Reading Hospital – Tower Health
Research Protocol

PI Name: Amir Behnam, M.D.

Study Title: Role of tranexamic acid (TXA) in the reduction of post-operative hematoma and seroma in patients undergoing panniculectomy or abdominoplasty, a pilot study

NCT04902950
February 27, 2020

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Other Investigators / Collaborators Kayla Humenansky, D.O., Christine Cho, D.O., Thomas Dooley, M.D., Scott Lindsay, D.O., Roman Gokhman, PharmD.

Funding Source(s): Investigators will apply for funding from the Reading Hospital Foundation. If funding from the foundation is unavailable, investigators will seek other funding sources. If no funding is acquired, the investigators will cover the cost of the study drug.

A.SPECIFIC AIMS

We aim to investigate the use of tranexamic acid (TXA) as a hemostatic agent in abdominoplasty/panniculectomy. We believe tranexamic acid to be effective in decreasing hematoma rates and drain output, allowing for earlier drain removal.

B. RESEARCH QUESTION AND HYPOTHESIS

Does the use of TXA soaked sponges decrease hematoma rates and drain output, resulting in earlier drain removal in patients undergoing panniculectomy or abdominoplasty? Comparative outcomes including return to operating room, fluid collection requiring additional procedures (i.e. aspiration or percutaneous drainage), hematoma rates, daily drain output and time to drain removal will be measured between the control group (normal saline) and the experimental group (TXA). We are evaluating the potential for TXA to reduce drain output and decrease time to drain removal.

C. BACKGROUND AND SIGNIFICANCE

The antifibrinolytic drug, tranexamic acid (TXA) has proven to reduce blood loss and transfusion requirements in other fields of surgery including orthopedic, cardiac, craniofacial and gynecologic surgery. Metanalysis performed by Ker et al. concluded that TXA reduced blood loss by 29 percent and the need for blood transfusion by 49 percent over a variety of surgical procedures.[1] Masoomi et al. reviewed 20,130 patients who underwent abdominoplasty from 2007-2011, noting that 9.3 percent required a post-operative blood transfusion.[2]

TXA has recently gained popularity in the field of plastic and reconstructive surgery.[3] Tranexamic acid is a synthetic lysine analogue which inhibits fibrinolysis and thus degradation of fibrin clots by competitively inhibiting the activation of plasminogen to plasmin. By inhibiting plasmin formation, TXA also provides an anti-inflammatory effect, as plasmin is responsible for several inflammatory activities.[3,4] Austen et al. demonstrated the efficacy of topical TXA in reducing drain output for patient undergoing reduction mammoplasty.[5]

The safety and efficacy of TXA has been well studied.[6] Historically administered intravenously, TXA is gaining popularity as a topical hemostatic agent. TXA administered topically has similar efficacy as intravenous administration while minimizing systemic exposure.[6] The Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage-2 trial (CRASH-2) found that the use of TXA provided a significant mortality benefit without an increased risk for thromboembolic events in adult trauma patients.

We believe topical TXA will decrease the rate of post-operative hematoma via its hemostatic effects, as well as decrease the overall drain output via its anti-inflammatory properties.

D. RESEARCH DESIGN AND METHODS (including data analysis)

Patients will be evaluated by the plastic surgeon for a symptomatic abdominal panniculus to determine their candidacy for elective or insurance authorized panniculectomy. Panniculectomy is defined as excision of excess lower abdominal skin and subcutaneous tissue. The term panniculectomy is often used interchangeably with abdominoplasty. Candidates for the study will be undergoing excision of excess abdominal skin and subcutaneous tissue with undermining of the abdominal flap to the xiphoid process superiorly and to the costal margin laterally; with or without rectus muscle plication. Signs and symptoms of a symptomatic abdominal panniculus include but are not limited to recurrent skin infections, difficulty with ambulation, interference with voiding or intercourse, as well as chronic lower back pain or difficulty finding appropriately fitting clothing.

Participating providers will include those physicians with operative privileges at Tower Health System Reading Hospital. Candidates for the procedure will be offered participation in the study preoperatively in the office setting by the provider performing the procedure. If they agree to participate, they will be consented appropriately with the attached IRB approved consent in addition to standard surgical consent.

This study will be double-blinded. Participating patients will be randomized to normal saline (control group) or tranexamic acid (study population) on the day of surgery by the pharmacist. All participants will have an order placed pre-operatively for tranexamic acid. Patient assignment will be determined by a random number table. A random number table is a series of digits 0, 1, 2, 3, 4, 5, 6, 7, 8, and 9 arranged randomly in rows and columns. Numbers in the list are arranged so that each digit has no predictable relationship to the digits that preceded it or to the digits that followed it. Each group will have 10 participants. One for each number in the table. Odd numbers will be assigned to the control group (Saline) and even numbers will be assigned to the study population (TXA). The pharmacist will have the table of random numbers and will assign patients appropriately. The pharmacist will send a 100cc bag of plain normal saline or 100cc bag of normal saline mixed with 3g of tranexamic acid. Tranexamic acid is supplied as 1g/10cc. Three grams of TXA will be mixed with 70cc of normal saline for a concentration of 3% and total volume of 100cc, as not to differ from the plain normal saline quantity. Either 100cc of plain normal saline or 100cc of 3% solution of TXA will be placed on the operative field prior to the start of the procedure. The solution will be placed into a sterile bowl on the operative field and three lap sponges will be placed in the solution at the beginning of the procedure. TXA is clear, odorless solution and will be indistinguishable from normal saline to the provider and operating room staff. To ensure the study providers remain blinded the pharmacist will control the randomization.

Each group will have 10 participants. Group 1 will undergo application of three normal saline soaked lap sponges to the surgical site, while Group 2 will undergo application of three TXA soaked lap sponges to the surgical site. After the abdominal skin and subcutaneous tissue is raised, the area will be irrigated, and hemostasis achieved using electrocautery. These steps are currently preformed with every panniculectomy. After hemostasis and irrigation, the soaked lap sponges will be unfolded and placed beneath the two lateral portions as well as the central area of the flap for 3 minutes. The lap sponges will not be “rung out” prior to placement. The time for TXA application is based on previous studies. The lap sponges will be removed after

three minutes. The surface area under the flap will be measured from the xiphoid process to the pubis, from the Xiphoid process to each anterior superior iliac spine (ASIS) and across from one ASIS to the other. These measurements will be used to calculate the surface area under the flap. These measurements will only be used in data collection and do not affect the principle aim of the study. The remainder of the surgical procedure will be the same for each patient. As currently practiced, two 15 round Blake drains will be placed for each patient. Patients will stay overnight for routine post-operative monitoring including vital signs and drain output or may be discharged home the same day of surgery if medically fit. Patients will also be monitored clinically at each post-operative visit for signs of post-operative hematoma or seroma.

After discharge, post-operative drain output will be monitored and recorded by the patient on the provided drain documentation sheet. This does not differ from the current standard of care regarding drain output recordings. All patients who receive a post-surgical drain are asked to document output. All patients will be educated on routine drain care and recording drain output prior to surgery, as well as post-operatively. Each patient will be given a standardized form to record their drain output. Post-operative drain output will be assessed during each post-operative visit. Drains will be removed when output is less than 30cc per drain in 24-hour period. Patients will track their 24-hour total drain output by recording the 24-hour total output at 10 am every day. If the output exceeds the drain capacity during the 24-hour interval but before the 10am empty time, the patient will empty the drain when full, record that output, allow the drain output to reaccumulate, and empty-record the drain output again at 10am or again when the output exceeds the drain capacity. The individual outputs recorded during the 24-hour interval will then be totaled to determine one output sum for the entire 24-hour time period between 10am time intervals. Each drain bulb will accommodate a maximum of 60cc of postoperative fluid. When less than 30 cc per drain in 24-hour period, patients will call to schedule drain removal. Drain recording policies do not differ from non-study patients. All post-operative panniculectomy patients are required to record their drain output. Each patient will be evaluated one week, three weeks, and eight weeks following their procedure to assess overall wound healing, post-operative fluid collections, drain output and overall well-being.

Data analysis for this project will consist of several parts. First it is important to analyze differences between the randomized control and treatment arms to test for bias. In order to do this, goodness of fit tests (GOF) will be performed on demographic variables such as age and gender. While the sample sizes are expected to be low, 10 for each arm, nonparametric tests consisting of Fisher's exact for discrete variables and Mann-Whitney U tests for continuous level data will be used. An omnibus p-value of 0.20 will be used to ensure there is no bias present in the samples. Secondly, efficacy analysis will be conducted on the outcome variables (drain output per day, total drain output, etc.) by use of Mann-Whitney U test. Statistically significant findings would be for a p-value less than 0.05 on any test. The samples are not expected to be large enough for the use of parametric measures so non-parametric methods will be used.

With a small sample of 10 patients per arm this analysis is viewed to be exploratory, and there will be no statistical corrections applied for multiple comparisons. Results of the GOF and efficacy analysis will be prepared and placed into tables for each group. In addition to the analysis mentioned above, power analysis will also be used to calculate the observed power for those tests with significant differences as well as to determine a sample size for those efficacy endpoints that did not achieve statistical difference. These power estimates will accompany the results in a separate table. Power analysis will be based on single tail alternative hypothesis with a power (1-B) of 80 percent and a p-value of 0.05. As this is an exploratory study, there will

be no interim analysis for efficacy or futility. The trial will be stopped after inclusion of twenty patients.

E. PROTECTION OF HUMAN SUBJECTS

1. RISKS TO THE SUBJECTS

a. Human Subjects Involvement and Characteristics

- Double-blind Prospective Randomized Control Trial
- Female or male patients 18 years or older
- Patients undergoing panniculectomy and agreeable to participate in the trial will be randomized to normal saline vs TXA
- Daily drain output will be monitored and recorded for each patient
- Rate of post-operative hematoma/seroma will be assessed by clinical evaluation to include palpation for ballotable fluid collection and assessment of skin for a shiny/tight appearance suggestive of an underlying fluid collection.
- Prisoners, pregnant or nursing women, persons under the age of 18, persons with preexisting coagulopathy, ongoing venous or arterial thrombosis, history of cerebral vascular accident, uncontrolled seizure disorder, documented administration of daily antiplatelet or anticoagulation (e.g. ASA, NSAIDs, Warfarin) or documented allergic reaction to tranexamic acid will be excluded from the study
- Patients can withdraw from the study at anytime

b. Sources of Materials

- All patient charts will be kept confidential, in compliance with HIPPA regulations
- All patient information will be stored on a password protected computer
- Normal saline and tranexamic acid are both products currently in use at the hospital in other plastic surgery procedures. They are indistinguishable in appearance, texture and odor; therefore, making them ideal substances for a double-blinded investigation
- No specimens will be stored

c. Potential Risks

- Potential risks include those risks associated with any surgical procedure.
- Patients will be monitored under standard operative protocols
- Although, the risks of topical use of TXA are not well known, there are known risks from oral and intravenous use. Those risks include:
    - Allergic reaction
    - Convulsions have been reported in association with intravenous tranexamic acid treatment in patients undergoing cardiovascular procedures
    - Retinal changes have been documented in some animals receiving intravenous TXA for extended periods of time (days to weeks)
    - Intravenous administration of tranexamic acid may cause dizziness
    - Gastrointestinal disturbances may occur with intravenous administration

2. ADEQUACY OF PROTECTION AGAINST RISKS

a. Recruitment and Informed Consent

- Female or male patients > 18 years for abdominal panniculectomy will be offered participation

- Consent will be obtained by the provider preforming the procedure
- Signed and witnessed consent will be placed within the patient's chart

b. Protection against Risk

- All patient charts will be kept confidential, in compliance with HIPPA regulations
- All patient information will be stored on a password protected computer
- All standard pre and post-operative photos will be stored on a password protected computer

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

- Our study aims to demonstrate a difference in hematoma rates as well as drain output between patients undergoing panniculectomy using topical tranexamic acid vs. normal saline. As a pilot study, these results could be used to encourage a larger investigation of the use of TXA in panniculectomy patients.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

- This study allows us to investigate additional methods to achieve low drain outputs in panniculectomy. The knowledge gained from our proposed study will be applicable to patients undergoing panniculectomy. In addition, this method of achieving hemostasis may lead to further research studies for various other surgical procedures.

5. SUBJECT SAFETY AND MINIMIZING RISKS (Data and Safety Monitoring Plan)

Subject safety will be monitored by the physician preforming the procedure.

- Subjects will be monitored for allergic reaction, wound healing complications, venous thromboembolism, drain output, and time to drain removal.
- Subjects will be monitored during their overnight hospital stay, if overnight admission is deemed appropriate. Participants will also be evaluated at each follow-up visit. Patients will be scheduled for follow-up at one week, three weeks, and eight weeks following their procedure.
- The physician performing the procedure will be responsible for the monitoring and evaluating patients postoperatively.
- This investigational study aims to assess for any difference in drain output, time to drain removal or return to the OR for hematoma or seroma evacuation.

F. REFERENCES/LITERATURE CITATIONS

1. Ker K., Beecher D., and Roberts I. Topical application of tranexamic acid for the reduction of bleeding. The Cochrane database of systematic reviews 2013; 7.
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3. Reed and Woolley. Uses of tranexamic acid. Continuing education in anaesthesia, Critical Care & Pain. 2015; 15(1):32-37.
4. Jimenez J., Iribarren J., Lorente L, et al. Tranexamic acid attenuates inflammatory response in cardiopulmonary bypass surgery through blockade of fibrinolysis: a case control study followed by a randomized double-blind controlled trial. Critical Care 2007; 11:R117.

5. Ausen K., Fossmark R., Spigset O., Pleym H. Randomized clinical trial of topical tranexamic acid after reduction mammoplasty. *Br J Surg.* 2015; 102:1348-1353.
6. Rohrich RJ and Cho MJ. The role of tranexamic acid in plastic surgery: review and technical considerations. Plast Reconstr Surg. 2018 Feb; 141(2):507-515.

G. CONSULTANTS
Our statistician is a consultant for the hospital.

H. FACILITES AVAILABLE
Our trial will be conducted through Tower Health Reading Hospital Medical Center and its associates.

I. INVESTIGATOR BROCHURE
N/A

J. APPENDIX
Attach any additional information pertinent to the project such as:
- surveys or questionnaires,
- diaries or logs,
- informed consent and/or HIPAA authorization documents, etc.