

2019

A randomized, double-blinded trial comparing the effectiveness of tranexamic acid and epsilon-aminocaproic acid in reducing bleeding and transfusion in cardiac surgery

J. Leff

A. Rhee

S. Nair

D. Lazar

S. Sathyanarayana

See next page for additional authors

Follow this and additional works at: <https://academicworks.medicine.hofstra.edu/articles>

 Part of the [Anesthesiology Commons](#)

Recommended Citation

Leff J, Rhee A, Nair S, Lazar D, Sathyanarayana S, Shore-Lesserson L. A randomized, double-blinded trial comparing the effectiveness of tranexamic acid and epsilon-aminocaproic acid in reducing bleeding and transfusion in cardiac surgery. . 2019 Jan 01; 22(3):Article 4784 [p.]. Available from: <https://academicworks.medicine.hofstra.edu/articles/4784>. Free full text article.

This Article is brought to you for free and open access by Donald and Barbara Zucker School of Medicine Academic Works. It has been accepted for inclusion in Journal Articles by an authorized administrator of Donald and Barbara Zucker School of Medicine Academic Works. For more information, please contact academicworks@hofstra.edu.

Authors

J. Leff, A. Rhee, S. Nair, D. Lazar, S. Sathyanarayana, and L. Shore-Lesserson

A Randomized, Double-Blinded Trial Comparing the Effectiveness of Tranexamic Acid and Epsilon-Aminocaproic Acid in Reducing Bleeding and Transfusion in Cardiac Surgery

Abstract

Objectives: To compare the effectiveness of epsilon aminocaproic acid (EACA) to tranexamic acid (TA) in reducing blood loss and transfusion requirements in patients undergone cardiac surgery under cardiopulmonary bypass. **Design:** Randomized, double blinded study. Outcome variables collected included; baseline demographic characteristics, type of surgery, amount of 24 hour chest tube drainage, amount of 24 hour blood products administered, 30 day mortality and morbidity and length of stay. We analyzed the data using parametric and non-parametric tests as appropriate. **Setting:** Single center tertiary-care university hospital setting. **Participants:** 114 patients who had undergone cardiac surgery under cardiopulmonary bypass. **Interventions:** Standard dose of intra-operative EACA or TA was compared in patients undergone cardiac surgery under cardiopulmonary bypass. **Results:** There was no statistically significant difference between groups when analyzing chest tube drainage. However, there was a significant difference in the administration of any transfusion (PRBC's, FFP, platelets) intra-operatively to 24 hours postoperatively, with less transfusion in patients receiving EACA compared to TA (25% vs. 44.8%, respectively $P = 0.027$). Additionally, there was no significant difference in terms of adverse events during the one month follow up period. **Conclusion:** The findings of this study suggest that EACA and TA have similar effects on chest tube drainage but EACA is associated with fewer transfusions in CABG alone surgeries. Our results suggest that EACA can be used in a similar fashion to TA which may result in a cost and morbidity advantage.

Keywords: Coronary artery bypass graft surgery, epsilon aminocaproic acid, epsilon-aminocaproic acid, tranexamic acid, tranexamic acid

Introduction

In the United States, cardiac surgery patients are transfused approximately 20% of the available blood supply.^[1,2] Massive bleeding is one of the most life-threatening complications associated with cardiac surgery. It has inevitable consequences in the perioperative period including; re-operation, increased transfusion requirements, and multiorgan dysfunction due to impaired perfusion and oxygenation. There are both physiologic and pharmacologic strategies to mitigate the risk of perioperative bleeding during cardiac surgery. Prophylactic use of the lysine analogs synthetic antifibrinolytic agents epsilon-aminocaproic acid (EACA) and tranexamic acid (TA) has been the primary pharmacologic approach to blood conservation in cardiac surgery since November 2007 when aprotinin was

removed from clinical use.^[3-5] The blood sparing properties of the two available lysine analogs (TA, EACA) have been shown to be inferior to the serine protease inhibitor (aprotinin); however, the side effect profile has proven to be favorable.^[6]

Currently, the choice of antifibrinolytic is dictated by hospital formulary or regional/geographic practices. There is little evidence to support the use of one antifibrinolytic over another regarding blood loss and transfusion requirements. A literature search reveals variable results. Some studies show no difference while others indicate that TA is a more potent blood sparing-agent than EACA.^[6-8] However, other literature highlights the potential negative side effects of large doses of TA that may be associated with seizure activity in both adult and pediatric cardiac patients.^[9-13] In addition, TA is approximately

Jonathan Leff,
Amanda Rhee¹,
Singh Nair²,
Daniel Lazar³,
Sudheera Kokkada
Sathyanarayana⁴,
Linda
Shore-Lesserson⁵

Montefiore Medical Center,
¹Department of Anesthesiology,
Icahn School of Medicine at
Mount Sinai, ²Department of
Anesthesiology, Montefiore
Hospital and Medical Center,
³Department of Anesthesiology,
North Shore Long Island Jewish
Health System, ⁴Department
of Anesthesiology, Lincoln
Medical Center, ⁵Department
of Anesthesiology, Hofstra
University, North Shore Long
Island Jewish School of
Medicine, New York, USA

Address for correspondence:
Dr. Singh Nair,
Department of Anesthesiology,
Montefiore Hospital
and Medical Center,
Bronx, New York, USA.
E-mail: sinair@montefiore.org

Access this article online

Website: www.annals.in

DOI: 10.4103/aca.ACA_137_18

Quick Response Code:



How to cite this article: Leff J, Rhee A, Nair S, Lazar D, Sathyanarayana SK, Shore-Lesserson L. A randomized, double-blinded trial comparing the effectiveness of tranexamic acid and epsilon-aminocaproic acid in reducing bleeding and transfusion in cardiac surgery. *Ann Card Anaesth* 2019;22:265-72.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

three times more expensive than EACA per dosing regimen. It is, therefore, critically important that in evaluating the efficacy of blood-sparing ability, that careful risk-benefit and cost-benefit analyses are performed.

The primary objective of this trial was to compare the effectiveness of EACA to TA in reducing 24-h chest tube drainage (blood loss) and transfusion requirements in patients undergoing cardiac surgery using cardiopulmonary bypass (CPB). Adverse effects of EACA and TA were also compared including renal dysfunction, myocardial infarction, death, respiratory arrest, stroke, seizure, and reoperation as secondary end-points.

Methods

Study design

This was a single-center double-blinded randomized controlled study comparing the effectiveness of EACA and TA in reducing 24 h blood transfusion and chest tube drainage. This study was approved by the internal review board at Montefiore Medical Center (MMC) and was conducted according to the Good Clinical Practice guidelines and in compliance with Office for Human Research Protection. All patients received detailed oral and written information during their preanesthesia consultation or as inpatients and gave their informed consent for the study. This study was registered on December 31, 2015, on clinicaltrials.gov and the principal investigator is Dr. Jonathan Leff. This manuscript adheres to the applicable Equator network guidelines.

Study population

From October 2008 to September 2011, patients >18 years of age, scheduled for cardiac surgery requiring CPB were consented. Eligible operations included; coronary artery bypass graft surgery (CABG), a heart valve repair/replacement, or a concomitant CABG and valve surgery were enrolled. Patients were excluded from the trial if they were unable to consent, were <18 years of age, or had religious reasons for refusing blood transfusions, had an allergy to either of the antifibrinolytic medications or were participating in another clinical trial. Additional exclusion criteria were concurrent renal dysfunction (diagnosis of Stage IV and Stage V chronic kidney disease) history of stroke and/or noncoronary thrombotic disorders (deep vein thrombosis, pulmonary embolism), known congenital bleeding disorders, and weight <50 or >150 kg.

Statistical analysis

Sample size

Sample size calculations were based on the incidence of blood transfusion reported in Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART).^[3] The proportion of patients receiving at least one red cell transfusion was 65.7% in the TA group. We calculated the

sample size based on the assumption that a 20% reduction in allogeneic transfusion would be clinically significant. The sample size of 196 patients was calculated with a power of 0.8 and with an alpha risk of 0.05 to detect a reduction of 20% transfusion in patients receiving TA when compared to the EACA group.

Interim analysis

The planned interim analysis was performed following the enrollment and completed data collection of 80 patients. An independent statistician who conducted the analysis reported futility of the study results and suggested continued enrollment was unlikely to yield a significant difference between the two medications. However, the study was kept open to evaluate secondary endpoints, particularly seizure related adverse events. Following the recruitment of an additional 34 patients (114 patients), the study was discontinued secondary to a lack of funding and resource availability in combination with the statistical information from the interim analysis.

Final statistical analysis

We performed an intention-to-treat analysis. Descriptive statistics were calculated for all the baseline characteristics. All the baseline variables were analyzed for differences between EACA and TA group using independent-sample Student's *t*-tests for continuous variables and Chi-square tests for categorical variables. The primary endpoint of the study, the chest tube drainage (in milliliters) was analyzed using Mann–Whitney Wilcoxon test and the proportion of blood products used was analyzed using Chi-square analysis. We also calculated Transfusion Risk Understanding Scoring Tool (TRUST) scores for all the patients enrolled in this study. TRUST score is an extremely validated tool for assessing transfusion risks in adult patients undergoing cardiac surgery.^[14] To address the differences in the baseline characteristics, a subgroup analysis was performed for the type of surgery and sex. Finally, we built a logistic model to predict the 24-h blood transfusion between the two groups. Type of surgery and sex were the only two explanatory variables that were included in the model. For all inferential statistical tests, a 0.05 two-tailed alpha risk was used. *P* values were reported unadjusted for multiple comparisons. Data analysis was performed with SPSS version 21.0 (SPSS Inc, Chicago, IL, USA). Data were reported as median 25th percentile–75th percentile and proportions as a percentage (number of patients) in each group.

Procedures

Consented patients were randomized into one of the two groups using a 1:1 randomization sequence generated by a computer program. Randomization sequence and the study drugs were kept in a locked box and were opened only by unblinded study personnel who were not involved in the clinical care of the patient. This person prepared

the study drug following the instructions of the study protocol, resulting in preparations of EACA and TA that contained equipotent similar volumes of the drug in the syringe, to ensure blinding. Antifibrinolytic study drug was administered following anesthetic induction. EACA was administered as a bolus loading dose of 150 mg/kg followed by a maintenance infusion of 15 mg/kg/h. TA was administered as a bolus dose of 30 mg/kg followed by a 16 mg/kg/h maintenance infusion.^[3] Maintenance infusion of both drugs was discontinued when the patient arrived in the cardiac surgical intensive care unit. In addition to routine blood sampling (standard of care in our hospital), patients had thromboelastogram (TEG) and D-dimer levels drawn at the following time points: post incision but before initial antifibrinolytic load, immediately following the antifibrinolytic loading dose, and postprotamine reversal of heparin. We transfused patients based on institutional restrictive transfusion practices which outline a threshold of hemoglobin <8 g/dl or hemodynamic instability with ongoing bleeding. Whenever available, TEG was utilized to determine the administration of fresh frozen plasma (FFP), platelets, and cryoprecipitate.

Measurement/endpoints

The primary endpoint was the amount of chest tube drainage and the amount of blood products used in the first 24 h following surgery (surrogate measurement for blood loss) was measured at 4, 8, 12, and 24 h after surgery. The incidence of packed red blood cells (PRBC), FFP, cryoprecipitate, and platelets administered during the first 24 h after surgery was collected. In addition, patients were monitored for any complications during their stay in the hospital and up to 30 days postoperatively. Complications included renal dysfunction (defined as the need for at least 1 hemodialysis or doubling of presurgical creatinine levels), stroke and seizures (clinically diagnosed), myocardial infarction (new Q waves in two electrocardiogram leads), cardiac arrest, respiratory failure, reoperation, and death. Monitoring of the patients

before discharge involved chart review during their stay in the hospital; if a postoperative complication was suspected, the complication was confirmed using MMC's carecast database, which contained independent results such as magnetic resonance imagings, computed tomography scans, or laboratories. In addition, computer records of the patients were searched to determine if there were documented complications in the 30-day postoperative period.

Results

From October 2008 to September 2011, a total of 114 patients undergoing cardiothoracic surgery under CPB were randomized into two groups, 56 in the EACA group and 58 in the TA group. All the subjects randomized were included in the analysis. Demographics, perioperative characteristics, and type of surgery were comparable between the EACA and TA groups [Tables 1 and 2]. The most commonly performed surgery was CABG, 75.4% in the EACA group versus 54.4% in the TA group ($P = 0.081$). The mean duration of surgery time, CPB time, and aortic cross-clamp time were comparable in the two groups ($P > 0.05$). There was no difference between the groups in the use of preoperative coagulation altering medication ($P > 0.05$) (data not shown) and no difference in other baseline laboratory values [Table 3].

The blood draws performed during the operation at time points; post incision but before antifibrinolytic load, postantifibrinolytic load, and postprotamine were performed to measure clotting characteristics as assessed with TEG. All values for TEG were recorded and analyzed to discern any perioperative differences which could account for the incidence of transfusion. TEG values collected revealed no difference in baseline characteristics and no difference in postprotamine fibrinolysis.

The TRUST score for the majority of patients enrolled in the study belonged to the high or very high-risk probability of

Table 1: Patient demographics and intraoperative variables

Variables	EACA (56)	TA (58)	P
BMI	28.51 (26-32)	27.67 (24-30)	0.432
Sex (female)	34% (19)	45.6% (26)	0.213
Age (years)	64 (54-76)	65 (57-76)	0.662
Weight (kg)	79 (70-88)	74 (64-77)	0.046
Temperature (end)	36.3 (36-37)	36.2 (36-37)	0.418
Temperature (low)	33.80 (33-35)	33.90 (33-34)	0.759
Initial heparin dose (units)	25,000 (22,000-29,250)	22,000 (20,000-27,250)	0.059
Total heparin dose (units)	35,500 (28,000-43,500)	36,500 (25,000-45,250)	0.836
Protamine (units)	250 (207-300)	262.50 (227-300)	0.162
Time surgery (min)	305 (256-352)	297 (261-351)	0.836
Time CPB (min)	101 (82-122)	102 (79.2-125)	0.728
Aortic clamp time (min)	74 (59-94)	76.5 (55-96)	0.612

Data presented as median (25th percentile and 75th percentile) and percentage (number of subjects) P values by Mann-Whitney U-test and Chi-square analysis. TA: Tranexamic acid, EACA: ϵ -aminocaproic acid, BMI: Body mass index, CPB: Cardiopulmonary bypass

exposure to transfusion category. The percentage of patients in the high-risk group was 23% (13) and 26% (15) in the EACA and TA, respectively. In addition, the percentage of patients in the very high-risk group was 32% (18) and 48.3% (28) in the EACA and TA, respectively.

One of the primary endpoints of the study the differences in the median amount of chest tube drainage values collected postoperatively at 4, 6, 12, and 24 h did not achieve statistical significance between the EACA and TA group [Table 4].

During the first 24 h postoperative period, 35% ($n = 40$) of the patients received any blood products. Percentage of patients receiving any form of blood product at any point of time during the first 24 h was 25% ($n = 14$) versus 44.8% ($n = 26$) in the EACA and TA group, respectively [Figure 1]. Patients receiving TA had 2.4 times higher odds of receiving any form of blood product at any point of time during the first 24 h (odds ratio [OR] = 2.4 95% confidence interval [CI], 1.1–5.4, $P = 0.027$) we also conducted a stratified analysis for type of blood products used in the first 24 h. The percentage of patients receiving PRBC alone during the first 24 h postoperatively was significantly higher in the TA group when compared to the EACA group, 34.5% ($n = 20$) versus 17.9% ($n = 10$) (OR = 2.4, 95% CI = 1.01–5.79, unadjusted $P = 0.044$). The mean number of blood products transfused was 0.59 ± 1.3 in the EACA group and 1.20 ± 2.2 in the TA group (unadjusted $P = 0.027$). The percentage of patients receiving FFP after the surgery but within the 24 h period was 5.4% (3) in the EACA

group versus 17.2% (10) in the TA group (OR = 3.6, 95% CI = 0.95–14.16, unadjusted $P = 0.046$). Other blood products transfused in the first 24 h postoperatively did not demonstrate the statistically significant difference between the two groups. Details of different blood products used at different time points are explained in [Table 5].

We additionally performed a subgroup analysis for type of surgery patients and for female patients. In patients undergoing CABG surgery alone, the percentage of patients receiving any blood transfusion in the first 24 h was 22% ($n = 9$) and 43.8% ($n = 14$) in EACA and TA group respectively (unadjusted $P = 0.047$). This difference in the blood transfusion between the groups was not seen when compared in valve alone surgery and valve combined with CABG surgery. In female patients who received TA, 75% received at least one blood transfusion during the first 24 h when compared to patients received EACA $P = 0.012$. However, in male patients, there was no statistically significant difference in blood transfusion between the groups.

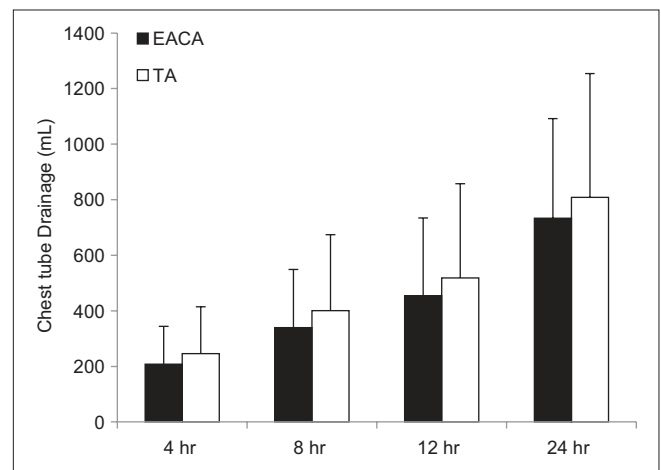


Figure 1: Amount of chest tube drainage 4 hours, 8 hours, 12 hours, and 24 hours post-operatively. The data shown represents the mean post-operative chest tube drainage (mL) and the error bars indicate one standard deviation

Table 2: Types of surgery

Type of surgery	EACA (56)	TA (58)	P
CABG alone	75.5% (42)	54.4% (32)	0.056
CABG + valve repair/replacement	9.4% (5)	22.8% (13)	
Valve repair/replacement alone	15.1% (9)	22.8% (13)	

Data presented in percentage (number of subjects), P values by Chi-square tests. TA: Tranexamic acid, EACA: ϵ -aminocaproic acid, CABG: Coronary artery bypass graft

Table 3: Baseline laboratory variables

	EACA (56)	TA (58)	P
ACT (s)	110 (105-129)	119 (108-129)	0.230
Serum creatinine (mg/dl)	1 (0.9-1.1)	1 (0.9-1)	0.729
RBS (mg/dl)	113 (88-145)	100 (92-148)	0.937
HCT (%)	39.8 (38-43)	39.65 (35-42)	0.234
Platelet ($\times 10^3/\mu$ l)	239 (202-279)	237 (187-304)	0.938
PTT (s)	27 (25-32)	26 (25-27)	0.065
Sodium (mmol/L)	141 (140-142)	141 (137-142)	0.735
Potassium (mmol/L)	4 (4-4)	4 (4-5)	0.608
D-dimer (mg/L)	1.1 (0.80-1.5)	1 (0.7-1.3)	0.448
Percentage of patients with abnormal LY 30 values	0	0	

Data presented as median (25th percentile and 75th percentile) and percentage P values by Mann-Whitney U-test and Chi-square analysis. TA: Tranexamic acid, EACA: ϵ -aminocaproic acid, ACT: Activated clotting time, RBS: Random blood sugar, HCT: Hematocrit, PTT: Partial thromboplastin time, LY: Lysis

The logistic regression model was poorly fitted and had a very weak relationship between the groups and the predicting factors, Nagelkerke's R^2 of 0.089. Patients received EACA were 0.417, (95% CI 0.174–0.997) times less likely to receive any blood transfusion in the first 24 h after surgery.

The most common adverse event encountered by the subjects in the two groups was a respiratory failure 18% ($n = 10$) in the EACA group and 9% ($n = 5$) in the TA group ($P = 0.21$). There was no difference in the incidence of stroke, renal dysfunction, cardiac arrest, reoperation, death, and seizure in the two groups [Table 6]. One patient from each group underwent re-operation for bleeding, and a surgical source was identified. The remaining patients from each group had reoperations for bleeding with no clear source recognized and were classified as a generalized coagulopathy.

Discussion

In this randomized controlled trial, the ability of EACA to decrease any transfusion intraoperatively to 24 h postoperatively was statistically significant compared to TA (25% vs. 44.8%, respectively $P = 0.027$). This trial further revealed EACA's ability to decrease chest tube

drainage, but the difference was not statistically significant. In addition, there were no significant differences in the evaluation of secondary endpoints (i.e., adverse events) comparing the two anti-fibrinolytic medications.

Our study represents one of the few which has directly evaluated TA versus EACA without the additional comparison with a lysine analog (Aprotinin) or placebo. The results of this trial revealed significantly more allogenic transfusions in the TA group compared to the EACA group [Figure 1]. A smaller study by Pinosky *et al.* examined 59 patients undergoing primary CABG and randomized them to EACA (150 mg/kg load and 10 mg/kg/h), TA (15 mg/kg load and 1 mg/kg/hr), or placebo.^[7] They showed no difference in perioperative transfusions between the groups; however, a significant increase in blood loss was observed at 6 and 12 h postoperatively in the patients receiving EACA as compared with TA. In our study, we did not include a placebo arm because the benefit of antifibrinolytic medication in reducing blood loss has been previously established and the administration of a lysine analogs in our institution is standard of care. This allowed our study to evaluate the effectiveness rather than the efficacy of using EACA or TA. A second study by Makhija *et al.* randomized 64 consecutive adult patients undergoing thoracic aortic surgery on CPB to receive either EACA or TA.^[15] EACA was given as a bolus of 50 mg/kg followed by maintenance infusion of 25 mg/kg/hr and the TA was a bolus of 10 mg/kg and maintenance of 1 mg/kg/h. In addition, Makhija *et al.* revealed no difference in overall transfusions between the two groups. It is worth mentioning that the dosing of antifibrinolytic medications in Makhija's study was considerably lower than our dosing regimen. We based our dosing regimen on the largest antifibrinolytic study (BART) which utilized a more aggressive dosing protocol.

Table 4: Chest tube drainage (mL)

Time interval after surgery (h)	EACA	TA	P
4	164 (115-250)	200 (130-313)	0.205
8	295 (197-400)	308 (210-512)	0.320
12	400 (280-520)	425 (285-680)	0.443
24	650 (500-940)	710 (447-1036)	0.516

Data presented as median (25th percentile and 75th percentile), P values by Mann-Whitney U-test. TA: Tranexamic acid, EACA: ϵ -aminocaproic acid

Table 5: Transfusion rate of intra-operative and 24 h postoperative blood products

Transfusions	EACA	TA	P
Intra-operative transfusions			
FFP	5.4% (3)	1.7% (1)	0.294
Platelets	10.7% (6)	5.2% (3)	0.273
PRBC	14.3% (8)	27.6% (16)	0.080
Transfusions within first 24 h postoperatively			
FFP*	5.4% (3)	17.2% (10)	0.046**
Platelets	8.9% (5)	15.5% (9)	0.284
PRBC	17.9% (10)	34.5% (20)	0.044**
Intra-operative transfusions+transfusions within first 24 h postoperatively			
FFP*	10.7% (6)	17.2% (10)	0.316
Platelets	17.9% (10)	19.0% (11)	0.879
PRBC	25% (14)	44.8% (26)	0.027
Any transfusion intra-operative (FFP/PRBC/platelets)	21.4% (12)	29.3% (17)	0.334
Any transfusion intra-operative + 24 h postoperative (FFP*/PRBC/platelets)	25% (14)	44.8% (26)	0.027**
Any transfusion within first 24 h postoperative (FFP/PRBC/platelets)	21.4% (12)	41.4% (24)	0.022**

**Statistically significant. Data presented as proportions in percentage (number), P values by Chi-square tests. TA: Tranexamic acid, EACA: ϵ -aminocaproic acid, FFP: Fresh frozen plasma, PRBC: Packed red blood cells

Table 6: 30-day postoperative complications

Complication	EACA	TA	P
Stroke	1.9% (1)	3.5% (2)	0.52
Renal dysfunction	1.9% (1)	3.5% (2)	0.52
Cardiac arrest	1.9% (1)	1.8% (1)	0.95
Respiratory failure	18% (10)	9% (5)	0.21
Re-operation within 24 h	5.7% (3)	7% (4)	0.77
Death	1.9% (1)	1.8% (1)	0.95
Seizure	0% (0)	0% (0)	

Data are presented as proportions in percentage (number of subjects), *P* values by Chi-square tests. TA: Tranexamic acid, EACA: ϵ -aminocaproic acid

The absence of a statistical difference between EACA and TA in chest tube drainage following cardiac surgery was similar to other studies that have compared the efficacy of EACA and TA.^[6,8,10,11] These studies include Martin *et al.* which found chest tube drainage of 41 ml/kg and 39 ml/Kg between EACA and TA, respectively. In addition, Makhija *et al.* observed a trend toward increased chest tube drainage in the TA group at all-time points (6, 12 and 24 h); however, this result did not reach statistical significance. This finding, which was also observed in our trial [Figure 2], is in disagreement with previous retrospective studies which pointed to TA as being slightly more effective in reducing blood loss.^[14,15]

The use of D-dimer can potentially indicate the effectiveness of an antifibrinolytic medication. Makhija *et al.* reported elevated postoperative levels of D-dimer in patients treated with EACA but noted no clinical sequelae. Our current study revealed no difference in D-dimer levels between the two lysine analogs assessed in the postbypass period and no incidence of thrombotic events in either group.

All secondary endpoints in this study were considered exploratory in nature; this study was not powered to find any significant difference between the groups. However, we noted similar rates of complications between the groups regarding renal dysfunction, strokes, seizure, death, and myocardial infarction. Our rate of renal dysfunction between the two groups is similar to the rate observed by Fergusson, *et al.* (4.5 per 100 patients for EACA and 4.0 per 100 patients for TA).^[3] Makhija *et al.* demonstrated a higher rate of renal dysfunction in patients receiving EACA versus TA, a finding also described by Eaton *et al.*^[16] Others are in agreement with our data and have shown no difference in renal outcome with the use of EACA compared with TA.^[17] The rate of stroke between our TA and EACA groups is comparable to that determined by Fergusson *et al.* (3.7 per 100 patients and 2.9 per 100 patients, respectively). There was a higher rate of respiratory arrest in the EACA group which was twice that compared to the TA group (18.9 vs. 8.6 per 100 patients, respectively); however, this did not reach statistical significance. The reason for the observed higher incidence

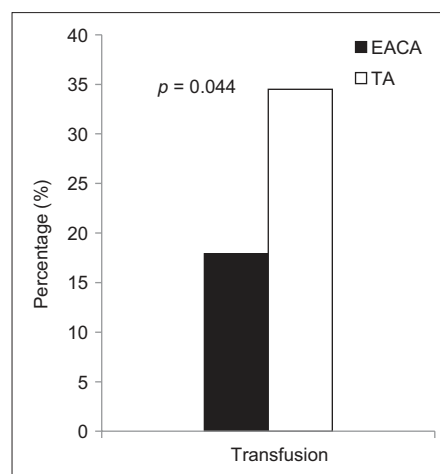


Figure 2: Percentage of patients that received packed red blood cell transfusions 24 hours post operation

of respiratory failure in the EACA group is unclear and given the number of patients, further investigation would be required to draw a conclusion. There is a higher rate of reoperation observed in the TA group compared to the EACA group which might indicate that there was an issue with surgical hemostasis in the TA study group and thus a need for more allogenic transfusion. A review of the patient records revealed that one patient from each group had a surgical source identified at the time of reoperation. All other reoperations for postoperative bleeding were described as “oozing” without a clear source.

Recent studies have cautioned about the effect of TA, and its role in promoting seizure activity.^[12,16,18,19] It has been suggested that this side effect is more pronounced at higher drug dosing regimens.^[13,20,21] Although our study did not reveal any seizures, we do recognize that we were not powered for this purpose. Moreover, there is a significant cost differential between the two medication with TA being approximately three times as expensive compared to EACA (\$30–100 per dosing vs. \$11–30 per dosing, respectively). Given the side effect profile demonstrated in previous studies and the cost of TA compared to EACA combined with the inability to show a patient benefit in decreasing bleeding and transfusion, it is prudent to consider EACA in patients undergoing cardiac surgery with CPB. Further, large multicenter randomized prospective studies would be required to definitively show the benefit of EACA over TA.

Limitations

There are several limitations to our study which must be considered. The primary objective of this trial was to compare the effectiveness of reducing blood loss and transfusion requirements between the two available lysine analogs (EACA vs. TA) during cardiac surgery. We powered the study based on a rate of transfusion of 61.8% (Fergusson), but in our study, we observed a lower

transfusion rate (35%). This lower rate of transfusion at our institution perhaps reflects that the BART study was more focused on a higher risk cardiac surgery population. The difference in transfusion requirements between the two groups is interpreted with caution because of the relatively small number of patients ($n = 114$); however, these results do bring into question previous studies which suggested TA as a more potent medication for reducing bleeding. We designed this as a pragmatic study; due to this reason blood transfusions did not follow an outlined standardized protocol. However, our institution adheres to restrictive transfusion practices, and the administration of PRBCs is based on a hemoglobin level <8 g/dl or hemodynamic instability with ongoing bleeding. In addition, whenever available TEG was utilized to guide the transfusion of FFP, platelets, and cryoprecipitate. As mentioned earlier, preoperative and intraoperative coagulation laboratory assessments were similar in the two groups.

In addition, while there was no statistically significant difference between the two study groups regarding the cardiac procedure, there were more CABG + valve operations in the TA group. The concomitant CABG + valve operation is associated with more intraoperative bleeding and potentially increasing the transfusion requirements appreciated in the TA group. Our analysis included the use of a trust score to assess the risks for patients receiving a transfusion. The trust score did reveal a difference between the groups with TA having a higher risk population which perhaps accounts for our observed difference in transfusions. Even though we reported that there is no statistically significant difference in postoperative morbidity between the two groups, this study was not adequately powered to find this difference. In addition, multiple comparisons including the interim analysis were performed as part of the study. The significance level reported for all the analyses are unadjusted for multiple comparisons. We recognize this is a single-center study, the results of the study may not be generalizable in other clinical care setting, and results may have been different if data from the projected sample size were analyzed. Overall results of this study needed to be interpreted cautiously because of the reason all the P values reported are unadjusted and the study is not powered to evaluate secondary endpoints reported.

A larger study would have yielded a stronger base for stating one antifibrinolytic is more effective over the other in preventing bleeding and transfusion. We also recognize that there exist a number of dosing regimens for both EACA and TA. At our institution, we adopted a similar dosing protocol as was performed by Fergusson, *et al.* in the BART trial. This was intentionally used because our study was designed using the transfusion rates available from this large international study.

Conclusion

The findings of this study suggest that EACA and TA have similar effects on chest tube drainage but EACA is associated with fewer transfusions in CABG alone surgeries but not in other high-risk cardiac surgeries. In our small sample size, the incidence of adverse events was also similar among the two groups. Our results suggest that EACA can be used in a similar fashion to TA which may result in a cost and morbidity advantage.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

- Ganz ML, Wu N, Rawn J, Pashos CL, Strandberg-Larsen M. Clinical and economic outcomes associated with blood transfusions among elderly Americans following coronary artery bypass graft surgery requiring cardiopulmonary bypass. *Blood Transfus* 2014;12 Suppl 1:s90-9.
- Bennett-Guerrero E, Zhao Y, O'Brien SM, Ferguson TB Jr., Peterson ED, Gammie JS, *et al.* Variation in use of blood transfusion in coronary artery bypass graft surgery. *JAMA* 2010;304:1568-75.
- Fergusson DA, Hébert PC, Mazer CD, Frenes S, MacAdams C, Murkin JM, *et al.* A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med* 2008;358:2319-31.
- Brown JR, Birkmeyer NJ, O'Connor GT. Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery. *Circulation* 2007;115:2801-13.
- Mangano DT, Miao Y, Vuylsteke A, Tudor IC, Juneja R, Filipescu D, *et al.* Mortality associated with aprotinin during 5 years following coronary artery bypass graft surgery. *JAMA* 2007;297:471-9.
- Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, *et al.* Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2011;4:CD001886.
- Pinosky ML, Kennedy DJ, Fishman RL, Reeves ST, Alpert CC, Ecklund J, *et al.* Tranexamic acid reduces bleeding after cardiopulmonary bypass when compared to epsilon aminocaproic acid and placebo. *J Card Surg* 1997;12:330-8.
- Chauhan S, Gharde P, Bisoi A, Kale S, Kiran U. A comparison of aminocaproic acid and tranexamic acid in adult cardiac surgery. *Ann Card Anaesth* 2004;7:40-3.
- Hunter GR, Young GB. Seizures after cardiac surgery. *J Cardiothorac Vasc Anesth* 2011;25:299-305.
- Martin K, Knorr J, Breuer T, Gertler R, Macguill M, Lange R, *et al.* Seizures after open heart surgery: Comparison of epsilon-aminocaproic acid and tranexamic acid. *J Cardiothorac Vasc Anesth* 2011;25:20-5.
- Martin K, Breuer T, Gertler R, Hapfelmeier A, Schreiber C, Lange R, *et al.* Tranexamic acid versus epsilon-aminocaproic acid: Efficacy and safety in paediatric cardiac surgery. *Eur J Cardiothorac Surg* 2011;39:892-7.
- Sharma V, Katznelson R, Jerath A, Garrido-Olivares L, Carroll J, Rao V, *et al.* The association between tranexamic acid and convulsive seizures after cardiac surgery: A multivariate analysis in 11 529 patients. *Anaesthesia* 2014;69:124-30.
- Murkin JM, Falter F, Granton J, Young B, Burt C, Chu M, *et al.* High-dose tranexamic acid is associated with nonischemic clinical seizures in cardiac surgical patients. *Anesth Analg* 2010;110:350-3.

14. Alghamdi AA, Davis A, Brister S, Corey P, Logan A. Development and validation of transfusion risk understanding scoring tool (TRUST) to stratify cardiac surgery patients according to their blood transfusion needs. *Transfusion* 2006;46:1120-9.
15. Makhija N, Sarupria A, Kumar Choudhary S, Das S, Lakshmy R, Kiran U, *et al.* Comparison of epsilon aminocaproic acid and tranexamic acid in thoracic aortic surgery: Clinical efficacy and safety. *J Cardiothorac Vasc Anesth* 2013;27:1201-7.
16. Martin K, Gertler R, Sterner A, MacGuill M, Schreiber C, Hörer J, *et al.* Comparison of blood-sparing efficacy of ϵ -aminocaproic acid and tranexamic acid in newborns undergoing cardiac surgery. *Thorac Cardiovasc Surg* 2011;59:276-80.
17. Eaton MP, Deeb GM. Aprotinin versus epsilon-aminocaproic acid for aortic surgery using deep hypothermic circulatory arrest. *J Cardiothorac Vasc Anesth* 1998;12:548-52.
18. Lecker I, Wang DS, Whissell PD, Avramescu S, Mazer CD, Orser BA. Tranexamic acid-associated seizures: Causes and treatment. *Ann Neurol* 2015;79:18-26.
19. Keyl C, Uhl R, Beyersdorf F, Stampf S, Lehane C, Wiesenack C, *et al.* High-dose tranexamic acid is related to increased risk of generalized seizures after aortic valve replacement. *Eur J Cardiothorac Surg* 2011;39:e114-21.
20. Goldstone AB, Bronster DJ, Chikwe J. Seizures after adult cardiac surgery. *J Cardiothorac Vasc Anesth* 2011;25:e25-6.
21. Kalavrouziotis D, Voisine P, Mohammadi S, Dionne S, Dagenais F. High-dose tranexamic acid is an independent predictor of early seizure after cardiopulmonary bypass. *Ann Thorac Surg* 2012;93:148-54.