NCT02753816

Document Date: 07/10/2018

1. TXA **Protocol Title:** The effect of tranexamic acid on blood loss and transfusion rates in burn wound surgery – A randomized, double-blinded placebo-controlled trial.

2. **Version Date: 7/10/18**

3. **Objectives:**
   - To determine the impact of perioperative administration of tranexamic acid on intra-operative blood loss and post-operative transfusion rates in burn wound surgery.

4. **Background:**
   An estimated 40,000 patients were hospitalized for burn related injuries in 2014.[1] Many of these patients required surgical excision and grafting. Early excision of burn eschar has been shown to reduce mortality, hospital stay, and time away from work. However, intraoperative blood loss and blood product transfusion rates have been shown to be higher.[2,3] Tangential excision of burns often causes large losses of blood, which have been estimated between 0.4 ml/cm^2 to 0.75 ml/cm^2 of debridement depending on timing of excision.[4] There are many techniques that have been described to help reduce the loss of blood in burn surgery. These include timing of excision, maintaining euthermia, extremity tourniquet control, dilute epinephrine tumescent infiltration, and topical application of epinephrine and thrombin.[5,6]

   Tranexamic acid (TXA) has been used as an adjuvant to reduce bleeding since the 1960's.[7] TXA acts by competitively binding to plasminogen leading to inhibition of its activation to plasmin. This is thought to inhibit fibrinolysis, maintain formed clot, and decrease perioperative bleeding.[8]

   Topical and intravenous uses of TXA have been studied in a variety of surgical specialties, including orthopedic surgery,[9] oral surgery,[10] cardiovascular surgery,[11] trauma,[12] as well as gynecology.[7] Impact on blood loss and decreased transfusion needs have been promising. Very little data exist on the use of TXA in burn surgery with only one case report and one prospective trial published.[13,14] Although a small sample size was used, results were encouraging for decreasing intraoperative blood loss. The effect on perioperative blood transfusion was not addressed in this study.

   Due to inhibition of fibrinolysis, a theoretical risk of venous thromboembolic (VTE) events is at the forefront for concern. Numerous studies have shown no increase in VTE events with perioperative use of TXA.[9,15] Although the reasons are unclear, incidence of VTE within the burn population are quite low (0.8%) compared to many inpatient populations.[16]

   We believe TXA has the potential to assist in perioperative control of hemorrhage during burn excision surgery leading to decreased blood loss and smaller transfusion rates. These potential improvements in care may translate into decreased surgical complications and a potential reduction in hospital stay and overall costs.

5. **Setting of the Research:**
   Spectrum Health Butterworth Campus

6. **Resources Available to Conduct this Research:**
   The Spectrum Health Regional Burn Center admits nearly 120 patients each year. Many of these patients require surgical management of their sustained injuries. Study personnel will

include attending burn surgeons and surgical residents with experience in surgical research and knowledge of surgical outcome measures. In addition, the Spectrum Health Office of Clinical Research Operations (OCRO) staff will assist with the informed consent process and subject enrollment, data collection and management, Institutional Review Board (IRB) communication and continuing renewal submission, ongoing subject management, and maintenance of the regulatory files and essential documentation for the study.

7. Study Design:

a. Recruitment Methods

Potential subjects will be recruited during the preoperative period for a planned procedure with any of the burn attending surgeons. A member of the Spectrum Health OCRO will obtain informed consent. This will take place in a private consultation room to ensure privacy and should take approximately 45-60 minutes. In order to minimize coercion, it will be made very clear to patients that their participation is strictly voluntary and that choosing not to participate will in no way affect their care at Spectrum Health.

Study Subjects

Potential subjects include all patients scheduled to undergo burn excision surgery with a deep partial or full thickness burn wound area of at least 350 cm^2 that meet all of the inclusion criteria, and none of the exclusion criteria. For a procedure to be included within the study, 96 hours must have elapsed since the previous procedure in which the patient was randomized to drug or placebo. If the patient has undergone a procedure outside the scope of this study, the 96-hour waiting period does not apply.

i. Inclusion Criteria

- Subjects undergoing burn excision surgery for standard of care purposes (to include: greater than or equal to 350 cm^2 of full thickness or deep partial thickness burns)
- Male or female $\geq$ 18 years of age
- Subject or subject's medical decision maker agrees to participate in this study and provides informed consent

ii. Exclusion Criteria

- Subjects with a history of hypercoagulopathy, deep vein thrombosis or pulmonary embolism
- Baseline creatinine level greater than 2.83 mg/dL
- Subjects with known hypersensitivity to tranexamic acid
- Patients with acquired defective color vision
- Patients with subarachnoid hemorrhage
- Children
- Pregnant women
- Prisoners

b. Study Endpoints

The primary outcome measures will be operative blood loss (measured and calculated) and red blood cell transfusion rates in subjects undergoing the eligible procedures. Secondary outcome measures will include total hospital length of stay, wound complication, transfusion reactions, and skin graft survival.

c. Procedures Involved in the Research

The study design will be a randomized, double-blinded, placebo-controlled trial, with the randomization to occur on a per procedure basis. Following satisfaction of inclusion/exclusion criteria and enrollment into the study by the Spectrum Health OCRO research staff, the subject and each procedure the patient undergoes will be assigned a study number. A single consent will be obtained for randomization of each procedure that a patient may undergo meeting inclusion criteria for the study. A single study participant could potentially be randomized to both treatments of the study if that participant undergoes two or more procedures. Each procedure a participating subject undergoes will be randomized based on a predetermined randomization schedule, created by an independent statistician at Grand Rapids Medical Education Partners (GRMEP) research department. The randomization schedule will be held by the pharmacists and checked prior to each procedure to determine the appropriate treatment (placebo or TXA). Surgical timing will be coordinated with the OCRO. The study participants will receive preoperative intravenous TXA or Normosol as placebo treatment. The preparation will be indistinguishable by nursing, surgical, or anesthesia staff. The TXA procedures will receive a 1000 mg dose immediately preceding surgical incision administered by the anesthesia provider, while the placebo procedures will receive an equivalent volume of Normosol. The dose will be administered via intravenous piggyback over 15 minutes. Operative details will be recorded including procedure performed, IV fluids received, estimated blood loss, lowest recorded body temperature, and transfused blood products. Perioperative hemoglobin level data will also be collected. Standard daily laboratory measurements will continue unless clinical conditions necessitate more frequent monitoring, per standard practice. Transfusion will take place for hemoglobin levels < 7.0 g/dL or hemoglobin level < 10 g/dL with clinical symptoms indicating need for transfusion, per standard practice. Final decision on transfusion will be made according to the staff surgeon's discretion.

It is anticipated that each patient will receive an average of three major surgical procedures during the treatment of their burn injury. The number of procedures may range from a single procedure to greater than 6 procedures for an individual patient depending on the extent of their injury. The time between subsequent procedures typically ranges from ten days to several weeks. Prior to each procedure, the patient will be re-randomized to receive TXA or placebo.

Data to be recorded includes patient demographics (age, sex, height, weight), burn injury characteristics (total body surface area, location, depth of burn), hospital admission date, hospital discharge date, past medical history, past surgical history, medications, and laboratory values. Data from operative records will include procedure date, procedure performed, wound measurements, lowest body temperature, operative blood loss, operative time, amount of fluid received, and intraoperative transfusion requirements. Postoperative data to be collected includes hemoglobin and hematocrit levels, transfusion requirements, surgical complications, skin graft survival (%), thromboembolic events, and length of hospital stay.

d. Data Management

The Spectrum Health OCRO research staff will collect outcome data at the time of each surgical procedure. Data will be stored in a password-protected REDCap

database. The OCRO will also keep a secure record of the procedures randomized to the TXA and placebo arms, which will be blinded from the study personnel.

e. Provisions to Monitor the Data for the Safety of Subjects
Adverse events including infections, allergic reactions, graft loss, respiratory failure, anaphylaxis, thromboembolic events and development of acute renal failure will be monitored and recorded at the time of occurrence by the Spectrum Health OCRO research staff. In the event an increased number of unanticipated events occur, the study will be temporarily stopped pending review. A review of unblinded data will be performed by an independent clinician and statistician at Grand Rapids Medical Education Partners to determine the need to discontinue or resume the study. If a significant increase in adverse events is noted in the treatment arm related to the study drug, the trial will be terminated. Decisions resulting from the review will be discussed with the primary investigator.

Interim reviews of unblinded data for statistically significant findings will be performed by an independent clinician, pharmacist, and statistician after the first 80 procedures have been completed. Findings will be reviewed with the investigators, and decisions will be made as to whether or not the research study continues. These interim reviews and outcomes will be reported to the IRB.

f. Withdrawal of Subjects
Subjects will be withdrawn from the study if they experience an adverse drug reaction defined as anaphylaxis. Other potential side effects such as nausea, vomiting, or diarrhea will be treated symptomatically per standard of care. If refractory to standard treatment for these side effects, subjects will be withdrawn from the study. Subjects experiencing any thrombotic event prior to completion of study drug dosing schedule will be withdrawn from study. Subjects may choose at any time to voluntarily withdraw from the study. If subjects choose to withdraw, No further data will be collected. Data already collected will be included in the study.

The primary investigator may remove a subject at any time from this research study if it is felt to be in the best interest of the subject.

8. Statistical Plan

a. Sample Size Determination
The primary outcome variable for the study is transfusion following a procedure. The analysis will be performed using generalized estimating equations (GEEs), as each individual may have multiple surgical procedures that may be randomized to either the control or TXA treatment prior to EACH procedure. An initial assessment for sample size for a McNemar test, assuming that the transfusion rate following a control procedure is 50%, the rate following a TXA procedure is 30%, $\alpha = 0.05$ and $\beta = 0.20$, indicates that 61 subjects would be needed. The control transfusion rate is based upon previous data at Spectrum Health, while the difference of 20 percentage points is based upon our estimate of what constitutes a clinically important effect. Due to the use of GEE for the analysis, a correction factor is needed.[17] From previous data from the Spectrum Health Burn Unit, we assume that there will be three procedures per patient. If we further assume that the intraclass correlation coefficient = 0.8 (postulated correlation of repeated measurements), we will be able to show a statistically significant effect with 53 subjects. With an average of 3 procedures per patient, the total procedures will be 159.

b. Statistical Methods

Summary statistics will be calculated. Quantitative data will be expressed as the mean±SEM and nominal data will be expressed as a percentage. Comparisons between groups for quantitative variables will be performed using the t-test. Nominal variables will be evaluated using the χ^2 test. The relationship between TXA administration and transfusion will be determined using GEE. Significance will be assessed at $p<0.05$. Analyses will be performed using intention to treat.

9. Risks to Subjects

TXA is an FDA approved medication. The safety of TXA has been demonstrated in a meta-analysis of the off-label use of TXA in the perioperative period. A theoretical risk of thromboembolic events exists, though no significant adverse outcomes have been reported with the proposed dosing schedule. Reported side effects include nausea, vomiting, diarrhea, and dizziness. Uncommon side effects include allergic dermatitis, giddiness, and hypotension. Rare side effects include blood clots, convulsions, and visual changes.

10. Potential Benefits to Subjects

Potential benefits include decreased surgical blood loss resulting in decreased transfusion requirements. Transfusion of packed red blood cells has been associated with numerous potential adverse events. In addition, decreased overall hospital cost may occur if the study subjects experience decreased complication rates.

11. Provisions to Protect the Privacy Interests of Subjects

The study, potential risks and benefits of treatment will be discussed extensively with each potential subject preoperatively in a private space. Any questions they have will be answered accordingly. Reported data will not contain identifiable information. Patient consent and all other research related activities will take place in a private exam room.

12. Provisions to Maintain the Confidentiality of Data

Identifiable study data will be kept in a secure password-protected file or locked cabinets by the Spectrum Health OCRO. The Spectrum Health OCRO will have record of the randomization of each individual subject stored in a controlled, secure area.

13. Medical Care and Compensation for Injury

Any medical or surgical complications experienced relative to this research will be treated in accordance with current standards of care. No study funds have been set aside to compensate subjects for injury.

14. Cost to Subjects

Study drug, placebo, and preparation/administration will be paid for by funds allocated to the study, and not billed to the subjects. All other aspects of the subject's care are considered standard of care, and will be billed to the patient and/or their insurance company.

15. Consent Process

Eligible subjects will be recruited during their inpatient stay. The potential risks and benefits of the study will be discussed in detail by a member of the Spectrum Health OCRO in a private space. All subjects will be ensured adequate time to read the research informed consent form, and all questions will be answered to their satisfaction. Subjects will be informed that the research is a voluntary option.

16. Vulnerable Populations

Patients with diminished decision-making will be included within the study as the possibility of direct benefit outweights the risks of the study drug. A patient will be considered to have diminished decision-making capasity if they have previously been assigned a gaudian in-charge of their medical decision making or if the patients medical condition interferes with their ability to communicate effectively or understand the medical decisions presented to them. If a patient is unable to make medical decisions due to circumstances surrounding their sustained injuries or they have an assigned legal gardian, patient recruitment will be done through the legally authorized representative. Written consent will be obtained prior to the first surgical procedure. If the patient's decision-making capacity becomes reestablished the patient will be reconcented through the standard informed consent process.

17. Sharing of Results with Subjects

At this time there are no plans to share study results with study participants.

18. References

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