Article Title: Tranexamic Acid for Prevention of Hemorrhage in Elective Repeat Cesarean Delivery – A Randomized Study

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Title: Use of tranexamic acid for prevention of hemorrhage in cesarean delivery

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Introduction and purpose:

Postpartum hemorrhage (PPH) affects 6 to 11 percent of birthing women worldwide[1]. It is the leading cause of maternal mortality, and results in approximately 100,000 deaths per year[2-4]. The prevention and treatment of obstetric hemorrhage has been identified as a national level of maternal care imperative [5].

Background:

Obstetric hemorrhage has been identified as a contributory cause for the United States' suboptimal and inequitable outcomes among pregnant women. As such, obstetric hemorrhage has become a formal focus point in a national agenda to improve maternal outcomes[5]. Strategies to identify maternal hypovolemia and treating obstetric hemorrhage are undergoing organized scrutiny in many states including Texas[12]. Tranexamic acid (TXA) treatment is receiving increased emphasis in obstetric care because TXA inhibits fibrinolysis. Increased clot stability offers the possibility of preventing blood loss (prophylaxis) as well as mitigating on going hemorrhage. TXA therapy has been principally studied in nonpregnant populations; results of studies in pregnant women have been lacking.

Tranexamic acid is an antifibrinolytic agent that acts as a competitive inhibitor at the lysine binding sites of plasminogen and inhibits the ability of protease plasmin to cleave the fibrin clot[6].

In large randomized controlled trials, it has been reported to be effective in decreasing perioperative blood loss in a variety of circumstances primarily involving trauma patients. Shakur and co-authors in a trial of 20,000 non-pregnant trauma patients reported a significant reduction in all-cause mortality after TXA administration[7]. In another large study (WOMAN trial), 20,000 pregnant women with hemorrhage where randomized to TXA or placebo. TXA was associated with a significant decrease in death due to bleeding[8].

Tranexamic acid's role in treating hemorrhage have been widely studied in non-pregnant populations. Studies of TXA in obstetrics are limited. The American College of Obstetricians and Gynecologists believes the data is insufficient to recommend tranexamic acid for prophylaxis[9].

We designed a randomized placebo-controlled trial comparing TXA dosing prior to incision for cesarean delivery with a repeat dose given at placental delivery. Our purpose is to quantify blood loss during uncomplicated repeat cesarean deliveries with and without TXA. We elected to study scheduled elective cesareans because such procedures are at low risk for profound hemorrhage. It is our intent to have a study cohort where the two treatment groups (TXA or placebo) are as comparable as possible, so we are not testing the efficacy of TXA in women with highly variable volumes of obstetric hemorrhage. TXA here-to-for has not been studied in a context where blood volume loss was quantified in both study groups.

Specific Aims:

Specific Aim 1: To determine the efficacy of perioperative TXA administration on reducing blood loss in women undergoing scheduled repeat cesarean delivery. We will use a method for calculating blood loss previously described by our group in an observational study of 1443 women with obstetrical hemorrhage[10]. Using this mathematical method to calculate maternal blood volume, pre- and post-cesarean, we hypothesize that an initial bolus of TXA with a second bolus at placental delivery will reduce blood loss in comparison to placebo.

Specific Aim 2a: To quantify maternal fibrinolytic activity with and without TXA in women undergoing cesarean delivery. In vitro serum markers of fibrinolysis (fibrinogen, plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator (t-PA), and D-dimer) and rotational thromboelastometry will be used to quantify fibrinolytic activity. Given that TXA is a lysine analog that prevents the conversion of plasminogen to plasmin, thereby inhibiting fibrinolysis[6], we *hypothesize* that in women given TXA , will have less evidence of fibrinolysis on measurement of serum markers and rotational thromboelastometry[11].

Specific Aim 2b: To ascertain if TXA effects on fibrinolysis dissipate by postoperative day 1. We *hypothesize* that by postoperative day 1, effects of TXA will have dissipated, as evidenced by comparable levels of fibrinolysis (serum markers and rotational thromboelastometry) in the TXA and placebo groups.

Concise Summary of Project:

This is the first trial to utilize a regimen of TXA that uses a prophylactic dose of TXA prior to incision followed by a subsequent prophylactic dose at placental delivery in obstetric patients undergoing scheduled cesareans. The outcome of interest is quantified blood loss.

We prepared a novel study of TXA designed to estimate the quantity of blood loss in women undergoing repeat cesareans. This group was chosen to minimize the large variability of hemorrhage in women after extreme hemorrhage has already commenced.

We are of the belief that careful study of TXA is imperative in any material or state level effort to mitigate obstetric hemorrhage's[12] impact on maternal health. If TXA is shown to quantitatively reduce obstetric hemorrhage in the highly controlled trial we now propose, then subsequent trials can be designed to test not only prophylaxis, but adjunct TXA therapy in the setting of ongoing severe maternal hemorrhage.

The training and research activities described in this application will occur in coordination with the Departments of Anesthesiology, and Obstetrics and Gynecology. Parkland Hospital is conducive to such a study because of a large delivery volume of >12,000 per year as well as a nationally recognized service.

Study Procedures: *Study Design*

This is a double-blind, randomized, placebo-controlled trial designed to assess the superiority of a prophylactic dose of TXA prior to skin incision with a repeated bolus at placental delivery compared to placebo. The outcome of interest is a reduction in blood loss in comparable women undergoing routine scheduled cesarean delivery. Women that meet inclusion criteria will be approached for informed consent **[Table 1]**. After written informed consent and HIPAA authorization is obtained, participants will be randomized to either 1) placebo-group: normal saline or 2) treatment group: TXA. Figure 3 illustrates the participant flow from screening through completion of this study.

Table 1 Inclusion/Exclusion Criteria.

Inclusion Criteria	Exclusion Criteria
• Age ≥ 18 • Intrauterine Pregnancy • Singleton pregnancy • Gestational age ≥ 37 weeks 0 days • Scheduled Cesarean Delivery • Second or third cesarean delivery	• First cesarean delivery • Four or more cesarean deliveries • Intrauterine fetal death • Fetal anomalies • Documented coagulopathy (Elevated Prothrombin Time (PT), Elevated Partial Thromboplastin Time (PTT), Elevated International Normalized Ratio (INR) • Thrombocytopenia (Platelet Count < 100k) • Internal bleeding, external bleeding, easy bruising • History of thrombotic event • Hypertension • Diagnosis of renal insufficiency (Creatinine > 1 mg/dL) • Insulin-treated diabetes • Suspected morbidly adherent placenta • Placenta previa • Multiple gestations • BMI ≥ 50 • HCT ≤ 25 • Blood transfusion within 24 hours prior to cesarean delivery • History of abnormal bleeding or blood disorder • Planned general anesthesia

Methods

All participants will receive an IV infusion, either saline (placebo) or TXA depending on randomization, prepared by the Parkland Investigational Drug Pharmacy, using identical blinded infusion bags with a unique identifier code.

Placebo group: Participants will receive an infusion of 100 mL of saline given intravenously over 10 minutes at least 10 minutes before skin incision. Subsequently, a 100 mL solution of saline will be infused over 10 minutes at the time of placental delivery.

Treatment group: Participants will receive an infusion of 1 g of TXA, diluted in 100 mL of saline, to be infused at least 10 minutes before skin incision. Subsequently, 1 g of TXA, diluted in 100 mL of saline, will be infused intravenously over 10 minutes at time of placental delivery.

Study Procedures

Written informed consent and HIPAA authorization will be obtained by the principal investigator (O.O.) and kept in the subjects' research chart along with a unique identifier of the solution infused. The principal investigator will be responsible for ordering TXA from Investigation Drug Services, and coordinating with the attending anesthesiologist. Research nurses will help screen patients for eligibility, and assist the principal investigator in obtaining consent. The research nurses will also assist in obtaining patient blood samples for hematocrit determination, markers of fibrinolysis, and ROTEM analysis. Research nurses will help maintain strict adherence to study protocol.

Figure 3 Timeline of data collection and outcomes of interest
Markers of fibrinolysis: tissue plasminogen activator, plasminogen activator inhibitor-1, D-Dimer & fibrinogen level

AIM-SPECIFIC APPROACH

Aim 1: To determine the efficacy of perioperative TXA administration on reducing blood loss in women undergoing scheduled repeat cesarean delivery.

Method: In each study group, we will calculate total blood volume lost using the mathematical method described in **Table 2[10].**

Table 2 Mathematical method for calculating total blood volume loss.

HCT: hematocrit; RBC: red blood cell

[a] Assumptions for transfused blood: (1) packed red blood cells contains 330 mL total volume with HCT 55 vol% or 182 mL RBC volume per unit; (2) whole blood contains 450 mL total volume with HCT 40 vol% or 180 mL RBC volume per unit.

Method for Calculation of Total Blood Volume Lost Due to Obstetric Hemorrhage	
Step 1	Calculate total non-pregnant blood volume: [(height in inches × 50) + (weight in pounds × 25)] ÷ 2
Step 2	Add 50% for average pregnancy volume expansion (i.e., hypervolemia of pregnancy)
Step 3	Pregnancy total blood volume× admission HCT (vol %) = admission RBC volume
Step 4	Assume total blood volume has returned at discharge to the non-pregnant total blood volume as a result of hemorrhage. Therefore, non-pregnant blood volume× discharge HCT (vol%) = discharge RBC volume
Step 5	Calculate total blood volume lost: (admission RBC volume− discharge RBC vol % + RBC volume transfused[a]) ÷ admission HCT (vol %)

Specific Aim 2a: To quantify maternal fibrinolytic activity with and without TXA in women undergoing cesarean delivery. In vitro serum markers of fibrinolysis (fibrinogen, plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator (t-PA), and D-dimer) and rotational thromboelastometry will be used to quantify fibrinolytic activity.

Specific Aim 2b: To ascertain if TXA effects on fibrinolysis dissipate by postoperative day 1.

Methods*:* For plasma *in-vitro* fibrinolytic activity (*To be collected before initiation of infusion of TXA or placebo, at placental delivery, and on postpartum day 1*)**:** quantitative t-PA and PAI-1 levels will be collected in a light blue top container with 3.2% sodium citrate. The specimens will be transported to the research lab, stored at -20ºC, and batch testing performed when appropriate. Fibrinogen levels and D-Dimer will be collected in a blue top container with 3.2% sodium citrate. The specimen for hematocrit will be collected in a lavender container.

For rotational thromboelastometry (ROTEM™), (*To be collected before initiation of infusion, TXA or placebo, at delivery, and on postpartum day one*)**:** a small aliquot of venous blood will be added to a disposable cuvette (measuring cell) in a heated cuvette holder. A disposable pin (sensor) fixed to a rotating shaft rotates back and forth 4.75 degrees. The exact position of the shaft is detected by reflection of light on a small mirror on the shaft. Data obtained from the reflected light is then computer processed into a graphical output with numerical values reported.

On ROTEM™ analysis, we will compare ML values at 60 minutes, CT, CFT, and MCF values, numerically and graphically. Normal levels are graphically depicted in **Fig. 4**, fibrinogen deficiency in **Fig. 5**, and hyperfibrinolysis in **Fig. 6**.

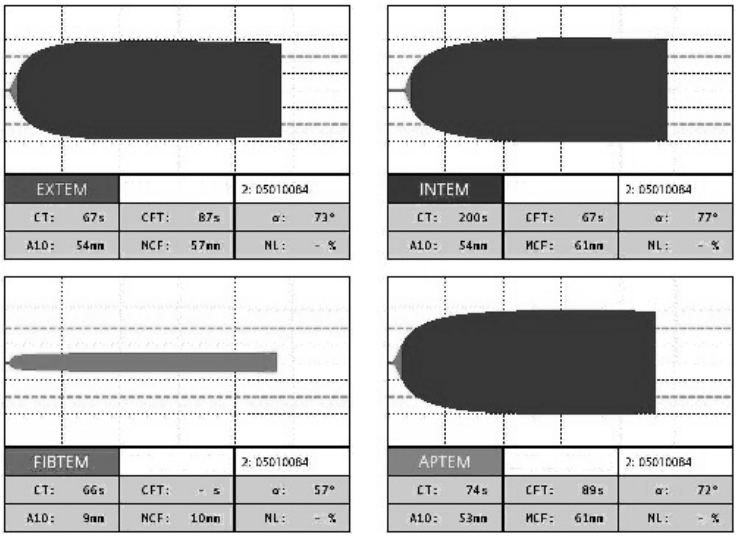

Fig. 4. Normal levels on ROTEM™.

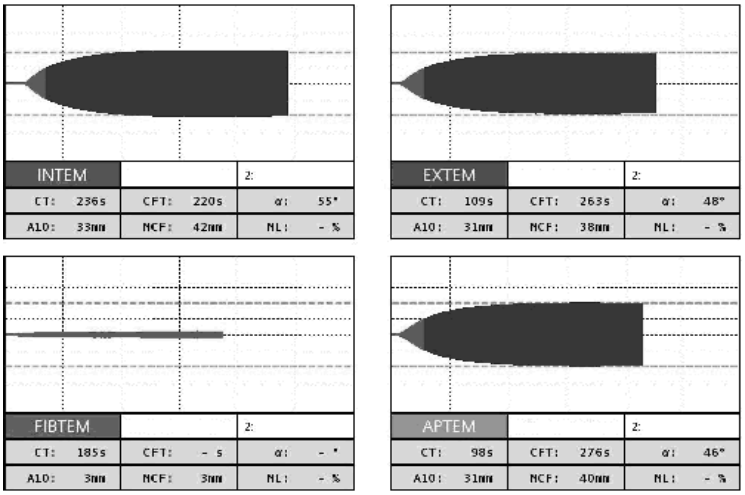

Fig 5. Fibrinogen deficiency on ROTEM™.

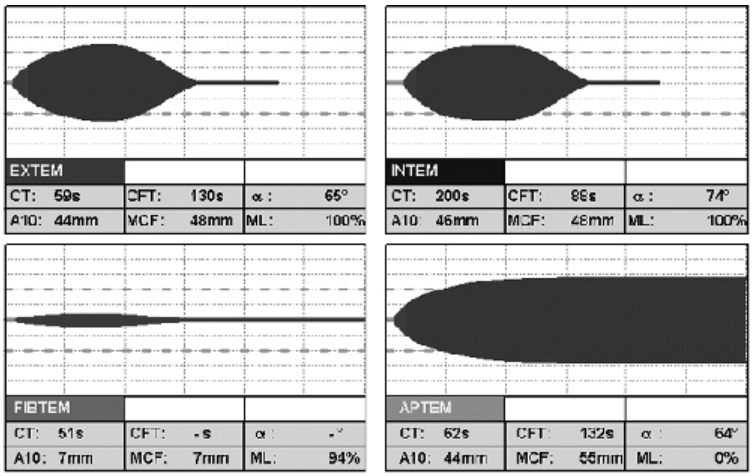

Fig. 6 Hyperfibrinolysis on ROTEM™.

Sources of Research Material: There are two electronic data sets to be used in this proposed study:

1) The Epic Electronic Medical Record (EMR) system at Parkland Hospital provides an integrated EMR system. Patient data is entered through a menu driven, formatted data entry screen and may be reviewed through similar processes. It was implemented at Parkland April 28, 2009. Epic is managed by Information Technology at Parkland and maintains strong security.
2) Selected obstetrical outcomes for all women who give birth at Parkland Hospital, as well as neonatal outcomes, are entered into a computerized obstetric database. Nurses attending each delivery complete an obstetrical data sheet, and research nurses assess the data for consistency and completeness before they are stored electronically. Data on neonatal outcomes are abstracted from discharge records. These data are stored on a secure file server maintained by the Department of Obstetrics and Gynecology.

Recruitment Methods and Consenting Process: Women scheduled for elective cesarean delivery Monday through Friday at Parkland Labor and Delivery and who meet the inclusion criteria will be eligible to participate. A research nurse will screen all women that meet study criteria. After identification of a potential subject, the principal investigator will discuss the research protocol, answer any questions, and obtain consent and HIPAA authorization. Consents will be available in English and Spanish, and an interpreter will be available.

Potential Risks:

	Frequent (30% of subjects)	Uncommon (<15% of subjects)
Major		Tranexamic acid: • Hypotension (rare) • Thromboembolism (Maternal **AND** fetal) (rare) • Seizures (rare) • Anaphylaxis (rare) Venous blood draw: • Excessive bleeding (rare) • Infection (rare) • Fainting (rare)
Minor		Tranexamic Acid: • Stomach discomfort • Nasal congestion • Headache • Joint and Muscle Pain • Vision changes Venous blood draw: • Discomfort at the needle site • Bruising • Clotting

Subject Safety and Data Monitoring:

Human Subjects Involvement and Characteristics:

We are proposing to enroll a total of 100 women into two study arms of 50 women each. Enrollment will be done exclusively at Parkland Hospital. Women who present for cesarean delivery will be screened by study team for eligibility. All women who volunteer to participate will sign a UTSW IRB-approved consent form and HIPAA authorization. Before being transported to the operating room, blood will be obtained by the study team for hematocrit (routine care), markers of fibrinolysis, & ROTEM analysis. The study team will then order "study drug" to be given:

1) TXA 1 gram (diluted in 100 mL normal saline) given intravenously over 10 minutes, 10 minutes before skin incision *followed by* TXA 1 gram (diluted in 100 mL normal saline) given intravenously over 10 minutes at time of placental delivery.
2) Placebo (100 mL of normal saline) given intravenously over 10 minutes, 10 minutes before skin incision *followed by* placebo (100 mL normal saline) given intravenously over 10 minutes at time of placental delivery.

Parkland's *Investigational Drug Pharmacy* will prepare a blinded solution containing TXA or saline with a unique identifier according to a computerized randomization allocation sequence generated by Dr. McIntire (statistician). The pharmacist on-call will deliver the solutions to an attending anesthesiologist. The study team which includes a research nurse will ensure that the solutions are infused per protocol. At delivery of the placenta & on postoperative day # 1, blood will be drawn for analysis of hematocrit, markers of fibrinolysis, & ROTEM by a study team member.

Sources of Materials:

Each participant will be assigned a unique study ID at enrollment. Blood samples collected from each participant will be appropriately labeled with the study ID number and will not contain patient identifiers. A master list linking the study ID with subject's information will be maintained by Dr. McIntire on a secure, password-protected computer in his locked office with automatic saving to a secure, password-protected, backup hard drive. A Microsoft Access® database containing the collected information will be maintained separately on a secure, password-protected server that is accessible only within the University of Texas Southwestern. The database will not include protected health-care information. All information and material will be obtained for research purposes only and kept in strictly confidential. Any paper documents resulting from the study are kept in locked file cabinets accessible only by authorized research personnel.

Research material will include a total of 36 mL of **maternal** venous blood (twelve mL x three collections) and clinical information. Clinical information will be collected from the electronic medical record and direct patient interview. Collected information includes demographic information, medical and surgical history, physical examination, laboratory, imaging, and pathology reports.

Potential Risks:

The potential **maternal** risks involved in this study include:

1) Venous blood draw: generally mild and include discomfort, bruising, and rarely, excessive bleeding, clotting, infection, or fainting.
2) Uncommon or rare complications of tranexamic acid administration include:
    a. Hematologic: Blood clot, bleeding, bruising
    b. Gastrointestinal: Stomach discomfort, diarrhea, nausea, vomiting
    c. Cardiovascular: Hypotension (with rapid I.V. injection)

d. Respiratory: Shortness of breath with exertion, nasal congestion
e. Central nervous system: Headache, giddiness, dizziness
f. Musculoskeletal: Muscle cramps, muscle spasm, joint stiffness, joint swelling
g. Hypersensitivity: Anaphylaxis, anaphylactoid reaction, allergic dermatitis
h. Ocular: Change in vision

3) Pregnancy and the immediate postpartum period are considered hypercoagulable states, and it is plausible that TXA could induce thromboembolism. Although this was not seen in the WOMAN trial of 10,000 TXA treated parturients.
4) Confidentiality: this risk is minimal with the study safeguards in place (see below).

There have been no **fetal** risks reported in the literature:

1. TXA is a Food and Drug Administration Pregnancy Category B drug; animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate well-controlled studies in pregnant women

ADEQUACY OF PROTECTION AGAINST SUBJECTS

a. Recruitment and Informed Consent:

All subjects will have the purpose of the study, risks, and benefits explained to them. All subjects who volunteer to participate will sign an IRB-approved consent form and HIPAA authorization. They will be informed that their voluntary consent can be withdrawn at any time, that they retain all legal rights to decision making, and will be provided with original signed copies of the consent form and HIPAA authorization including Dr. Ogunkua's contact information.

b. Protection Against Maternal Risk:

1) Venous blood draw: generally mild and include discomfort, bruising, and rarely, excessive bleeding, clotting, infection, or fainting. *Whenever possible, blood samples will be performed simultaneously with clinical blood draws to avoid the need for additional venipuncture. Blood will be drawn using aseptic technique by trained personnel.*
2) Tranexamic acid administration: *To avoid hypotension and assess for allergic reactions, the infusion will be delivered from a programmed infusion pump to avoid rapid administration. Subjects will be continuously monitored for the 1st 2 hours of administration for complications.*

3) Confidentiality: this risk is minimal with the study safeguards in place: *A strictly enforced policy of confidentiality is in place for all research staff and included completion of Collaborative Institutional Training Initiative (CITI) in the protection of human subjects. Any paper documents resulting from the study are kept in locked file cabinets. Subjects' electronic data records are stored in restricted computer files on non-networked computers. Direct identifiers such as name, address, and social security number, will be removed from subject data and replaced with a study based unique identification code. All data and documentation storage devices are accessible only by authorized study personnel. At the completion of the study, any information containing patient identifiers will be destroyed by confidential means.*

c. Protection Against Fetal Risk:

For this study, TXA is administered maternally 10 minutes before incision. Although there is a degree of placental transfer of TXA, the administration so close to delivery largely reduces fetal exposure. There have not been any reports in the literature of adverse fetal outcomes. We have assembled a team of experts to monitor for potential issues and the possible call for early termination if warranted.

POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECT AND OTHERS

The potential benefits include determining if intravenous tranexamic acid therapy is efficacious in reducing blood loss in women undergoing cesarean delivery. Uterine atony is the leading cause of postpartum hemorrhage often occurring in women with no previous risk factors. Theoretically, some of the study patients will benefit from TXA prophylaxis. This study poses minimal & infrequent maternal risks and there are no adverse fetal effects reported in the literature. This study has the potential to significantly impact maternal morbidity and mortality due to obstetric hemorrhage.

DATA AND SAFETY MONITORING PLAN

A data and safety monitoring board assembled of diverse specialists including Dr. Scott Roberts Obstetrics, Dr. Weike Tao and Dr. Rhonda Arnette Anesthesiology will meet quarterly to monitor for protocol adherence and adverse events. Dr. Donald McIntire, Biostatistician, will lead this board.

BIOSTATISTICS

Sample Size (total sample size=100, power 0.80, two-sided)

We selected a pilot of 20 patients randomly from schedule cesarean deliveries at Parkland Hospital. For this sample we performed the blood loss calculation for each delivery. This resulted in a mean blood loss of 2224 mL and a standard deviation of 362 mL. The trial is designed to observe a 205 mL reduction in the TXA arm over the placebo arms as from 2224 mL (placebo arm) to 2019 mL (TXA arm) with 80% power. This requires fifty patients randomized to each arm (one hundred total patients) using a two-sided test of significance level 0.05 using a Student's t-test.

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