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Efficacy and Safety of Tranexamic Acid Versus ε-Aminocaproic Acid in Cardiovascular Surgery

Olabisi Falana, PharmD, BCPS[1], and Gourang Patel, PharmD, MSc, BCPS[2]

Abstract

Background: Blood conservation is a major concern in the management of surgical patients because of transfusion-related complications, limited supply, and health care costs. Tranexamic acid (TXA) and ε-aminocaproic acid (εACA) are lysine analogue antifibrinolytics used to reduce surgical bleeding and transfusions. **Objective:** To evaluate the efficacy and safety of TXA compared with εACA in the management of cardiovascular surgical bleeding at an academic medical center. **Methods:** This single-center, retrospective, observational cohort study included 120 patients undergoing cardiovascular surgery with or without cardiopulmonary bypass, who received at least 1 dose of perioperative TXA or εACA. The efficacy outcome—massive perioperative bleeding—was a composite end point of chest tube drainage >1500 mL in any 8-hour period after surgery, perioperative transfusion of 10 or more units of packed red blood cells, reoperation for bleeding, or death from hemorrhage within 30 days. The safety outcomes were incidence of thromboembolic events, postoperative renal dysfunction, seizure, and 30-day all-cause mortality. **Results:** The primary end point—massive perioperative bleeding—occurred in 10 patients (16.7%) in the TXA group compared with 5 patients (8.3%) in the εACA group ($P = 0.17$). There were no significant differences in the secondary end points of 30-day all-cause mortality, thromboembolic events, renal dysfunction, and seizure. **Conclusions:** There were no differences in the efficacy and safety outcomes between TXA and εACA in the management of cardiovascular surgical bleeding at our institution. Considering the substantial cost difference and comparable efficacy and safety, εACA may have better value over TXA for reducing cardiovascular surgical bleeding.

Keywords

cardiovascular surgery, cardiopulmonary bypass, antifibrinolytic, hematology, bleeding, cost

Introduction

There are more than a million cardiovascular surgeries performed in the United States every year.[1] Perioperative bleeding is a major complication of cardiovascular surgery, which increases morbidity and mortality.[2,3] The use of cardiopulmonary bypass further increases this risk because of increased fibrinolysis.[4] Other common risk factors associated with significant bleeding include older age, preoperative anemia and coagulopathy, use of anticoagulant medications, and critical illness.[5-7]

Of the approximately 15 million units of packed red blood cells (pRBCs) that are transfused every year in the United States as a result of surgical bleeding, 80% are in cardiovascular surgery.[8] Blood conservation is a major concern because of limited supply, costs (up to $522 to $1183 per unit of pRBC), and risks associated with transfusion-related complications.[9,10] Tranexamic acid (TXA) and ε-aminocaproic acid (εACA) are lysine analogue antifibrinolytics administered to reduce surgical bleeding and have been demonstrated to decrease the number of blood transfusions during surgical procedures.[11] Both TXA and εACA inhibit fibrinolysis by interacting with the lysine-binding site of plasminogen, thereby inhibiting the activation of plasmin. These lysine analogues are the only antifibrinolytic agents currently available for intravenous administration in the surgical setting in the United States. TXA is about 10 times more potent and significantly more expensive than εACA.[11-14] Safety concerns with these agents include risk of thromboembolism and reduced clearance in patients with renal impairment.[13-16] The clinical studies that reported renal dysfunction are mainly in cardiovascular surgery with cardiopulmonary bypass.[17,18] Some

[1]The University of Chicago Medicine, Chicago, IL, USA
[2]Section of Pulmonary and Critical Care Medicine, Rush Medical College, Rush University Medical Center, Chicago, IL, USA

Corresponding Author:
Olabisi Falana, Neurocritical Care Pharmacist Specialist, Department of Pharmacy, The University of Chicago Medicine, 5841 S Maryland Ave, MC 0010, Chicago, IL 60637, USA.
Email: Olabisi.Falana@uchospitals.edu

retrospective studies have also observed increased seizure risk with intravenous TXA.[18-20]

The Society of Thoracic Surgeons and Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines recommend the use of lysine analogues for blood conservation in cardiac surgery patients (level of evidence IA).[5,6] The American Society of Anesthesiologists (ASA) Guidelines for Perioperative Blood Transfusion and Adjuvant Therapies, however, recommends against the routine use of intravenous antifibrinolytics for the treatment or prevention of surgical bleeding, except for consideration in patients at high risk for major bleeding (eg, repeat cardiac surgery).[7] In 2008, Fergusson et al[17] published the Blood Conservation using Antifibrinolytics in a Randomized Trial (BART) comparing the efficacy and safety of aprotinin and lysine analogs (TXA and εACA). A 2011 reanalysis of the BART study by Raghunathan et al[21] concluded that εACA has increased clinical value in high-risk cardiac surgery. The clinical value equation used for this analysis assessed quality and volume per cost, including patient satisfaction and clinical and functional outcomes.[21]

At Rush University Medical Center (RUMC), εACA is the formulary antifibrinolytic agent for the prevention of cardiovascular surgical bleeding. However, εACA has experienced some national supply shortages because of manufacturing issues in 2011 and more recently in 2013.[22] As a result, RUMC changed its formulary antifibrinolytic agent to TXA in October 2011. Our goal is to evaluate the efficacy and safety of TXA compared with εACA in the management of cardiovascular surgical bleeding at our institution for reasons of national εACA shortage.

Methods

The study was a single-center, retrospective, observational cohort study at RUMC, a 673-bed tertiary care academic medical center located in Chicago, Illinois. About 20 500 surgeries are performed annually at RUMC, of which about 1600 are cardiovascular surgeries. Prior to the commencement of this study, Midwestern University and RUMC institutional review boards approved the study.

Study Population

Patients were included if they were 18 years of age or older, undergoing major cardiac surgery with or without cardiopulmonary bypass, and received at least 1 dose of TXA between October 2011 and October 2012 (group TXA) or εACA between January 2010 and October 2011 (group εACA). Patients undergoing one or more of the following cardiac surgeries were included: coronary artery bypass graft (CABG), aortic valve replacement or repair, mitral valve replacement or repair, tricuspid valve replacement or repair, and aortic surgeries. Patients undergoing cardiac transplant, left-ventricular assist device implantation, or congenital defect surgery were excluded from the study. Patients who did not receive antifibrinolytic therapy or those who received multiple antifibrinolytic agents were excluded from this study. If a patient had a repeat operation for nonbleeding reasons during the same admission, only data from the first operation were included in the analysis.

There are several dosing regimens (fixed and weight-based) for TXA and εACA.[2,12] The dosing strategy for our study was based on the standard RUMC dosing regimen of TXA 1-g bolus, followed by a 500-mg/h infusion over 5 hours, and εACA 10-g bolus, followed by a 1-g/h infusion over 5 hours. These dosing schemes were developed in collaboration with pharmacy, surgical, nursing, and anesthesia leadership. Demographic data, baseline characteristics, and primary and secondary outcomes were collected for each patient using our electronic medical record.

Outcomes

The objective of this study was to evaluate the efficacy and safety of TXA compared with εACA in the management of cardiovascular surgical bleeding at an academic medical center for reasons of national shortage of εACA. The hypothesis was that TXA and εACA would have similar efficacy and safety for the prevention of cardiovascular surgical bleeding. The efficacy outcome of this study—massive perioperative bleeding—was a composite of chest tube drainage greater than 1500 mL in any 8-hour period after surgery, perioperative transfusion of 10 or more units of pRBCs, reoperation for bleeding, or death from hemorrhage within 30 days. The safety outcome measures were incidence of thromboembolic events, postoperative renal dysfunction, seizure, and 30-day all-cause mortality. Thromboembolic events were defined as any new myocardial infarction, deep-vein thrombosis, pulmonary embolism, or cardioembolic stroke. Renal dysfunction was defined as postoperative doubling of baseline serum creatinine or initiation of renal replacement therapy. Investigators also conducted analyses on additional outcomes, including postoperative 8-hour and 24-hour chest tube output, total chest tube output, number of blood products administered, and total blood products given within the 24-hour perioperative period, to better comprehend blood product(s) use in our cardiovascular surgery population.

Statistical Methods

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS v.18) statistical software. Nominal variables were analyzed using a χ^2 test or Fischer's exact test, and continuous variables were analyzed using a Student t test or Mann-Whitney U test, as appropriate. Descriptive data are presented as mean ± standard deviation

for normally distributed data or as medians and interquartile ranges for skewed distributions, as appropriate. All tests were 2-sided, with a 5% level of significance—that is, a *P* value ≤0.05 indicating statistical significance.

Results

A total of 967 orders (780 TXA orders and 187 εACA orders) were identified using an interface between EPIC electronic medical record and University HealthSystem Consortium database. Of these, 60 patients in the TXA group met the inclusion criteria for the study; 79 patients from the εACA group met the inclusion criteria, and the first 60 patients were selected for a 1:1 patient ratio for comparison with the TXA group. Patients were excluded if they were younger than 18 years old and had had left-ventricular assist device implantation, congenital defect surgery, orthopedic surgery, or neurosurgery. A total of 120 patients were included in our study, of whom 34 (56.7%) and 30 (50%) were male in the TXA and εACA group, respectively. The mean age was 64.2 ± 14.3 years in the TXA group and 65.9 ± 13.8 years in the εACA group. There were no statistically significant differences in any of the baseline characteristics, except for higher ASA scores (P = 0.05) and higher intraoperative protamine doses (P = 0.003) in the εACA group (Table 1). The ASA score is an assessment of the physical health of a patient prior to surgery but does not predict surgical risk or outcome. Mean length of hospital and intensive care unit stays were 12.7 ± 8 and 8.7 ± 13.9 days in the TXA group, and 12.9 ± 6.7 and 5.1 ± 3.9 days in the εACA group. Although not statistically significant, the difference in the length of intensive care unit stay (9 days in the TXA vs 5 days in the εACA group, P = 0.06) between the 2 groups is clinically significant. The majority of patients were admitted for elective surgery (Table 1) and had multiple procedures—that is, valve replacement or repair with CABG (Figure 1). In addition, there was a statistically significant difference in patients undergoing repeat cardiac surgery (12% in the TXA vs 33% in the εACA group, P = 0.04; Figure 2).

Among the 120 patients, the primary efficacy outcome of massive perioperative bleeding occurred in 10 (16.7%) in the TXA group and 5 (8.3%) in the εACA group (P = 0.17), as described in Table 2. This difference was largely driven by reoperation for bleeding in the TXA group (11.7% vs 3.3%; P = 0.16). There were no significant differences in the individual components of the primary efficacy outcome: chest tube drainage greater than 1500 mL in any 8-hour period after surgery (8.3% in each group, P = 1.00), perioperative transfusion of 10 or more units of pRBCs (5.0% vs 3.3%, P = 0.65), reoperation for bleeding (11.7% vs 3.3%, P = 0.16), and death from hemorrhage within 30 days (1.7% in each group, P = 1.00). Additionally, there was no statistically significant difference in the safety end points of 30-day all-cause mortality (6.7% vs 3.3%, P = 0.68), thromboembolic events (13.3% vs 5.0%, P = 0.28), postoperative renal dysfunction (20.0% vs 8.3%, P = 0.11), and development of a seizure (no incidence in either treatment group). On average, the total chest tube output was 2643 mL in the TXA group compared with 1677 mL in the εACA group (P = 0.08). Patients in the TXA group also received more blood products compared with those in the εACA group (8.2 units vs 5.4 unit, P = 0.11). However, there was a significant difference in autologous (Cell Saver) blood transfusion (523 mL in the TXA vs 678 mL in the εACA group, P = 0.04) between the 2 groups (Table 2).

Discussion

Blood conservation is a principal goal in the management of patients undergoing major surgical procedures.[23-26] Previous studies comparing the efficacy and safety of TXA and εACA in cardiovascular surgery have demonstrated no clinically relevant difference in efficacy and safety between the 2 agents.[11,17,21] The results from our study support these clinical findings. The outcome trends demonstrated in our study are similar to the BART outcomes: 12.1% in each group for the primary outcome and 3.9% and 4% for 30-day all-cause mortality.[17,21] In addition, the investigators also observed trends toward less bleeding, reoperation for bleeding, and exposure to blood products in the εACA group. The increased volume of autologous (Cell Saver) blood transfusion in the εACA group may have contributed to less allogeneic blood product transfusions in that group. Despite higher protamine doses in the εACA group, this did not affect the clinical outcome of our study because this correlated with the heparin doses administered during surgery.

One difference between this study and the BART study was the fixed-dose versus weight-based regimens. The dosing scheme used in the BART was as follows: TXA, 30-mg/kg loading dose followed by a 16-mg/kg/h infusion for the duration of surgery; εACA, 10-g loading dose followed by a 2-g/h infusion for the duration of surgery. On average, we use 3.5 g of TXA and 15 g of εACA per surgery at our institution compared with 8.8 g of TXA and 20 g of εACA with the BART regimen (assuming surgery duration of 5 hours for an 80-kg patient). In rare cases (3 out of 120 cases), the anesthesiologist chose to administer half dose in patients with renal dysfunction and/or other risk factors for thromboembolic complications. Given the discrepancy in dosing regimens, it is uncertain if our outcomes would be different using the BART dosing. At our institution, the pharmacy acquisition cost per cardiovascular surgery for TXA was $145.25, which was about 40 times more than the cost of $3.66 for εACA in 2013.

There were several limitations to our study. The BART study design only included patients undergoing high-risk cardiac surgeries, defined as a surgical intervention with an

Table 1. Baseline Characteristics.

Demographic Data	TXA (n = 60)	εACA (n = 60)	*P* Value
Age (mean ± SD)	64.2 ± 14.3	65.9 ± 13.8	0.51
Male	34 (56.7%)	30 (50%)	0.46
Body mass index	27.8 ± 5.9	28.2 ± 6.6	0.73
Race			0.20
African American	23 (38.3%)	14 (23.3%)	
Caucasian	30 (50.0%)	35 (58.3%)	
Hispanic	3 (5.0%)	2 (3.3%)	
Length of hospital stay (mean ± SD)	12.7 ± 8.0	12.9 ± 6.7	0.86
Length of ICU stay (mean ± SD)	8.7 ± 13.9	5.1 ± 3.9	0.06
American Society of Anesthesiologists score			0.05
Score 3	23 (38.3%)	11 (18.3%)	
Score 4	36 (60.0%)	48 (80.0%)	
Score 5	1 (1.7%)	0	
Unknown	0	1 (1.7%)	
Admission status for surgery			
Elective	31 (52%)	32 (53%)	
Urgent	18 (30%)	15 (25%)	
Emergent	11 (18%)	13 (22%)	
Comorbidities prior to admission			
Stroke	11 (18.3%)	10 (16.7%)	0.81
Thromboembolism	11 (18.3%)	10 (16.7%)	0.81
Myocardial infarction	27 (45.0%)	21 (35.0%)	0.26
Heart failure	24 (40.0%)	21 (35.0%)	0.57
Ejection fraction < 40%	7 (11.7%)	5 (8.3%)	0.54
Renal insufficiency	19 (31.7%)	12 (20.0%)	0.08
Acute	4 (6.7%)	2 (3.3%)	
Chronic	9 (15.0%)	7 (11.7%)	
End-stage renal disease	6 (10.0%)	3 (5.0%)	
Severe liver disease	2 (3.3%)	5 (8.3%)	0.44
Diabetes mellitus	15 (25.0%)	23 (38.3%)	0.12
Cancer	11 (18.3%)	7 (11.7%)	0.31
Medications prior to admission			
Digoxin	6 (10.0%)	7 (11.7%)	0.77
ACE inhibitor	31 (51.7%)	30 (50.0%)	0.86
Nitrates	10 (16.7%)	6 (10.0%)	0.29
β-Blocker	42 (70.0%)	31 (51.7%)	0.04
Calcium channel blocker	16 (26.7%)	17 (28.3%)	0.84
Diuretic	27 (45.0%)	29 (48.3%)	0.72
Warfarin	13 (21.7%)	7 (11.7%)	0.19
Aspirin[a]	39 (65.0%)	43 (73.3%)	
Last dose >24 hours	31 (51.7%)	39 (6.7%)	0.43
Last dose <24 hours	8 (13.3%)	4 (21.7%)	0.26
P2Y12 inhibitor (clopidogrel, prasugrel)[b]	12 (20.0%)	13 (21.7%)	0.82
Heparin	19 (31.7%)	24 (40.0%)	0.34
≤10 000 units/d	6 (10.0%)	9 (15.0%)	0.51
>10 000 units/d	13 (21.7%)	16 (26.7%)	
GIIb/IIIa receptor inhibitor	1 (1.7%)	1 (1.7%)	1.00
Thrombolytic therapy	0	0	1.00
Perioperative medications and labs			
Heparin dose (units, mean ± SD)	30 283 ± 8622	31 375 ± 7780	0.47
Protamine dose (mg, mean ± SD)	211 ± 69	251 ± 69	0.003
Preoperative INR 1.5-3.0	5 (8.3%)	0	0.06
Preoperative hemoglobin			0.30
11-14 g/dL	35 (58.3%)	37 (61.7%)	
>14 g/dL	4 (6.7%)	8 (13.3%)	
24-Hour postoperative hemoglobin			0.75
11-14 g/dL	54 (90.0%)	55 (91.7%)	
>14 g/dL	6 (10.0%)	5 (8.3%)	
Surgery time			
Cardiopulmonary bypass (minutes, mean ± SD)	166 ± 83	159 ± 67	0.61
Cross-clamp time (minutes, mean ± SD)	119 ± 61	118 ± 53	0.91

Abbreviations: TXA, tranexamic acid; ε-ACA, ε-aminocaproic acid; ICU, intensive care unit; ACE, angiotensin-converting enzyme; INR, international normalized ratio.
[a]All aspirin doses were ≤325 mg.
[b]All patients on a P2Y12 inhibitor discontinued it 5 to 7 days prior to surgery.

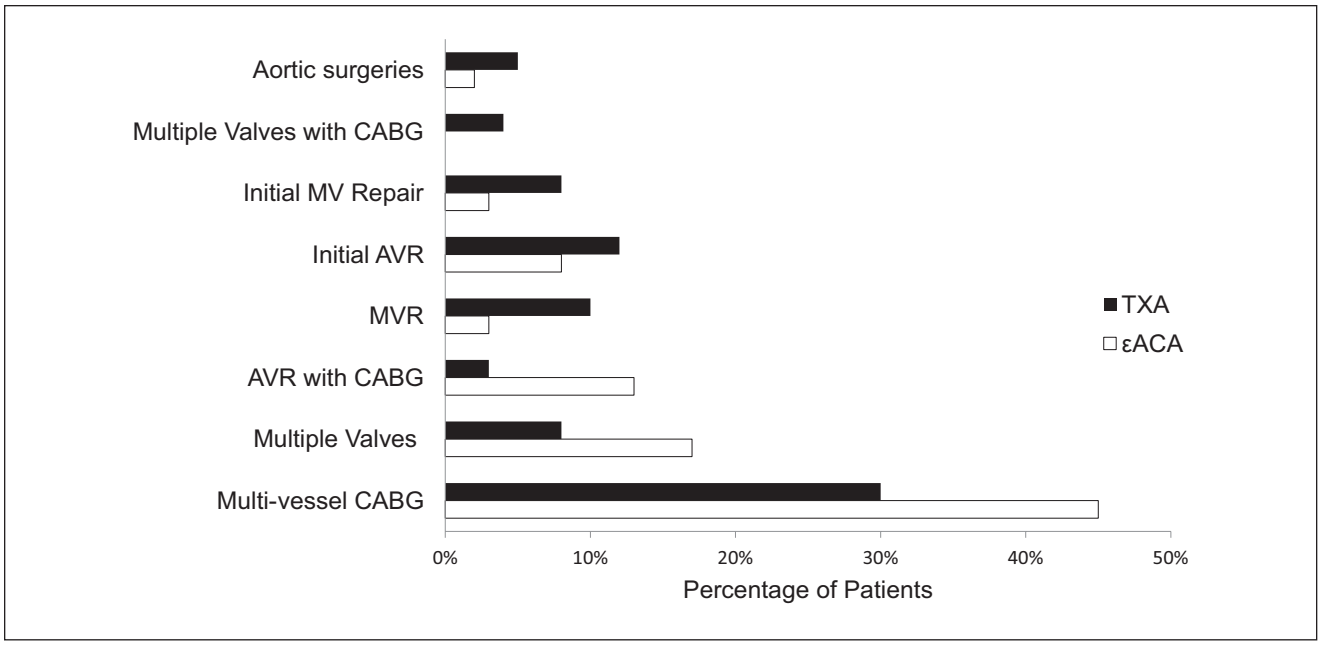

Figure 1. Type of surgery.
Abbreviations: CABG, coronary artery bypass graft; MV, mitral valve; AVR, aortic valve replacement; MVR, mitral valve replacement; TXA, tranexamic acid; εACA, ε-aminocaproic acid.

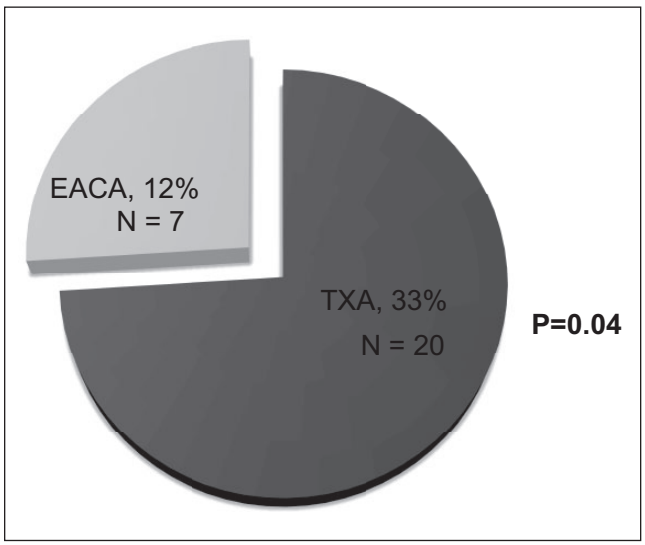

Figure 2. Re-do sternotomy patients.
Abbreviations: TXA, tranexamic acid; EACA, ε-aminocaproic acid.

average mortality of at least twice of an isolated primary CABG and a risk of repeat surgery >5%.[17] Patients who were undergoing lower-risk surgeries, such as isolated primary CABG with or without cardiopulmonary bypass, isolated mitral-valve repair, or aortic-valve replacement, were excluded.[17] One limitation of our study was that we included patients undergoing high- and low-risk cardiac surgery rather than isolated high-risk cardiac surgery. Therefore, it is difficult to determine if antifibrinolytic agents are more beneficial in a certain subset of cardiac surgery patients. However, this study is reflective of the patient populations who receive antifibrinolytic agents at our institution. Another limitation was the retrospective nature of our study; the accuracy of data collection was highly dependent on proper and accurate documentation. In addition, data for each agent were collected during different time periods; thus, variation in surgeons, surgical technique, or clinical practice could have affected our results. TXA was used for a period of about 12 months, which constricted our sample size. Larger sample sizes are needed to more effectively evaluate the impact of this study at our institution and reduce any type II error. Finally, a major limitation was that patients were not matched based on surgery types, and difference in acuity of patients may have skewed the results.

Because of continued drug shortages with εACA at the time of the writing of this article, we are currently using TXA as an alternate therapy at our institution. Given the results from this study, we plan to switch back to εACA as soon it is available on the market. Our future direction includes continued data collection for a larger sample size with the continued use of TXA.

Conclusion

In summary, there were no significant differences in the efficacy and safety outcomes between TXA and εACA for the management of cardiovascular surgical bleeding at our

Table 2. Outcomes.

	TXA (n = 60)	εACA (n = 60)	*P* Value
Major primary outcome			
Massive perioperative bleeding	10 (16.7%)	5 (8.3%)	0.17
Bleeding from chest tubes	5 (8.3%)	5 (8.3%)	1.00
Massive transfusion	3 (5.0%)	2 (3.3%)	0.65
Death from hemorrhage	1 (1.7%)	1 (1.7%)	1.00
Reoperation for bleeding	7 (11.7%)	2 (3.3%)	0.16
Major secondary outcomes			
30-Day all-cause mortality	4 (6.7%)	2 (3.3%)	0.68
Thromboembolic event	8 (13.3%)	3 (5.0%)	0.28
Myocardial Infarction	0	1 (1.7%)	
Stroke	0	0	
Deep-vein thrombosis	3 (5.0%)	1 (1.7%)	
Pulmonary embolism	1 (1.7%)	0	
Other	4 (6.7%)	1 (1.7%)	
Renal impairment	12 (20.0%)	5 (8.3%)	0.11
Doubling of baseline creatinine	6 (10.0%)	4 (6.4%)	
Postoperative renal replacement therapy	6 (10.0%)	1 (1.7%)	
Seizures	0	0	1.00
Other outcomes			
Bleeding from chest tubes			
8 Hours after surgery (mL)	705 ± 988	591 ± 588	0.45
24 Hours after surgery (mL)	1093 ± 1141	1013 ± 1055	0.69
Total chest tube(s) output (mL)	2643 ± 3931	1677 ± 1523	0.08
Blood products administered (units)			
Total (mean ± SD)	8.2 ± 10.6	5.4 ± 7.6	0.11
Packed red blood cells (mean ± SD)	3.3 ± 4.6	2.5 ± 3.0	0.25
Fresh frozen plasma (mean ± SD)	1.8 ± 3.1	1.2 ± 2.2	0.21
Platelets (mean ± SD)	2.4 ± 2.9	1.4 ± 1.9	0.02
Cryoprecipitate (mean ± SD)	0.7 ± 1.2	0.4 ± 1.1	0.22
Cell Saver (mL) (mean ± SD)[a]	523 ± 316	678 ± 457	0.04

Abbreviations: TXA, tranexamic acid; ε-ACA, ε-aminocaproic acid.
[a]Cell Saver is autologous blood transfusion from the patient's salvaged blood during surgery.

institution. Considering the substantial cost difference and comparable efficacy and safety, εACA may have better value over TXA for reducing cardiovascular surgical bleeding. TXA may be used as an alternative to εACA for reducing cardiovascular surgical bleeding during periods of εACA drug shortages. Larger sample sizes are needed to more effectively evaluate the impact of this study at our institution.

Authors' Note

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Declaration of Conflicting Interests

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