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Original Article

Blood Conservation Using Tranexamic Acid versus Epsilon Aminocaproic Acid in Cardiac Surgery: A Randomized Controlled Trial

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ABSTRACT

Background: This study compares the efficacy of tranexamic acid (TXA) to epsilon aminocaproic acid (EACA) in reducing blood loss in patients undergoing cardiac surgery.

Methods: This was a double-blinded randomized trial. Patients (n = 100) undergoing cardiac surgery were randomized to receive either TXA (10 mg/kg bolus followed by an infusion of 1 mg/kg/hr) or EACA (150 mg/kg bolus followed by an infusion of 20 mg/kg/hr). The primary outcome measure was a difference in transfusion amounts. Secondary outcomes measured included: the amount of transfusion during the operative procedure, calculated Red blood cell (RBC) volume change, postoperative creatinine, time to extubation, chest tube output and length of ICU stay.

Results: A total of 100 patients consented, of whom 82 completed participation in the study (EACA arm = 42 patients and TXA arm = 40 patients). There was no difference in patient demographics. Similarly, there was no difference between the type of cardiac surgery, cardiopulmonary bypass (CPB) time, intraoperative fluids, and procedure time. Primary marker comparison showed no difference in the frequency or amount of transfusion between groups in the operating room, ICU, or in total. Additionally, there was no difference in hematocrit (Hct), chest tube output, time to extubation, and length of stay. Post Hoc analysis indicated that red blood cell volume change through postoperative day 2 was larger in TXA than EACA; P = 0.03).

Conclusion: There was no difference in clinically significant outcome criteria between the TXA and EACA groups. Given the lower cost of EACA, this study further supports EACA as an appropriate antifibrinolytic agent for cardiac surgery. (Funded by the Department of Anesthesiology, Loma Linda University Medical Center; ClinicalTrials. gov number, NCT01248104.)

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Intraoperative and postoperative blood loss in patients undergoing cardiac surgery involving cardiopulmonary bypass (CPB) has remained a constant challenge to both the anesthesiologist and surgeon. Transient platelet dysfunction and excessive fibrinolysis are proposed mechanisms by which CPB results in excessive blood loss that results in a higher incidence of blood product transfusion (1). The increased in-hospital mortality, high cost, and infectious risk seen in patients receiving allogenic transfusions have driven the search for an ideal blood conserving strategy in cardiac surgery (2). Antifibrinolytic use is one means to address this issue and has become the standard of care for these patients (3). However, the superiority of one agent over another has remained unclear (3).

In the United States currently available antifibrinolytics include tranexamic acid (TXA) and epsilon aminocaproic acid (EACA), two synthetic lysine analogues that have been shown in randomized controlled trials to also decrease blood loss when compared to placebo (3). Aprotinin is a serine protease inhibitor whose distribution was halted in 2008 by the FDA after evidence from the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) suggested aprotinin was associated with a higher 30-day mortality than either TXA or EACA (4). Subsequent reviews of existing data have validated concerns regarding the safety of aprotinin, and have recommended the use of the lysine analogues as safer alternatives to reduce blood loss in these patients (5).

Although numerous studies have validated the efficacy of the lysine analogues in reducing blood loss when compared to placebo, few have compared them to each other in adult patients undergoing cardiac surgery. An updated Cochrane review published in 2011 evaluated the use of the three antifibrinolytics for minimizing perioperative allogeneic blood transfusion in major surgery. Of the 252 randomized controlled trials, 8 compared TXA to EACA in head-to-head trials and found no statistical difference in the rate of allogenic blood transfusion, volume of blood transfused, post-operative blood loss, rates of reoperation for bleeding, mortality or hospital length of stay. Six of the eight were performed in cardiac surgery (one study was conducted in liver transplant and one in orthopedic surgery) and subgroup analysis showed that the risk of receiving an allogenic blood transfusion was slightly higher in patients treated with TXA compared to EACA (RR=1.07) [2]. A study published in 2011 by Raghunathan et al reanalyzed data from the BART authors and compared the TXA and EACA arms to each other. Of the 1556 included patients, no significant difference in massive bleeding and other related parameters was found between the two groups. Of note, there is considerable cost difference between the two lysine analogues, with the authors reporting TXA costing approximately 225 times more than EACA at their institution. Thus, they concluded that based on non-inferiority, EACA should be the drug of choice in these patients (6). Recently, Blaine et al compared the efficacy of EACA and TXA and demonstrated no difference in postoperative bleeding or red cell transfusions but did demonstrate a trend for the EACA group to receive more hemostatic medications (7).

Current evidence supporting the use of one lysine analogue over the other is far from robust and recent research suggests a "trend" between EACA use and less bleeding, reoperation for bleeding, and exposure to blood products (8). Thus, we designed a prospective double-blinded randomized trial in an attempt to detect a difference between TXA and EACA in reducing transfusion in patients undergoing cardiac surgery.

METHODS

This study was approved by our Institutional Review Board and registered in ClinicalTrials.gov (NCT01248104). Written informed consent was obtained from adult patients scheduled for primary cardiac surgery with anticipated CPB. Patients were excluded if they weighed < 30 kg, had pre-existing coagulopathy (INR > 1.5, platelets < 100 ×109/L), had renal failure (defined as BUN/Cr ⩾ 20:1), had severe liver disease (AST&ALT > 3x normal), or were undergoing cardiac surgery known to be associated with greater risk for bleeding and transfusion such as complex aortic surgery, or combination valve replacement with coronary artery bypass graft surgery. The research pharmacist used computer randomization to assign patients to receive

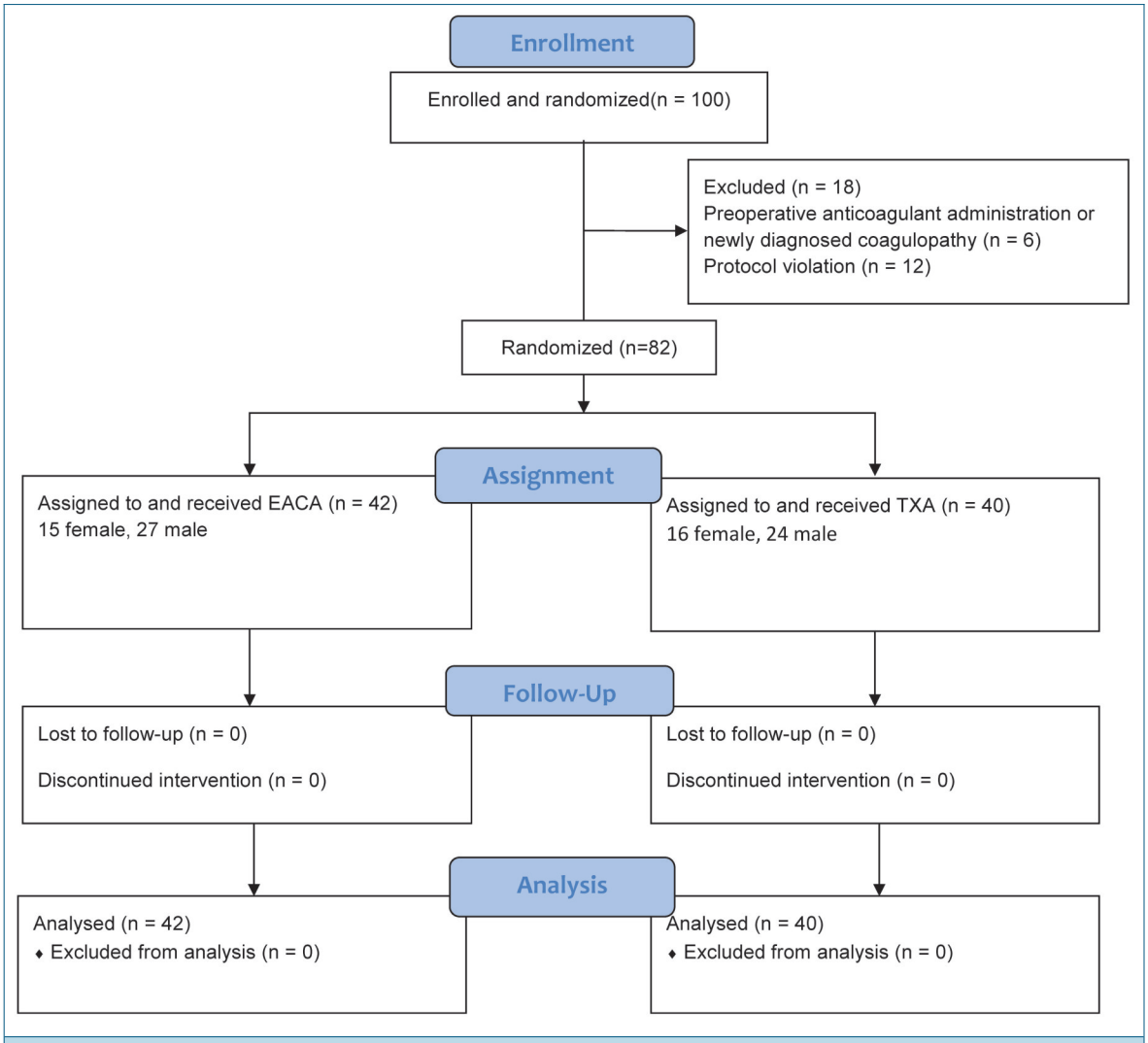

Figure 1. The CONSORT diagram.

either TXA or EACA. Researchers, patients, surgeons, and nurses caring for the patients were unaware of the study group assignments throughout hospitalization. Dosing was chosen based on published equivalency data (approximately tenfold greater potency of TXA compared to EACA) (9) and drugs were delivered by the pharmacy in a blinded fashion. The infusion and bolus drug doses were prepared by the pharmacy with study drug concentrations adjusted based on patient weight, so that each drug was provided in identical volumes and delivery rates to facilitate blinding. The EACA group received a bolus of 100 mg/kg given over 15 minutes shortly after induction of anesthesia followed by an infusion of 10 mg/kg/hr. The TXA group received a bolus of 10 mg/kg over 15 minutes followed by an infusion of 1 mg/kg/hr. All intraoperative care decisions regarding transfusion were left to the discretion of the attending anesthesiologist. Our institutional protocol follows published guidelines, with an intraoperative hemoglobin target range of 6 to 8 g/dl (10).

Data Collection

Patients undergoing primary cardiac surgery at Loma Linda University Medical Center were screened and 100 patients underwent randomization. In addition, patient demographics, type of surgery, duration of CPB, total surgery time,

Table 1. Demographic Data.

Demographic Parameters	EACA	TXA	P value
Gender (male : female) — no.	15 : 27	16 : 24	0.69
Age (range) — yr	63 (54 - 69)	64 (54 - 69)	> 0.99
BMI (range) — kg/m^2	30 (27 - 33)	29 (25 - 31)	> 0.99
Estimated blood volume (range) — ml	5158 (4732 - 5824)	5191 (4392 - 5738)	> 0.99
Preop Hct (range) — %	39 (37 - 43)	41 (38 - 43)	> 0.99
Cardiopulmonary Bypass Time (range) — min	117 (102 - 151)	127 (107 - 143)	> 0.99
Operative Time (range) — min	371 (325 - 417)	382 (339 - 435)	> 0.99
Surgical Procedure (Valve : CABG) — no.	18 : 24	23 : 17	0.24

BMI, body-mass index; EACA, epsilon aminocaproic acid; TXA, tranexamic acid; Hct, hematocrit; CABG, coronary artery bypass grafting.

chest tube output in operating room (OR) and postoperative day (POD) 1, blood loss and transfusion (mL) in the operating room and during the first 48 hours in the ICU, POD 1 creatinine, and length of ICU stay were also recorded. The RBC volume was calculated from hematocrit (Hct) multiplied by estimated blood volume derived from the equation developed by the International Council for Standardization in Hematology (11). This equation uses age, gender, and body surface area derived from height and weight to estimate blood volume. The RBC volume was calculated at baseline, at end of surgery, on POD 1, and on POD 2. Change in RBC volume was calculated as the difference from baseline plus the average Hct of packed RBC (0.55) times the volume of packed RBC transfused documented in transfusion records.

Statistical Analysis

The primary outcome measure was the intergroup difference in total transfusion amounts up to POD 2. A power analysis based on the comparison of a 15% difference in total transfusion amounts up to POD 2 between the treatment groups indicated a total sample size of 80 with a power of 0.8, confidence interval 0.9, and p= 0.05. Primary and secondary continuous variables were compared by multivariate linear regression analysis to adjust for possible covariates of intraoperative fluids, age, bypass time, and procedure time. Tukey-Kramer test was then used to compare for specific differences between groups for each variable. Categorical data were compared using Fisher's exact test. All comparisons were made at a significance level of 0.05, and analysis was performed with Minitab version 17 (Minitab Inc, State College, PA, USA).

RESULTS

Of 100 originally enrolled in the study, 82 patients completed participation. As shown in the CONSORT diagram (Figure 1), 6 patients were excluded secondary to being on anticoagulants and / or having newly diagnosed coagulopathy; 12 patients were excluded secondary to protocol violation in TXA or EACA administration. Patient demographic data are summarized in Table 1. There was no significant difference in age, gender, the body-mass index (BMI; the weight in kilograms divided by the square of the height in meters), estimated blood volume, and baseline Hct. There was also no difference in type of surgical procedure, cardiopulmonary bypass time, or operative time between groups (Table 1). The primary outcome measure showed that there was no difference in PRBC transfusion frequency or amounts in the operating room or the in ICU up to POD 2 (Table 2).

Post hoc analysis of this primary outcome measure demonstrated that the EACA group had a significantly smaller decrease in RBC volume change on POD 2 compared to the TXA (481 ml ± 153 vs. 579 ml ± 214, $P < 0.04$) (Table 2 and Figure 2). The percent decrease in RBC volume change difference was 17% between the TXA and EACA groups. Analysis of secondary mea-

Table 2. Study Outcome Comparisons.

Outcome Parameters	EACA	TXA	P value
Transfused PRBC in OR — no. (%)	7 (17)	10 (25)	0.35
Transfused PRBC in OR or ICU — no. (%)	10 (24)	14 (35)	0.18
PRBC transfusion in OR & ICU — ml	116 ± 296	161 ± 274	0.82
PRBC transfusion in OR — ml	108 ± 283	131 ± 247	0.99
FFP transfusion in OR & ICU — ml	63 ± 164	98 ± 277	0.90
FFP transfusion in OR — ml	51 ± 146	71 ± 239	0.99
Cell saver transfusion — ml	671 ± 208	664 ± 226	0.89
POD 1 Hct (range) — %	32 (29 - 35)	32 (28 - 36)	0.99
Chest Tube Output up to POD 1 (range) — ml	565 (341 - 767)	437 (318 - 673)	0.60
Creatinine POD 1 (range) — mg/dl	0.9 (0.7 - 1.1)	0.9 (0.8 - 1..1)	0.99
Intraoperative crystalloid (range) — ml	1200 (912 - 1647)	1262 (900 - 1620)	0.98
Time to extubation (range) — min	192 (158 - 269)	229 (131 - 424)	0.45
Length of stay (range) — day	4 (4 - 5)	4 (4 - 5.3)	0.99
RBC volume decrease to POD 2 — ml	481 ± 153	579 ± 214	0.04

EACA, epsilon aminocaproic acid; TXA, tranexamic acid; PRBC, packed red blood cells; OR, operating room; ICU, intensive care unit; FFP, fresh frozen plasma; POD, post-operative day; RBC, red blood cell.

sures showed no difference between the groups in: FFP transfused, change in POD 1 Hct, chest tube output, POD 1 creatinine, intraoperative crystalloid, time to extubation, and length of stay (Table 2). Only one patient in the TXA received platelets and no patients received cryoprecipate. There was also no difference in adverse events between the TXA and EACA groups and no patients were required re-exploration secondary to post-operative bleeding. Specifically, no patient in the TXA or EACA groups suffered: renal failure, seizures, stroke, or post-surgical myocardial infarction. Additionally, no mortality was reported in either group at thirty days.

DISCUSSION

Conservation of blood transfusion is of utmost importance for patients undergoing cardiac surgery, and use of antifibrinolytics to facilitate this goal has become routine. Previous works comparing the efficacy of TXA and EACA have demonstrated no significant differences (2, 6, 12). However, there are few studies that have directly compared EACA to TXA in a prospective double-blinded fashion. Our results support previous studies in that we did not find a difference in transfusion rate between patients treated with EACA and those treated with TXA. Similarly, we did not find a difference in postoperative renal function, time to extubation, or length of stay between the groups. This is in concordance with the reanalysis of the data from the BART study (6).

While these prior reports have shown that both EACA and TXA can reduce blood loss in patients undergoing cardiac surgery involving CPB, there are some differences with our study design. Previous studies compared different dosing regimens (i.e. bolus dosing of one drug compared with infusion dosing of the other)(13). We corrected for this difference by standardizing the dosing regimen based on published equivalent potency between TXA and EACA. Further, prior studies did not always standardize drug infusion dosing according to the length of surgery (1, 13-15). Our patients were given continuous infusions of the study drugs for a defined length of time beyond separation from CPB, to adjust for potential differences attributable to variation in bypass times and duration of heparinization. These differences may account for our finding of less RBC volume decrease in the EACA group vs. TXA. However, it is important to note that our study did not demonstrate this difference to impact transfusion, length of stay, time to extubation, and post-operative Hct.

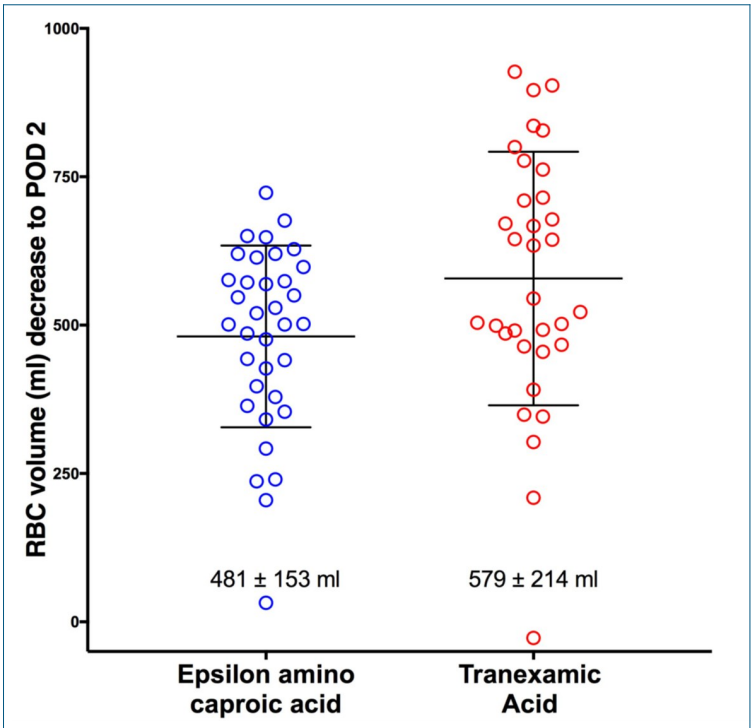

Figure 2. Comparison of RBC Volume Change on Postoperative Day Two.

The association of TXA as an independent predictor of postoperative seizures in patients undergoing cardiac surgery has been suggested (16). While this study was not powered to detect a difference in adverse events, our data exhibited no difference between groups. This data further supports the equal efficacy between EACA and TXA.

Our study does have limitations. There was no placebo control arm to which TXA or EACA could be compared as we felt antifibrinolytic treatment was appropriate care for this group of patients. The sample size for this study is small. The study was powered as a superiority trial for a difference in blood transfusion volumes between the groups and was not designed as equivalence or non-inferiority trial. Also, there was no risk stratification for high-risk to low-risk cardiovascular surgical procedures but the similarity of operative time and case type between groups suggests that procedures were of similar risk between groups. Similarly, there was no protocolization of fluid administration and while there was no difference between intraoperative fluids, it is important to highlight the potential impact on anticoagulation and RBC volume decrease that can accompany excessive hemodilution (17) particularly in patients whose blood volume is small compared to cardiopulmonary bypass circuit or crystalloid infusion volumes (18). In addition, we did not compare the groups for differences in: pre and intra-operative anticoagulants, baseline comorbidities, or preoperative laboratory values. Also only one dosage strategy of TXA and EACA was implemented for this study. The use of 15% difference of total volume transfused was determined, a priori, to detect any difference between the two study antifibrinolytic agents despite its small clinical volume. Finally, patients in this study did not receive functional coagulation studies such as thromboelastography.

Recently, the availability of EACA has become an issue in the United States (8). While the evidence supporting the safety of TXA and EACA is growing, further evaluation of possible administration strategies of these medications along with a continued prospective evaluation of these medications is warranted.

CONCLUSIONS

In summary, this prospective double-blinded study demonstrated no difference in transfusion or safety outcomes between TXA and EACA groups. Continued evaluation of these widely-used medications for cardiac surgery is warranted.

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The authors have no other potential conflicts of interest for this work.

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