Mount Sinai	Protocol Name:	EFFICACY OF TRANEXAMIC ACID IN FOOT AND ANKLE SURGERIES - A RANDOMISED CONTROLLED TRIAL
	Principal Investigator:	YAN LAI MD,MPH.
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	Study Number:	IF# 2089572, GCO#17-04301

HRP-503 PROTOCOL TEMPLATE

- *Note that, depending on the nature of your research, certain questions, directions, or entire sections below may not be applicable. Provide information if and when applicable, and in cases where an entire section is not applicable, indicate this by marking the section "N/A". Do not delete any sections.*
- ***For any items below that are already described in the sponsor's protocol, the investigator's protocol, the grant application, or other source documents, you may simply reference the title and page numbers of these documents in the sections below, rather than cutting and pasting into this document. Do not refer to the Sample Consent document, or information on the application form in this document..***
- *Keep an electronic copy of this version of the document. You will need to modify this copy when making changes.*

Brief Summary of Research (250-400 words):

In foot and ankle surgery, the prevention of postoperative hematoma in a confined space in the wound has a crucial impact on perioperative outcomes. There has been growing emphasis on the role of antifibrinolytics to minimize bleeding and the formation of postoperative hematoma. Approximately 20% of all foot and ankle fractures are open. Excellent operative field without measurable bleeding remain prerequisite of most orthopedic procedures. Increase blood loss can increase the risk of infection, hematoma formation and wound complications. Presence of blood in synovium not only has direct corrosive effects but also causes increased intra capsular pressure leading to capsular fibrosis culminating as ankyloses.

Traditionally, tourniquets are employed to optimize surgical field visualization thereby limiting operative duration and improving technical precision. There are several unwanted effects that can arise from use of tourniquet like neurapraxia, vascular injury, post operative swelling etc. Hence there is a growing interest in achieving the same operative goals without the use of tourniquet.

Antifibrinolytics can be utilized to achieve a blood sparing effect. Its efficacy in reducing intra operative and post operative blood loss is well documented in cardiac surgery, joint replacement surgery, and spine surgery. Tranexamic acid is a synthetic antifibrinolytic drug that competitively blocks the lysine-binding sites of plasminogen, plasmin and tissue plasminogen activator, thereby delaying

fibrinolysis and blood clot degradation. It has been effectively used as intravenous (IV), oral, topical, as well as intra articular routes of administration. The effects of IV administration lasts 8-17 hours after the initial dose. Orthopedic surgeons have incorporated TXA into multiple elective surgeries as a means of reducing blood loss and transfusion requirements.

Effectiveness of Tranexamic acid (TXA) in postoperative outcomes is unknown in foot and ankle surgeries. The aim of this study is to evaluate effectiveness of intraoperative doses of intravenous TXA in reducing postoperative bleeding and hematoma formation after foot and ankle surgeries.

1)Objectives

Research Question*:* Does intraoperative administration of intravenous TXA reduce postoperative bleeding and hematoma formation after foot and ankle surgeries?

Primary outcome: The incidence of wound complications classified as dehiscence, hematoma, necrosis and infection. Wound healing time and length of stay will be evaluated. The first follow up at surgeon's office will be included.

Secondary outcome: The amount of intra operative and post operative blood loss during the first 24 hours in patients undergoing foot and ankle surgeries. Post-operative complete blood count (CBC), duration of surgery and intra operative fluid resuscitation will be recorded. Intraoperative and post operative narcotic consumption.

2)Background

See above. Effectiveness of Tranexamic acid (TXA) is unknown in foot and ankle surgeries. The aim of this study is to evaluate effectiveness of intravenous TXA in reducing post operative blood loss during foot and ankle surgeries.

3)Setting of the Human Research

Prospective triple blinded randomized control trial in patients undergoing foot and ankle surgeries. The research study will take place at Mount Sinai West hospital. The site PI is Yan Lai, MD, MPH.

4)Resources Available to Conduct the Human Research

For n=200, the feasibility of recruitment is manageable. Recruitment will be done through a coordination of the operating schedule and the surgeon's office. Patients presenting for preoperative visits at the surgeon's office or the preoperative joint clinic will be approached. The surgeon will also provide study information (protocol, consent, general information) to patients in the surgeon's office. After confirmation on the operating schedule, patients will be provided detailed instructions the day before surgery and the final consent will be obtained at the surgeon's office or joint clinic for patients at Mount Sinai West hospital. On the day of the surgery, the subject will meet the research team in the holding area. The team will finalize participation and ask the subject about the signed consent forms and answer any additional questions. The staff members on this protocol are all employees of Mount Sinai and will either be a resident or attending physicians that are included on the IRB protocol. There are three primary members of the research personnel:

a)Yan Lai, MD, MPH – Roles for Dr. Lai in this study include serving as primary investigator responsible for study design and planning, data collection, subject recruitment, manuscript writing and preparation, data analysis, safety monitoring, and responding to adverse events and/or complications. He is certified in PPHS/IRB protocols, all Citi/IRB required training in human subject protection, and has prior clinical research experience. He is also a board certified anesthesiologist and assistant professor of anesthesiology with the Icahn School of Medicine and the Mount Sinai Health System.

b) Poonam Pai B.H MD – Roles for Dr. Pai include serving as primary research coordinator involved in data collection, subject recruitment, manuscript writing and preparation, data analysis, safety monitoring, and responding to adverse events

and/or complications. She has completed all of her required CITI training to be IRB certified and has experience in clinical research. In addition she has been a resident physician in anesthesiology with the Icahn School of Medicine in good standing for the previous three years going on her fourth.

c) Ettore Vulcano MD- Roles for Dr Vulcano in this study include serving as co-investigator responsible for study design and planning, data collection, subject recruitment, manuscript writing and preparation, data analysis, safety monitoring, and responding to adverse events and/or complications. He is certified in PPHS/IRB protocols, all Citi/IRB required training in human subject protection, and has prior clinical research experience. He is also a board certified orthopedic surgeon and assistant professor, department of Orthopedic surgery with the Icahn School of Medicine and the Mount Sinai Health System.

There are institutional processes to ensure that all persons assisting with the protocol will be well informed. The research personnel will conduct regular meetings and department email updates to review the results and safety data of the study. The research personnel will initiate the formation of a safety monitoring board for adverse effects, complications, or complaints from patient subjects.

5) Study Design

Prospective triple blinded randomized control trial. The surgeon will also provide study information (protocol, consent, general information) to patients in the surgeon's office. Recruitment will be done through a coordination of the operating schedule and the surgeon's office. Patients presenting for preoperative visits at the surgeon's office or the preoperative joint clinic will be approached. On the day of the surgery, the subject will meet the research team in the holding area. The team will finalize participation and ask the subject about the signed consent forms and answer any additional questions. All patients will be provided with copies of the IRB protocol and consent if they wish to have it. Copy of the consent form will be sent in a secured email to the potential subject. The email will be secured by

entering in [SECURE] in the e-mail subject line. Once recruited blinding assessments will be done by the study team.

Patients will be assigned randomly using a computer- generated table of numbers to either TXA group (Tranexamic acid group) or placebo (saline group). Patients assigned to TXA group will receive 10mg/kg IV TXA in a 100cc normal saline bag at the time of induction and a second dose prior to skin closure. Patients in the placebo group will receive 100cc normal saline IV at the time of induction and a second dose prior to skin closure. Otherwise, the patient, surgeon, and anesthesiologist in the case will be blinded.

a) **Recruitment methods:** Patients will be recruited and consented at the surgeons office or pre-operative testing/Joint clinic.

b) **Inclusion and Exclusion Criteria**

Inclusion criteria: ASA (American Society of Anesthesiology) class I-IV, age 18-75.

Exclusion criteria: ASA class V, patient refusal, patients with known coagulopathy disorder, renal insufficiency, hepatic dysfunction, serious cardiac disease, patients receiving antiplatelet and/or anticoagulant drugs, or an allergy to TXA or will be excluded.

c)Number of Subjects

We intend to recruit 200 patients.

Based on a confidence level of 99% with a Z score of 2.58, standard deviation of .5 and a confidence interval of 10% our sample size should be 166. For ease of statistical calculations we rounded up to 200 patients. Literature search reveals only one previous study where TXA has been used in calcaneal fractures. Xie et al concluded in a study with 90 patients that TXA reduces post operative blood loss. We intend to use a higher sample size to see any statistical significance.

$$ss = \frac{Z^2 * (p) * (1-p)}{c^2}$$

Where:

Z = Z value (2.58 for 99% confidence level)
p = percentage picking a choice, expressed as decimal (.5 used for sample size needed)
c = confidence interval, expressed as decimal (e.g., .01= ±1)

Sample size= [(2.58^2)(.5)(.5)]/(.1^2)=166 subjects
For effect size, we expect a Cos d medium effect of 0.5.

Intergroup comparisons will be performed using the Mann-Whitney U test. Qualitative data will be compared using the chi-square test or Fisher's exact test. Only $p < .05$ will be considered statistically significant.

d)Study Timelines

2018-2019 and subsequent data analysis. The subject's participation will be from time of enrollment in the pre-operative period until first postoperative day. The first follow up visit at the surgeons office will be included as well. Estimated date of enrollment completion will be when 200 eligible subjects are enrolled in final data analysis. Estimate date for study completion will be June 2018.

e)Endpoints

Conclusion of data analysis and evaluation of significance of findings, as measured by primary and secondary outcomes listed under Objectives (item #1) for purposes of quality improvement.

f)Procedures Involved in the Human Research

Prospective randomized controlled trial and data analysis only. TXA group and placebo group. Intraoperative care of the patient will be provided by an anesthesia team member who is a part of the Mount Sinai System. The anesthesia provider will not be aware of the randomization of the patient. Standard post-operative orders will be written for patients during their time in the PACU.

g)Specimen Banking

N/A

h)Data Management and Confidentiality

Data collected in excel file to be de-identified after initial collection. Excel file be subsequently encrypted and shared only between the above listed investigators via secure Mt. Sinai (chpnet) electronic mail.

The information included in the data will be medical record number, age, gender, ASA class, type of surgery, duration of surgery, the amount of intra operative and post operative blood loss during the first 24 hours in patients will be collected. Wound complications (eg dehiscence, hematoma, necrosis and infection), wound healing time and length of stay will be evaluated. Post operative complete blood count will be recorded. The first follow up at surgeon's office will be the other data collected.

Only the research personnel will have access to the data. The data will be stored as a hard copy files and on a secure spreadsheet. The research personnel is responsible for the receipt of the data. The PI will keep the hard copies secure and any electronic data will be encrypted. No personal identifiers will be used. The data will undergo statistical analysis

i)Provisions to Monitor the Data to Ensure the Safety of Subjects

Part I: Elements of Data and Safety Monitoring Plan

MSSM Principal Monitor:

Last Name: Lai
First Name: Yan
Academic Title: Attending Physician, Assistant Professor
Department: Anesthesiology
Mailing Address: Mount Sinai West 1000 10th Avenue, New York, NY 10019
Phone: 212-523-6915
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MSSM Additional Monitor:

Last Name: Pai B.H
First Name: Poonam
Academic Title: Research Personnel, Physician
Department: Anesthesiology
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MSSM Additional Monitor:

Last Name: Vulcano
First Name: Ettore
Academic Title: Attending Physician, Assistant Professor
Department: Orthopedic Surgery
Mailing Address: 425, west 59th street, 5th floor, New York, NY 10019
Phone: 212-523-7342
Fax:
E-mail: Ettore.vulcano@mountsinai.org

The principal monitor is a board certified anesthesiologist thus minimizing the risk to the subjects and further optimizing their health and wellbeing. Adverse events will be monitored as a standard of care everyone receives regardless of participation in the study. The safety and data information will be reviewed on a daily basis until the desired sample size is achieved. All temporary and/or permanent suspensions will be reported. Prospective chart review for quality data analysis without potential for danger to subjects.

All anesthesiologists involved in patient care will be prepared for the prevention and rescue for any complications involving IV TXA.

j) Withdrawal of Subjects

Patients may withdraw from the study at any given time by contacting any member of the research study group. Data will not be collected on patients who wish to withdraw. Patients do not need to withdraw consent in writing.

6) Risks to Subjects

If patients are injured or made sick from taking part in this research study, medical care will be provided. Generally, this care will be billed to the patient or their insurance in the ordinary manner and the patient will be responsible for all treatment costs not covered insurance, including deductibles, co-payments and coinsurance. This does not prevent the patient from seeking payment for injury related to malpractice or negligence. Contact the investigator for more information.

As with any medication, there is a possibility of an allergic reaction. Although rare, possible complications include hypersensitivity reaction, bleeding or local site infection, and chance of any vascular event. There is a possible risk of private information with procedures in place to minimize the risk.

7)Provisions for Research Related Harm/Injury

If patients are injured or made sick from taking part in this research study, medical care will be provided. Generally, this care will be billed to the patient or their insurance in the ordinary manner and the patient will be responsible for all treatment

costs not covered insurance, including deductibles, co-payments and coinsurance. This does not prevent the patient from seeking payment for injury related to malpractice or negligence. Contact the investigator for more information.

8)Potential Benefits to Subjects

It is important to know that you may not get any benefit from taking part in this research. Others may not benefit either. However, possible benefits may be improved with knowledge about how the reduced blood loss helps in better surgical outcome.

9)Provisions to Protect the Privacy Interests of Subjects

Patients will be appropriately educated about the research study. Any questions or concerns they have will be adequately addressed and patients will have the option to decline participation. Patients will be given as much time as they need to review the consent form. The study personnel will be approaching the subjects. Privacy will be maintained by not including any identifiers such as names or addresses in the data collected.

The identities of human subjects whose data is being studied will be de-identified as per HIPAA Privacy Rule.

10)Economic Impact on Subjects

Patients will not incur any additional cost for participating in the study. The medications used are part of a standard anesthetic regimen that will be billed to subject's insurance as bundled standard of anesthesia care. The cost of the procedure is overall unaffected.

11)Payments to Subjects

Patients will not be reimbursed for their participation.

12)Consent Process

Informed consent will be obtained prior to the procedure. Both the HRP-090 (SOP) Informed Consent Process for Research and the HRP-091 (SOP) Written Documentation of Consent will be followed by the study team. These documents are both available at http://icahn.mssm.edu/research/resources/program-for-the-protection-of-human-subjects/irb-members-palette.

13)Process to Document Consent in Writing

The patients will receive a paper copy of the IRB approved consent packet and will sign in the designated areas to confirm consent of participation. They will have the option of have a copy of the consent and may ask for a personal copy of the consent.

14)Vulnerable Populations

Indicate specifically whether you will include (target) or exclude each of the following populations:

Include	*Exclude*	*Vulnerable Population Type*
	X	*Adults unable to consent*
	X	*Individuals who are not yet adults (e.g. infants, children, teenagers)*
	X	*Wards of the State (e.g. foster children)*
	X	*Pregnant women*
	X	*Prisoners*

15)Multi-Site Human Research (Coordinating Center)

This study will be performed within the Mount Sinai West Hospital. No additional centers will be involved.

16)Community-Based Participatory Research

This does not apply to our study.

17)Sharing of Results with Subjects

Results will not be shared with the patients since the study will take time to complete. Patients can request results if they contact the PI by writing.

18)External IRB Review History

This does not apply to our study.

19)Control of Drugs, Biologics, or Devices

Not applicable. IV TXA are routinely used in orthopedic surgeries.