1. **Protocol Title:** The effect of tranexamic acid on blood loss and transfusion rates in major oncologic surgery.

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4. **Objectives:**
   - To determine the impact of preoperative administration of tranexamic acid on blood loss and transfusion rates in major oncologic surgery.
   - To evaluate the cost-effectiveness of tranexamic acid in major oncologic surgery.

5. **Background:**
   Tranexamic acid was first introduced in the 1960's as a treatment for heavy menstrual bleeding.[1] This medication inhibits fibrinolysis by inhibiting multiple plasminogen binding sites. In the past two decades, it's use has been incorporated into surgical practice for patients undergoing open-heart surgery, liver transplantation, and urologic surgery.[2-4] Recent reports of decreased mortality in patients with traumatic hemorrhage receiving tranexamic acid have shown significant promise.[5-6] A 2006 study published out of Taiwan demonstrated decreased blood loss, reduced transfusion rates, and decreased overall hospital cost in patients undergoing liver resections for both benign and malignant conditions.[7]

   Major oncologic surgeries involving the liver and gastrointestinal tract involve extensive dissection, which can result in significant operative blood loss requiring intra- or postoperative transfusion. Tranexamic acid may be a useful addition in procedures with significant blood loss, as previous studies indicate it is both safe and affordable. While reports of seizure activity have been published when used at high doses (100 mg/kg), standard dosing regimens have proven to be safe and effective.[8,9] The beneficial effect of reduction in bleeding has been demonstrated without an increase in thromboembolic events.[6] We believe tranexamic acid has potential to reduce bleeding in major oncologic surgery resulting in reduced blood loss and lower transfusion rates. An improvement in the rate of surgical complications related to bleeding may also result in decreased hospital costs as well.

6. **Setting of the Research:**
   Spectrum Health Butterworth Campus. Lemmen-Holton Cancer Pavilion.

7. **Resources Available to Conduct this Research:**
   Approximately 15 major oncologic surgeries are performed on a monthly basis at the Spectrum Health Butterworth Campus. All individuals scheduled to undergo these surgeries that meet the eligibility criteria will be recruited for enrollment. Study personnel will include surgical residents with experience in surgical oncology research and knowledge of surgical outcome measures, with monitoring by a staff surgical oncologist.

8. **Study Design:**
   a. <u>Recruitment Methods</u>
      Potential subjects will be recruited at their preoperative office visit with their surgeon or, if applicable, during their inpatient stay prior to surgery. Informed consent will be obtained by the Spectrum Health Oncology Research staff. The potential subjects include all patients scheduled to undergo major oncologic surgery that meet all of the

inclusion criteria, and none of the exclusion criteria. There will be no payment to study subjects. We plan to enroll a total of 200 subjects, unless planned interim analyses determine otherwise.

b. Inclusion Criteria

- Subjects undergoing major oncologic surgery for standard of care purposes (to include, but not limited to: liver resections, radical cholecystectomy, pancreaticoduodenectomy (Whipple procedure), esophagectomy, gastrectomy, colectomy, and debulking with hyperthermic intraperitoneal chemotherapy, prostatectomies, nephrectomies, and partial neprectomies)
- Male or female $\geq$ 18 years of age
- Subject agrees to participate in this study and provides informed consent

Exclusion Criteria

- Subjects with a history of hypercoagulopathy, deep vein thrombosis or pulmonary embolism
- Subjects that are on anticoagulation or antiplatelet medications at the time of surgery other than Aspirin
- Subjects with a history of TIA or Stroke
- Subjects with a history of atrial fibrillation
- Subjects with a known thrombus
- Baseline creatinine level greater than 2.83 mg/dL
- Subjects with known hypersensitivity to tranexamic acid
- Adults unable to provide informed consent
- Children
- Pregnant women
- Prisoners
- Non-English speaking subjects
- Any other medical condition including mental illness or substance abuse deemed by the investigator to be likely to interfere with a subject's ability to provide informed consent, cooperate and take part in this research study

c. Study Endpoints

The primary outcome measures will be operative blood loss and transfusion rates in subjects undergoing the eligible procedures. Secondary outcome measures will include cost of hospitalization, intensive care unit length of stay, and total hospital length of stay.

d. Procedures Involved in the Research

The study design will be a randomized, double-blind, placebo-controlled trial. Following satisfaction of inclusion/exclusion criteria and enrollment into the study, designated pharmacy staff will be notified of the patient's enrollment and scheduled timing of surgery. Designated pharmacy staff will randomize the patient and assign the patient a unique study number. The subject will be randomized based on a predetermined algorithm by the pharmacy staff to receive preoperative intravenous tranexamic acid or preoperative intravenous isotonic electrolyte solution as placebo. The preparation will be indistinguishable by nursing, surgical, or anesthesia staff. The tranexamic acid group will receive a 1000 mg dose immediately preceding surgery, administered by the anesthesiologist. Both the tranexamic acid and placebo will be administered via intravenous piggyback over 15 minutes. Standard daily

laboratory measurements will continue unless clinical conditions necessitate more frequent monitoring. 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 surgical oncologist's discretion.

Data to be recorded from operative records will include operative blood loss, operative time, amount of fluid received, and intraoperative transfusion requirements. Postoperative data including hemoglobin levels, transfusion requirements, surgical complications, thromboembolic events, length of ICU stay, length of hospital stay, and cost of inpatient stay. Subjects will be followed for 90 days postoperatively. Additionally, re-admission to the hospital during this time will also be recorded with associated complications.

e. Data Management

The study personnel will collect outcome data on a weekly basis. Data will be stored in a password-protected file for security. Pharmacy staff will keep a secure record of subjects randomized to the tranexamic acid and placebo arms respectively, which will be blinded from the study personnel.

f. Provisions to Monitor the Data for the Safety of Subjects

Adverse events including thromboembolic events and development of acute renal failure will be monitored and recorded on a weekly basis by study personnel. In the event an increased number of unanticipated events occur, the study will be temporarily stopped pending review. Review of unblinded data will be performed by an independent clinician, pharmacist, and statistician to determine the need to discontinue or resume the study. If a significant increase in adverse events is noted in the treatment arm, 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 every 50 subjects complete the study. 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.

g. 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, their data will not be included for analysis if they did not complete the proposed dosing regimen.

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.

**9. Statistical Plan**

a. Sample Size Determination

We anticipate a 15-20% reduction in transfusion rates in the tranexamic arm when compared with placebo treatment. A sample size of 200 total subjects, 100 in each arm of the study, will be required to obtain a statistically significant result with $p < 0.05$. Randomization will ensure an equal number of respective surgeries between the treatment and placebo arms of the study. All subjects who consent to the trial who meet the above inclusion criteria and complete the proposed dosing regimen will be included in the sample size.

b. Statistical Methods

Summary statistics will be calculated. Quantitative data will be expressed as the mean$\pm$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 $c^2$ test. Significance will be assessed at $p<0.05$.

**10. Risks to Subjects**

Tranexamic acid is an FDA approved medication. The safety of tranexamic acid has been demonstrated in a meta-analysis of the off-label use of tranexamic acid in the perioperative period. A theoretical risk of thromboembolic events exists, though no significant adverse outcomes have been reported with the proposed dosing schedule. Refer to Pfizer Physician Prescribing Information document for a listing of potential adverse effects.

**11. 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.

**12. Provisions to Protect the Privacy Interests of Subjects**

The study, potential risks and benefits of treatment will be discussed extensively with each potential subject at their preoperative office visit (or as an inpatient, if applicable) in a private space. Any questions they have will be answered accordingly. Reported data will not contain identifiable information.

**13. Provisions to Maintain the Confidentiality of Data**

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

**14. 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.

**15. 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.

**16. Consent Process**

Eligible subjects will be recruited at their scheduled preoperative office visit. In rare circumstances recruitment will take place in the inpatient setting if a preoperative visit is not scheduled to occur. The potential risks and benefits of the study will be discussed in detail by the Spectrum Health Oncology Research staff 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. The subject may choose to sign the research consent at the time of the office visit. If the subject desires additional time to consider the study, they may take a research consent home for review purposes, and they may choose to consent to involvement in the study at any time up to the date of their scheduled surgical procedure.

**17. Vulnerable Populations**

There will be no involvement of vulnerable populations in this study.

**18. Sharing of Results with Subjects**

Study results will not be shared with subjects until formal publication of the data. Results will be shared as requested at that time.

**19. References**

1) Vermylen J, et al. A double blind study of the effect of tranexamic acid in essential menorrhagia. Thromb Diath Haemorrh 1968;20(3):583-7.

2) Casati V, et. al. Tranexamic acid in off-pump coronary surgery: A preliminary, randomized, double-blind, placebo-controlled study. Ann Thorac Surg 2001;72:470-5.

3) Massicotte L, et. al. Aprotinin versus tranexamic acid during liver transplantation: Impact on blood product requirements and survival. Transplantation 2011;91:1273-8.

4) Crescenti A, et. al. Intraoperative use of tranexamic acid to reduce transfusion rate in patients undergoing radical retropubic prostatectomy: double-blind, randomized, placebo-controlled trial. BMJ 2011;343:d5701.

5) CRASH-2 trial collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomized, placebo-controlled trial. Lancet 2010;376:23-32.

6) Cap AP, et. al. Tranexamic acid for trauma patients: A critical review of the literature. J Trauma 2011;71:S9-14

7) Wu CC, et al. Perioperative parenteral tranexamic acid in liver tumor resection. Ann Surg 2006;243:173-80.

8) Kalavrouziotis D, et. al. High-dose tranexamic acid is an independent predictor of early seizure after cardiopulmonary bypass. Ann Thorac Surg 2011;(epub ahead of print).

9) Henry DA, Carless PA, Moxey AJ, et. al. Anti-fibrinolytic use for minimising perioperative allogenic blood transfusion. Cochrane Database Syst Rev. 2011;16(3):CD001886.