STUDY PROTOCOL

TITLE: Prophylactic use of Tranexamic acid versus Saline to prevent Bleeding during Transbronchial Biopsy in Lung Transplant Recipients– A Randomized Double-Blind Trial (Protest Trial)

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KEY PERSONNEL

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I. OBJECTIVES

Primary Objective:
To determine if endobronchial (topical) tranexamic acid used prophylactically prior to performing transbronchial biopsies in lung transplant recipients reduces bleeding risk.

Secondary Objectives:

1. To determine if the use of tranexamic acid prophylactically reduces procedure time
2. To determine if the use of tranexemic acid results in greater diagnostic yield of tissue samples

II. BACKGROUND AND SIGNIFICANCE

Surveillance bronchoscopy with transbronchial biopsy is routinely performed in lung transplant patients to monitor for rejection. While the frequency of life-threatening bleeding post biopsy is rare, transbronchial biopsy is a risk factor for moderate to severe bleeding[1]. Lung transplant patients particularly have an increased risk of bleeding compared to the general population.[2] Significant bleeding prolongs procedure time and complication rate and can result in decreased diagnostic yield due to early procedure termination or inability to obtain adequate samples.

There is no standardized process for performing transbronchial biopsies, therefore, practice patterns vary among proceduralists regarding methods used to control bleeding. Due to the inability to predict bleeding severity among patients, the use of medications pre-biopsy to prevent bleeding is rarely used. Instead, efforts to control bleeding are most often performed post-biopsy with medications such as cold saline, topical epinephrine, and topical thrombin.

Tranexamic acid (TXA) is an antifibrinolytic agent. It forms a reversible complex that displaces plasminogen from fibrin resulting in inhibition of fibrinolysis. It also inhibits proteolytic activity of plasmin. TXA is frequently used in clinical practice and can be administered via multiple delivery methods, including intravenous, nebulized, and topical. It has been shown to reduce blood loss in a variety of clinical settings without significant adverse effects.[3] It has also been evaluated for prophylactic use with mixed results in reducing bleeding[4-7]. In our current general pulmonary practice, topical TXA is used variably by pulmonologists during bronchoscopy for post-biopsy bleeding or pulmonary hemorrhage.

A recent randomized control trial was performed comparing prophylactic topical TXA to placebo during transbronchial biopsies. The results showed that patients in the TXA group had less bleeding than the placebo group without adverse reactions.[8] This study did not include lung transplant patients.

The purpose of this research study is to determine if prophylactic topical TXA can reduce bleeding risk in lung transplant patients who undergo transbronchial biopsies. A finding of reduced bleeding would be significant as it could improve clinical outcomes, allow for improved diagnostic yield of biopsy samples, and improve patient experience. It therefore has the potential to change clinical practice and standardize bronchoscopy procedures.

III. RESEARCH STUDY DESIGN, INTERVENTION AND PROCEDURES

The study design will be a single-center, randomized, double-blinded, placebo-controlled study. The control group will receive topical saline (placebo) and the experimental treatment group will receive topical TXA (active drug). The investigational pharmacist will be responsible for randomizing on the day of bronchoscopy to placebo or TXA in a 1:1 fashion using REDCap software. The pharmacist will be the only individual aware of the randomization assignment. All other study personnel will be blinded to the randomization assignment.

Research will be conducted in the endoscopy department at Butterworth Hospital by the pulmonary transplant medical team and research team. Patients may be recruited from inpatient or outpatient settings.

The study population will be stable inpatient or outpatient lung transplant recipients (ages 18 and over) undergoing routine surveillance bronchoscopy at varying intervals within the first 18 months post lung transplant as well as lung transplant recipients who undergo bronchoscopy for evaluation of rejection due to lung function decline. These are all patients already established with the Lung Transplant Registry. The investigator will evaluate each potential participant to ensure that they meet inclusion criteria and do not meet any exclusion criteria prior to enrollment activities occurring. Subjects may enter the study only once during the study period. Total number of subjects to be enrolled = 94 (47 per group).

Inclusion:

1. single or double lung transplant recipients
2. patients >18 years old
3. willingness and ability to sign an informed consent for study participation

Exclusion:

1. platelet count (<50k/uL)
2. INR (>1.6)
3. active bleeding
4. decompensated liver disease
5. history of uremic bleeding or BUN >50
6. severe pulmonary hypertension (mean PA pressure >40 mmHg on RHC or estimated PA systolic pressure >62 mmHg on TTE within one year of procedure)
7. known bleeding disorder
8. allergy to TXA
9. prior history of severe TBBx-related airway bleeding requiring admission or advanced maneuvers for hemostasis (examples including intubation, bronchial artery embolization, surgical intervention)
10. contraindications to topical TXA
11. pregnancy
12. vulnerable populations
13. Adults of limited English proficiency/non-English speakers

Exclusion criteria contain factors that may affect risk of bleeding and are excluded in order to minimize confounding factors.

Duration of the study will be 6-12 months. Currently approximately 6-8 bronchoscopies per week are scheduled. Eligible participants are those who meet inclusion criteria and requirements for diagnostic bronchoscopy in either the outpatient or inpatient setting. Eligible participants will be approached/included only once to either treatment versus placebo group during study timeframe. Total visits will include the screening visit and treatment visit. Treatment time is not expected to be significantly longer than standard procedure. There will be no follow-up visits, but patients can comment on their experience at the end of the study, when all data has been collected.

Procedure:
The bronchoscopy will be conducted in standard fashion. Level of sedation will be determined by the bronchoscopist. Therapeutic anticoagulation and antiplatelet agents will be discontinued with the exception of aspirin.

Randomization: Randomization will be completed by the investigational pharmacist who will use REDCap for randomization in a 1:1 fashion. The randomization will be blinded to the proceduralist and the research team. Placebo and TXA will be identical to each other and all unblinding records will be kept by the investigational pharmacists. Should a safety event occur, the investigator will contact the pharmacist who will reveal the assigned treatment group.

Data to be collected from the medical records and put into REDCap:
Demographic data (age, gender, race, and ethnicity)
Transplant related data (laterality, date of surgery)
Indication for procedure
Bronchoscopy approach (trans oral, trans nasal, endotracheal tube, tracheostomy)
Timing from bronchoscope insertion and final bronchoscope removal
Number of biopsies passes (as documented by proceduralist)
Number of tissue samples (as documented on pathology report)
Amount of Bleeding during the procedure
Performance of other bronchoscopy procedures (i.e., airway stent placement, endobronchial ultrasound)
Recording of vitals during procedure (heart rate, blood pressure, oxygen saturation)

These measures are currently being collected on patients routinely by the Epic procedure form and will require no additional documentation.

Bleeding severity will be documented in the categories of none, mild, moderate, severe, and massive bleeding which will be documented in the procedure note. The definition of each category will be as stated below:

- **No bleeding:** no evidence of bleeding and no intervention required
- **Mild bleeding:** evidence of bleeding but no intervention required
- **Moderate bleeding:** bleeding that requires bronchoscopic tamponade or instillation of topical cold saline
- **Severe bleeding**: bleeding that requires topical epinephrine or topical thrombin or which causes premature termination of the procedure
- **Massive bleeding:** life threatening bleeding which requires interventions such as endotracheal intubation or bronchial artery embolization.

The type of intervention required for management of bleeding will also be documented in the procedure note.

Safety Review:
The participants' clinical stability will be monitored per standard measures by the bronchoscopy team who is trained in assessing patients who undergo moderate or deep sedation. This includes monitoring of consciousness, vital signs, and airway. The proceduralist will be responsible for documenting all procedure complications at the end of the case. This includes the complications mentioned under section XVII related to bronchoscopy (risks to participants). Immediate unblinding will not be necessary, even if major complications do arise.

The investigator is responsible for recording and reporting unanticipated problems related to research that occur during and after study treatment.

IV. ADVERSE EVENTS, SERIOUS ADVERSE EVENTS AND UNANTICIPATED PROBLEM REPORTING

Adverse Events
An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

Assessment and Reporting of Adverse Events
Adverse events will be evaluated by the principal investigator or a qualified and delegated study sub-investigator.

Reporting of Adverse Events
Serious Adverse Events will be reported to the Spectrum Health IRB within 5 business days of their discovery per the investigator responsibility policy. Adverse events will be recorded and summarized for safety monitoring and reported in alignment with GCP requirements and clinicaltrials.gov results reporting requirements.

Serious Adverse Events
An AE should be classified as an SAE if any of the following criteria are met:

- It results in death (i.e., the AE causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., it may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

Adverse Event Grading
Adverse events (AE) for this protocol will be monitored and graded defined by the Common Terminology Criteria for Adverse Events (CTCAE) v5.0, November 27, 2017.[29]

Unanticipated problems
Unexpected adverse events are those not listed in the Package Insert (PI) or current I.B or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. Patients will be asked to report any new adverse effect experienced while on study medication. The unit staff will be monitoring for any unusual signs or symptoms that are new to the patient, as well as the clinical research staff will evaluate the patient. If any new adverse event is experienced while on study medication, even if it is not one of the common or rare side effects of the study medication, the clinical research staff and PI will be notified. In the event an unforeseen adverse event is being seen among patients in the study, the clinical research staff and PI will stop the study medication to identify if it is possibly the culprit of the unforeseen adverse event. If a new unforeseen adverse event is witnessed throughout the study and the study medication cannot be ruled out as causing the adverse event the IRB will be notified and the study will be temporarily stopped pending IRB review.

Reporting Plans
The Principal Investigator will report Unanticipated Problems and Serious Adverse Events, to the Spectrum Health IRB in accordance with IRB policies:

- Unanticipated problems occurring at Corewell Health will be reported to the Spectrum Health IRB within 7 days of the investigator learning of the event.

Stopping Rules
The study has no pre-defined stopping rules.

V. SAMPLE SIZE DETERMINATION

Necessary minimum sample size was calculated using G*Power 3.1.5. For this sample size calculation, we used prior research that showed a proportion of bleeding for the placebo group was 29% and 7.7% for the treatment group[8]. Using these numbers in a one-tailed two proportions test, with alpha of 0.05, power of 0.85, and a 1:1 allocation ratio we determine the minimum number of patients is 94 total patients (47 per group).

VI. STATISTICAL METHODS

Summary statistics will be provided. Numeric data will be expressed as mean ± standard deviation or median [25th, 75th percentile], depending on distribution of the data. Categorical data will be expressed as count (percentage). The primary outcome will be analyzed using a Chi-Square or Fishers Exact test depending on if more than 20% of the expected cell counts are less than 5. For secondary outcomes and demographic data that are numeric those will be analyzed using two-sample independent t-test or Wilcoxon Rank Sum, depending on assumptions being met. The secondary outcomes and demographic data that are categorical will be analyzed using Chi-Square or Fishers Exact Test. All analyses will be assessed at a 0.05 level.

VII. DRUG ADMINISTRATION

The product under investigation is Tranexamic Acid.

Dosing and administration will be 1000mg/10mL diluted in 10mL of saline and will be administered as endobronchial topical application prior to transbronchial biopsy tissue collection.

Placebo will be 20 mL of normal saline drawn up in a syringe and administered as endobronchial topical application.

Study drug will be maintained and dispensed by Corewell Health Investigational Drug Services. Study personnel will pick up the drug and deliver it to the procedure room.

Storage requirements: room temperature (68°F to 77°F). Temperature will be monitored and recorded via electronic monitoring systems. Temperature logs are electronically archived, but specific time frames can be downloaded and made available.

Accountability: The Investigational Drug Services staff will maintain accountability logs for study placebo and investigational product. They will also procure the saline and TXA used for this trial.

Labeling: To maintain the blind, labeling will be identical between placebo and active treatment.

Saline:
Saline has been selected as the placebo drug in the control group because it is a safe medication that is administered in various clinical settings and has almost zero side effects. Should there be an intolerance to topical saline, this would be clinically indistinguishable from a participants' general intolerance to bronchoscopy. In addition, saline is used routinely during bronchoscopy for clearing the working channel of the scope and aiding in secretion clearance. Additional advantages are that it has the same visual appearance as TXA to aid in blinding of the bronchoscopy staff and its use does not affect bleeding risk.

TXA:
The preparation and dose of TXA is the same dosing used in the published study that showed a reduction in bleeding in non-transplant participants undergoing transbronchial biopsy [8]. Both saline and TXA vials will be prepared in a sealed syringe containing either 10mL saline or tranexamic acid (1000mg/10mL). Each vial will be diluted in another 10mL of saline for a total volume of 20mL to be instilled for endobronchial application. There will be no dose modifications. Both

saline and TXA will be dispensed by Corewell Health Investigational Drug Services. Both drugs will be stored at room temperature (68°F to 77°F).

Should severe bleeding occur, the proceduralist can use all usual interventions to control bleeding. This includes and is not limited to cold saline instillation, topical TXA, topical thrombin, and topical epinephrine. If the participant is in the experimental group and receives initial application of topical TXA, they can safely receive additional doses as determined by the proceduralist to control bleeding and unblinding is not required.

VIII. IND EXEMPTION JUSTIFICATIONS

A clinical investigation of a marketed drug is exempt from the IND requirements if all of the criteria for an exemption in § 312.2(b) are met:

• The drug product is lawfully marketed in the United States. TXA and Saline are lawfully marketed in the United States

• The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug. This trial is not intended to be reported to the FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any changes to the labeling of TXA or Saline.

• In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug. This study activity is not intended to support a significant change in the advertising for TXA or Saline.

• The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)).

The investigation will be conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).

- This study will follow all requirements set forth by IRB and will obtain IRB approval. Patients will receive and must sign an informed consent to be included in the study.

The investigation will be conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product)

- This study will not be used with the intention of promoting or commercializing Tranexemic acid for the purpose of reducing bleeding risk in lung transplant recipients receiving transbronchial biopsies.

IX. VULNERABLE POPULATIONS

We do not intend to include vulnerable populations. Vulnerable populations would include those cognitively impaired, non-English speaking individuals, prisoners, those under the age of 18, involuntary behavioral health patients, pregnant women.

X. COMPENSATION

There will be no compensation for participants.

XI. CONSENT PROCESS

Identified patients may be contacted by the study team to gauge their interest. The study team will request to provide them with an electronic version of the consent via secure email or a hard copy of the consent via mail. The purpose of this will be to allow the participant time to review the consent with family and friends and compile a list of questions. Written informed consent will be obtained during a clinic visit (in a private exam room) prior to their bronchoscopy appointment. A hard copy of the signed informed consent form will be provided to the patient to take home and an electronic copy will be uploaded to their chart in EPIC. The original signed consent form will be stored in the research office with the study files.

XII. IRB REVIEW

The protocol and consent form will be reviewed and approved by the IRB prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the Investigator will keep the IRB informed as to the progress of the study. The Investigator will obtain assurance of IRB compliance with regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB'S unconditional approval will be transmitted by the Investigator to the pharmacy prior to the release of the study drug to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

XIII. DATA MANAGEMENT

All data will be stored in REDCap, Florence, and a secured folder such as M-drive or other platforms designated by Corewell Health IS. Access to the study's data in REDCap will be restricted to the members of the study team and members of the Data Acquisition personnel team and biostatisticians in SHORE by username and password. The data for these protocols will follow the safe-harbor method of de-identifying and creating limited datasets. Data that are direct identifiers within the REDCap database will be marked as such and will not be exported where de-identified or limited datasets are required. User Rights will be used to limit exposure of marked identifiers. Any extracted de-identified and/or limited datasets will be stored in a password protected file on secured servers as mentioned above. De-identified and when appropriate limited datasets will be transferred via secure file transfer port or on an encrypted portable hard drive. At Corewell Health, all study records and data are kept and accessible for review and audit for at least 7 years. The information will be destroyed in accordance with the Corewell Health documentation destruction policy.

XIV. PROVISIONS TO MAINTAIN CONFIDENTIALITY OF DATA

All data and records generated during this study will be kept confidential in accordance with institutional policies. Patient name, date of birth, MRN may be used in the patient database for correlation purposes but will be stored in a password-protected environment and only accessible to IRB-approved study staff. This data will not be sent outside of Corewell Health.

Authorized representatives may inspect all documents and records required by the investigator, including medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The PI will oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan.

XV. STUDY MONITORING

The PI and study personnel will meet to discuss after the first 5 patients have been enrolled in the study. Subsequent meetings will occur after every 10 patients to review data. They will complete a monitoring report form, which will include summary of findings, protocol version, summary of enrollment, informed consent review, protocol deviations, serious adverse events, and action items.

XVI. WITHDRAWAL OF PARTICIPANTS

Any requests by subject for withdrawal from study will be recognized and study investigators will comply. Data collected before the withdrawal will be kept for analysis, but no further data will be collected upon receipt of the withdrawal notification.

A subject may be discontinued from study treatment at any time if the investigator feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up

XVII. STUDY RISKS

Risks of TXA include nausea, vomiting, diarrhea, allergic dermatitis, giddiness, hypotension, seizure, dizziness, visual disturbances, hypersensitivity reactions, and thromboembolic events.[12] Prior studies have not shown increased risk of thromboembolic events with use of topical tranexamic acid.[11]

Other potential risks and discomforts experienced by participation will be the same as those of routine surveillance bronchoscopy with bronchoalveolar lavage and transbronchial biopsy. Common risks include adverse reaction to sedation (hypotension, tachycardia, respiratory depression), hypoxia, pneumothorax (2%), epistaxis, bleeding, coughing, vomiting, bronchospasm, and laryngospasm [13]. Other standard of care procedures and their risks and benefits will be discussed with the patient by the provider. AE and SAE's will be monitored as defined previously.

XVIII. MANAGEMENT OF RISKS

No additional monitoring will be needed other than what is usually required for post-bronchoscopy care.

XIX. POTENTIAL BENEFITS

The study participant may experience the benefit of reduced bleeding, shortened procedure time, and adequate biopsy specimens should prophylactic TXA provide reduced bleeding compared to placebo. In cases of moderate bleeding, patients experience more discomfort and anxiety related to recovery from the current procedure and for future procedures. In addition, if a procedure is terminated early due to bleeding complications, insufficient tissue may be collected resulting in a non-diagnostic bronchoscopy which leads to the need for an additional procedure. Because the risks associated with use of topical TXA are minimal, these potential benefits greatly outweigh the risks.

The overall benefit of the study will be providing evidence for standardization of practice. If the use of prophylactic TXA provides a benefit, our study will provide evidence-based practice among patients undergoing transbronchial biopsies. If the study shows no difference, it will provide evidence to avoid unnecessary cost and utilization of prophylactic topical TXA during bronchoscopy.

XX. PROVISIONS TO MONITOR THE DATA FOR THE SAFETY OF PARTICIPANTS

In the event of a serious safety concern that necessitates unblinding, such action will be taken to reveal their treatment assignment to guide medical management.

XXI. PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

Names and medical record numbers will be removed from the primary data to protect privacy. All study activities and conversations will take place in a private setting. Only IRB study personnel will have access to protected health information.

XXII. 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.

XXIII. COST TO PARTICIPANTS

There will be no costs to the participants due to the nature of the study

XXIV. REGULATORY

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

This trial will be registered on Clinicaltrials.gov and updated according to applicable regulations.

XXV. SHARING OF RESULTS WITH PARTICIPANTS

At study completion, participants will be informed of which group they were randomized to and any preliminary results of the study, if available at the time.

Results of the study will be submitted for publication.

XXVI. REFERENCES

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