

TXA (Tranexamic Acid) vs. Amicar (Aminocaproic Acid) in Total Knee and Hip Arthroplasty- Effectiveness,
Safety, and Cost Analysis

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TXA (Tranexamic Acid) vs. Amicar (Aminocaproic Acid) in Total Knee and Hip Arthroplasty- Effectiveness, Safety, and Cost Analysis

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Research Summary

2. Purpose

Minimization of perioperative discomfort and complications, such as increased blood loss and length of hospital stay is a mutual goal amongst both patients and surgeons alike. To our knowledge, there have been no studies in the US and only one small study in Europe comparing the efficacy of tranexamic acid (TXA) and ε-aminocaproic acid (EACA or ACA, Amicar®) in TKA and total hip arthroplasty (THA). A double blind, randomized and placebo controlled trial in Spain involving 127 patients sorted into three different arms found that there was significant reduction of blood transfusions in the TKA and Amicar arms, and also less of a reduction in hemoglobin levels by post-op day 5.¹ There were no statistical significance in the 35 patients administered TXA compared to the 32 patients administered EACA, and authors noted that the limited number of patients may have prevented any findings.¹ Given the potency of TXA, it may in fact be more efficacious than Amicar, leading to improved patient outcomes. Despite the clinical advantages to using TXA vs. placebo, it is frequently felt to be financially prohibitive. TXA currently costs between \$100-200 per each IV dose. A unit of RBC costs between \$500-1000 dollars. A recent study comparing the cost of TKAs using TXA vs. those that did not found that although the pharmacy cost increased by \$140, the total hospital cost was decreased by about \$900 (looking at OR, blood, and total costs associated with admission).² Amicar is significantly less expensive than TXA, and given its theoretically similar mechanism of action, is used as the agent of choice in many hospitals in the United States. Currently TXA is being used at Duke University for total joint arthroplasty. There are limited data comparing the clinical efficacy and cost effectiveness of the two anti-fibrinolytics. Given the increased potency of TXA, it may be more efficacious and ultimately more cost effective than Amicar. The primary objective of this study is to determine the effectiveness of TXA vs. Amicar by determining the percentage of patients requiring transfusions and blood loss in total joint arthroplasty. A secondary objective is to determine the overall cost of hospitalization when the two different products are used. We hypothesize that TXA will decrease the transfusion rate in patients as compared to Amicar. We also hypothesize that the overall cost of hospitalization will be less in patients with TXA, despite the increased pharmacy cost.

3. Background Information

Hemostasis is an essential part of any surgical procedure, and especially in the case of total joint surgical procedures. Hemostasis is achieved through the steps of vasospasm, platelet adhesion, contact phase, and then fibrinolysis. Increased fibrinolysis can lead to increased intra-operative blood loss.³ Tourniquets during surgical procedures, such as the ones used during Total Knee Arthroplasty (TKA), have been shown to increase fibrinolysis during deflation, despite there being no change in circulating clotting factors.⁴ Medications that either retard or stop fibrinolysis potentially would decrease the breakdown of a clot leading to decreased operative blood loss while not impacting the risk of systemic thrombosis.⁵

Currently there are three FDA-approved antifibrinolytic agents. Aprotinin is currently not being used in the US market as a study in 2007 suggested that there might be an increased mortality associated with its use during cardiac surgery.⁵ While that conclusion was based largely on observational studies, A Cochrane review published in 2011 and a meta-analysis in 2012 concluded, regardless of the questionable increased risk caused by aprotinin, ϵ -aminocaproic acid and tranexamic acid are safer in terms of risk of death and myocardial infarction than aprotinin.⁶⁻⁸ These lysine analogues have also been used to control non-surgical bleeding control such as the use of Amicar in thrombocytopenia and TXA in the treatment of uterine bleeding.^{9,10} Amicar and TXA are currently approved for non-surgical settings of excessive bleeding where fibrinolysis is a contributing factor, like ocular bleeding, menorrhagia, cirrhosis, and placental abruption. Both of these agents are reversible competitive inhibitors of plasminogen/plasmin and are widely used in the fields of orthopaedics, cardiothoracic surgery, and transplantation to reduce blood loss. Amicar was the first agent to be used in hopes of reducing blood loss during major surgery, however shift began due to a worldwide shortage of Amicar. Although this shortage has since been corrected, TXA began being used as a result and is showing early promising results. TXA is 6-10 times more potent but has a similar toxicity profile.⁵ Amicar continues to still be widely used in cardiac surgery.

TXA can be administered in both a topical or intravenous manner. Topical administration of TXA vs. placebo in a randomized controlled trial after cementing the implants resulted in higher postoperative hemoglobin and lower total blood loss.¹¹ Studies using administration of intravenous TXA vs. placebo also initially demonstrated decreased blood loss and fewer transfusions of blood products. However, there has been concern that these studies were not able to detect if there was an increase in thromboembolic risk.¹² A meta-analysis of 15 clinical randomized trials on TXA use demonstrated an average perioperative blood loss of 504 ml less than the placebo group. Patients also used 1.4 times more units of blood compared with placebo, and were about six times less likely to need the transfusion. There was no difference in the rate of thromboembolic events.¹³

4. Study Design

This is a randomized prospective trial. Eligible patients will include those who do not screen positive for any of the exclusion criteria (history of stents, myocardial infarction, cerebrovascular accident or stroke, deep venous thrombus, pulmonary embolus late onset color blindness, and hypercoagulable state). Subjects will be identified during clinic visits with their provider before their procedure. After the patient's agreement to be enrolled in the study and formal consent process during preoperative screening, they will be randomized to either the TXA or the Amicar arm.

Primary total hip or knee surgery will be performed as per the standard of care as determined by the subject and the attending surgeon, with the exception of the administration of the type of antifibrinolytic product. There is no consensus as to the dosing of either Amicar or TXA in the literature. Previous studies have ranged in dosing of TXA from 10-150 mg/kg administered over different time periods and dosed Amicar at 10 mg/kg.^{1,5} This is consistent with the fact that TXA has been shown to be 6-10 times more potent in binding to plasminogen and plasmin.⁵ Dosing guidelines for TXA and Amicar will be based on the dosing regimens approved at Duke. These doses are currently used at Duke for TKAs and THAs per standard of care by the orthopaedic team. If patients are not willing to participate in this study they will still receive the same dosage of either drug as prescribed by the ordering physician if they are screened and indicated for these medications.

All data needed for this study including blood loss, need for transfusion, preoperative and lowest postoperative hematocrit and hemoglobin, and complications will be collected during the hospitalization. Subject's study participation will end at hospital discharge. Costs of each component of the hospital stay will also be obtained and recorded. Adverse events will be recorded on case report form and submitted to the Duke IRB per Adverse Event policy.

The recruitment goal of this study is to enroll 75% of eligible subjects electing to undergo either primary hip or knee arthroplasty performed by three attending surgeons at this institution over a year time period.

5. Selection of Subjects

Adult patients aged 18 and over electing to undergo primary total hip or knee arthroplasty will be considered for inclusion in the proposed study and identified preoperatively.

6. Subject Identification, recruitment, and compensation

Adult patients aged 18 and over electing to undergo primary total hip or knee arthroplasty will be considered for inclusion in the proposed study and identified preoperatively. Exclusion criteria will include history of stents, MI, CVA, DVT, PE,

color blindness, and hypercoagulable state. Females of childbearing age will also have a serum pregnancy test drawn before inclusion in this study. A positive pregnancy will result in exclusion from the study. We aim to recruit 400 subjects, 200 total hip and 200 total knees. Subjects may withdraw at anytime. Post operatively, surgery data will be collected via the electronic medical record. Consent will be signed and witnessed before surgery takes place in clinic.

7. Consent Process

The investigator or his/her authorized designee will inform the subject of all aspects pertaining to the subject's participation in the study during the consent process. The process of obtaining informed consent will be in accordance with all applicable regulatory requirements (Federal Register Vol. 48, No. 17, 1982, pp 8951-2).

8. Subject's Capacity to Give Legally Effective Consent

Each patient aged 18 years or older will consent for him or herself. If the patient is less than 18 years of age they will not be considered for the study.

9. Study Interventions

Subjects will be randomly assigned in a 1:1 ratio to either an Amicar or TXA arm which are both standard of care at Duke. Subject's study participation will end at hospital discharge.

10. Risk/Benefit Assessment

Potential Benefits: Despite being off-label, TXA and Amicar are already both being used across various fields, including orthopaedics, for their benefit in reducing blood loss, the need for transfusion, and a drop in hemoglobin during major surgery and have shown to be safe to use.^{1,14,15} Patients given TXA or Amicar will likely experience decreased blood loss and decreased risk of transfusion and as a result may experience shorter hospital stay, fewer complications and decreased cost. Both are currently used as standard of care in total hip and knee replacements.

Potential risks: Although initially there was a fear that TXA or EACA would increase the risk of death and thromboembolic events, current evidence suggests that this increase is not statistically significant.⁸ TXA is currently used as the standard of care at Duke University Hospital.

However, subjects in the TXA arm may experience the following adverse effects including GI disturbances (nausea, vomiting, diarrhea), allergic dermatitis, giddiness, and hypotension. The FDA also lists the risk of serious rare side effects including thromboembolic events (such as deep vein thrombosis, pulmonary embolism, cerebral thrombosis, acute renal cortical necrosis, and central retinal artery and vein obstruction), convulsion, chromatopsia, and visual impairment.

Adverse effects associated with Amicar include edema, headache, malaise, hypersensitivity (anaphylaxis), cardiovascular effects (bradycardia, hypotension, peripheral ischemia, thrombosis), GI disturbances (abdominal pain, diarrhea, nausea, vomiting), hematologic effects (agranulocytosis, coagulation disorder, leukopenia, thrombocytopenia), musculoskeletal effects (CPK increase, muscle weakness, myalgia, myopathy, myositis, rhabdomyolysis), neurologic complications (confusion, convulsions, delirium, dizziness, hallucinations, intracranial hypertension, stroke, and syncope), respiratory effects (dyspnea, nasal congestion, pulmonary embolism), rash, pruritis, tinnitus, decreased vision, watery eyes, and urogenital effects (increased BUN and renal failure). Amicar is less potent than TXA so it may lead to increased blood loss and therefore increased risk of transfusion according to one study.¹

Many of the above side effects for both TXA and Amicar have been reported in patients with hemophilia.

11. Costs to the Subject:

Subject or **their** insurance provider will be responsible for all costs related to your medical care, including the drugs used in this study.

No direct monetary compensation will be offered for inclusion in the proposed study.

12. Data Analysis & Statistical Considerations

Subject characteristics and study results including those outlined above (considered complications or adverse events) will be recorded. ¹ The primary endpoint for this study is the percentage of patients requiring transfusions. The secondary endpoint include total blood loss (recorded as estimated blood loss intraoperatively as determined by anesthesia staff, and postoperatively recorded by nurses from the output in drains), change in hemoglobin (preoperative vs. postoperative hemoglobin that is routinely measured before discharge), and the total cost of hospitalization as billed by Duke University (including pharmacy cost, price each night in hospitalization, all other charges incurred during admission). Binary variable results will be compared using chi-square and Fisher's exact tests (where appropriate). We plan a comparison of continuous variable results using Wilcoxon rank sum and *t*-tests (where appropriate). We will consider multivariable logistic regression in determination of TXA and Amicar and their correlation with the above listed complications and adverse events. Anesthetic techniques will be recorded for analysis and covariate analysis will be performed at the end of the study. In order to perform a cost analysis, total cost of hospitalization including pharmacy cost, potential transfusion costs, and cost of stay. Based on the one small European study, sample size for finding the difference between two proportions was calculated using a proportion of 0.125 patients given Amicar were transfused (n=32 vs. 0.028 (n=35) given TXA. Using an alpha value of .05 and power of .90 it was determined that there

would need to be 154 patients in each sample size to find a significant difference in independent samples. Our goal of enrolling 400 patients total (200 in each arm) will therefore be appropriate for this study

13. Data & Safety Monitoring

The primary investigator will collect data from the subject's electronic medical record and will extract necessary study data and then transfer this data into a limited access electronic Excel spreadsheet housed on the Duke Orthopaedic share drive. We will have an independent safety reviewer in lieu of a formal DSMB committee to ensure the safety of subjects. Dr. Steve Olson, head of the orthopaedic clinical research unit will be asked to serve in this role. He will review available safety data, including thrombotic complications after 100, 200, and 300 patients are enrolled.

During collection, data will be indexed by the subject's medical record number. After data collection, a case number will be assigned to the data, and the medical record number, name and any dates associated with clinical care (the only identifying data collected) will be stripped from the database. The code linking medical record number to case number will be kept in an Excel spreadsheet with access limited to the primary investigator and his research team. Electronic research records will be stored on a DHTS server in the following limited access folder O:\CLINICAL RESEARCH DATA\JOINT\50108 - Bolo TXA vs. Amicar. Paper research documents will be stored in the PI's locked research office in a locked cabinet with keys in possession of the CRC. Paper documents will be housed in the PI's locked research office in a locked cabinet with access limited to his research team and keys in possession of the CRC. When the study is complete, the code linking medical record numbers to case numbers will be destroyed. During data collection and review, protected health information will be available only to the primary investigator and will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study.

14. Privacy, Data Storage & Confidentiality

All data collection will be performed on a secure PIN station protected by DHT firewalls. Only researchers participating in the study will have access to the data. With the exception of medical records numbers, data collection will not contain patient identifiers as specified in the HIPPA regulations (45CFR164.514(b)(2)(i)). All data will be stored as outlined in the research data security plan (RDSP) included with this submission. Subject identity will be made anonymous after completion of the data accrual and prior to statistical analysis to assure confidentiality. Original signed consent forms and collected data will be kept in subject folders in a locked secure location.

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