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A Randomized Control Trial Investigating the impact of High dose Prophylactic Tranexamic acid on blood loss at the time of minimally invasive myomectomy – Protocol

Proposed Research Study:

A Randomized Control Trial Investigating the impact of High dose Prophylactic Tranexamic acid on blood loss at the time of minimally invasive myomectomy

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Specific aim:

1. To compare the volume of blood loss in patients undergoing minimal invasive myomectomies who received prophylactic tranexamic acid vs placebo
2. To compare the number of blood products received during/post procedure in patients received tranexamic acid prophylactically vs placebo

This will be conducted as a double blinded randomized control trial. Data will be collected over a 3 year period with the goal of recruiting 50 patients per arm

Background and Significance

In minimal invasive gynecologic surgeries, operative blood loss is a common complication that affects postoperative morbidity and recovery (1). Antifibrinolytic drugs are well established in the management of surgical and traumatic bleeding(1–3). Tranexamic acid (TXA) is a synthetic lysine derivative that binds to plasminogen and inhibits the enzyme from breaking down fibrin deposits. In a recent Cochrane review last updated in 2015 that investigated the use of TXA in general surgery, TXA was found to reduce intraoperative and postoperative blood loss by 414 mL (95% confidence interval [CI] −525 to −303 mL) in comparison to placebo(4). In another Cochrane review 16 trials involving benign obstetrics and gynecologic were included. 14 studies involved women undergoing elective Cesarean deliveries and 2 studies involved women having abdominal myomectomy. No studies involving hysterectomy were identified and no studies involving minimal invasive myomectomies were identified(1)(5). Only recently, the first Randomized controlled double blind study was completed at George Washington University (6).

The results of this study have yet to be published. We hope to attempt to show the efficacy of prophylactic TXA use in minimal invasive myomectomies in reducing blood loss.

Study Design

This is a Double-blinded randomized placebo-controlled trial based at Eastern Virginia Medical School. Subjects who are identified in clinic having menorrhagia or abnormal Uterine bleeding (AUB) due to uterine fibroids and meet inclusion criteria based on the ultrasound (US) or Magnetic Resonance Imaging (MRI), aged 18-45 undergoing laparoscopic or Robotic assisted myomectomies. These subjects will be then approached for consent during their pre-op visit 1-2 weeks prior to their surgery. The setting for consent will be in a patient consultation room. A total of 50 women in each arm of the study with symptomatic fibroids meeting any of the following criteria will be included in the study:

1) At least one fibroid greater than or equal to 6 cm (7)

2) Any intramural or broad ligament fibroid greater than or equal to 4 cm (7)

3) At least 3 total fibroids based on preoperative imaging. (8)

Randomization will be performed using an automated randomization website (9)(Supplement 1)

Patients will be randomized to receive a single IV bolus injection of TXA 30mg/kg in 50ml of normal saline (intervention group) versus an IV bolus injection of normal saline of equivalent volume (placebo group) 15 minutes prior to initial surgical incision. This dosage will not be adjusted for patients with renal insufficiency as they will be excluded from the study. Preparation of the medications will be performed by anesthesia who have both medication and normal saline available to them on short notice. No prior preparation by pharmacy will be required. Tranexamic acid is readily available in a 10 ml vial, which does not need a pharmacist to prepare for administration. The vial is mixed with 50 ml of saline in the operating room. This is the same process that occurs outside of any study with any medication that is administered intra-operatively. This will in no way impact the patient's safety during the surgery, especially since it is administered 15 minutes prior to the start of the procedure.

The dosage of TXA is considered a high dose and has been shown in cardiothoracic, orthopedic and trauma surgery to be reduce blood loss and transfusion need in comparison to regular dosing. There has been no reported increases in TXA side effects with higher dosing of TXA in the literature. (10–12)

Both surgeon and patient will be blinded to the treatment arm. This dosage has been used previously in both obstetric and gynecological procedures and is the same dose recommended by the WHO for preventing post-partum hemorrhage(13).

The surgery itself will be scheduled at either Sentara Norfolk General, Sentara Leigh hospital, and Sentara Princess Anne hospital. These are the three sites that the investigators already perform Minimally invasive myomectomies.

An envelope will be given to the anesthesiologist prior to the procedure informing whether they are to receives TXA or the placebo. Blood loss will be estimated by the surgeon performing the procedure. Hemoglobin and hematocrit will be obtained 24 hours post procedure. The patient will be assessed for reported side effects from the medication given will be assessed by a questionnaire that will be given at their post-op appointment at the 2 week and 6-week mark. During these two visits a physical exam is performed, checking incision sites, and patient symptoms, all of which are standard of care for any minimally invasive procedure. The patients will be seen at the EVMS outpatient clinic for Gynecology or

depending with the physician who performed the surgery. Data will be collected from both Allscripts and EPIC charts.

Primary Outcomes measured

1. Estimated blood loss at time of procedure completion; using volume of cannister and weight of lap sponges
2. Calculated Blood loss, using pre-operative hematocrit, postoperative hematocrit and estimated blood volume x Body Mass Index
3. Number of blood products received during admission that is directly due to blood loss at time of procedure

Secondary outcomes

1. Duration of surgery
2. Length of hospital stay
3. Number of fibroids removed
4. Fibroid types 0-8
5. Total Weight of fibroids removed
6. Pain index on post-operative day 1, and 2-week post-operative visit
7. Post-operative complications
    a. Readmission
    b. Postoperative fever
    c. Postoperative infection
8. Reported mild side effects of medication (Supplement 2)
    a. Diarrhea
    b. Nausea
    c. Headache
9. Reported Serious Side effects of medication (Supplement 2)
    a. Shortness of breath
    b. Deep vein thrombosis
    c. Pulmonary Embolism

Patient data will be collected in a data collection tool with the subjects de-identified.

A subject identifying tool will also be sued to identify the subject with their EPIC and Allscripts MRN.

Both epic and Allscripts will be used to collect patient data

Inclusion Criteria

1. Female
2. Age 18-45

3. Undergoing laparoscopic myomectomy
4. At least one fibroid greater than or equal to 6 cm
5. Any intramural or broad ligament fibroid greater than or equal to 4 cm
6. At least 3 total fibroids based on preoperative imaging

Exclusion Criteria

1. Severe existing medical complications involving the heart, liver, or kidney
2. Moderate to severe renal impairment (serum creatinine > 1.4)
3. Blood clotting abnormalities
4. Age <18
5. Known Allergies to tranexamic acid
6. Known Contraindications to Minimally invasive myomectomies
7. If you are pregnant
8. History of a prior blood clot in the lung, arm, or leg, known as pulmonary embolism or deep vein thrombosis
9. Any active blood clots, clotting disease, pulmonary embolism, cerebral thrombosis, estrogen use, renal impairment, elevated creatinine level
10. History of a stroke or mini-strokes
11. History of prior seizures
12. Concurrent oral contraceptive use
13. Contraindications to receiving Tranexamic acid
    i. In patients with acquired defective color vision, since this prohibits measuring one endpoint that should be followed as a measure of toxicity
    ii. In patients with subarachnoid hemorrhage. Anecdotal experience indicates that cerebral edema and cerebral infarction may be caused by tranexamic acid in such patients.
    iii. In patients with active intravascular clotting.
    iv. In patients with hypersensitivity to tranexamic acid or any of the ingredients

Statistical Analysis

Descriptive statistics will be calculated. Continuous variables will be compared with t-test and categorical variables will be compared with Chi-square. P-values of less than 0.05 will be considered significant. A logistic regression will be performed to calculated the adjusted odds ratio.

Sample size calculation was set at 90 % power to detect a 150 ml difference in blood loss, with a significant level of 5 % and a one-sided alpha of 0.05 and beta (β)-set at 0.1.

The sample size was calculated using the formula below.

$N=2\Sigma^2 (z\alpha+Z1/2\beta)^2/r^2$

Substituting with figures:
$N=2\times135\times135(1.96+1.282)^2/150^2=17$ patients in each group.(14)
However, we wish to include 50 patients on each arm to try to increase the chances of identifying any side effects associated with the procedure

Risks of Study

There are few risks associated with this study beyond the standard risks of confidentiality breach of patient private information and the general risks of minimally invasive gynecologic surgery.
Tranexamic acid is commonly used for surgical procedures and reduces blood loss significantly. It is used in multiple specialties, such as general surgery, trauma surgery, gynecologic surgery, and obstetric surgery to minimize and prevent blood loss in patients. Even though it is an off-label use it has been studied extensively and is considered a safe and standard method to prevent /minimize blood loss. It is readily available intraoperatively at all Sentara facilities for use in a situation of excessive intraoperative blood loss. It is subject to shortages and unavailability as with any other medication.

Available below is the associated side effects of prolonged usage of IV tranexamic acid

>10%:

- Central nervous system: Headache
- Gastrointestinal: Abdominal pain
- Neuromuscular & skeletal: Back pain
- musculoskeletal pain
- Respiratory: Nasal signs and symptoms

1% to 10%:

- Central nervous system: Fatigue
- Hematologic & oncologic: Anemia
- Neuromuscular & skeletal: Joint pain
- Muscle cramps
- Muscle spasm

This study will only administer a single dose use of tranexamic acid, and we believe that there will be minimal side-effects comparatively.

In the event there are any serious adverse events, the principal investigator will notify FDA MedWatch, using their standard operating procedure, and the EVMS IRB using the Serious Adverse Event form appended to the protocol

Another risk associated with the study is health information confidentiality breach. To minimize the risk, the patient data will be stored in a single desktop computer located in the EVMS outpatient facility, with a password protected account. Access will be given only to those listed as coinvestigators on the study. The risks of the surgery and the drug cannot be minimized further.

Budget

Cost of tranexamic acid will be covered as medications given during surgery; It is covered by insurance for gynecologic surgery because it is considered a primary method of hemostasis for surgery. This medication is used routinely in myomectomies, and there has been no issue covering the cost of the medication as part of the surgery outside of this study. Since anesthesia is administrating the medication and will be the only person not blinded to the study, they will also bill for the medication. This is usually how the medication is billed under normal circumstances.

Since there is no current funding for this study, the patient will be informed of the cost of the medication and they can refuse to participate if they do not want to pay for such medication.

The placebo will be normal saline that will be administered by anesthesia. It is not considered an additional cost to the surgery because of its normal use during any procedure

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