Document date: 6/4/2016 **NCT02806024**

ID: 2016036 Perioperative Administration of Tranexamic Acid for Placenta Previa and Accreta Study

Perioperative Administration of Tranexamic Acid for Placenta Previa and Accreta Study (TAPPAS): A Randomized, Placebo-controlled Double Blind Trial

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Brief Synopsis

The purpose of this pilot study is to determine if intravenous tranexamic acid (TXA) is effective for reducing blood loss during high risk surgical procedures related to placenta previa and placenta accreta. TXA is currently used in other types of surgery for patients who are expected to have a large blood loss, such as orthopedic or cardiac surgery. The drug will be given AFTER delivery of the baby, so there is no risk of harm to the infant when participating in the study.

Background

Significance: The incidence of morbidly adherent placenta is rising due to increasing cesarean rates, and is currently estimated at 1 in 500 to 700 deliveries. Placenta accreta, a condition in which the placenta abnormally invades the uterine wall, carries a high risk of operative complications and often requires cesarean hysterectomy. Cesarean hysterectomy leads to higher intraoperative blood loss and morbidity when compared to a routine cesarean delivery. Retrospective reviews estimate there a 40% risk of requiring blood transfusion over ten units, and a 7% risk of maternal death (1).

Placenta accreta can be suspected antenatally based on certain risk factors, such as prior cesarean delivery and abnormal placenta location. For example, a woman with 3-4 prior cesarean deliveries and a placenta previa (low lying placenta) has a 60% risk of placenta accreta (14). Additional ultrasound and/or MRI studies can identify suspicious imaging features. However, diagnosis cannot be confirmed until the time of surgery, at which point abnormal placental behavior (hemorrhage, or failure of the placenta to detach) may be observed. The diagnosis is confirmed by final pathology report. Women with multiple prior cesarean sections, placenta previa, and placenta accreta have greater expected intraoperative blood loss, perioperative complications and morbidity than primary (first-time) cesarean sections (14).

Placenta accreta is as challenging to treat as it is to diagnose. The only commonly described innovation thus far is interventional radiology preoperative placement of balloon catheters in the uterine arteries to reduce intraoperative bleeding. Yet the evidence supporting this practice is mixed and in some series has not been shown to provide a statistically significant reduction in blood loss (2). Additionally, some motivated patients with accreta who wish to preserve the uterus do not undergo hysterectomy, and instead are given methotrexate after delivery to encourage absorption of the placenta. This approach frequently results in failure and hysterectomy at a later date. Current recommendations include referral of patients with a high suspicion of accreta to a tertiary care center for delivery, preparedness for a massive transfusion protocol if needed, and a planned, late preterm delivery to occur with coordinated support of surgical subspecialists (such as oncology backup) if bladder or other visceral organ involvement is suspected.

Innovation: To date, no novel or pharmacologic methods of reducing blood loss have been described for women at risk for placenta accreta. Intravenous tranexamic acid (TXA), a drug with

anti-fibrinolytic activity, is routinely used in elective orthopedic and cardiac surgery to reduce blood loss. Intravenous tranexamic acid is currently FDA approved for use in patients undergoing cardiac surgery or total knee arthroplasty or total hip arthroplasty to reduce peri- and post-operative blood loss and to reduce the need for blood transfusion. Although off label, the use of TXA in trauma patients with massive blood loss is also well described (3,4). The FDA states that prospective studies investigating the optimal use of tranexamic acid in trauma and other settings are needed and encouraged (5).

There has been growing interest in the application of tranexamic acid in obstetrics and gynecology. In multiple international studies, intravenous TXA has been shown to significantly reduce blood loss when given prophylactically with cesarean delivery or vaginal delivery without an increase in morbidity from adverse thrombotic events (6-9). Currently, a large, international (n=15,000) clinical trial is being conducted in middle- and low-income countries investigating the use of TXA for post-partum hemorrhage after vaginal delivery (10). A recent Danish study has also been completed regarding the use of TXA in benign gynecologic surgeries, i.e. routine hysterectomy (11). Furthermore, in March of 2016, Pacheco et al released new guidelines recommending the use of TXA in all obstetrical cases requiring massive transfusion protocol. TXA is recommended to be given in round three of obstetrical hemorrhage cases (1 gram intravenously over 10 minutes). (15). The authors called for more research to clarify the role and timing of administration of the drug in high risk obstetrical populations. Lastly, the 2015 Cochrane review of more than 3,000 obstetrical patients given TXA showed reduction in bleeding with no increase in adverse events including thromboembolism (16).

To date, TXA has not been studied in the particular population of patients requiring cesarean hysterectomy for placenta previa or accreta. This inexpensive, low risk medication has potential to greatly reduce perioperative morbidity and cost when used in a uniquely high risk obstetrical population.

Hypothesis

We predict tranexamic acid will reduce intraoperative bleeding associated with cesarean hysterectomy in patients with suspected placenta accreta compared to placebo. We aim to perform a pilot study showing a 25% reduction in estimated blood loss versus placebo.

Methods

Study design: This pilot study will be conducted as a randomized, placebo-controlled, double blind trial in the CRMC obstetrical department. The subjects will be recruited from outpatient clinics by the principal investigator or co-investigators during their routine antenatal care. Study consent will be secured during a routine antepartum outpatient visit, or sometimes during an antenatal admission to Labor and Delivery. The majority of patients at CRMC and CCMC with suspected placenta accreta are referred to the perinatologists at the Prenatal Diagnostic Center, and we anticipate most patients will be recruited from this practice. We will not attempt to recruit new patients who are in active labor, or those with medical acuity who require immediate intervention.

Study population: A consequence of studying pregnant women is that all of our study subjects will represent a vulnerable population. Based on our patient demographics, we anticipate a large proportion of the women in our study will be of Hispanic ethnicity, and will be preterm (before 37 weeks gestation). In general, patients with suspected placenta previa have a planned preterm delivery at 34-36 weeks.

Inclusion criteria:
- English and Spanish speaking pregnant

- Any order pregnancy (singleton, twin gestation, etc)
- With a suspected accreta based on ultrasound or MRI imaging studies
- All women evaluated for placenta accreta and deemed to be high risk for this disease (≥40% risk) [14], meaning women diagnosed with a placenta previa and greater than or equal to 2 prior c-sections

Exclusion criteria:
- Women less than 18 years of age
- Women with a personal history of venous or arterial thrombosis (deep vein thrombosis, pulmonary embolism, myocardial infarction, or stroke
- Women with a personal history of clotting disorder, such as anti-phospholipid syndrome
- Women who do not have a good understanding of either English or Spanish will be excluded.
- Women with defective color vision (color-blindness) [See Appendix A]

Pharmacy and Drug Delivery Protocol:

Drug purchasing: Per CRMC policy, the pharmacy cannot charge a patient for an approved drug in a research protocol. However, the CRMC pharmacy regularly purchases the study drug for use in surgical patients. The CRMC pharmacy has agreed to purchase the study drug for the principle investigator (Dr. Kremer), and the studies' grant money will be used to reimburse the pharmacy at cost. Each vial of 1 gram of tranexamic acid for intravenous administration costs the pharmacy $16.70. An initial box of ten vials has been purchased and additional boxes will be ordered after five patients are enrolled.

Randomization protocol: The drug and placebo will be stored, logged, and dispensed from the CRMC Inpatient Pharmacy. A recruited patient will be labeled study subject number one, and so on, by the study investigators. The name and study number will be given to Inpatient Pharmacy. Inpatient Pharmacy staff will randomize the subject to treatment or placebo using a blocked randomization technique and a computer protocol designed with assistance from Dr. Paul Mills. The block size will be set at 4-6 to ensure that the number of treatment and placebo subjects are as close to equal as possible. Inpatient Pharmacy will assign that patient to receive drug or placebo prior to the scheduled surgery. The randomization assignments for each study subject will be located in a study binder in the research pharmacy space. Inpatient Pharmacy staff members will be the only unblinded study staff. The study investigators, clinicians, patient, and hospital staff will be blinded to treatment assignments.

Pharmacy and Drug Delivery Protocol:

Drug purchasing: Per hospital pharmacy policy, the study drug must be ordered from an outside pharmacy. The study drug will be purchased by the investigator from a non-CRMC pharmacy using her DEA number and delivered to the research pharmacy technician. The online pharmacy will be accredited with the National Association of Boards of Pharmacy member and recommended by chief hospital pharmacist.

Drug delivery: In orthopedic and cardiac surgery, 1 gram of intravenous TXA is routinely given 15 minutes before incision time. TXA is typically prepared at CRMC by removing 20cc of fluid from a small IV bag of 5% dextrose in plain water and then injecting the drug into the remaining 30 cc. This is then delivered with an IV piggyback with the patient's preoperative fluids.

In our study in pregnant patients, 1 gram intravenous TXA (or placebo) will be administered immediately after delivery of the infant and after clamping of the umbilical cord to avoid any potential fetal effects. The drug will be prepared and ready to hang at the beginning of the case.

Drug preparation will include the following: Removal of 20 ml from a 50 ml bag of D5W and injection of 10 milliliters of 100mg/ml TXA resulting in a final total volume of 40 ml. Placebo will be prepared by removing 10 ml from a 50 ml bag of D5W. The final volume of the study drug and the placebo bags will be the same and identical in appearance.

Anesthesia staff (physicians and nurse anesthetists) working in the trauma operating rooms will have an in-service about the research study and procedures at a weekly staff meeting to ensure proper education and compliance with study protocol. Intravenous TXA or placebo will be given to the randomized patients by CRMC anesthesia staff after the cord has been clamped and cut based on the intraoperative findings.

All patients undergoing cesarean at high risk for accreta at CRMC have two large bore IVs placed preoperatively. The patient will not require an additional IV for the study drug. TXA is delivered in 5% dextrose plain water and this can be hung as a piggyback with the patient's intraoperative fluids. TXA is clear and colorless and will be visually indistinguishable from the placebo. The hospital pharmacy will be able to provide the placebo.

Primary outcome: The primary endpoint will be estimated intraoperative blood loss (EBL), which is routinely recorded at the end of all operative cases. EBL is *estimated* by the operating room team following a discussion between the surgeon and anesthesia staff based on number of tapes / sponges used, amount of fluid in suction canister, amount of blood on the floor, etc. Secondary endpoints will include amount of blood transfusion, preop and post operative hemoglobin levels, length of hospital stay, ICU admission rates and length of stay, and post-operative complications (DVT, PE, surgical site infection). Maternal demographic information, medical comorbidities, and infant outcomes (weight, Apgar scores, NICU admission) will also be recorded with chart review.

The pilot trial is planned to last 24-36 months with possible extension if needed to meet study enrollment targets. All final results from the study will be submitted for publication in recognized peer-reviewed obstetrical journals. After completion of the pilot study, a future goal is to approach the Maternal Fetal Medicine Unit Network (MFMU) to organize a larger multi-center trial with additional academic centers (https://www.nichd.nih.gov/research/supported/Pages/mfmu.aspx). The MFMU is a national network established by the NIH to reduce maternal, fetal, and infant morbidity, and to provide the rationale for evidence-based, cost-effective obstetric practice.

Sample Size Calculation

Sample Size: Given the low incidence of placenta accreta at CRMC (approximately 10-15 cases per year), we propose performing a pilot / feasibility study that will include approximately 40 cases over the study period of 3 years. Prior studies using TA in elective cesarean deliveries and post-partum hemorrhage found a 30-33% reduction in estimated blood loss (9, 12). A power analysis with a conservative estimate of 25% reduction in predicted blood loss constraining type I errors to 95% and type II errors to 50% requires 29 patients in each sample given our known average and standard deviation of blood loss in accreta patients from the past year.

Statistical Analysis: Categorical data will be compared using the Chi-square test. Continuous variables, such as estimated blood loss, will be analyzed by comparing means using the Student t-test.

Adverse Events Monitoring *(and explanation of routine patient care)*

The principle investigator Dr. Kremer does not typically scrub on planned cesarean hysterectomy cases. These surgeries are typically performed by UCSF faculty sub-specialists, Dr. William Rich (oncology) or Dr. Michael O'Shaughnessy (Urogynecology). However, a coinvestigator (UCSF

resident) will be present in the operating room for all cases, and directly involved in patient care throughout the patient's hospitalization.

All UCSF generalists (including Dr. Kremer) and residents (co-investigators) will be involved in the post operative care of these patients. There is an "attending of the day" for Labor & Delivery who rounds on high risk post partum patients with the residents and directly supervises resident care of these patients. A resident co-investigator will closely follow the patient throughout their post-operative course. Standard clinical care involves a "PM check" (evening visit to see the patient on the day of surgery), as well as daily morning rounding by a resident and attending faculty. *The principle investigator Dr. Kremer will be notified of all potential adverse events by frequent communication with the resident team and with chart review, starting on post operative day zero, and continuing daily throughout the length of the patient's hospitalization.*

Patients will be called by the PI or a co-investigator 24-48 hours after discharge to evaluate for any clinical needs at home and to monitor for potential adverse events. Patients will be seen at 2 and 6 weeks post operatively in clinic (if their health insurance allows this) by a resident co-investigator and UCSF faculty which is standard for post partum / post surgical care. If a patient no-shows to a post partum visit, they will be called to ask them to reschedule, and a letter will be sent to the home address to improve follow up rates.

Patients will not be followed beyond the 6 week post partum visit. A copy of the consent form, including the drug risks, will be provided to each patient in the study to be given to their primary care doctor for future care.

If a significant adverse event occurs at any point during the study, the research pharmacy technician will be notified and that patient will be unblinded to the lead study investigator. The principle investigator will present the patient and adverse events to the safety monitoring committee for discussion and potential action in a timely fashion (within 48 hours for significant adverse events (blood clot, patient death) and within one week for minor adverse events (rash, nausea/vomiting).

Risks to Human Subjects

The proposed research activities qualify as Human Subjects Research and meet the definition of clinical research, as described fully below.

Potential Risks: Because TXA inhibits fibrinolysis, it carries a theoretical risk of thrombosis especially in patients with a previous history of thrombosis. However, large systematic reviews of randomized clinical trials for TXA use in elective surgical patients show no significant increase in the incidence of myocardial infarction, stroke, DVT, or pulmonary embolus (13). Furthermore, although pregnancy and the post partum period represent a hypercoagulable state, the risks of thrombosis in pregnancy are comparable to that of the orthopedic surgical population, in which TXA has well documented safety. TXA so far has not been shown to have any adverse effects in existing clinical trials involving pregnant women, and is currently being investigated in several large international trials in pregnant and post partum women to evaluate its promise in the treatment of post partum hemorrhage.

Please see Appendix A for the Lexicomp drug monograph with on and off label dosing, and risks of adverse events.

Breastfeeding: TXA is category B in pregnancy with no evidence of adverse events in pregnancy in animal studies. For comparison, TXA is safer than Tylenol use, which is category C with some evidence for adverse events in animal studies. TXA is compatible with breastfeeding.

Standard of Care: The current standard of care for patients with suspected accreta is to perform cesarean delivery at a tertiary care hospital with experienced surgical teams. Planned late preterm delivery at 34-36 weeks gestation is recommended. Patients are expected to have two large bore IVs placed and be typed and crossed for transfusion, with the ability to activate a massive transfusion protocol if needed. Depending on surgeon preference, preoperative prophylactic placement of balloons in the arteries leading to the uterus to attempt to lower blood loss may also be performed. Research participants will be receiving the standard of care regardless of whether they choose to participate in the study. By choosing to participate, a patient's regular treatment plan for placenta previa or placenta accreta is completed in addition to the administration of study drug at the time of surgery.

Confidentiality and Privacy: The patients' information will be accessed through electronic charts maintained by CRMC Health Information Management. The patients will only be identified by a non-identifying code assigned to their medical record number. This data will be stored on a password protected Excel spreadsheet, accessible only to IRB approved investigators, and maintained on the UCSF-Fresno secure server.

Data Security: The data will be saved on an Excel spreadsheet and the patients will only be identified by the non-identifying code. Protected health information will not leave the study site and only IRB approved investigators would have access to it. Any data leaving the secure study site or seen by investigators not approved by the IRB will be de-identified.

Conflicts of Interest

The PI has no conflicts of interest to report.

Funding

A research grant from CCFMG was awarded to assist with the completion of this project. The final budget is attached. The grant will assist with remuneration of study subjects, support staff, and statistical support. The study investigators will not receive any payment through the grant.

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