardiac surgeries.

Both TA and EACA have been shown to reduce bleeding associated with cardiopulmonary bypass.<sup>[4,5]</sup> Role of TA in decreasing bleeding in OPCAB surgeries is also evaluated.<sup>[3]</sup> Studies demonstrating topical use of EACA in OPCAB surgery have documented positive outcome in reducing postoperative hemorrhage.<sup>[12]</sup> However, the literature regarding its systemic use in OPCAB is sparse. There are no large trials comparing the effectiveness of both drugs in OPCAB surgeries.

The present study is aimed at comparing the effectiveness of both drugs in reducing postsurgical bleeding in off-pump CABG surgeries with respect to blood loss at 4 hours and 24 hours as the primary outcome and rate of transfusion of packed red blood cells (PRBC), fresh frozen plasma (FFP) and platelets, re-exploration rates, postoperative D-dimer, and fibrinogen levels as secondary outcomes.

## Materials and Methods

Eighty patients who were admitted for elective CABG by off-pump technique, belonging to American Society of Anesthesiologist category I or II, were enrolled for the study after the approval of Institutional Ethical committee, between June 2017 and June 2018. Patients with concomitant valvular heart disease, recent myocardial infarction (MI <4 weeks ago), ejection fraction <40%, pre-existing neurological, pulmonary, renal or hepatic dysfunction, and known allergy to study drugs were excluded. Oral antiplatelets were stopped 5 days prior and patients were put on low molecular weight heparin, which was withheld 12 hours before surgery. Written informed consent was taken from all the patients. Four patients were excluded as they did not meet the criteria (2 patients required cardiopulmonary bypass owing to hemodynamic collapse after induction and 2 other patients developed acute MI, hence the surgery was postponed). Remaining 76 patients were randomly allocated to Group TA (Tranexamic acid group,  $n = 38$ ) and Group EA (Epsilon-amino-caproic acid group,  $n = 38$ ) [Figure 1]. Randomization was done with sealed envelopes and group allocation was done by random drawing of these envelopes by the patients. The envelopes contained designated group label. Drugs were prepared by an anesthetist who was not involved in the study. The preloaded infusions bearing a label of specific infusion rate were handed over by the anesthetist to one of the authors,

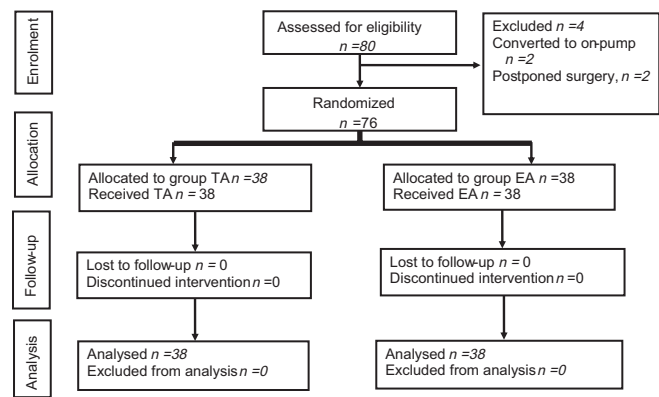


Figure 1: Randomization, group allocation and assessment of the patients

who administered the study drugs according to the study protocol.

For induction of anesthesia, a standard cardiac induction protocol<sup>[13]</sup> was followed including fentanyl, midazolam, and rocuronium for induction and sevoflurane with oxygen-air mixture for maintenance. Myocardial stabilization was aided with the help of Octopus stabilizer with negative suction arms. Internal mammary with either a radial artery or a saphenous vein or both were harvested for all cases. Heparin was administered in a dose of 2 mg/kg IV to a target activated clotting time (ACT) of >300 seconds. Group TA received tenexemic acid at a dose of 10 mg/kg IV at induction over 20 min and 1 mg kg<sup>-1</sup> h<sup>-1</sup> thereafter throughout the surgery. Group EA received amino-caproic acid in dose of 100 mg/kg IV over 20 min, followed by 10 mg kg<sup>-1</sup> h<sup>-1</sup> through the completion of surgery. Previous studies have reported both weight-based and fixed-dose regimen for TA and EACA,<sup>[10,14]</sup> however, a weight-based dosing regimen was opted for in the present study for the purpose of standardization.<sup>[7]</sup> Protamine was administered as 1 mg per mg of heparin dose.

After the surgery patients were shifted to ICU following standard protocol. Blood loss was analyzed at 4 and 24 hours after shifting. Packed cell transfusion was given if hemoglobin <8 g%. FFP was transfused if specific factor deficiency was documented or postoperative drain output >250 ml/h in the first hour. Platelet transfusion was indicated if platelet count <50000/mm<sup>-3</sup>. Postoperative fibrinogen levels and D-dimer levels were also analyzed at 4 and 24 hours. Surgical re-exploration was considered if bleeding >300 ml/h in the first 2 hours, or if >200 ml/h for 4 consecutive hours, with normal coagulation data. Patients were observed for postoperative complications (MI, stroke, DVT, PE, renal dysfunction, and seizures) for 48 hours after shifting to the ICU. Seizure was defined as altered sensorium with uprolling of eyes, with or without tonic clonic movements of one or more extremities, renal dysfunction was described as doubling of serum creatinine from the baseline value at 24 hours. Thromboprophylactic measures were started on the first postoperative day in

the form of aspirin 100 mg/d and low molecular weight heparin (weight-adjusted dose).

Statistical analysis was performed using Statistical Package for the Social Sciences software, version 19.0 (SPSS Inc., Chicago, IL) Assuming a difference of 420 ml in the postoperative blood loss at 24 hours between the control group and tenexemic acid group, and a standard deviation (SD) of 106 ml (pooled SD of 120 and 90 ml) between the groups, based on a previous study,<sup>[11]</sup> a sample size of 32 was found sufficient for each group, at a significance level of 5% and study power of 80%. Assuming a dropout rate of 10%, a total of 80 patients were enrolled. Nonparametric data was represented as median with interquartile range and analyzed using Mann–Whitney U-test. Categorical data was represented as mean with standard deviation and was analyzed using Student's *t*-test. Nominal data was analyzed using Chi-square tests. *P* value <0.05 was considered significant.

Both groups were comparable with respect to demographic variables (age, weight, height, and male: female ratio) [Table 1]. Bleeding at 4 hours did not show any significant difference between the groups, however, bleeding at 24 hours was significantly lesser in group TA compared to group EA (*P* = 0.0022) [Table 2]. Two patients in TA group and three patients in EA group required PRBC transfusion (*P* > 0.05). One patient in each group required FFP transfusion (*P* > 0.05). None of the patients in either group required platelet transfusion. Transfusion rate was nonsignificant between the groups. None of the cases had re-exploration due to excessive bleeding. There was no significant difference in the rate of postoperative thromboembolic events (i.e., MI, Stroke, DVT, PE) (*P* > 0.05). One patient in TA group had an episode of seizure and one patient in EA group had renal dysfunction postoperatively [Table 3]. D-dimer levels were comparatively lesser at all time points in group TA compared to EA but did not differ significantly (*P* > 0.05) [Figure 2]. Serum levels of fibrinogen were fairly preserved in both groups with no significant difference (*P* > 0.05) [Figure 3].

## Discussion

OPCAB surgeries have shown to be associated with lesser postoperative bleeding compared to conventional CABG by surpassing cardiopulmonary bypass altogether.<sup>[15,16]</sup> Despite this, the crude evidence of increased fibrinolysis and increased concentration of inflammatory mediators has urged researchers to investigate the probable role of antifibrinolytics in OPCAB surgeries.<sup>[17]</sup> Likewise in the present study, the effectiveness of both antifibrinolytic agents (TA and EACA) in decreasing postoperative blood loss in off-pump CABG was compared.

There was no significant difference in the amount of postoperative bleeding at 4 hours between the groups, however, at 24 hours, group TA showed significantly less bleeding compared to group EA. Similar findings were

**Table 1: Baseline demographics**

Parameters	Group TA (n=38)	Group EA (n=38)	<i>P</i>
Age (years)	64±2	63 +/-3	0.967
Weight (kg)	70±3	72+/-4	0.271
Height (cm)	161±3	158 +/-6	0.118
M/F (Gender)	25/13	27/11	0.739

TA: Tranexamic acid, EACA: Epsilon-amino-caproic acid. Data represented as Mean±Standard deviation or proportion. Student's *t*-test or Chi-square test were used as applicable to compare groups

**Table 2: Comparison of primary and secondary outcomes**

Parameters	Group TA (n=38)	Group EACA (n=38)	<i>P</i>
Bleeding at 4 h (ml)	180 (80-250)	200 (100-310)	0.0321
Total bleeding at 24 h (ml)	350 (130-520)	430 (160-730)	0.0022
Patients transfused with PRBCs (n)	2	3	0.921
Patients transfused with FFP (n)	1	1	1
Patients transfused with PC (n)	0	0	1
Number of re-explorations (n)	0	0	1

Data represented as median (quartiles) or percentage.

PRBC: Packed red blood cells, FFP: Fresh frozen plasma,

PC: Platelet concentrate. Mann–Whitney U-test and Chi-square test were used to compare groups as applicable

**Table 3: Comparison of postoperative complications between groups**

Parameters	Group TA (n=38)	Group EACA (n=38)	<i>P</i>
Thromboembolic events	0	0	-
MI (n)	0	1	0.981
Stroke (n)	1	1	1
DVT (n)	0	0	-
PE (n)			
Renal dysfunction			
Doubling of S.Cr (n)	0	1	0.981
Seizures (n)	1	0	0.981

MI: Myocardial infarction, DVT: Deep vein

thrombosis, PE: Pulmonary embolism, S.Cr: Serum creatinine.

Data represented as percentage. Chi-square test was used to compare groups

obtained by Karski *et al.*<sup>[18]</sup> in a study comparing TA and aminocaproic acid with placebo. This also could be the result of the fact that TA is ten times more potent than aminocaproic acid.<sup>[19]</sup>

The study showed no significant difference in the rate of postoperative transfusion of PRBC, FFP, or platelets or the rate of reopening operations for excessive bleeding. Chauhan *et al.*<sup>[11]</sup> and Falana *et al.*<sup>[14]</sup> have demonstrated

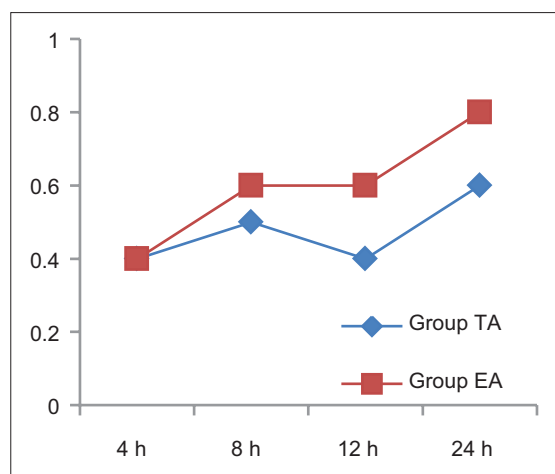


Figure 2: Levels of D-dimer. Median D-dimer level between groups. Mann-Whitney U-test was used for comparison,  $P = 0.0734$

similar results in their respective studies comparing the two drugs. Martin *et al.* also reported that both drugs similarly decreased transfusion requirement in pediatric population undergoing cardiac surgeries.<sup>[20]</sup> It is known that intraoperative or postoperative blood transfusion after CABG is associated with increased long-term mortality.<sup>[21]</sup> Thus, it can be inferred that both drugs have a positive role in decreasing transfusion rates in OPCAB surgeries.

Further, there was no difference in the rate of thromboembolic complications (MI, stroke, DVT, or PE) found between the two groups. The incidence of stroke and DVT that occurred were not statistically significant. Hardy *et al.* also demonstrated no significant difference in the rate of thromboembolic events in their study comparing the two drugs.<sup>[22]</sup> Hence, it can be elucidated based on the present study that neither of the antifibrinolytics led to an additional risk of thrombosis, and thus can potentially become a standard of care for blood conservation in OPCAB surgeries.

No increased incidence of renal dysfunction was reported in the present study with either of the drugs. Although EACA has been associated with significant risk of renal dysfunction,<sup>[23,24]</sup> the rate in the present study did not reach level of significance. The dose variation and low sample size of the study could have led to such a difference in the outcome.

There was no significant difference between the groups with respect to incidence of seizures. This was in accordance with the findings of a previous study by Makhija *et al.*<sup>[23]</sup> In earlier studies, TA has been known to be associated with postoperative seizures.<sup>[24,25]</sup> The mechanism involved is thought to be inhibition of gamma-amino-butyric acid neurons. Nevertheless, the present study did not report additional risk of seizures which could have been due to a lower dose of TA employed in the present study.

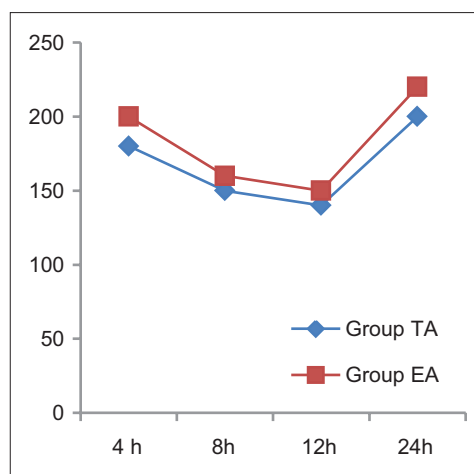


Figure 3: Levels of fibrinogen. Mean fibrinogen levels between groups. Data represented as mean  $\pm$  standard deviation. Student's *t*-test was used for comparison. No significant difference was found between groups ( $P = 0.096$ )

Levels of fibrinogen were fairly preserved at all time points in both the groups, which implies adequate plasminogen binding. Similar results were found in a study by Chauhan *et al.*<sup>[11]</sup> In addition, both groups showed low levels of FDP with no significant difference, indicating effective inhibition of fibrinolysis. Same findings were reported in a prior study.<sup>[22]</sup>

Thus, based on the results of the present study it can be stated that both TA and EACA are effective inhibitors of fibrinolysis associated bleeding in OPCAB surgeries, however, TA was slightly better with respect to significant reduction in post-operative bleeding at 24 hours.

Lack of standardized, surgery-specific dosing of both agents could be listed as the biggest drawback of this study. Differences in the results of the reported literature could have been subject to the variegated dosing regimen adopted by researchers. Second, timing of the drug administration also requires standardization. Third, the sample size was comparatively smaller to precisely determine the difference in complication rates. Larger trials are warranted in off-pump CABG surgeries to further substantiate the findings of the present study.

#### Financial support and sponsorship

Nil.

#### Conflicts of interest

There are no conflicts of interest.

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