Title: Randomized Study on the Topical Application of Tranexamic Acid to the Wound Bed of Granulating Defects for Hemostasis in the Setting of Mohs Micrographic Surgery

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1. ABSTRACT

Mohs micrographic surgery (MMS) is considered the gold standard for treatment of high-risk non-melanoma skin cancer. Postoperative bleeding is a complication that can lead to further complications including necrosis, infections, take-down of repairs, patient distress and unnecessary return visits including possibly to emergency rooms after hours. Tranexamic acid is an antifibrinolytic drug that prevents the breakdown of blood clots. The topical application of TXA has been shown to reduce intraoperative and postoperative bleeding in orthopedic, plastic, and maxillofacial surgeries. It has also been used topically as a hemostatic agent in anterior epistaxis and superficial oral trauma. This study aims to determine the efficacy of topical TXA in preventing postoperative bleeding when used as an adjunct to wound care on granulating defects in the setting of MMS.

2. OBJECTIVES

To perform a prospective randomized controlled trial to determine the hemostatic effect of TXA soaked gauze (intervention) versus normal saline soaked gauze (control) when applied to granulating defects in the setting of Mohs micrographic surgery by collecting the following data:

1. Rate of postoperative hemorrhagic complications.
2. Types of postoperative hemorrhagic complications.

3. BACKGROUND AND SIGNICANCE

Mohs micrographic surgery (MMS) is considered the gold standard for treatment of high-risk non-melanoma skin cancer.[1] Bleeding complication rates and severity are very low in cutaneous surgery,[2] but hematoma formation can lead to other complications such as infections, necrosis, and take-down of repairs such as grafts and flaps. The risk for bleeding complications is increased in some populations because anticoagulant and antiplatelet agents are typically not discontinued prior to Mohs surgery[3]. Intraoperatively, the modalities commonly used to decrease intraoperative and postoperative bleeding include the addition of adrenaline to local anesthetic, use of electrosurgery, suture ligation, and placement of topical hemostatic agents, such as absorbable hemostatic foam inserts.[4] Postoperatively, pressure dressings are the standard preventative measure utilized in wound care to decrease risk of postoperative hemorrhage.[5]

Antifibrinolytics decrease bleeding by preventing the natural breakdown of formed blood clots. Several different pharmaceutical formulations are available, including tranexamic acid (TXA). TXA is a synthetic lysine analogue that blocks binding sites of plasminogen to lysine, thus preventing plasminogen activation to plasmin and the subsequent enzymatic lysis of polymerized fibrin in blood clots.[6] TXA can be administered intravenously, orally, subcutaneously, or topically, for the reduction of bleeding.

Although only the oral form of TXA is FDA approved to reduce bleeding in women with heavy menstrual cycles,[7] it is administered intravenously in a wide range of surgical specialties including cardiothoracic[8], obstetric,[9] orthopedic[10], and trauma[11] to reduce risk of blood loss, and thus blood transfusions. Several studies have shown there is no increased risk of thrombotic events with this intervention[6-9].

The topical application of TXA has been shown to reduce intraoperative and postoperative bleeding in cardiothoracic[12], orthopedic[13], plastic[14], and maxillofacial[15] surgeries, as well as for anterior epistaxis.[16] A recent meta-analysis of 71 RTCs, mostly in the setting of orthopedic surgery, showed that topical TXA can reduce the incidence of blood transfusions by 70%.[17] Systemic absorption and cytotoxicity to ex vivo skin is negligible under concentrations of 25mg/ml.[18,19] There is no increased risk of thromboembolic events or myocardial infarction when TXA is applied topically.[17] To our knowledge, there has been no study in which topical TXA has been added to wound care in the setting of MMS with the aim to reduce postoperative bleeding.

4. STUDY PROCEDURES

A. Study design
   I. Prospective randomized controlled trial
   II. Location: University of Missouri Columbia Dermatologic Surgery Unit (Columbia, MO)
   III. Patients: All adult (18 years or older) patients presenting for Mohs micrographic surgery (MMS) for the treatment of melanoma or nonmelanoma skin cancer (NMSC) with a wound that will be healing by granulation
   IV. Patients meeting inclusion criteria will be randomized into two arms once enrolled in the study and will be randomized using computerized randomization software. The study personnel will randomize patients on the day of surgery.
      a. One arm will serve as the control group and will receive normal saline soaked telfa pads to the wound bed upon completion of MMS.
      b. A second arm will receive TXA 25mg/ml soaked telfa pads to wound bed upon completion of MMS. This concentration is based on studies showing possible decrease in re-epithelization with chronic exposure to *in vitro* and *ex vivo* cutaneous wound bed models, as well as decreased viability of bovine and human cartilage, above this selected concentration.[19-21]
   V. Both solutions of the intervention and control are clear liquids that cannot be differentiated from one another. As such, the research staff will provide the surgeon with an unmarked sample cup of the either the saline solution or TXA solution, as selected by the randomization process for that individual patient. This will ensure that the surgeon, fellow, nursing staff, patient and family of patient are blinded to the intervention.

VI. TXA will be provided by IDS and stored on-site/in-clinic in a temperature controlled and temperature monitored refrigerator. The volume of TXA solution needed for the intervention, see below, will be diluted to 25mg/ml by research staff and provided to surgeon once patient is enrolled.

VII. Volume of both intervention and control substance will be determined by size of defect. All defects will be considered circles for the purposes of calculating wound area. The radius of the greatest dimension of the defect will be used to calculate the surface area using the formula, $A = \pi r^2$. A volume of 1ml per 1cm^2 will be dropped onto a Telfa pad that has been placed on the wound bed. A standard pressure dressing will be applied overtop.

VIII. All patients will receive the same standardized post-operative wound care management instructions (see Appendix I)

IX. Post-operative bleeding complications will be determined using the following data points (see Appendix II):

a. Did patient call with concern for post-operative bleeding on the same day of surgery, or post-operative day 0 (POD0)? YES/NO
b. Did patient call with concern for post-operative bleeding on POD1? YES/NO
c. Did patient call with concern for post-operative bleeding on POD2? YES/ NO
d. Did patient return to clinic within post-operative days 0-2 for evaluation of post-operative bleeding complication? YES/ NO
e. Did patient receive postoperative intervention of any kind for hemorrhagic complication? YES/NO
f. Type of intervention performed for bleeding complication.
g. Perceived side-effects, if any, by patient due to study intervention.

X. Study patients will be called 3 days after their surgical procedure to be asked the above data points in case a patient received outside care that was not disclosed to office or research staff.

XI. Patients' medical charts will be reviewed for and patients will also be asked to divulge the following medical history for demographic and sub analysis purposes (see AppendixIII):

a. Age, sex, race
b. Medical history including hypertension, coronary vascular disease, liver disease, renal disease
c. Medications including anti-platelet agents and anti-coagulants

B. Study duration and number of study visits required of research participants.

I. Duration sufficient to enroll 124 patients (62 per treatment arm). No additional patient visits will be required beyond the visit normally required for their procedure and/or suture removal.

II. The initial visit for this study will take place after already scheduled Mohs micrographic surgery which will take no longer than one additional hour during the surgical visit.

III. Participation includes a total of three days, specifically postoperative days 0-2.
IV.

C. Blinding, including justification for blinding or not blinding the trial, if applicable.
    I. Double-blinded trial in which patients and surgeons will be masked to which treatment arm participants are assigned
D. Justification of why participants will not receive routine care or will have current therapy stopped.
    I. Care will be identical in both arms except for addition of topical application of TXA vs normal saline soaked gauze to wound bed at completion of MMS.
E. Justification for inclusion of a placebo or non-treatment group.
    I. There will be a control group of patients who do not receive the intervention, topical TXA, and instead will receive topical application of normal saline in order to provide a blinded comparison to the intervention arm. This will prevent unconscious bias from affecting patient and surgeon perception of postoperative bleeding complications.
F. Definition of treatment failure or participant removal criteria.
    I. Patient will be removed from the study if
        i. Patient removes bandage and cleans wound within 24hrs
        ii. Patient seeks postoperative care from outside institution within study timeframe (POD0-2), thus not allowing researchers to evaluate postoperative complication. This will be elucidated with a phone call three days after surgery.
    II. Patients may also voluntarily leave the study. Only patients who complete all steps of the study will be included in data analysis, but the number of enrollees who do not complete the study will be tabulated to track if there is a significant difference between the groups.
G. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.
    I. There will be no effect on the patient.

5. INCLUSION/ EXCLUSION CRITERIA

A. Adult (18 years or older) patients being treated with Mohs micrographic surgery will be included in this study.
B. Surgical procedure must include one of the following:
    a. Any defect being healed by granulation
        i. Including periocular defects[22]
        ii. Including defects with fenestrated cartilage[20,21]
        iii. Including skin graft donor sites left to heal by granulation
C. Patients must not

a. be pregnant or breastfeeding
    i. urine qualitative pregnancy test will be obtained in-office, prior to surgery, from women of childbearing potential
    ii. pregnancy test not required on post-menopausal women or women with history of tubal ligation, ablative uterine procedure or salpingo/oophor/hyster-ectomy
b. Have a known allergic reaction or sensitivity to TXA
c. Have an international normalized ratio (INR) out of therapeutic range if on warfarin; all patients on warfarin will be tested within one week of surgery
    i. INR level will be obtained within 1 week prior to time of intervention
    ii. therapeutic range INR 2.0-3.0
    iii. if high-risk prosthetic heart valve, therapeutic range INR 2.5 – 3.5

6. DRUGS/ SUBSTANCES/ DEVICES

A. Active intervention group: application of TXA soaked gauze on open wound defect, held in place by standard postoperative pressure bandage
B. Control group: Identically placed sterile normal saline soaked gauze, held in place by standard postoperative pressure bandage

7. STUDY STATISTICS

A. Primary outcome variable.
    I. Determination of effects of topical TXA on postoperative hemorrhagic complications and need for additional visits for care related to bleeding complications within the first 2 days following Mohs surgery with a wound allowed to heal by granulation
B. Secondary outcome variables.
    I. Determination of possible adverse effects, if any, that are different between the intervention and control arms.
C. Statistical plan including sample size justification and interim data analysis
    I. The statistical analysis will be performed by the University of Missouri biostatistics group. The sample size was calculated using a power analysis with the alpha set to 0.05 and the power set to 80%. Dichotomous variables were assessed with an anticipated change of bleeding of 10% in the intervention group and 30% in the control group based on prior clinical experience. No interim data analysis is planned.
    II. Data will be analyzed on an intention to treat basis.
D. Early stopping rules.
    I. Study will end early if severe or high rate of adverse events occur.

8. RISKS

A. Medical risks, listing all procedures, their major and minor risks and expected frequency.

I. Topical TXA application
   a. potential local allergic reaction

B. Steps taken to minimize the risks.
   I. Plan for reporting unanticipated problems or study deviations.
      a. Will report all deviations and problems to IRB.
   II. Legal risk such as the risks that would be associated with breach of confidentiality.
      a. Participants will be assigned a study number, which will have no identifiable information. Key to match study number with patient will be located and protected on encryption secured software with access only available to research team. Hard copy will be located in research office in locked cabinet with key only available to research team.
   III. Financial risks to the participants.
      a. In the case of adverse events related to study, participants may incur medical fees associated with treatment of the adverse events.

9. BENEFITS

A. Description of the probable benefits for the participant and for society.
   I. Patients may have reduced post-operative bleeding complications and improved overall surgical experience if in the intervention arm.
   II. If this intervention is helpful, then the intervention may serve as an additional hemostatic wound care option in cutaneous surgery to prevent postoperative bleeding complications and the costs and angst associated with such complications

10. COSTS

A. An application for funding will be made for the MU Department of Dermatology Dyer research fund and from the MU MSDO Procedural Fellowship Endowment.
B. Participants will not incur any costs during this study, outside of standard of care procedural costs billed to their insurance, including INR or pregnancy testing as indicated. Patients will not be billed for intervention or placebo drug.

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