Blood Loss in Arthroplasty with Oral Versus IV Tranexamic Acid

FUNDER: Department of Anesthesiology

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TABLE OF CONTENTS

PROTOCOL SYNOPSIS

Protocol Title:	Blood Loss in Arthroplasty with Oral Versus IV Tranexamic Acid
Protocol Number:	2019_0882
Protocol Date:	3/8/2022
Sponsor:	Department of Anesthesiology
Principal Investigator:	Stavros Memtsoudis, MD PhD
Objective:	Tranexamic acid (TXA) is an antifibrinolytic medication used to reduce bleeding in a variety of medical settings. The use of TXA in total hip arthroplasty (THA) and total knee arthroplasty (TKA) has resulted in dramatic decreases in operative blood loss and transfusion rates, revolutionizing the field of arthroplasty. The use of TXA, now common, has made autologous blood donation programs largely obsolete. Additionally, it has made perioperative blood transfusion uncommon. While AAOS guidelines suggest that all three available preparations of TXA (oral, IV, topical) are effective, preferred route of dosing varies by provider and institution. These preferences are based on habit, understanding of pharmacodynamics, and logistical issues regarding effective dosing. Oral TXA is the cheapest option, but some surgeons prefer IV dosing due to concerns regarding efficacy and controlled dosing. In this study, we seek to compare the efficacy of a single pre-operative oral dose of TXA to a single pre-operative IV dose of TXA.
Study Design:	Randomized controlled clinical trial
Enrollment:	400
Subject Criteria:	1. Patients undergoing total hip arthroplasty (THA) through a posterior approach 2. Patients undergoing total knee arthroplasty (TKA) 3. Patients between the ages of 18-80
Data Collection:	Sources: EPIC, Patient and Medical Records. Variables: Name, MRN, DOB, Race/ethnicity, sex, Co-morbidities, diabetes, heart disease, prior use of blood thinners, patient weight/height/BMI, Date of surgery, Time PO txa given in holding, surgeon, time of IV txa infusion (start, end), surgery start/end time, incision time, Procedure (TKA or THA), Tourniquet use (onset, release, duration, inflation pressure), Anesthesiologist, ASA physical status, Anesthesia start/end times, Constavac drainage, Transfusion volume, incidence of

	DVT/PE, LOS, transfer to higher level of care, CBC (at PSS, upon PACU entry, at AM labs POD1), Post-Transfusion (if transfusion required).
Statistical Analysis:	• Proposed analysis (e.g., student's t-test, ANOVA, chi-square, regression, etc.): Non-inferiority tests for two primary outcomes: a t-test or Mann Whitney U test will be used for calculated blood loss and chi-square or Fisher's exact test will be used for proportion of blood transfusions • Interim analysis planned? Yes • Alpha level: 0.025 • Beta or power level: 0.80 • Primary outcome variable estimate (mean +/- s.d. for continuous outcome, frequency/percentage for categorical variable): Two primary outcomes for joint hypothesis: 1—Calculated blood loss: 1173±479mL for IV TXA (Jules IV vs Topical TXA); 20% (235 mL) increase in blood loss clinically meaningful difference (based on clinical experience) 2—Blood transfusion: 3% average proportion of cases requiring transfusions; 20% difference clinically meaningful (both based on clinical experience) • Number of groups being compared (use 1 for paired analysis within the same subjects): 2 • Resulting number per group: 200 THAs, 200 TKAs • Total sample size required: 400

1.0 INTRODUCTION

The interventions to be studied are oral and IV tranexamic acid. The conditions to be studied are blood loss and transfusion rate.

Tranexamic acid (TXA) is an antifibrinolytic medication used to reduce bleeding in a variety of medical settings. The use of TXA in total hip arthroplasty (THA) and total knee arthroplasty (TKA) has resulted in dramatic decreases in operative blood loss and transfusion rates, revolutionizing the field of arthroplasty. The use of TXA, now common, has made autologous blood donation programs largely obsolete. Additionally, it has made perioperative blood transfusion uncommon. While AAOS guidelines suggest that all three available preparations of TXA (oral, IV, topical) are effective, preferred route of dosing varies by provider and institution. These preferences are based on habit, understanding of pharmacodynamics, and logistical issues regarding effective dosing. Oral TXA is the cheapest option, but some surgeons prefer IV dosing due to concerns regarding efficacy and controlled dosing. In this study, we seek to compare the efficacy of a single pre-operative oral dose of TXA to a single pre-operative IV dose of TXA.

The standard oral TXA dose is 2g and costs about $2 per dose. The standard IV TXA dose is 1g and costs about $4 per dose (plus the cost of extra equipment such as syringes). Some surgeons prefer IV over oral TXA because it has rapid onset and the dosing can be easily timed with regard to incision. Oral TXA, on the other hand, would have to be taken at some time prior to surgery since its peak plasma concentration is achieved 3 hours after administration (Pilbrant, PMID 7308275). With oral dosing, operating room delays could potentially mean that the peak effect of oral TXA would not coincide with surgery. The benefits of giving oral rather than IV TXA include a significant cost savings and not having to administer an IV medication. A recent meta-analysis (Wang, PMID 30200167) showed similar blood loss and transfusion rate in patients given oral TXA vs IV TXA.

Data and guidelines suggest no functional difference between oral and IV TXA use (Della Valle PMID 29805106). Prior work has investigated oral and IV TXA head-tohead (Kayupov PMID 28244907, Fillingham, PMID 27113948), finding equivalent reductions in blood loss but with great cost savings for oral TXA. This study will attempt to corroborate these findings. However, it will also function as a feasibility study in investigating whether oral TXA can effectively be administered consistently in a pre-operative setting.

2.0 OBJECTIVE(S) OF CLINICAL STUDY

Primary questions

1. Does oral TXA dosing in THA/TKA result in more blood loss compared to IV TXA dosing?
2. Does oral TXA dosing in THA/TKA result in more transfusions compared to IV TXA dosing?

Secondary question

3. Does oral TXA dosing in THA/TKA result in longer length-of-stay (LOS) after THA/TKA compared to IV TXA dosing?

If we further establish that oral TXA can effectively be administered prior to surgery with comparable results to IV TXA, it could potentially shift use away from IV toward oral dosing. This would create an enormous cost savings for our hospital (estimated between $100,000 and $200,000) and might make perioperative workflows function more smoothly, as well.

3.0 STUDY HYPOTHESES

1. Oral TXA administration results in no greater blood loss compared to IV TXA administration.
2. Oral TXA administration results in no increased transfusion rate compared to IV TXA administration.
3. Oral TXA administration results in no increased LOS compared to IV TXA administration.

4.0 STUDY DESIGN

4.1 Endpoints

4.1.1 Primary Endpoint

- Calculated blood loss (CBL) in cc, to be calculated according to Gao (PMID 26521781).
- Transfusion during hospital stay (both binary yes/no and discrete volume transfused)

4.1.2 Secondary Endpoints

- Time to discharge from PT
- Length of stay

4.2 Study Sites

This study will take place at the main campus of the Hospital for Special Surgery (HSS).

5.0 STUDY POPULATION

5.1 Number of Subjects

400

5.2 Inclusion Criteria

Subjects of either gender will be included if:

1. Patients undergoing total hip arthroplasty (THA) through a posterior approach
2. Patients undergoing total knee arthroplasty (TKA)
3. Patients between the ages of 18-80

5.3 Exclusion Criteria

Subjects will be excluded from the study if:

- Patient declines enrollment
- Patients greater than 80 years if age or less than 18 years of age
- Patients with a BMI over 40
- Patients undergoing general anesthesia
- Patients with a history of major ipsilateral joint surgery
- Patients on pre-operative anticoagulation or anti-platelet drugs (other than aspirin)
- Patients with a history of bleeding disorders
- Patients with platelet levels less than 100/nl
- Patients with new-onset/active atrial fibrillation
- Patients with a history of myocardial infarction in the past year
- Patients with a history of a stroke in the past year

6.0 PROCEDURES

6.1 Intraoperative Protocol

Two blocked, 1:1 patient randomization schedules (one for THA and one for TKA patients) will be created using SASsoftware by a biostatistician not otherwise involved in the trial. Randomization cards will be sealed in opaque envelopes and given to the anesthesiologist once the patient consents.

A total of 400 patients will be enrolled, 200 THA patients and 200 TKA patients.

200 THA (posterior approach) patients will be randomized to receive either:
Oral TXA (1950mg) in holding area (N=100)
IV TXA 1g upon transfer to OR (N=100)

200 TKA patients will be randomized to receive either:

Oral TXA (1950mg) in holding area (N=100)
IV TXA 1g upon transfer to OR (N=100)

6.2 Postoperative Protocol

CBC at AM labs done on POD1

6.3 Data Collection

The following data will be collected:

Pre-operative/Baseline

- Time PO txa given in holding

Post-Operative

- Name
- MRN
- DOB
- Race/Ethnicity
- Sex
- Co-morbidities, diabetes, heart disease, prior use of blood thinners
- Patient weight/height/BMI
- Date of surgery
- Surgeon
- Time of IV txa infusion (start,end)
- Surgery start/end time
- Incision time
- Procedure (TKA or THA)
- Tourniquet use
- Anesthesiologist
- ASA physical status
- Anesthesia start/end time
- Constavac drainage

Post-Discharge

- Transfusion volume
- Incidence of DVT/PE
- LOS
- Transfer to higher level of care
- CBC at PSS, upon PACU entry, at AM labs POD1
- Post-transfusion

7.0 STATISTICAL ANALYSIS

- Proposed analysis: Non-inferiority tests for two primary outcomes: a t-test or Mann Whitney U test will be used for calculated blood loss and chi-square or Fisher's exact test will be used for proportion of blood transfusions
- Interim analysis planned: Yes
- Alpha level: 0.025
- Beta or power level: 0.80
- Primary outcome variable estimate: Two primary outcomes for joint hypothesis: 1—Calculated blood loss: 1173±479mL for IV TXA (Jules IV vs Topical TXA); 20% (235 mL) increase in blood loss clinically meaningful difference (based on clinical experience) 2—Blood transfusion: 3% average proportion of cases requiring transfusions; 20% difference clinically meaningful (both based on clinical experience)
- Number of groups being compared: 2
- Effect size or change expected between groups: N/A
- Resulting number per group: 200 THAs, 200 TKAs
- Total sample size required: 400

Outcome	*Calculated Blood Loss*	*Blood Transfusion*
Test	*Non-inferiority*	*Non-inferiority*
Non-inferiority margin	*20%*	*20%*
Clinically meaningful difference	*235 mL*	*20%*
True difference in means/proportions	*0 mL*	*0%*
Pooled SD	*479 mL (Jules, IV vs Topical TXA)*	
Alpha (one-sided)	*0.025*	*0.025*
Power	*80%*	*80%*
Sample size required per group	*67*	*28*
Total sample size required	*134*	*56*
Total sample size required + 20% to account for attrition/withdrawal	***168****	***68***
Total sample size will be N = 400 (200 hips, 200 knees). For the joint hypothesis, sample sizes were calculated for each hypothesis separately. The calculated blood loss hypothesis resulted in a larger sample size (168 compared to 68), so this will be considered a sufficient sample size to power for both portions of the joint hypothesis. We rounded this up to 200 to ensure sufficient power and intend to test both hypotheses separately for hip and knee patients.		

Outcome	**Analysis**		**Possible Confounders**
CBL (1° outcome) (continuous, cc)	t-test or Mann-Whitney U		Surgeon, surgery (TKA vs THA), demographic info, comorbidities
Transfusion (1° outcome) (binary)	Chi-square or Fisher Exact		

Transfusion (1° outcome) (binary) Transfusion volume (discrete, # units)	Chi-square or Fisher Exact t-test or Mann-Whitney U		**Groups** IV vs PO
Transfusion volume (discrete, # units) Change in hemoglobin Preop-POD1 (continuous, mg/dL)	t-test or Mann-Whitney U t-test or Mann-Whitney U		**Notes** Baseline characteristics will be compared between groups using standardized differences, if differences in baseline variables are found, we will conduct regression analyses (linear for calculated blood loss and logistic for blood transfusions) to account for these.
Change in hematocrit Preop-POD1 (continuous, %)	t-test or Mann-Whitney U		All analyses will be conducted separately for hips and knees.
LOS (discrete, nights)	t-test or Mann-Whitney U		
Transfer to higher level of care (binary)	Chi-square or Fisher Exact		

Calculated blood loss (CBL) in cc, to be calculated according to Gao (PMID 26521781). We will calculate CBL according to all 4 methods described by Gao and plan to use the Hb-balance equations, since it is thought to be most reliable. We will compare the 4 CBL calculations as well as EBL to assess the validity of our CBL calculations

8.0 ADVERSE EVENT ASSESSMENT

All Adverse Events (AEs) will be reported in the final study report.