Prevention of Postpartum Hemorrhage With Tranexamic Acid
8/9/2018

NCT#03287336

RESEARCH PROTOCOL

TITLE: Prevention of postpartum hemorrhage: pharmacokinetics (PK) and pharmacodynamics (PD) of Tranexamic acid

RESEARCH PLAN

A. Specific Aims

The purpose of this study is to characterize the pharmacokinetics of TXA when given prophylactically at time of delivery. In addition we aim to determine the mechanism of action and pharmacodynamics (PD) of TXA in the peripartum period

B. Background and Significance

Postpartum hemorrhage (PPH) is a significant contributor to maternal morbidity and mortality and is worldwide responsible for approximately *10 maternal deaths every hour*.[1,2] Prediction for who is at risk for severe hemorrhage is not reliable based on current methods.[3,4] National organization leaders have called for improvement of recognition and prevention of postpartum hemorrhage.[5] Aside from uterotonic agents for treatment and/or prevention, few other simple medical interventions exist in the peripartum period.

Tranexamic acid (TXA) is an inexpensive and easy to administer anti-fibrinolytic agent routinely used in cardiac, trauma and orthopedic patients to prevent hemorrhage and reduce mortality. Most of the evidence to support dosing recommendations for clinical studies are based on pharmacokinetic (PK) data from non-pregnant patients.[4] High dose exposure to TXA among non-pregnant patients is associated with gastrointestinal side effects, seizures and a potential increase in thrombotic risk.[5-7] Thus, US obstetricians and anesthesiologists are hesitant to use TXA in the peripartum period especially for prevention of PPH due to uncertainty of an optimal dose and safety profile.[8]

C. Research Design and Methods

The study will seek to enroll 45 3rd trimester pregnant women scheduled for non-emergent cesarean section who are at high risk for hemorrhage towards a target of 30 study subjects to conduct a prospective, open-label, dose finding PK study. We will administer three doses of the drug (5 mg/kg, 10 mg/kg and 15 mg/kg) in an escalating fashion by cohort with the lowest dose first. The drug will be administered intravenously at the time of umbilical cord clamping for a non-emergent cesarean section. A maximum of 1 gram will be administered. TXA serum levels at several time points after delivery will be assayed to see if they reach the target plasma concentration of 10 microg/mL. A PK model will be constructed for determining the optimal TXA dose administered at parturition.

Of note, GW currently has an ongoing randomized clinical trial using tranexamic acid to reduce blood loss in surgery for uterine fibroids (IND# 125089). This study is nearly halfway with recruitment and the research coordinator who is helping with this study will also help with the current proposed study.

Group	N	TXA Dose
1	10	5 mg/kg
2	10	10 mg/kg*
3	10	15 mg/kg*

*max 1 gram dose

Plasma sampling: TXA will be administered by intravenous infusion given over 15 minutes using an infusion pump at the time of umbilical cord clamping. Timing of samples will be relative to the end of the infusion intravenous infusion (start of infusion is t=0) and include before receiving the drug, within 10 minutes, 30-60 minutes, 1.5-3 hours, 4-6 hours,7-8 hours and 24 hours after the drug load. Each volume of blood draw will be approximately 2-5 mL. The first 10 enrolled patients will receive 5 mg/kg, then the second 10 patients will receive 10 mg/kg and the final set of 10 patients will receive 15 mg/kg. Actual times of plasma sampling will be documented. A second IV will be required for participating in the study. Citrated plasma samples will be centrifuged and supernatant will be stored at -70 degree Celsius for further. Breast milk sampling of no more than 2 cc per time point will occur at time points coinciding with maternal feedings.

1) Subject recruitment and consent. Subject recruitment will take place in the GW MFA routine prenatal clinic among other prenatal patients. In addition, inpatient charting will utilize a screening tool developed for research projects at GW called 'Power Trials' to help screen eligible subjects admitted to L&D. Interested subjects will be consented by either a physican investigator or Research Coordinator as described below. The subjects serum creatine levels will be obtained if indicated at the time of delivery.

2) Drug doses will be given in cohort fashion as outlined above with the lowest drug concentration first (5 mg/kg). This will be continued to enroll all participants until the maximum dose of 15 mg/kg (with the absolute max dosage of 1 gram).

3) The MFA Investigational Drug Services Pharmacy will provide the drug at the different doses requested. 30 patients in the intervention group will be given a single bolus intravenous injection as described above of TXA at least 10 minutes before.

4) Estimated intraoperative blood loss (EBL) will be calculated by measuring the volume in the suction apparatus and weighing the sponges. The weights of dry sponges will be subtracted from the weights of sponges used during the operation. The weight of a sponge found in grams will be translated to ml by using blood density (1.050 g/ml). Thus, estimated intraoperative blood loss will be defined as the blood volume found in the suction apparatus (minus irrigation used) plus the volume calculated for the used sponges. The total perioperative blood loss will be a measure of the intraoperative and postoperative blood loss. In addition, if a patient has an Hb< 7 g/dl and has clinical

symptoms of anemia will be given a blood transfusion. The number of transfusions given will be recorded.

5) The pharmacodynamic testing to be performed includes blood coagulation assays outside the body using patient blood samples. They will assess whole blood clot formation and break down real time and help demonstrate the effects TXA has on these properties. This technology is not routinely used in clinical obstetric care so therefore the information will not be available to be applied to patient care. However, this technology is routinely used for other fields such as cardiac and transplant surgery.

6) Hospital (operative and pathology reports) and clinic (clinical visit notes) reports will be reviewed to compare baseline demographics, preoperative Hb, past surgical history, past medical history and operative time.

D. Study Population:

Inclusion Criteria:

a. Women who are undergoing medically indicated cesarean section at greater than 34+0 weeks gestation or women undergoing elective cesarean section at 39+0 weeks gestation in accordance with recommendations from the American Congress of Obstetricians and Gynecologists
b. pregnant women with normal serum creatinine (serum creatinine < 0.9)
c. Women between the ages of 18 and 50 years old

Exclusion criteria:

a. Patients younger than 18 or older than 50
b. women with active thrombotic or thromboembolic disease
c. Women with a history of arterial or venous thromboembolic event
d. Women with inherited thrombophilia or preexisting conditions that predisposes them to thromboembolic events (i.e. lupus, antiphospholipid syndrome)
e. Women with a subarachnoid hemorrhage
f. Women with acquired defective color vision
g. history of seizure disorder
h. known renal dysfunction (serum creatinine >2.0)
i. multiple gestations (Twin or triplet pregnancies)
j. Hypersensitivity to Tranexamic acid or anti-fibrinolytic therapy
k. History of liver dysfunction

Subject Discontinuation Criteria:

a. Women who experience any serious adverse side effect (including unknown hypersensitivity (hives, shortness of breath, angioedema) or acute thrombosis) while undergoing TXA infusion will be terminated from the study and the infusion of study drug will be discontinued immediately.

The maximum number of patients to be recruited for the study will consist of 30 subjects (10 patients at each dose of the drug specified). This number was chosen as an appropriate sample size for the pilot study.

The Department of Obstetrics and Gynecology at the MFA has seen a dramatic increase in their volume over the past few years. The George Washington University Medical Center (GWUMC) Department of Obstetric Anesthesiology serves a busy Labor and Delivery unit that includes 10 private suites, 4 triage beds, 2 perioperative beds and 2 operating rooms. Obstetrics, nursing and anesthesiology staff are available, in-house 24/7, including resident and attending faculty. It is anticipated that the study coordinator will be available daily during business hours and by an on-call arrangement at other times. Our Labor and Delivery unit has **approximately 3,400 deliveries per year**. The approximate rate of PPH is estimated to be about the national average rate in the US, at 3-5%. Research ROTEM machine and reagents will be provided by ROTEM Inc. and a location for the machine to be stored on Labor and Delivery has been secured. I will use my prior training and experience using ROTEM technology to oversee the PD portion of this project. Frozen samples will be stored in lab space occupied by the Anesthesia department on the 5th floor of Ross Hall.

Study participants will be identified from patients presenting to the GWU Medical Faculty Associates for routine prenatal care. Data including age, pregnancy history such prior cesarean section, uterine fibroids, anemia, prior history of postpartum hemorrhage or blood transfusion will be collected and used to screen for eligible patients.

E. Recruitment and Informed Consent

Recruitment will be performed by one of the prenatal providers who will mention the study to each eligible patient during the patient's routine clinic appointment. The clinician will minimize undue influence by emphasizing the voluntary nature of participation. Furthermore, whenever possible consent procedures will be performed by the research coordinator and not by that patient's physician. A partial HIPAA waiver has been requested in order to review medical records to identify potential participants.

Patients who express interest in the study during scheduled prenatal clinic visits (recruitment) will be contacted directly or by phone by the study's research coordinator. The consenter will ask to meet the patient during her scheduled pre-admission blood work appointment, next scheduled clinic visit, or the day of surgery. Whenever possible, the research coordinator will meet each patient individually to explain the study in greater detail and get each patient's informed consent.

The list of study participants will be maintained in a de-identified coded spreadsheet on the study coordinators password protected computer. The code, linking patient number to MFA medical record number will be separately maintained in a locked file cabinet in the OB/GYN fellow's office.

Informed consent will be obtained by one of the investigators in a non-coercive manner in a private location. All risks, benefits and alternatives to participation will be discussed and the participant will be notified that her decision to or not to participate in the study will in no way influence the quality of care she will receive. The consenter will answer any questions the subject may have. After the study has been explained in detail and they have agreed to participate, signed consent will be obtained and kept on file in a locked cabinet accessible only to research personnel. Subjects will receive a copy of the

signed consent form at the time of consent. Subject recruitment will take place during scheduled preoperative patient visits. Subjects who complete the study will be compensated $200.00 in the form of a gift card to Target or a Medela breast pump. They will receive the compensation after they have undergone delivery and blood samples are collected.

Subjects will be given the chance to ask questions and to opt out of the research at the recruitment session (during the clinic appointment), the recruitment follow-up (when the research coordinator contacts patients who expressed interest during their clinic appointment) and also at the consent session. Subjects will be reminded of the study on the day of surgery and will have another opportunity to opt out of the study prior to surgery if they wish.

F. Risks and Side Effects:

Potential Risks*:*

1. *Psychological*: emotional discomfort if a participant assumes a different level of care will be given to those who do or do not participate in this study. However, all efforts will be made to assure patients that participation in this study will not affect the quality of care received. Additionally, patients will undergo informed consent privately in the absence of the clinicians.

2. *Privacy*: There is also a risk of breach of confidentiality. All efforts will be made to ensure that confidentiality is protected. Risk of breach of privacy will be minimized by undertaking both recruitment and consent in the clinic and hospital, at patients' appointments in a private office or exam room. The research coordinator and the clinicians will practice discretion in choosing when to discuss the patient's involvement in the study.

   Demographic and study data will be collected and stored in secure password protected digital locations in a de-identified manner. The code linking the study participant number with a patient identifier (MFA medical record number) will be stored in a locked file cabinet in the research coordinators locked office at the MFA. The link between the patient identifiers and the study-related documents will be destroyed 12 months after completion of the study.

3. *Physical*: Tranexamic acid has been studied in a broad range of surgical and obstetrics literature and the risk for venous thrombosis (VTE) is largely theoretical. In the small randomized trials thus far in obstetric literature, there is no increased risk for VTE found. There may be other risks associated with this drug not yet known/published.

   Physical risks will be minimized by excluding patients with a prior history suggesting an increased risk for VTE, history of seizure disorder, history of renal (Cr >2.0) or liver dysfunction, women older than the age of 50, women less than the age of 18. A full listing of exclusions can be found under section.

Potential harm to the neonate should be assessed by asking the mother to self-report any medical diagnosis of the neonate at the 1-2 week follow up call and the 6-week follow up appointment.

We will reassess thromboembolic events for trial participants at thte time of discharge from the hospital, 1-2 weeks from C-section by phone call (asking about symptoms such as asymmetrical leg swelling, pain or redness and also shortness of breath) and at 6-week routine postpartum visit.

G. Benefits:

Potential Benefits:
The direct benefit to the patient is that participants in the intervention group may benefit from decreased complications, need for blood transfusions and faster recovery if tranexamic acid does minimize blood loss during cesarean section. Additionally, as many patients with cesarean sections may get repeat operations for delivery during their lifetime, results of this study may inform management of repeat cesarean sections in the future.

The potential indirect benefits of the study are also significant. This research may provide a method to make a common and necessary procedure safer. It may potentially help future studies designed to identify the lowest safest dose for women to use in peripartum period for prevention of postpartum hemorrhage.

H. Costs To Subjects:

1. There is no additional cost to the patient.

I. Conflicts Of Interest:

1. I have a ROTEM Inc Research Machine on loan to conduct the research of my choice. The company has no influence in study design or carrying out the study.

J. Confidentiality:

Each participant will be assigned a study number at the time of consent to participate in the study. All data (demographic, sample labeling, and analytic) will be attached to the study number. No identifiable participant information will be included with these data. De-identified data collection forms will be maintained in secure locked filed cabinets in the research coordinator's office. De-identified data will be entered into spreadsheets on password-protected computers in the research coordinator's office.

The code linking study number to MFA medical record number will be maintained in a single locked file cabinet separate from de-identified data collection sheets by the study research coordinator at the MFA. Access to the participant's medical record will only be available to the study's clinicians and the MFA research coordinator through the MFA's HIPAA compliant, password protected, firewalled electronic medical record (Allscripts).

Following completion of this pilot study and all associated academic publications, presentations, or follow-up grant proposals the de-identified data collection sheets and the code linking participant study number to the MFA medical record number will be destroyed.

K. Subject Compensation:

The subjects who complete the study will be compensated $200.00 in the form of a gift card to Target or choose to obtain a Medela breast pump valued at $250. They will receive the compensation after they have undergone delivery and collection of blood samples.

L. Facilities and Equipment

This study will be conducted at George Washington University Hospital Labor and Delivery Operating Room and the GW Medical Faculty Associates OB/Gyn Clinic. All equipment used will be the equipment already planned to be used for the subjects scheduled surgery. No additional surgical equipment necessary. The study drug (IV tranexamic acid) along with associated vials will be purchased.

M. Adverse Event Monitoring and Reporting

Participants will be monitored for adverse events (AEs) by a physical exam performed by the PI or other OB/Gyn physician within 24h hours of administration of the drug. All adverse events will be recorded in real time in an AE log maintained by study staff. AEs will be immediately reviewed and if appropriate, an IND Safety Report will be completed and submitted to the FDA pursuant to CFR Title 21 Part 312 Subpart B §312.32 IND Safety reporting. Additionally, all AEs will be reported to the IRB overseeing the trial in accordance with their requirements.

N. Study Discontinuation

This trial will be stopped and the IRB and FDA immediately notified if any of the following events occur:

a. Death of one participant
b. prevalence rate of thromboembolic events in patients that receive TXA exceeds the prevalence background rate of thromboembolic events in this patient population

O. References & Literature Cited

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