Effect of Tranexamic Acid on Postoperative Bleeding Following Sinus and Nasal Surgery

Study Protocol and Statistical Analysis Plan

NCT04754230

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1. PURPOSE OF THE STUDY

a. Brief Summary

The purpose of the research is to assess the effectiveness of a medication called tranexamic acid (TXA) when given intraoperatively to reduce bleeding postoperatively after sinonasal surgery (e.g. septoplasty, endoscopic sinus surgery). This medication has already been shown to decrease blood loss during surgery, but the implications for bleeding after surgery are unclear. Any impact on postoperative bleeding from the nose will be assessed over the first 7 days following surgery leading up to the first postoperative clinic visit.

b. Objectives

We hope to learn whether use of the tranexamic acid (TXA) lowers the amount of bleeding after surgery as well as the need for repeat evaluation and additional intervention including nasal packing, cautery, and return trips to the OR. If the medication proves effective in doing so, this knowledge will help provide a rationale for sinus surgeons to routinely use this medication intraoperatively to reduce postoperative bleeding, thereby improving the patient experience and reducing use of hospital resources, both in terms of physical and human capital.

c. Rationale for Research in Humans

This study evaluates the clinical effect of tranexamic acid (TXA) on bleeding followed sinonasal surgery. As a clinical study, it necessarily involves the use of human subjects to assess the impact. The study will also evaluate the patient experience and the impression that patients have of their own bleeding following these procedures.

2. STUDY PROCEDURES

a. Procedures

After a patient in the outpatient clinic has been recommended for and agreed to sinonasal surgery (e.g. septoplasty, turbinate reduction, endoscopic sinus surgery), they will then be eligible for screening for the study. Patients will only be informed of the existence of the

study in a clinical context if they meet the screening requirements. Screening may occur either at the preoperative visit that is part of the standard of care, or on the morning of surgery during the surgical consent process if the patient decided to schedule surgery remotely without a preoperative visit. For any patients who have their pre-op visit via telehealth instead of in-person, it will still be brought up in the clinical context of that pre- operative visit. If a patient is interested, the patient will receive more information regarding the study details, and if the patient wishes to participate after a full informed consent process, written consent will be obtained. Patients will need to be able to provide voluntary consent; those who cannot will be excluded. Patients will be excluded if they under 18 years of age, are pregnant or may become pregnant by time of surgery, are prisoners, are international participants, are unable to provide consent, or are non-English speaking. Patients will also be excluded if they have known pro-thrombotic clotting disorders. Other patients that are not specifically targeted but will not necessarily be excluded include employees and students, as long as they are able to provide voluntary consent. Once a patient has had all questions answered and has voluntarily enrolled in the study, the patient will be provided with a bleeding diary template to record the postoperative experience which include VAS evaluation postoperative bleeding and number of gauze changes per day. They will use this diary template daily postoperatively. Patients will be randomized to receive either the study medication (TXA with saline infusion) or not (saline infusion alone). The surgeon will be blinded to this selection. The anesthesiologist will not be blinded. However, the patient's participation in the study will be announced during the surgical time out, and it will be announced that the attending surgeon is blinded to the patient's participation. The patient will undergo general anesthesia and undergo their sinonasal surgery as routine. The study intervention will occur 15 minutes before completion of the surgery. At this time, a 1,000 mg IV dose of tranexamic acid will be added to the saline infusion by the anesthesiologist for patients randomized to the intervention. Patients randomized to placebo will continue to receive their routine infusion of normal saline, which is administered throughout surgery. The anesthesiologist will be asked only to state 'study medication administered" at the time of administration, whether the infusion consists of saline alone or with the addition of TXA. This will be the only way in which the two study arms differ. To standardize patient management, packing materials (e.g. nasopore, surgical, Floseal) will not be used at the end of a surgery. However, if a patient experiencing clinically concerning bleeding at the termination of surgery that requires use of these materials (or the clinically indicated use of a dose of TXA), they will be unblinded, removed from the protocol, and managed accordingly. Patient safety will always take priority. After reversal of anesthesia and extubation, patients will be transported to recovery as per standard of care. They will be discharged home when meeting routine post-anesthesia criteria (tolerating oral intake, control of nausea, control of pain, etc). After discharge home and through the following week leading up to their postoperative visit, all patients will fill out the diary template outlined above to characterize their daily postoperative bleeding. Patients will then follow up for their first postoperative clinic visit one week after surgery which is the standard of care. They will turn in their postoperative bleeding diary entries at this time. Their active obligation at this point is over, but they will always have the right to have their data removed from analysis if they wish to withdraw. They will not be contacted for research purposes after this point in regards to this specific study, but will continue to follow up clinically as per standard of care. They will have no clinic visits exclusively for

research purposes; the only visits will be part of the standard of care. Surgical residents will maintain a list of study patients on whom they are called to evaluate for postoperative bleeding in the recovery unit. They will be blinded to whether the patient received the study medication or placebo. Records (i.e. via STARR) will be queried to determine the frequency with which patients in each group call the clinic or answering service with bleeding- related concerns. Records of further intervention (nasal packing, cautery, return to OR) will also be gathered. These outcomes will be used to determine the difference between groups. Patients will have received the standard of care for postoperative epistaxis in all these scenarios, identical to patients who are not enrolled in the study. The primary outcome is the patient-reported VAS bleeding score after surgery. This methodology has been used by other published work to assess the impact of agents used at the end of procedures to reduce the rate of postoperative bleeding after sinonasal surgery (https://journals.sagepub.com/doi/10.1016/j.otohns.2009.06.078). Using their results as a reference, we may expect that the VAS score on postoperative day one may drop from a 4 to a 2. Assuming an SD of 1.6-1.8 for the purpose of estimations, we would need 24-28 total cases to detect the effect size of 2 in VAS if using 1:1 ratio with 80% power. The secondary outcome is the frequency with which the service is requested to evaluate patients in the recovery unit for postoperative bleeding concerns after sinonasal surgeries. Anecdotal feedback from the resident service suggests that they are requested to evaluate roughly 30% of these patients. With the hypothesis that the TXA could reduce the frequency by roughly half to 15%, we will require 118 patients in each group (total N=236) to achieve 80% power to detect a difference between the two group proportions of 15% (with 30% in placebo, 15% in TXA group). This estimate uses two sided Z-test while assuming type I error=0.05.

b. Procedure Risks

These procedures involve the delivery of routine standard of care in all facets of sinonasal surgery with the addition of a single medication intervention to be delivered intraoperatively while under the direct care and supervision of the anesthesiology service. Any unexpected hemodynamic or clinical side effects can therefore be immediately assessed and addressed. The planned medication dose is based on previous studies and has been extremely well tolerated during studies evaluating its use in endoscopic sinus surgery to assess the effect on intraoperative bleeding. Higher doses have been used for other indications including orthopedic surgery, however we plan to utilize this lower dose with a proven safety record.

c. Use of Deception in the Study

N/A

d. Use of Audio and Video Recordings

N/A

e. Alternative Procedures or Courses of Treatment

The alternative is not to participate and to receive the routine standard of care with no change in risks. This involves observation after surgery with traditional management of epistaxis if it occurs (oxymetazoline nasal spray and pressure, Floseal hemostatic matrix,

formal nasal packing as required). These will still all be available for patients, as their utilization is one of the endpoints of the study. No care or alternative medications are being withheld in order to participate in this study. This is an additional intervention to the routine standard of care. All patients will continue to be treated as clinically indicated.

f. Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

Patients will receive the appropriate standard of care both during and after the conclusion of the study. Nothing will change in regards to their normal clinical management by participating in the study.

g. Study Endpoint(s)

Patients data will be gathered for one week postoperatively and their direct participation will end at the first clinical visit one week after surgery (their data will still be analyzed after that time). The primary endpoint is the patient VAS assessment of postoperative bleeding over the first week, and the patient report of gauze usage over the first week. Secondary endpoints to be evaluated will include the proportion of patient in recovery on whom the nurses contact the on-call resident for assessment with postoperative bleeding, the need for interventions to address postoperative bleeding (cautery, nasal packing, return to OR), and frequency of patient calls to clinic after discharge home with bleeding concerns. If during interim data analysis a significant difference in postoperative bleeding is noted without an increase in adverse events, discussion could be had with the IRB over developing a new standard of care, however we would anticipate continuing with the standard of care through the end of the study.

3. BACKGROUND

a. Past Experimental and/or Clinical Findings

The rationale for this study is based on the findings from other groups that have consistently demonstrated a reduction in intraoperative bleeding with the use of tranexamic acid (TXA) without any significant adverse events. A systematic review and meta- analysis of 5 RCTs including 192 patients receiving a variety of routes of administration TXA (incuding IV, oral, and topical) demonstrated a mean decrease in operative blood loss and resulting improved surgical field quality without any difference in adverse events.(1) A more recent meta-analysis came to the same conclusions by evaluating 11 RCTs.(2) A study examining only IV TXA given at induction of anesthesia demonstrated a significant reduction in bleeding with no incidence of thrombosis in either group, one of the main theoretic concerns of TXA. (3) One patient in the study required intervention for epistaxis, and this patient was in the placebo group. A recent publication in the Laryngoscope evaluated 7 RCTs with a total of 562 patients and found reduced blood loss with TXA versus placebo with no difference in hemodynamics, coagulation profiles, emesis, or thrombotic events.(4) Numerous additional studies have proven the benefit of topical and IV TXA used intraoperatively to reduce intraoperative blood loss, with a recent randomized clinical trial demonstrating no increase in MAP, HR, PT, or PTT. (5) Given the robustness of these findings but without clear evidence to date on postoperative bleeding, nor the resource utilization spent on evaluation by the surgical

service in the recovery unit, a Cochrane protocol was developed in 2017. (6) Among the secondary outcomes of the protocol includes complications and postoperative bleeding, however the protocol has not been published and no studies since that time have answered this particular question.

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2. Ping WD, Zhao QM, Sun HF, Lu HS, Li F. Role of tranexamic acid in nasal surgery: A systemic review and meta-analysis of randomized control trial. Medicine (Baltimore). 2019;98(16):e15202.
3. Alimian M, Mohseni M. The effect of intravenous tranexamic acid on blood loss and surgical field quality during endoscopic sinus surgery: A placebo-controlled clinical trial. J Clin Anesth [Internet]. 2011;23(8):611–5. Available from: http://dx.doi.org/10.1016/j.jclinane.2011.03.004
4. Kim DH, Kim S, Kang H, Jin HJ, Hwang SH. Efficacy of tranexamic acid on operative bleeding in endoscopic sinus surgery: A meta-analysis and systematic review. Laryngoscope. 2019;129(4):800–7.
5. El-Din El-Ozairy HS, Mady OM, Tawfik GM, Elhennawy AM, Teaima AA, Ebied A, Huy NT. Outcomes of combined use of topical and intravenous tranexamic acid on surgical field quality during functional endoscopic sinus surgery: A randomized controlled trial. Head & Neck. 2021, early view.
6. Ravesloot MJL, Lourijsen E, Avdeeva K, Pundir V, Fokkens W. Tranexamic acid for the reduction of bleeding during functional endoscopic sinus surgery. Cochrane Database Syst Rev. 2017;2017(11).

b. Findings from Past Animal Experiments

N/A

4. RADIOISOTOPES OR RADIATION MACHINES

N/A

5. DEVICES USED IN THE STUDY

N/A

6. DRUGS, BIOLOGICS, REAGENTS, OR CHEMICALS USED IN THE STUDY

a. Investigational Drugs, Biologics, Reagents, or Chemicals

N/A

b. Commercial Drugs, Biologics, Reagents, or Chemicals

Commercial Product 1	
Name:	Tranexamic acid
Dosage:	1000 mg

7. DISINFECTION PROCEDURES FOR MEDICAL EQUIPMENT USED ON BOTH HUMANS AND ANIMALS

N/A

8. PARTICIPANT POPULATION

a. Planned Enrollment

All patients will be recruited at Stanford Sinus Center. Given the expected number of patients to power the study based on the calculations listed in section 2a, this will include approximately 250 total patients. To be included, patients will have to be scheduled for sinonasal surgery, as this is the population of interest. While students and employees will not be specifically targeted, they also will not be specifically excluded. Patients with surgery for sinonasal cancer will be excluded as this study will focus on routine sinonasal surgery for nasal obstruction and/or chronic rhinosinusitis.

b. Age, Gender, and Ethnic Background

Patients will include both men and women 18 years of age or older from all ethnicities that present to Stanford outpatient clinics.

c. Vulnerable Populations

Children, pregnant women, homeless, and decisional impaired patients will be excluded from the study. Students, employees, and economically and educationally disadvantaged patients will be offered the opportunity to participate in the study, however it will be made clear that if they choose not to participate they will otherwise still receive the identical standard of care. There will be no pressure to participate given the high volume of patients that are scheduled for surgery through the sinus center.

d. Rationale for Exclusion of Certain Populations

This study will only be implemented at the adult hospital. Children do not receive surgical care at the adult hospital, but rather only at LPCH. As such, by necessity, they will be excluded.

e. Stanford Populations

Laboratory personnel, employees, and students are eligible for the study, but will not be specifically targeted. All those who have been scheduled for sinonasal surgery who do not meet the exclusion criteria (pregnant women, children, prisoners, international, etc) will be offered participation in the study. No participants will receive compensation.

f. Healthy Volunteers

N/A - all patients will have a diagnosis code requiring sinus or nasal surgery

g. Recruitment Details

Patients seen in the outpatient clinic and offered to schedule elective sinus or nasal surgery will automatically be screened for inclusion into the study. Advertisements will not be used; rather the clinician will inform the patient of the research trial and if the patient expresses interest a member of the research team will discuss the details of the trial with the patient, answer further questions, and obtain consent.

h. Eligibility Criteria

i. Inclusion Criteria

Scheduled to undergo elective sinus or nasal surgery (e.g. septoplasty, inferior turbinate reduction, endoscopic sinus surgery)
Age 18 or greater
English-speaking
Able to provide consent

ii. Exclusion Criteria

Minors (age<18)
Pregnant or may become pregnant by time of surgery
Prisoners
Non-English speaking
Foreign citizens
Unable to provide consent
Known pro-thrombotic coagulation disorders
Active intranasal drug use (e.g. cocaine)
Surgery is for a sinonasal tumor or other sinus pathology not described in inclusion criteria
Enrollment is in conflict with existing study participation

i. Screening Procedures

Patients will be screened in the outpatient clinic for inclusion in the study once electing to schedule sinonasal surgery. Their past medical history will be obtained at this time to determine eligibility. If the patient is pregnant or has a reported history of a pro-thrombotic coagulopathy, they will be excluded from the study. Medication history will also be evaluated to determine whether a patient is on blood thinners to provide context to outcomes for subset analysis. Standard of care will be used in regards to medication management before and after surgery; there will be no alteration in medication management as a result of inclusion in the study.

j. Participation in Multiple Protocols

The patient may potentially be enrolled in other unrelated study protocols. They will be asked about participation in other studies at the time of enrollment in this study to confirm there is no conflict by enrolling in this study.

k. Payments to Participants

N/A

l. Costs to Participants

Only the costs of routine medical care associated with the surgery and postoperative care will be charged to the patient, as is routine. There will be no additional costs to the patient by participating in this study.

m. Planned Duration of the Study

Once enrollment begins, the expected duration of the study is expected to be 6-12 months depending on speed of enrollment. Screening will take roughly 10 minutes during the preoperative clinic visit. Active participation in the study will last from the day of surgery to the first scheduled clinical visit one week later. Analysis of patient data will be performed quarterly.

9. RISKS

a. Potential Risks

i. Investigational devices

N/A

ii. Investigational drugs

N/A

iii. Commercially available drugs, biologics, reagents or chemicals

Tranexamic acid:
Safety: Higher total IV doses (eg, ≥50 mg/kg), such as those given perioperatively, may be associated with an increased risk of seizures; lower doses (eg, 1 or 2 g given in the first 8 hours of trauma) do not appear to increase the risk of seizure or venous thromboembolism (CRASH-3 Trial Collaborators 2019; Fillingham 2018a; Lecker 2016; Myles 2017; Sigaut 2014).

Of note, this study will utilize a single 1g dose toward the end of surgery, therefore no risk of these issues would be expected in our study.

Less common side effects such as low blood pressure, nausea and vomiting are also more often seen at the high dose if medication, but may be possible at the low dose as well.

iv. Procedures

Risks of sinus and nasal surgery are reviewed with every patient during informed consent for the surgical procedure itself in the outpatient setting. These risks remain the same regardless of participation in the study. These risks include infection, bleeding, damage to surrounding structures such as the orbit or intracranial cavity, persistent olfactory dysfunction, septal hematoma/perforation, hypoesthesia of

dentition and/or face, need for revision surgery to achieve optimal result, and risks associated with general anesthesia. Patients must accept these risks before being scheduled for elective surgery.

v. Radioisotopes/radiation-producing machines

N/A

vi. Physical well-being

The risks to physical well-being are those associated with underlying disease process and indicated surgery as above. Participation in the study does not alter these risks.

vii. Psychological well-being

The risks to psychological well-being are those associated with underlying disease process and indicated surgery as above. Participation in the study does not alter these risks.

viii. Economic well-being

The risks to economic well-being are those associated with underlying disease process and indicated surgery as above. Participation in the study does not alter these risks.

ix. Social well-being

The risks to social well-being are those associated with underlying disease process and indicated surgery as above. Participation in the study does not alter these risks.

x. Overall evaluation of risk

Low

b. International Research Risk Procedures

N/A

c. Procedures to Minimize Risk

The intervention medication will be administered in the operating room under the supervision of the anesthesia team. Any unexpected side effects will be identified and addressed at that time. As a matter of routine, patients are watched in the recovery unit after surgery for a period of approximately two hours. The half-life of the IV formulation of tranexamic acid is 2 hours, and so any side-effects should be noted prior to discharge home.

To reduce the risk of data breach, data will be coded after the completion of the patient's participation, which will terminate at the first clinical follow-up visit one week after surgery, at which time they will submit their bleeding journal template. Data will be stored only on a encrypted laptop, and if sharing is required will be done through Stanford-sponsored secure data sharing platforms such as Box.

d. Study Conclusion

As above, active individual patient participation terminates at one week postoperatively. All the data necessary for analysis will have been gathered at this time. This data will still be analyzed along with the remainder of the patients until the time of study completion, which is expected to be 6-9 months later once an adequate number of patients have been recruited.
As above, patients will continue to receive the routine standard of care during this study. Epistaxis is expected after sinonasal surgery and is addressed in a variety of ways (observation, holding pressure, nasal sprays, nasal packing, return to OR). The purpose of this study is to determine whether this inherent risk of bleeding can be reduced. All of these interventions are still available and will be used as clinically indicated.

e. Data Safety Monitoring Plan (DSMC)

i. Data and/or events subject to review

Data that will be collected include study-related adverse events (e.g. thrombosis, nausea requiring overnight admission) and any serious adverse events (e.g. death), suspected serious adverse reactions, and unanticipated problems. Outcomes data will be analyzed every 3 months to assess progress toward study endpoints and to ensure no unanticipated risks of study participation.

ii. Person(s) responsible for Data and Safety Monitoring

Dr. Zara Patel (PD)

iii. Frequency of DSMB meetings

Meetings will occur quarterly. If deemed necessary by the IRB, written recommendations will be submitted after each meeting, to include plans to continue the study as designed, continue with modification, temporarily suspend, or terminate.

iv. Specific triggers or stopping rules

The study will end when recruitment targets are reached or if interim data analysis demonstrates a statistically significant difference in endpoints between groups. If Suspected Unexpected Serious Adverse Reactions or Unanticipated Problems (UPs) are encountered, the study will be halted and possibly terminated early if the issue cannot be resolved.

v. DSMB Reporting

The outcome of the review will be disseminated to the co-investigators and the IRB.

vi. Will the Protocol Director be the only monitoring entity? (Y/N)

Yes

vii. Will a board, committee, or safety monitor be responsible for study monitoring? (Y/N)

No

f. Risks to Special Populations

N/A

10. BENEFITS

Participants in the study may receive direct benefit if the administration of tranexamic acid does indeed reduce postoperative bleeding, and assuming the participant receives tranexamic acid rather than placebo. Because this is not yet proven, and this study is designed to evaluate this, this is a potential benefit and not a certain benefit. Furthermore, if the patient receives placebo, they will receive no benefit, and will have received the routine standard of care.

If the data gathered from the study is able to show a benefit without additional risks with the administration of a dose of tranexamic acid, then future patients may benefit from this knowledge with a change in the routine standard of care. Given that this type of surgery is one of the most common in the United States, many future patients may have a more favorable postoperative course if the volume of bleeding is able to be reduced effectively.

11. PRIVACY AND CONFIDENTIALITY

All participant information and specimens are handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and privacy policies of Stanford University, Stanford Health Care, and Stanford Children's Health.