The Effect of Topical and Intravenous Tranexamic Acid (TXA) on Thrombogenic Markers in Patients Undergoing Total Knee Replacement (TXA Knee)

FUNDER: Research & Education Fund, Department of Anesthesiology, Critical Care & Pain Management

PROTOCOL NO.: 2015-210

VERSION & DATE: 12/3/19

PROTOCOL SYNOPSIS

Protocol Title:	The Effect of Topical and Intravenous Tranexamic Acid (TXA) on Thrombogenic Markers in Patients Undergoing Total Knee Replacement (TXA Knee)
Protocol Number:	2015-210
Protocol Date:	5/13/19
Sponsor:	N/A
Principal Investigator:	Kethy JulesElysee, MD
Products:	NA
Objective:	This study will investigate the effect of both topical and intravenous (IV) administration of tranexamic acid (TXA) on thrombogenic markers in patients undergoing total knee arthroplasty.
Study Design:	Randomized Controlled Trial
Enrollment:	76
Subject Criteria:	1. Patients undergoing primary unilateral total knee arthroplasty with a participating surgeon (Drs. Mayman, Sculco, Su, McLawhorn) 2. Patients aged 18-80
Study Duration:	11/2016-12/2017
Data Collection:	• Age • Gender • Race • Ethnicity • BMI • History of systemic or pulmonary hypertension • Anesthesia time –duration • Surgery time – duration • Tourniquet time – duration • Time of TXA/Placebo administration(s) • Time of blood collection - Before TQ onset (after time out), before final TQ release, 1-hour post-TQ release, 4-hours post-release • Color/condition of blood samples after centrifugation • Amount of Constavac drainage

	• Blinding Assessment • Amount of blood loss • Number of intraoperative and postoperative blood transfusions • Hcb and Hct levels • Incidence of DVT/PE • Range of Motion
Outcome Parameters:	• Levels of plasmin anti-plasmin (PAP), a marker of fibrinolysis - measured from peripheral blood and wound drainage 4 hours after tourniquet (TQ) release.
	• Serum and wound levels of prothrombin fragment 1.2 (PF1.2), plasmin anti-plasmin (PAP), and IL-6 – prior to TQ release, and 1-hour after TQ release (serum only) and 4-hours post-TQ release • Serum and wound levels of TXA – prior to TQ release, and 1-hour after TQ release (serum only) and 4-hours post-TQ release to determine whether IV TXA diffuses into tissue readily and to what extent topical TXA is absorbed. • Blood loss – measured up until hospital discharge. Blood loss will be determined using an equation that calculates • the patient's blood volume based on their height and weight, then multiples the patient's blood volume by the • change in hematocrit after surgery compared to before surgery. • Hemoglobin (Hgb) levels – measured up until hospital discharge • Hematocrit (Hct) levels - measured up until hospital discharge • Constavac drainage – measured 4-hours postoperatively • Incidence of thrombosis (DVT/PE) – measured up until 2 weeks after the date of surgery • Units of intraoperative and postoperative blood transfusions administered – measured up until hospital discharge • Time to PT Discharge – PT discharge during hospital stay • Length of Stay – time of discharge
Statistical Analysis:	Proposed analysis (e.g., student's t-test, ANOVA, chi-square, regression, etc.): Two-sample t-test Alpha level: 0.05 Beta or power level: 0.80

	Primary outcome variable estimate (mean +/- s.d. for continuous outcome, frequency/percentage for categorical variable): Based on results from the control group of a previous study (IRB #11007) the mean + standard deviation PAP level 4-hours post-operatively in unilateral TKA patients = 1086.6 + 536.3 µg/mL Number of groups being compared (use 1 for paired analysis within the same subjects): 2 (IV TXA vs. topical TXA) Effect size or change expected between groups: There is no information in the literature regarding a clinically meaningful difference in PAP level. Based on clinical experience, a difference of 400 µg/mL in mean PAP level between IV and topical TXA groups was estimated to be clinically meaningful. Resulting number per group: 30 Total sample size required: After inclusion of 6 additional patients (+10%) to account for potential withdrawals and/or protocol violations, the total sample size It was determined that a sample size of 30 patients per group would achieve 80% power at alpha = 0.05 to detect a 400 µg/mL difference in mean PAP level 4-hours post-operatively between the IV and topical TXA groups assuming a common within-group standard deviation of 536.3 µg/mL using a two-sided two-sample t-test. After addition of 10% to the sample size to account for potential withdrawals and/or protocol violations, the total sample size required was 66 patients. The primary outcome (PAP level 4 hours postoperatively) will be compared between the IV and topical TXA groups using a two-sample t-test or the Wilcoxon rank-sum test, depending upon the distribution of the data. Continuous secondary outcomes will be compared between groups using two-sample t-tests or Wilcoxon rank-sum tests, as appropriate. Differences between groups will be expressed as differences in means or Hodges-Lehmann estimate of location shift with 95% confidence intervals. Categorical secondary outcomes will be compared between groups using chi-square or Fisher's exact tests, as appropriate. The magnitude of the effects will be expressed as odds ratios with 95% confidence intervals.

1.0 INTRODUCTION

Tranexamic acid (TXA), a lysine analog and antifibrinolytic agent, is being used more frequently at HSS in order to decrease blood loss associated with total knee replacement (TKR). It can be used intravenously or topically prior to tourniquet release. One of the concerns while using TXA is the possibility of deep vein thrombosis (DVT) or pulmonary embolism (PE). According to HSS medical guidelines, there are specific contraindications to use of IV TXA, but none for topical use of TXA. Interestingly, in a recent study done by one of the co-investigators (Dr. Mayman), 2 patients in a group of 320 patients who received topical TXA developed DVT while none of the IV group (320 patients) developed signs of thrombosis. This may be a coincidence since the total number of patients is small, but it raises concern about the safety of topical application. According to Wong et al, topical application of TXA at a dose of 3gm led to serum levels of 8.05 (7.2-9.9 mg/ml). The therapeutic level of TXA is considered to be 10 mg/ml. If topical and IV TXA have a similar effect on thrombotic markers, topical administration may have the same risk of thrombosis as the intravenous form.

If we find that the IV form of TXA has mostly a local effect, should we give it only topically? These are some of the questions this study will help answer.

This study will examine thrombotic markers when TXA is given both IV and topically. We will also measure levels of TXA as well and establish a correlation if possible from peripheral blood and Constavac drainage.

2.0 PRODUCT DESCRIPTION

N/A

3.0 OBJECTIVE OF CLINICAL STUDY

1) Similarly to IV TXA, does topical use of TXA also lead to systemic changes in fibrinolysis in blood after TKR, since it may get systemically absorbed?

2) Is there a difference with thrombotic markers between topical and IV use of TXA?

3) Does IV TXA exert its effects systemically and/or locally?

4.0 STUDY HYPOTHESES

Topical application of TXA is absorbed through tissue and may lead to the same effect on thrombogenic markers as when given intravenously.

5.0 STUDY DESIGN

5.1 Study Duration

11/2016-12/2017

5.2 Endpoints

5.2.1 Primary Endpoint

- Levels of plasmin anti-plasmin (PAP), a marker of fibrinolysis - measured from peripheral blood and wound drainage 4 hours after tourniquet (TQ) release.

5.2.2 Secondary Endpoints

- Serum and wound levels of prothrombin fragment 1.2 (PF1.2), a marker of thrombin generation – measured at pre-incision (serum only), prior to TQ release, and 1-hour after TQ release (serum only) and 4-hours post-TQ release
- Serum and wound levels of TXA – measured prior to TQ release and 1-hour post-TQ release (serum only) to determine whether IV TXA diffuses into tissue readily and to what extent topical TXA is absorbed.
- Blood loss – measured up until hospital discharge. Blood loss will be determined using an equation that calculates the patient's blood volume based on their height and weight, then multiples the patient's blood volume by the change in hematocrit after surgery compared to before surgery.
- Hemoglobin (Hgb) levels – measured up until hospital discharge
- Hematocrit (Hct) levels - measured up until hospital discharge
- Constavac drainage – measured 4-hours postoperatively
- Incidence of thrombosis (DVT/PE) – measured up until 2 weeks after the date of surgery
- Units of intraoperative and postoperative blood transfusions administered – measured up until hospital discharge

5.3 Study Sites

Hospital for Special Surgery – Main Campus

6.0 STUDY POPULATION

6.1 Number of Subjects

76

6.2 Inclusion Criteria

Subjects of either gender will be included if they:

1. Patients undergoing primary unilateral total knee arthroplasty with a participating surgeon (Drs. Mayman, Sculco, Su, McLawhorn)
2. Patients aged 18-80

6.3 Exclusion Criteria

Subjects will be excluded from the study if they:

1. All patients on steroid therapy regardless of dose, duration, or treatment or those requiring stress-dose steroids preoperatively
2. Patients who will require postoperative use of Coumadin, Xarelto, or Plavix
3. Use of non-steroidal anti-inflammatory drugs (NSAIDs) within 1 week of surgery
4. Hypersensitivity to tranexamic acid
5. Contraindication to use of IV tranexamic acid as per HSS guidelines, which includes:
    a. Renal dysfunction (Creatinine clearance <40 ml/min)
    b. Hepatic dysfunction (AST or ALT 2x upper limit of normal)
    c. Cardiac exclusions: coronary stent, history of MI, positive stress test or atrial fibrillation, advanced CAD
    d. Advanced COPD or advanced interstitial lung disease
    e. History of venous thromboembolism (VTE)
    f. Hypercoagulability (e.g. antiphospholipid syndrome, genetic hypercoagulability with or without prior VTE)
    g. History of stroke or TIA

6.4 Randomization

This is a double-blinded study; group assignment will be concealed from both patients and the treating physicians/researchers. A computer-generated randomization table will be generated by a statistician. After a patient is enrolled in the study, the pharmacist will provide 2 vials of study medication (TXA or placebo) to be given intravenously (one intraoperatively, one postoperatively), as well as a syringe containing study medication (TXA or placebo) to given topically.

Randomization was performed prior to enrollment start. Due to methodological and sample collection issues, the first 10 patients enrolled using this randomization scheme are excluded from data analysis. In order to meet the required sample size, the target enrollment number will be increased by 10 patients and a new randomization scheme will be created for the required sample size (66 patients) prior to enrolling the 11th patient.

7.0 PROCEDURES

7.1 Surgical Procedure

Total knee arthroplasty

7.1.1 Investigational Product Application

N/A

7.2 Data Collection

Data will be collected by an investigator or research assistant. Sources of data include medical records and patient physical assessments conducted by study personnel. Data will be recorded and managed using REDCap electronic data capture tools hosted at the Clinical and Translational Science Center (CTSC) at Weill Cornell Medical College. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Connection to REDCap occurs via the hospital's encrypted cable and wireless networks, and data will be entered through a password-protected computer terminal or iPad.

7.3 Schedule of Assessments

Study Visit #	Randomization	Surgery	Administration of IV Study Medication	Administration of Topical Study Medication	Blood Draw (from existing catheter)	Collection of Drained Blood from Wound
#1 OR, Before TQ onset	X	SOC	X		X	
#2 OR, Before final TQ release				X	X	X (Surgeon collects pooled blood around wound)
#3 PACU, 1 hour after TQ release			X		X	
#4 PACU, 4 hours after TQ release					X	X (Taken from surgical drain)

X= Research Procedures

SOC= Standard of care (care you would receive if you were not participating in this study)

OR = Operating Room; PACU = Post-Anesthesia Care Unit; TQ = Tourniquet; IV = Intravenous

8.0 STATISTICAL ANALYSIS

Proposed analysis (e.g., student's t-test, ANOVA, chi-square, regression, etc.): Two-sample t-test
Alpha level: 0.05
Beta or power level: 0.80
Primary outcome variable estimate (mean +/- s.d. for continuous outcome, frequency/percentage for categorical variable):
Based on results from the control group of a previous study (IRB #11007) the mean + standard deviation PAP level 4-hours post-operatively in unilateral TKA patients = 1086.6 + 536.3 µg/mL
Number of groups being compared (use 1 for paired analysis within the same subjects): 2 (IV TXA vs. topical TXA)
Effect size or change expected between groups:
There is no information in the literature regarding a clinically meaningful difference in PAP level. Based on clinical experience, a difference of 400 µg/mL in mean PAP level between IV and topical TXA groups was estimated to be clinically meaningful.
Resulting number per group: 30
Total sample size required: After inclusion of 6 additional patients (+10%) to account for potential withdrawals and/or protocol violations, the total sample size

It was determined that a sample size of 30 patients per group would achieve 80% power at alpha = 0.05 to detect a 400 µg/mL difference in mean PAP level 4-hours post-operatively between the IV and topical TXA groups assuming a common within-group standard deviation of 536.3 µg/mL using a two-sided two-sample t-test. After addition of 10% to the sample size to account for potential withdrawals and/or protocol violations, the total sample size required was 66 patients.

The primary outcome (PAP level 4 hours postoperatively) will be compared between the IV and topical TXA groups using a two-sample t-test or the Wilcoxon rank-sum test, depending upon the distribution of the data.

Continuous secondary outcomes will be compared between groups using two-sample t-tests or Wilcoxon rank-sum tests, as appropriate. Differences between groups will be expressed as differences in means or Hodges-Lehmann estimate of location shift with 95% confidence intervals. Categorical secondary outcomes will be compared between groups using chi-square or Fisher's exact tests, as appropriate. The magnitude of the effects will be expressed as odds ratios with 95% confidence intervals.

Outcomes measured at multiple timepoints will be analyzed using the generalized estimating equations (GEE) method.

9.0 ADVERSE EVENT ASSESSMENT

All Adverse Events (AEs) will be reported in the final study report. Definitions for Adverse Event (AE) used in this study are listed below and are based on FDA and international guidelines:

9.1 Adverse Event (AE)

Tranexamic acid (TXA) is routinely used at HSS to reduce postoperative blood loss after total knee arthroplasty and potentially reduce the need for transfusion. Risks associated with TXA administration are rare.

One risk of participating is this study is having blood drawn. The risks of blood drawing include mild pain, bruising, and very rarely infection at the place of the needle insertion. However, the likelihood of these risks occuring is rare, as an arterial line catheter is routinely placed in TKA patients. The purpose of this catheter is to continuously monitor blood pressure during and after surgery. We expect to draw blood using the pre-existing catheter.

9.2 Serious Adverse Events (SAE)

Due to the pro-clotting nature of TXA, there have been long-standing concerns about the potential for thromboembolic events, including: deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), transient ischemic attack (TIA), and stroke. However, intravenous administration of TXA has been widely studied and has been shown to reduce the need of blood transfusions without an increase in risk of complications (Poeran et al, 2014). Moreover, TXA is contraindicated in patients with a history or high risk of thromboembolism. It is currently unknown whether topical TXA administration has similar risks in regards to thromboembolism.

9.3 Subsequent Surgical Interventions Definitions

If a patient is found to have an allergy/hypersensitivity to TXA, they will immediately be withdrawn from the study and kept at HSS for observation and treatment. Based on the current literature, the doses that are used in this study have not been found to result in any toxicity level in patients. However, if this occurs, patients will immediately be withdrawn from the study. If any mortality is seen, or if there is any increase in DVT or PE rates from the established incidence in the literature, the DSMB will recommend termination of the study.

9.4 Adverse Event Reporting

All adverse events will be reported to the DSMB and IRB within five working days of the event.

10.0 INVESTIGATOR RESPONSIBILITIES, RECORD AND REPORTS

10.1 Subject Consent and Information

Written/signed consent will be collected from participants in the holding area before surgery.

10.2 Subject Data Protection

- HSS tries to minimize those risks by (i) removing some direct identifiers from information stored [(i.e., names, social security numbers, medical record numbers)]; (ii) securing, in a separate location, and limiting access to information linking codes (i.e., linkage codes)

assigned to the registry information with direct participant identifiers; and (iii) limiting access to information stored to HSS investigators.

- Access to the REDCap program is password-protected, and access to a specific study's information within the program is limited to the research assistant and other IRB-approved study personnel who have been given permission to view and/or enter study data. REDCap program access is authorized by the CTSC; particular study access is granted by the research assistant. For data exports, fields marked as protected health information (PHI) in REDCap will be de-identified, if feasible.
- All transmission of data will occur via encrypted networks in password-protected files. Any paper-based data sheets utilized for the study will have personal identifiers removed whenever possible and will be stored in the department's locked office. Each subject will be assigned a unique study number for identification, and that number will not be derived from or related to information about the individual. Presentations and publications that result from this study will not contain any individual identifiers (at most the unique study numbers may be referred to). Thus our research presents a minimal risk of harm to subjects' privacy.