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Comparison of Tranexamic Acid and Aminocaproic Acid in Coronary Bypass Surgery

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COMPARISON OF TRANEXAMIC ACID AND AMINOCAPROIC ACID IN CORONARY BYPASS SURGERY

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Abstract

OBJECTIVE: Tranexamic acid (TXA) and ε-aminocaproic acid (EACA) are used in coronary bypass surgery for anti-fibrinolytic therapy. Since the removal of aprotinin, data directly comparing their blood sparing effect and their side effects is still missing.

METHODS: Fifty patients undergoing coronary bypass cardiac surgery at a community teaching hospital were evaluated in a retrospective cohort study. Perioperative data was collected by a thorough chart review. Patients received EACA from 01/01/2013 to 04/05/2013 or TXA from 05/07/2013 to 12/31/2013. Primary outcome was the amount of chest tube output throughout the hospital stay. Secondary outcomes were the amount of blood transfusion requirements, post-operative complications, number of ICU days, need for re-exploration, and in-hospital mortality.

RESULTS: All demographic and pre-operative parameters were well comparable for patients who received EACA (n = 25) and those who received TXA (n = 25). There was no difference in chest tube output (EACA 942 ± 371 mL vs. TXA 1162 ± 480 mL, p = 0.077). There were also not any differences in blood transfusion requirements (EACA 4.92 ± 3.29 units vs. TXA 3.44 ± 2.10 units, p = 0.064), nor in post-operative complications such as atrial fibrillation, unstable blood pressure, pneumonia, or pleural effusions related to surgery (EACA 20% vs. TXA 32%, p = 0.520). There were not any patients in the study who experienced a need for re-exploration or in-hospital mortality. The number of days spent in the ICU (EACA 1.60 ± 1.35 vs. TXA 1.08 ± 0.4, p = 0.0717) were also found to be statistically non-significant.

CONCLUSIONS: TXA and EACA are comparable in the effect of chest tube output and blood transfusion requirements, as well as their adverse event profile. Although the number of days spent in the ICU approached statistical significance for favoring TXA, either agent would be appropriate to be utilized in coronary bypass cardiac surgery.

Background

Cardiopulmonary bypass (CPB), or the 'heart-lung machine,' is an essential part of cardiac surgery. It allows the blood to be oxygenated and dissipates carbon dioxide while the heart and lungs are at rest. In order for CPB to be fully safe and effective, reversible anticoagulation must be used and the blood must be pumped without destruction of red blood cells or other blood components.[1] To achieve this, the patient is systemically heparinized and the CPB components are heparin coated.[2] Although protamine can be utilized to reverse the effects of heparin, cardiac surgery patients are still at an increased bleeding risk.[3,4,5] Up to 10% of cardiac surgery patients experience massive blood loss after CPB. Massive blood loss is defined as chest tube bleeding >2 L up to 24 hours post-operatives, ≥10 units of packed red blood cells (RBC) transfused, or bleeding requiring a re-exploration surgery. This coagulopathy related to CPB is multifactorial by alterations in the coagulation cascade, inflammatory processes, and fibrinolysis.[3]

During CPB, the coagulation cascade is altered by heparin and anti-platelet use. CPB also requires hemodilution of the blood volume which results in decreased numbers of coagulation factors and causes platelet dysfunction. When activated, certain coagulation factors are pro-inflammatory, such as factor Xa and thrombin. The resultant inflammation can ultimately cause end-organ damage, such as renal dysfunction. For adequate clot formation after CPB, fibrinogen levels should be maintained at ≥200 mg/dL. Fibrinolysis can occur as a result of decreased levels of fibrinogen and the release of endogenous fibrinolytics. Endogenous fibrinolytics, such as urokinase and tissue plasminogen activator (tPA), can split fibrin and fibrinogen into inactive segments. These inactive segments are called D dimers, and they have no coagulation activity.[3] To manage perioperative bleeding from the CPB-related coagulopathy, various medications are given prophylactically. Fibrinogen concentrate can be given to increase fibrinogen levels.[6] Also, anti-fibrinolytics, such as aminocaproic acid (EACA)[7] and tranexamic acid (TXA)[8], are given in the majority of cardiac surgeries that use CPB. Anti-fibrinolytics are utilized to diminish the effects of endogenous fibrinolytics which are released in response to CPB-related coagulopathy.[4]

CPB-related coagulopathy greatly increases the bleeding risk in patients. Anti-fibrinolytics are used preoperatively to minimize the incidence of postoperative bleeding, but no head-to-head trials exist to compare TXA and EACA. Both medications came to market based on non-inferiority studies to aprotinin, which was pulled from the market due to post-marketing safety

studies. Increased bleeding can increase the patient's mortality, increase the hospital length of stay, and increase the amount of hospital resources utilized.[3] The Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists currently recommend anti-fibrinolytics to be a Class I, level of evidence A guideline recommendation for them to be used in perioperative blood conservation in cardiac surgery.[4]

The objective of this study is to evaluate the difference between EACA and TXA in cardiac bypass surgery. If a difference is shown preferring either agent in blood conservation, an argument will be able to be made to utilize this agent preferably in an effort to decrease other hospital costs and conserve the blood bank.

Methods

Based on previous non-inferiority studies of EACA and TXA to aprotinin, a power of fifty patients was found to be adequate for this study. Inclusion criteria were any patient undergoing coronary bypass cardiac surgery at a community teaching hospital from 4/6/2013 to 5/6/2013. Exclusion criteria were any patient who was pregnant or under 18 years of age. This month duration was the transition period of switching medications and there was the possibility of prescriber bias for which patient received either medication. In this retrospective cohort study, patients were randomly selected until there were twenty-five patients who had received TXA and twenty-five patients who had received EACA. Primary outcome was the amount of chest tube output throughout the hospital stay. Secondary outcomes were the amount of blood transfusion requirements, post-operative complications, number of ICU days, need for re-exploration, and in-hospital mortality.

Patients were identified by billing records for EACA or TXA during 2013. Perioperative data was collected by a chart review conducted by the secondary investigators. Baseline characteristics collected were age, gender, race, weight, smoker status, and past medical history. Past medical history included chronic hypertension, type 2 diabetes mellitus, history of arrhythmia, previous MI, previous thromboembolic event, number of prior surgeries. All surgeries were included, with the exception of orthopedic, ophthalmic, or otorhinolaryngologic interventions. Medications accounted for at baseline included aspirin, clopidogrel, and anticoagulation use. Pre-operative laboratory values evaluated were serum creatinine (SCr), estimated creatinine clearance (CrCl), hemoglobin (Hgb), hematocrit (Hct), activated partial thromboplastin time (aPTT), prothrombin time (PT), fibrinogen, and international normalized ratio (INR). Patient confidentiality was ensured by

maintaining information on an encrypted jump drive and will not be destroyed for two years after data collection. IRB approval was granted from the community teaching hospital and the affiliated university. As a retrospective cohort study, there were no ethical or safety issues in completing this study.

Demographic characteristics and all categorical data points were evaluated by a Fischer's exact test with a two-tailed *p* value. Fischer's exact test was chosen over the chi-square test, due to some demographic characteristics, such as race or past medical history, which had numerical values less than five. Continuous data points, such as laboratory values, were evaluated by an unpaired t-test with a two-tailed *p* value. The unpaired t-test was chosen over the paired t-test, due to nature of the study comparing two independent patient groups. Alpha was set at 0.05. Due to the lack of post-operative laboratories that were evaluated, this was not included as a data collection endpoint. The specific dosing regimen for each patient was unable to be acquired; however, the collective amount of EACA or TXA billed to the patient was included in the original patient identification process.

Results

Patients received EACA from 01/01/2013 to 04/05/2013 or TXA from 05/07/2013 to 12/31/2013. There were not any patients evaluated that met the exclusion criteria. All demographic and pre-operative parameters were well comparable (**Tables 1** and **2**).

All patients underwent a coronary artery bypass graft due to coronary atherosclerosis. Each patient's antiplatelet therapy (aspirin, clopidogrel) was held for 24 hours prior to surgery, if applicable. During the surgery, each patient was systemically heparinized and was given EACA or TXA according to the dosing protocols.

There was no difference in the primary outcome of chest tube output (EACA 942 ± 371 mL vs. TXA 1162 ± 480 mL, $p = 0.077$). See **Figure 1**. There were also not any differences in blood transfusion requirements (EACA 4.92 ± 3.29 units vs. TXA 3.44 ± 2.10 units, $p = 0.064$), nor in the amount of patients who required platelets, fresh frozen plasma, cryoprecipitate, factor VII, or prothrombin complex concentrate (EACA 28% vs. TXA 24%, $p = 1.000$). Also, post-operative complications such as atrial fibrillation, unstable blood pressure, pneumonia, or pleural effusions related to surgery (EACA 20% vs. TXA 32%, $p = 0.520$) were not found to be statistically significant. There were not any patients in the study who experienced a need for re-exploration or in-hospital mortality. Finally, the number of days spent in the

ICU (EACA 1.60 ± 1.35 vs. TXA 1.08 ± 0.4, $p = 0.0717$) were also not found to be statistically significant.

Demographics	**Aminocaproic Acid (n=25)**	**Tranexamic Acid (n=25)**	**P value**
Age (mean)	64 ± 9 years	67 ± 8 years	0.189
% Smokers	72% (18)	64% (16)	0.762
% Male	68% (17)	92% (23)	0.074
% Non-Hispanic White % African American % Arab American % Hispanic American	80% (20) 20% (5)	88% (22) 4% (1) 4% (1) 4% (1)	0.702
Weight (mean) BMI (mean)	97 ± 22 kg 32 ± 5.4 kg/m^2	91 ± 16 kg 30 ± 4.2 kg/m^2	0.247 0.136
Past Medical History			
Chronic Hypertension	88% (22)	80% (20)	0.702
Type 2 Diabetes Mellitus	32% (8)	44% (11)	0.561
History of Arrhythmia	8% (2)	16% (4)	0.667
Previous MI	20% (5)	16% (4)	1.000
Previous thromboembolic event (DVT, PE, TIA/CVA)	16% (4)	12% (3)	1.000
Amount of prior surgeries (All included except orthopedic, ophthalmic, or otorhinolaryngology surgeries)	8% (2)	8% (2)	1.000
ASA therapy alone before surgery	52% (13)	56% (14)	1.000
Clopidogrel therapy alone before surgery	12% (3)	4% (1)	0.609
ASA + clopidogrel therapy before surgery	12% (3)	12% (3)	1.000
No antiplatelet therapy before surgery	24% (6)	28% (7)	1.000
Anticoagulation therapy (warfarin, rivaroxaban, apixaban, dabigatran)	0%	0%	1.000

Table 1. EACA & TXA demographic parameters.

Laboratories (mean)	**Aminocaproic Acid (n=25)**	**Tranexamic Acid (n=25)**	**P value**
Pre-op SCr	1.21 ± 0.74 mg/dL	1.23 ± 0.72 mg/dL	0.923
Pre-op CrCl	68 ± 29.5 ml/min	67 ± 25.1 ml/min	0.894
Pre-op Hgb (12.8-16.9 g/dL) Post-op Hgb	13.7 ± 1.9 g/dL 11.03 ± 1.03 g/dL	14.5 ± 1.8 g/dL 11.15 ± 1.05 g/dL	0.082 0.521
Pre-op Hct (38.8-50.2%) Post-op Hct	40.5 ± 5.5% 32.7 ± 3.1%	42.3 ± 5.2% 32.6 ± 3.1%	0.176 0.832
Pre-op aPTT (12.1-33 sec)	30.3 ± 4.9 sec	30.5 ± 6.8 sec	0.618
Pre-op PT time (9.5-11.9 sec)	12.2 ± 1.1 sec	11.9 ± 1.2 sec	0.184
Pre-op fibrinogen (179-381 mg/dL)	209 ± 81.4 mg/dL	198 ± 55.6 mg/dL	0.484
Pre-op INR	1.13 ± 0.11	1.10 ± 0.12	0.318

Table 2. EACA & TXA pre-operative parameters.

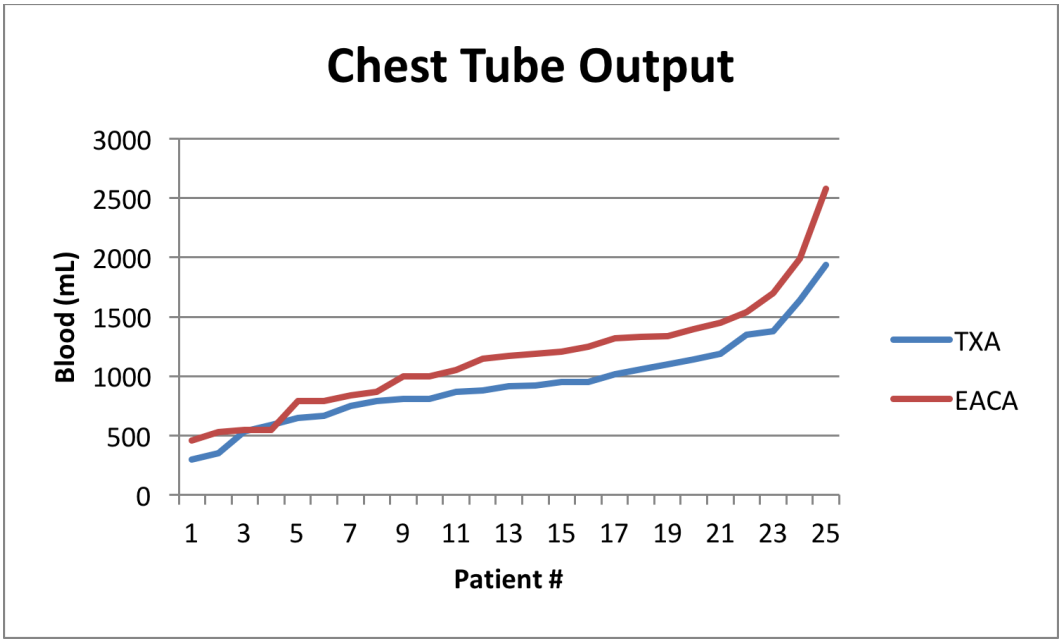

Figure 1. Primary outcome of chest tube output.

Discussion

Patients received EACA from 01/01/2013 to 04/05/2013 or TXA from 05/07/2013 to 12/31/2013. There were not any patients evaluated that met There have been three anti-fibrinolytics that have been on the market: aprotinin, EACA, and TXA. Aprotinin is a peptide serine protease inhibitor that inhibits fibrinolysis and affects the inflammatory process. Aprotinin was consistently shown to be efficacious in decreasing the need for transfusions. However, in two large observational studies it was shown to have an increased mortality rate and increased serum creatinine levels leading to kidney injury. Therefore, aprotinin was removed from market in November 2007.[3-4]

The other two anti-fibrinolytics are lysine analogs: EACA and TXA. These medications compete with fibrin for binding sites which then inhibits the conversion from plasminogen to plasmin. The dosing of these medications typically includes a CPB priming dose, loading dose, and maintenance dose. Various dosing regimens have been utilized. There are multiple ways to dose EACA and TXA. At the community hospital studied, EACA is dosed as 5-10 grams loading dose, then 1-2.5 grams/hr maintenance dose, until the end of the operation. On average, this calculates out to a 75 mg/kg loading dose, then a 10-15 mg/kg/hr until the end of the surgery. For TXA, a 2mg/kg CPB prime, 30 mg/kg load, and 16 mg/kg/hr maintenance dose was utilized.[3] As for the efficacy, the studies to date are done in comparison to aprotinin and both have been found to be alternatives to aprotinin.

In 2001, a randomized, double-blind, placebo-controlled, non-inferiority trial was completed comparing EACA and aprotinin in 81 patients undergoing CABG with CPB. EACA was shown to be non-inferior to aprotinin by the surrogate marker of D-dimer formation for fibrinolysis reduction and the endpoint of blood loss measured by 24-hour chest tube drainage. For D dimer formation, the results were: aprotinin 608 ± 279 μg/L vs EACA 612 ± 335 μg/L (difference -3.58 μg/L, 95% CI -203 to 195 μg/L). For the amount of chest tube drainage, the results were: aprotinin 685 ± 505 mL vs. EACA 715 ± 394 mL (difference 67 mL, 95% CI -90 to 230 mL).[9] Both the surrogate marker of D dimer formation and endpoint of chest tube drainage was a non-significant difference between aprotinin and EACA. This shows that EACA is noninferior to aprotinin and can therefore be utilized as an alternative in patients undergoing CABG with CPB.

In 2004, a randomized, double-blind, prospective trial was completed comparing TXA and aprotinin in 118 patients undergoing CABG with CPB. TXA was shown be an alternative to aprotinin by the end points of total blood

loss and transfusion requirements. For total blood loss, the results were: aprotinin 756 mL ± 347 vs TXA 896 mL ± 354, p = 0.03. For RBC transfusion, the results were: aprotinin 1.5 units ± 1.7 vs. TXA 1.5 units ± 1.5, p = 1.0. The blood loss was concerning because the difference was found to be statistically significant; however, the transfusion requirements for both aprotinin and TXA patients were shown to be statistically insignificant.[10]

In this retrospective cohort study at a community teaching hospital of fifty patients, EACA and TXA were not found to be statistically different. Both are comparable for efficacy in regards to the amount of chest tube output, blood transfusion requirements, and amount of days spent in the ICU. Since the *p* value for the amount of days spent in the ICU approached statistical significance in favor of TXA, a future study with a larger sample population and greater power is warranted. The tolerability of EACA and TXA was shown to be similar, due to the lack of difference in re-exploration rates, mortality, or adverse effects.

As a retrospective cohort study, the ability for controlling confounding variables through non-statistical approaches is limited. One limitation to the data collection process is the lack of selection randomization. The investigators did randomly select patients, but this process was not formalized. Although a sample of fifty patients was found to be adequate for this study, the wide variation in standard deviation indicates that a type II error may have occurred. The comparable patient characteristics pre-operatively benefited this study and increased its validity.

Conclusion

EACA and TXA are comparable in the amount of chest tube output and blood transfusion requirements, as well as their adverse outcomes. A future study with a greater sample population could increase the power of this retrospective cohort study. Although the number of days spent in the ICU approached statistical significance for favoring TXA, either agent would be appropriate to be utilized in coronary bypass surgery.

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