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TRANEXAMIC ACID (TXA) TO REDUCE VOLUME OF BLOOD TRANSFUSED IN PEDIATRIC AND YOUNG ADULT CANCER PATIENTS UNDERGOING LIMB SALVAGE PROCEDURE OF A LOWER EXTREMITY

IND 147543

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Protocol Summary

TXAKIDS – Tranexamic Acid (TXA) to Reduce Volume of Blood Transfused in Pediatric and Young Adult Cancer Patients Undergoing Limb Salvage Procedure of a Lower Extremity
Principal Investigator: Michael D. Neel, MD
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Brief Overview: This is a clinical trial evaluating the number of pediatric and young adult cancer patients undergoing a limb salvage procedure that frequently requires perioperative or post-operative transfusions of blood products. Tranexamic acid (TXA) will be tested in pediatric and young adult patients with a history of bone malignancy. TXA will be administered perioperatively in a randomized double-blind control trial.
Intervention: Eligible participants undergoing limb salvage procedures will be randomized to receive either TXA or placebo peri-operatively – one dose at initiation of surgical preparation and a second dose 6 hours after the first.
Brief Outline of Treatment Plan: The initial dose of tranexamic acid will be given at the initiation of surgical preparation. The second dose will be given 6 hours after the first dose (either intraoperatively or post-operatively). All doses will be given intravenously at 10 mg/kg with a maximum dose of 1 g. Doses will be double-blinded and randomized for each surgical procedure.
Study Design: Prospective Randomized Double-blind Control Trial (TXA versus placebo)
Sample Size: We estimate a total accrual of 39 limb salvage patients will be needed for the study to yield 38 evaluable subjects**.**
Data Management: Data management and statistical analysis will be provided locally by the Surgery Department and Biostatistics Department at St. Jude Children's Research Hospital.
Human Subjects Per Clinical Trials.gov, pediatric trials have reported minimal adverse events using TXA. Patients will be informed of this and other side effects during the informed consent discussion. Adverse events will be monitored and reported and treated appropriately.

CONTENTS

1. OBJECTIVES

1.1 Primary Objective

1.1.1. To evaluate the difference in intra-or post-operatively transfused blood volume (mL/kg) for patients undergoing limb salvage procedures of the distal femur or proximal tibia who are randomized to receive perioperative tranexamic acid (TXA) versus placebo.

- Study endpoint: intra- or post-operatively transfused blood volume (mL/kg), continuous measurement.

1.2 Secondary Objectives

1.2.1. To evaluate changes in platelets and in hemoglobin from pre-op to post-op level for patients randomized to receive perioperative TXA versus placebo.

- Study endpoint: changes in platelets and in hemoglobin from pre-op to post-op level, continuous measurement.

1.2.2 To evaluate differences in post-operative daily surgical drain output for patients randomized to receive perioperative TXA versus placebo.

- Study endpoint: postoperative daily surgical drain output, continuous measurement, for the duration of the drain.

1.2.3. To evaluate changes in estimated blood loss (EBL) for patients randomized to receive perioperative TXA versus placebo.

- Study endpoint: estimated blood loss, continuous measurement.

1.2.4. To evaluate the association between the intra-or post-operatively transfused blood volume and estimated blood loss (EBL) for patients randomized to receive perioperative TXA and placebo, respectively.

- Study endpoint: intra- or post-operatively transfused blood volume, continuous measurement, until resumption of chemotherapy; estimated blood loss (EBL), continuous measurement.

1.3 Exploratory Objectives

1.3.1. To evaluate differences in functional outcomes post-operatively for patients randomized to receive perioperative TXA versus placebo.

- Study endpoint: Functional Mobility Assessment (FMA), quality of life endpoints and Patient-Reported Outcomes Measurement Information System (PROMIS), quality of life endpoints.

1.3.2. To explore if significant correlations are observed between parameters reported with rotational thromboelastometry (ROTEM®) and EBL and transfusion requirements

in pediatric and young adult patients undergoing limb salvage procedure who are randomized to perioperative TXA versus placebo.

- Study endpoint: rotational thromboelastometry (ROTEM), continuous measurement; intra- or post-operatively transfused blood volume (mL/kg), continuous measurement; estimated blood loss (EBL), continuous measurement.

1.3.3. To evaluate differences in the prevalence and management of wound complications such as superficial or periprosthetic infections, wound dehiscence, contact dermatitis, post-operative hematomas, or any other clinically significant wound complication between patients randomized to receive perioperative TXA versus placebo.

- Study endpoint: Number of patients with the wound complications of interest.

2. BACKGROUND AND RATIONALE

2.1 Background

Limb salvage procedures in pediatric and young adult cancer patients are at high risk for perioperative bleeding with the resultant need of blood product transfusions. Limb salvage procedures may be performed at various anatomic sites with two of the most common sites being the distal femur and proximal tibia.

Perioperative bleeding can result in significant post-operative hematoma, which can affect wound healing and function. Additionally, platelet-derived growth factors are a vital part of the wound healing process. Thrombocytopenia secondary to perioperative blood loss contributes to wound healing complications. Delayed healing of wounds can adversely affect resumption of chemotherapy and rehabilitation. Patients with significant perioperative anemia requiring transfusion are more likely to be tachycardic, light-headed and unable to fully participate with rehab thus adversely affecting early mobilization and its benefits. The use of tranexamic acid has been shown to reduce the incidence of post-operative hematomas[27].

The use of antifibrinolytic drugs is one of the strategies for reducing perioperative blood loss. Antifibrinolytics such as aminocaproic acid, tranexamic acid, and aprotinin have been shown to reduce perioperative blood loss, autologous and/or allogenic blood transfusions, and associated costs in pediatric and adolescent patients who underwent major spinal, craniofacial or cardiac surgery[1-4]. Since the restriction of aprotinin use in

2008, the most commonly used antifibrinolytic drugs have been the lysine analogs, tranexamic acid (TXA) and □-aminocaproic acid (EACA), which inhibit the conversion of plasminogen to plasmin and decrease the degree of fibrinolysis. These agents reduce perioperative blood loss by inhibition of clot breakdown[5-7]. Prospective, randomized studies have shown that the use of these agents in adults can be effective in reducing the perioperative blood loss and transfusion requirements in total joint arthroplasty and reconstructive surgery of the spine[8-12]. In pediatric patients, the efficacy of antifibrinolytics such as TXA has been demonstrated in cardiac surgery, spine deformities surgery and craniofacial surgery[1,2,13-15]. TXA is the most common antifibrinolytic used worldwide because EACA is not available in many countries[1].

Tranexamic acid (TXA) is FDA approved for pediatric and adult hemophilia patients for tooth extraction at 10 mg/kg/dose IV immediately before surgery, then 10 mg/kg/dose IV 3 to 4 times daily for 2 to 8 days. Randomized controlled trials and systematic reviews support the use of TXA to decrease blood loss and transfusion requirements in pediatric patients undergoing cardiac surgery, spine deformities surgery, craniofacial surgery and pediatric trauma. Per Clinical Trials.gov, pediatric trials have reported minimal adverse events as referenced in Appendix II. Some concerns exist about increased thrombotic events with the use of these agents, but large meta-analyses suggest that antifibrinolytics can be safely and efficaciously employed in pediatric patients.

2.2 Rationale

Children, adolescents and young adults undergoing major surgery are frequently exposed to a high risk of perioperative bleeding with concomitant requirement of blood product transfusion. This increases the risk of postoperative adverse outcomes, resulting in longer length of hospital stay and increased morbidity and mortality. The underlying mechanisms that increase the bleeding risk differ depending on the type of surgery performed. Increased fibrinolysis has been implicated as a contributing factor in excessive blood loss in pediatric spinal surgery, adult arthroplasty (TKA) and other major surgeries. Studies utilizing TXA in pediatric orthopedic surgery support its use to reduce perioperative blood loss, drain output and post-operative hematoma. [1,2,11,15]

Because of the significant risks and complications associated with blood loss and allogenic transfusions, efforts to identify safe and effective ways of minimizing blood loss perioperatively are crucial. Reducing blood loss and transfusion needs minimizes post-operative complications, hospital stay length, and decreases risk of development of transfusion related complications such as allergic or transfusion reactions, transfusion-related acute lung injury (TRALI), or risk of transmission of blood borne illness[18,19]. Maintaining a nearer to normal Hgb and Hct allows the patient to undergo more aggressive physical therapy sooner. Higher postoperative Hgb and Hct levels promote improved wound healing as well. The use of antifibrinolytic drugs will help to improve clinical care and functional outcome of children undergoing limb salvage operations.

The administration of antifibrinolytics, such as TXA and EACA, has been shown to reduce bleeding in various surgeries including cardiac, trauma, hip, and knee arthroplasty, gynecological, and urologic procedures in adolescents and young adults.[1,2] Since January of 2014 to December of 2017, 39 patients at our institution underwent limb-sparing tumor resections of the proximal tibia or distal femur that met the inclusion criteria for our proposed study. All 39 patients received either an intraoperative or postoperative blood transfusion. The average total blood volume transfused was 19.78 mL/kg with a standard deviation of 11.38 mL/kg. The average number of transfusions received was 2.95 with a standard deviation of 1.83. The average Estimated Blood Loss per Kilogram of Body Weight was 17.84 mL/kg with a standard deviation of 16.28 mL/kg.

2.3 Background and Rationale for Ancillary and Exploratory Studies

ROTEM® is an established viscoelastic measurement of hemostasis of whole blood at low shear forces. The results of a ROTEM are reported as a reaction curve which shows the elasticity over time when a blood clot forms and dissolves. The measurement parameters available are as follows:

- CT (Clotting time): The CT is the latency time from adding the start reagent to blood until the clot starts to form.
- CFT (Clot formation time) and alpha-angle: The alpha angle is the angle of

tangent between the curve while CFT is the time from CT until a clot firmness of 20 mm point has been reached. These parameters denote the speed at which a solid clot forms and are primarily influenced by platelet, fibrinogen and coagulation factors.

- MCF (Maximum clot firmness): MCF is the greatest vertical amplitude of the trace. It reflects the absolute strength of the fibrin and platelet clot.
- A10 and A20 values: These values describe the clot firmness (or amplitude) obtained after 10 and 20 minutes and provide a forecast on the expected MCF value at an earlier stage already.
- LI 30 (Lysis Index after 30 minutes) and ML (Maximum Lysis): The LI30 value is the percentage of remaining clot stability in relation to the MCF value at 30 min after CT. The ML parameter describes the percentage of lost clot stability (relative to MCF, in %) viewed at any selected time point or when the test has been stopped. A low LI (X) value or a high ML value indicates hyperfibrinolysis. While in normal blood fibrinolysis activity is quite low, in clinical samples a more rapid loss of clot stability by hyperfibrinolysis may lead to bleeding complications which can be treated by the administration of antifibrinolytic drugs.

Of particular interest for this randomized trial will be the association with the LI30 to EBL, transfusion requirements and clinical outcomes, because the addition of an antifibrinolytic agent like TXA should have a direct impact on this value.

3. RESEARCH PARTICIPANT ELIGIBILITY CRITERIA AND STUDY ENROLLMENT

According to institutional and NIH policy, the study will accession research participants regardless of gender and ethnic background. Institutional experience confirms broad representation in this regard.

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than 7 days at the start of therapy. If a post-enrollment lab

value is outside the limits of eligibility, or laboratory values are > 7 days old, then the following laboratory evaluations must be re-checked within 72 hours prior to initiating therapy: CBC with differential, PT, PTT, INR, Fibrinogen, Pregnancy Test and Comprehensive Metabolic Panel (CMP).

3.1. Inclusion Criteria

3.1.1. Participant undergoing limb salvage procedure of malignant bone tumor of the distal femur or proximal tibia, which typically requires blood transfusions.

3.1.2. Patient under the age of 25

3.1.3. Organ Function Requirements:

a. Adequate bone marrow function defined as:
   - Upward trending peripheral absolute neutrophil count (ANC)
   - Platelet count ≥ 100,000/mm^3 (transfusion independent defined as no platelets required for 4 days)
   - Hemoglobin ≥ 8.0 g/dL
   - No RBC transfusion within 24 hours

b. Adequate renal function defined as:
   - Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73m^2

OR

Maximum Serum creatinine based on age/gender as follows: (threshold creatinine values were derived from the Schwartz formula for estimating GFR) (Schwartz GJ, Gauthier B. J Pediatr 1985; 106: 522-6)

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 day to < 1 years	0.6	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1.0	1.0
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

c. Adequate liver function defined as:
   - Total bilirubin ≤ 1.5x the institutional upper limit of normal (IULN) for age
   - ALT (SGPT) and AST (SGOT) ≤ 2.5x IULN for age (or <5x IULN for patients with documented disease involving the liver or 10x IULN for patients receiving HDMTX)
   - Serum albumin > 2 g/dL

d. Adequate coagulation function as defined by International Normalized Ratio (INR) ≤ 1.5

3.1.4 Female participants of child-bearing potential (>10 years old) must have a negative serum or urine pregnancy test within 72 hours of sedation

3.2. Exclusion Criteria

3.2.1. Participants whose limb salvage procedure may require significant manipulation of major blood vessels.
3.2.2. Participants with known bone marrow deficiency resulting in red blood cell deficiency (e.g. Diamond-Blackfan anemia)
3.2.3. Participants receiving erythropoietin-stimulating agents (e.g. epoetin alfa)
3.2.4. Participants with active hemorrhagic cystitis (e.g. alkylator-induced) with gross hematuria or >50 RBCs per high powered field on urinalysis
3.2.5. Participants actively receiving all-trans retinoic acid (ATRA) or isotretinoin (Accutane)
3.2.6. Participants with known allergies to antifibrinolytics
3.2.7. Participants with known hypercoagulopathies
3.2.8. Personal history of a thrombosis or active thrombus
3.2.9. Participants currently on anticoagulation medications (e.g. warfarin, enoxaparin)
3.2.10. Participants with a history of seizures. Patients with a history of febrile seizure are eligible.
3.2.11 Persisting toxicity related to other systemic therapies (e.g. chemotherapy) which constitutes an unacceptable safety risk based on the judgment of the PI and/or the primary treating physician
3.2.12. Female participants who are currently pregnant or actively breastfeeding.
3.2.13. Female participants who are currently receiving estrogen-based contraception therapy.
3.2.14. Inability or unwillingness of research participant or legal guardian/representative to give written informed consent.
3.2.15 Participants enrolled in another clinical trial utilizing an IND/IDE experimental therapy.
3.2.16 Participants with a history of CNS disease.
3.2.17 Participants with known bleeding disorder.
3.2.18 Participants with known platelet dysfunction.

3.3 Research Participant Recruitment and Screening

This clinical trial will be conducted solely at St. Jude Children's Research Hospital (SJCRH). Recruitment will begin in Year 1 and will be completed when a total accrual of 39 limb salvage patients (to yield 38 evaluable subjects) is reached. Subjects will be approached and enrolled during regular surgery consult visits when surgery is being planned. We plan on approaching all available eligible participants until enrollment is completed. The study will be discussed with each potentially eligible family by the PI and/or designee in an unbiased basis until enrollment goals are met.

3.4. Enrollment on Study at St. Jude

A member of the study team will confirm potential participant eligibility as defined in Section 3.1 -3.2, complete and sign the 'Participant Eligibility Checklist'. The completed

checklist will be faxed to Clinical Trials Operations at [redacted]; followed by a phone call to [redacted] to ensure that the fax is received. Eligibility will be reviewed and entered into the Clinical Trials Management System. A research participant-specific consent form and assent document, where applicable, will be generated. The signed consent/assent form must be faxed or emailed to Clinical Trials Operations (CTO) at [redacted] in order to complete the enrollment. To assist with enrollments and consent release, the Clinical Trials Operations (CTO) staff is available Monday through Friday. After hours and on weekends and holidays, the study team is referred to the CTO webpage for additional resources and instructions. Link: [redacted]

3.5. Procedures for Identifying and Randomizing Research Participants

Prior to initiating the study, a workshop will be held at SJCRH with team members participating. The background to the study, study procedures, consent processes, data transfer, and plans to monitor intervention integrity and data quality will be the content for that workshop.

Following the workshop and preparation for data collection, screening for eligible research participants will begin. Eligibility of newly admitted research participants will be confirmed during daily discussions between the PI, designee, and attending physician. The PI or designee will then approach the parent or participant regarding the study and only after the parent/participant has given permission for such will the PI or designee discuss the study with the research participant. If both the research participant and parent agree to participate, the randomization plan established by the study biostatistician will be accessed according to Section 11.1.

4. TREATMENT PLAN

4.1 Study Treatment

Upon participant enrollment, a SJCRH Pharmaceutical Services Department pharmacist will randomize each participant to one of two possible treatment arms (see section 11 for randomization).

To allow for the study team and participants to remain blinded to the treatment assignment, the study drug will be labeled as Tranexamic Acid/Placebo (TXAKIDS) followed by applicable dose and administration instructions.

Study treatment order entry will be managed by study staff according to protocol and institutional policies for medication administration. Any modifications to the study treatment (frequency or discontinuation) will be done by the study team.

4.1.1. Active Treatment Arm

At initiation of surgical preparation, participants randomized to the active treatment arm will receive tranexamic acid 10 mg/kg (max 1 g), given via syringe pump programmed to infuse over 15 minutes. If infused over 15 minutes, the maximum possible rate will be 67 mg/min (for the maximum 1g dose).

4.1.2. Placebo Treatment Arm

At initiation of surgical preparation, participants randomized to the placebo treatment arm will receive 0.9% sodium chloride. It will be matched in appearance, volume, and administration to the active treatment arm with tranexamic acid.

4.1.3 Second Dose

If no unacceptable toxicities occur, a second dose of tranexamic acid/placebo (TXAKIDS) 10 mg/kg (max 1 g) IV push over 5 to 15 minutes will be given 6 hours (with a window of +/- 30 minutes) after the first dose (either intra- or post-operatively).

4.2. Dose Modifications

4.2.1. Check BUN/serum creatinine on post-op day 3.

4.2.2. If the patient has a seizure after the first dose and prior to the second dose, the second dose will not be given.

4.2.3. An anaphylactic reaction will be considered if the patient experiences any of the following 2 symptoms during infusion: nausea/vomiting; hives, pruritis or angioedema; dyspnea, wheezing or hypoxemia; syncope; or incontinence. A sudden decrease in systolic blood pressure by >30% based on age will also be considered evidence of anaphylaxis.

4.2.3.1. In case of anaphylactic reaction, immediately discontinue infusion of study agent.

4.2.3.2. Administer diphenhydramine 1 mg/kg IV (max dose 50 mg) and epinephrine 1 mg/ml (1:1000) 0.01 mg/kg IM, max dose 0.5 mg.

4.2.3.3. Additional supportive care including oxygen, bronchodilators, steroid and vasopressor support may be administered as appropriate.

4.2.3.4. The anesthesia provider will monitor continuously for signs of allergic reaction. These signs may include bronchospasm (increased airway pressures, difficulty with ventilation), and/or skin rash. Hypotension and tachycardia can be seen when an allergic reaction progresses to anaphylactic shock and may be suspected for hypotension unresponsive to fluid bolus. If an allergic reaction is suspected, a serum tryptase level will be drawn, while

treatment for allergic reaction (i.e., Epinephrine, anti-histamines) is commenced.

4.2.3.5. Medication Hypersensitivity and Anaphylaxis Treatment Guidelines can be found at:

[redacted]

4.3. Concomitant Therapy

4.3.1. Non- Allowed Concomitant Therapies

4.3.1.1. Herbal remedies that may impact coagulation (e.g. St. John's Wort) or have unknown effects on coagulation.

4.3.2. Allowed Concomitant Therapies

4.3.2.1. Patients may receive systemic therapies in accordance with their diagnosis, i.e., chemotherapy for patients with malignancy.

4.3.2.2. Patients with a history of reactions to transfusions may receive appropriate pre-medications (e.g. acetaminophen, diphenhydramine).

4.3.2.3. Medications that cause temporary impairment of platelet function should be used with caution.

4.3.2.4. All concomitant and supportive care medications should be documented.

4.3.3. NSAIDS will be given per standard postoperative pain protocol which is immediately after surgery.

4.4. Supportive Care

4.4.1. Central Venous Catheter

While not required for the purposes of this study, many participants will have a central venous catheter/line (CVL) in place for intravenous (IV) administration of medications and blood products. The CVL may be used for administration of the investigational agent/placebo as well as for blood draws, transfusions and other needs based on best medical practice.

It is possible that the risk of forming a blood clot in a deep vein or developing problems with the central line function may be higher than expected in the group that receives TXA. The children in this study are at higher risk of these complications than people in previous studies using TXA because of their cancer diagnosis and the fact that they may have a central venous line.

4.4.2. Additional Post-Operative Supportive Cares

Participants will receive standard post-operative supportive measures including IV hydration, pain medications, nutritional supplementation, and antibiotics per standard procedures as indicated by the responsible members of Surgery, Anesthesiology, Critical Care, and the primary treating service.

5. DRUG INFORMATION

5.1 Tranexamic Acid (Cykloapron®)

Source and Pharmacology: Tranexamic acid is antifibrinolytic, antihemophilic and hemostatic agent that forms a reversible complex that displaces plasminogen from fibrin resulting in inhibition of fibrinolysis. It also inhibits the proteolytic activity of plasmin. By reducing plasmin activity, tranexamic acid also reduces activation of complement and consumption of C1 esterase inhibitor (C1-INH), thereby decreasing inflammation associated with hereditary angioedema.

Formulation and Stability: Tranexamic acid is available as an intravenous solution at a concentration of 1000mg/10mL (10mL vial). Room temperature storage is recommended (25°C or 77°F, with temperature excursions permitted from 15°C to 30°C (59°F to 86°F)).

Supplier: Commercially available from Pfizer as Cyklokapron® or generic manufacturers.

Toxicity: Adverse reactions associated with the injection of Tranexamic acid include (frequency not defined): hypotension with rapid IV injection (>1 mL per minute), dizziness, allergic dermatitis, menstrual disease (unusual menstrual discomfort), diarrhea, nausea, vomiting, and blurred vision. Adverse reactions seen with all formulations that were observed to be rare (< 1%), through post marketing, and/or case reports include: allergic skin reaction, anaphylactic shock, anaphylactoid reaction, cerebral thrombosis, deep vein thrombosis, diarrhea, dizziness, nausea, pulmonary embolism, renal cortical necrosis, retinal artery occlusion, retinal vein occlusion, seizure, ureteral obstruction, visual disturbances (including impaired color vision and vision loss), and vomiting.

Dosage and route of administration including infusion times: The first dose will be given at initiation of surgical preparation, and the second dose will be given 6 hours after the first dose (either intra- or post-operatively). Dose will be given by intravenous push over 5 to 15 minutes at 10mg/kg with a maximum dose of 1 g. Dose will not be injected more rapidly than 1 mL per minute to prevent hypotension.

Dose rounding at St. Jude will be allowed according to institutional policy (See St. Jude Institutional Policy 20.03.004).

5.2 Placebo

Participants randomized to the placebo arm will receive 0.9% sodium chloride. It will be matched in appearance, volume and administration to the active treatment arm with Tranexamic acid.

5.3 Drug Management

St. Jude Pharmaceutical Services Department is experienced with managing study drugs for clinical trials and will store and control Tranexamic acid and Placebo. Drug Accountability Record Forms will be maintained to account for the inventory and disposition of the investigational agent including receipt, dispensing, returns and destruction. Participant specific doses will be ordered by investigators in the St Jude electronic medical record after enrollment. All doses will be dispensed from the SJCRH pharmacy with labels per our standard SOPs including at least participant name, medical record number, dose, and date. If a dose cannot be given, it should be returned to the SJCRH Pharmaceutical Services Department to be disposed with documentation.

To allow for the study team and participants to remain blinded to the treatment assignment, the study drug will be labeled as Tranexamic Acid/Placebo (TXAKIDS) followed by applicable dose and administration instructions.

6. REQUIRED EVALUATIONS, TESTS, AND OBSERVATIONS

6.1. Pre-Study Evaluations

All entry/eligibility studies must be performed within 1 week prior to entry onto the trial (unless otherwise specified).

Pre Study Evaluation – must be obtained before enrollment	Within 1 week of enrollment
History and physical exam with height (cm), weight (kg), and BSA	X
Laboratory Studies: CBC with Diff, CMP, Urinalysis, PT, PTT, fibrinogen, UA	X
Pregnancy test	Within 48 hours

6.2. Evaluations During Therapy

6.2.1 Intra-operative labs per Anesthesiology

6.2.1.1. ABGs q1 hour during the case (if arterial line present)

6.2.1.2. Intraoperative transfusion will occur for all patients with a Hb less than 8.0, and/or for patients with Hb between 8.0 and 9.0 AND a base deficit greater than or equal to -5. The transfusion dose will be 10 mL/kg for patients <30 kg and 1 full unit of packed red blood cells for patients >30 kg. A patient may receive multiple transfusions.

6.2.1.3. There may be a need for blood transfusion prior to Hb measurement in the setting of massive or brisk blood loss. This will be dictated by hemodynamic instability and/or obvious massive hemorrhage on the surgical field. Volume expanders other than packed red blood cells (i.e., Albumin) may be considered to allow time for Hb measurement and will be given at the discretion of the attending anesthesiologist.

6.2.2 CMP

6.2.3 Estimated Blood Loss (EBL)

6.2.3.1. At conclusion of surgery

6.2.3.2. EBL measured using Neptune system and weight of surgical laps, calculated by Surgery, Anesthesia, and circulating nurse.

6.2.4 CBC

6.2.5 Transfusions (intra-operatively and post-op)

6.2.5.1. Intra-operatively see 6.2.1.2.

6.2.5.2. Post-operative transfusion criteria

6.2.5.3. Hgb <7.0

6.2.5.4. Hgb <8.0 if unstable, tachycardic, or symptomatic, or at clinician's discretion

6.2.5.5. Volume of and number of patients receiving transfusion

6.2.6 Post-op coags

6.2.7 ROTEM

6.2.8 Management of drain and drain output

6.2.8.1. Drain emptied and recorded at discharge from PACU

6.2.8.2. Measured and recorded when drainage collection system bag is full and/or every 8 hours.

6.2.8.3. Drains will be placed to Hemovac or Somavac collection system. "Wall suction" will not be utilized.

6.2.8.4. Daily measurement of drain output will be tabulated (over a 24 and 48-

hour period)

6.2.8.5. Negative pressure wound therapy (if used) “output” will be measured and recorded per routine.

6.2.8.6. Patient to remain on antibiotics while drain is in.

6.2.8.7. Drains will be pulled when output is 75 ml or less per 24- hour period

6.2.9 Incisional care

6.2.9.1. Wound care nursing will evaluate the incision at first dressing change and at the first post-operative visit then subsequent visits up to 12 weeks post-op.

6.2.9.2. Starting at the first post-op visit, high risk incisions (patients receiving neoadjuvant chemotherapy) will be monitored every 7-14 days up to 12 weeks post-op or completion of chemotherapy

6.2.10 Incisional healing

6.2.10.1. Presence or absence of dehiscence

6.2.10.2. Presence or absence of clinically significant hematoma

6.2.11 Functional Assessment

6.2.11.1. All patients enrolled on the study will receive a standard physical therapy evaluation at the same timepoints (with a window of +/- 2 weeks for all):

- weeks post-operatively
- 3 months post-operatively
- 6 months post-operatively

6.2.11.2 Additionally, during each physical therapy evaluation, participants will complete the FMA, PROMIS, and ROM assessment of the lower extremities.

6.2.11.3 See Appendix V.

Please see the table below for more detail and obtain other tests as needed for good patient care.

REQUIRED EVALUATIONS, TESTS, AND OBSERVATIONS

STUDIES TO BE OBTAINED	Pre-Op	In surgery/PACU/ Post-op	End of Study
History	X	with each outpatient visit	X
Physical Exam (Ht, Wt, BSA, VS, BMI)	X	with each outpatient visit	X
Type and screen	X		
CBC with differential, platelets	X	In PACU; daily while inpt; 1 week post-op	X
Urinalysis	X		
ROTEM		X In PACU	
Transfusions (amount in cc)		X	
Drain output (amount in cc)		X, daily until pulled	
Incisional healing (visualization)		X Post-op	X
Estimated Blood Loss		X At conclusion of surgery	
CMP	X	In surgery; daily while inpt; post-op day 3; 1 week post-op	X
Wound f/u		Daily until hospital discharge. At week 1 +/- 4 d for all pts; Every 10-14 days +/- 4 d for "high risk" participants; Every 7-10 days +/- 4 d for wounds undergoing active management of problems; At 6,12 weeks +/- 2 wks. for "low risk" participants; All pts. at 2 & 3 months +/- 3 wks.	X
PT, INR, PTT, fibrinogen	X	PACU; Inpt; 1 week post-op	X
Pregnancy Test*	X		
Physical therapy attendance	X	Inpt, 1, 2, 4 and 6 weeks post op +/- 2 wks; 2 and 3 mos. post op +/- 2 wks	X
Functional Mobility Assessment (FMA)		6 wks., 3 mos. post op +/- 2 wks	X
PROMIS	X	6 wks., 3 mos. post op +/- 2 wks	X
ROM	X	6 wks., 3 mos. post op +/- 2 wks	X

* The St. Jude IRB requires that a female patient of childbearing potential must have a negative pregnancy test as a condition of clinical research eligibility.

Obtain other studies as needed for good patient care. End of study for each participant will be after the 6-month evaluation (+/- 1 month) has been completed.

6.3 Response Evaluations

6.3.1. Wound care follow up to include photo documentation for anyone on chemotherapy or undergoing radiation therapy or who develops a wound problem.

6.3.2. For high risk participants who are not at SJ weekly, local wound care must be found. These individuals must provide SJ with photo documentation of wound care follow up.

6.3.3. Wound complications will be graded using CTC AE version 5.0.

6.4. Off-Study Evaluations

6.4.1. Wound evaluation

6.4.2. Functional assessment by physical therapy

6.5 Long-Term Follow-up Evaluations

None.

7. EVALUATION CRITERIA

7.1. Toxicity Evaluation Criteria

The Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 will be used for toxicity and performance reporting. A copy of CTCAE Version 5.0 can be downloaded from the CTEP home page https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

8. CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF-STUDY CRITERIA

8.1. Off-study criteria

8.1.1. Death

8.1.2. Lost to follow-up

8.1.3. Request of the Patient/Parent

8.1.4. Completion of all study-related treatment and follow-up

8.1.5. Discretion of the study PI

8.1.6. Found after enrollment to be ineligible

8.1.7. Seizure

8.2. Off-therapy criteria

8.2.1. Development of unacceptable toxicity during treatment:

8.2.1.1. Acute kidney injury (defined by doubling of creatinine)
8.2.1.2. Anaphylaxis (grade 3 or 4).
8.2.1.3. Seizure

8.2.2. Did not receive second dose of TXA/placebo due to unacceptable toxicity

8.2.3. Completed both doses of TXA/placebo

9. SAFETY AND ADVERSE EVENT REPORTING REQUIREMENTS

9.1. Reporting Adverse Experiences and Deaths to St. Jude IRB

9.1.1. Only "unanticipated problems involving risks to participants or others" referred to hereafter as "unanticipated problems" are required to be reported to the St. Jude IRB promptly, but in no event later than 10 working days after the investigator first learns of the unanticipated problem. Only adverse events that constitute unanticipated problems are reportable to the St. Jude IRB. The Common Terminology Criteria for Adverse Events (CTCAE) version 5 will be used to grade adverse events. As further described in the definition of unanticipated problem, this includes any event that in the PI's opinion was:

- Unexpected (in terms of nature, severity, or frequency) given (1) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, as well as other relevant information available about the research; (2) the observed rate of occurrence (compared to a credible baseline for comparison); and (3) the characteristics of the subject population being studied; and
- Related or possibly related to participation in the research; and

- Serious; or if not serious suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unrelated, expected deaths do not require reporting to the IRB. Though death is "serious", the event must meet the other two requirements of "related or possibly related" and "unexpected/unanticipated" to be considered reportable.

Deaths meeting reporting requirements are to be reported immediately to the St. Jude IRB, but in no event later than 48 hours after the investigator first learns of the death.

9.1.2. The following definitions apply with respect to reporting adverse experiences:

9.1.2.1. Serious Adverse Event: Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include: any substantial disruption of the ability to conduct normal life functions, allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse), a congenital anomaly/birth defect, secondary or concurrent cancer, medication overdose, or is any medical event which requires treatment to prevent any of the medical outcomes previously listed.

9.1.2.2. Unexpected Adverse Event:

- Any adverse event for which the specificity or severity is not consistent with the protocol-related documents, including the applicable investigator brochure, IRB approved consent form, Investigational New Drug (IND) or Investigational Device Exemption (IDE) application, or other relevant sources of information, such as product labeling and package inserts; or if it does appear in such documents, an event in which the specificity,

severity or duration is not consistent with the risk information included therein; or

- The observed rate of occurrence is a clinically significant increase in the expected rate (based on a credible baseline rate for comparison); or
- The occurrence is not consistent with the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

9.1.2.3. Internal Events: Events experienced by a research participant enrolled at a site under the jurisdiction of St. Jude IRB single-center research projects.

9.1.2.4. Unanticipated Problem Involving Risks to Subjects or Others: An unanticipated problem involving risks to subjects or others is an event which was not expected to occur and which increases the degree of risk posed to research participants. Such events, in general, meet all of the following criteria:

- unexpected;
- related or possibly related to participation in the research; and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. An unanticipated problem involving risk to subjects or others may exist even when actual harm does not occur to any participant.

Although some adverse events will qualify as unanticipated problems involving risks to subjects or others, some will not; and there may be other unanticipated problems that go beyond the definitions of serious and/or unexpected adverse events. Examples of unanticipated problems involving risks to subjects or others include:

- Improperly staging a participant's tumor resulting in the participant being assigned to an incorrect arm of the research study;
- The theft of a research computer containing confidential subject information (breach of confidentiality); and
- The contamination of a study drug. Unanticipated problems generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others.

9.1.2.5 There will be an assessment for the existence of adverse events with each study participant encounter, i.e. during each history and/or physical, as depicted in Appendix I. The study team will capture all Grade 3-5 adverse events, including lab toxicities. All adverse events will be assessed for seriousness, grade,

attribution/ causality, and duration. Adverse events will be recorded in the database and reported as per institutional policy. The study team and the PI will review adverse events/toxicities during regular study team meetings. Once adverse events/toxicities have been reviewed, the PI will sign and date a study AE document.

9.2 Emergency Unblinding

In the case of a medical emergency or in the event of a serious medical condition, when knowledge of the investigational product is essential for the clinical management or welfare of the participant, an investigator or other physician managing the participant may decide to unblind that participant's treatment code.

The physician managing the medical emergency or serious condition should attempt to contact the principal investigator to discuss options prior to unblinding, and the principal investigator should approve the unblinding, when applicable. However, ensuring patient safety is the primary objective when the decision to unblind the treatment assignment is made.

The principal investigator or designated study personnel will request to unblind the participant's treatment arm. The principal investigator or treating clinician will contact St. Jude Pharmaceutical Services Department to receive the unblinding information.

All occurrences of emergency unblinding will be reported to the IRB according to the criteria established in protocol section 9.0, the DSMB, and the FDA, when applicable. In a majority of cases, emergency unblinding will occur while managing a serious adverse event (SAE), and will therefore be reported with the SAE. If the unblinding event is not directly associated with an SAE, the same timeline and mechanism for reporting SAEs will be used to notify the IRB of the event (section 9.1).

9.3 Reporting to the Sponsor and/or Federal Agencies

9.3.1. Notification of Federal Agencies by Investigator

Any unanticipated fatal or unanticipated life-threatening event judged by the PI to be at least possibly due to the study treatment, will be reported to the DSMB by e-mail and the FDA by telephone or fax as soon as possible but no later than seven calendar days after notification of the event and followed by a written safety report as complete as possible within eight additional calendar days (i.e., full report 15 calendar days total after notification of event).

Unanticipated, non-fatal and non-life-threatening adverse events that occur in on-study patients and that are considered due to or possibly due to the investigational agent, will be reported to the FDA by written safety report as soon as possible but no later than 15 calendar days of the notification of the occurrence of the event. Expected SAEs, even unexpected fatal SAEs, considered by the PI to be not related to the study, will be

reported to the FDA in the Annual Review Report along with non-serious AEs. All FDA correspondence and reporting will be conducted through the St. Jude Office of Regulatory Affairs.

Copies of all correspondence to the St. Jude IRB, including SAE reports, are provided to the St. Jude Regulatory Affairs office by the St. Jude study team. FDA-related correspondence and reporting will be conducted through the Regulatory Affairs office.

9.3.2 Recording Adverse Events and Serious Adverse Events

Adverse events and serious adverse events will be recorded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

9.4 Data and Safety Monitoring Board

This study has been referred to the St. Jude Data and Safety Monitoring Board (DSMB) for regular monitoring and has been sent to the DSMB. The DSMB is charged with advising the Director and other senior leaders of St. Jude Children's Research Hospital (SJCRH) on the safety of clinical protocols being conducted by SJCRH investigators and on their continuing scientific validity. The DSMB will monitor this protocol every six months for safety events/ toxicity. Refer to the DSMB Charge and Criteria for Protocol Referral for more information regarding DSMB review.

10. DATA COLLECTION, STUDY MONITORING, AND CONFIDENTIALITY

10.1 Data Collection

Electronic case-report forms (e-CRFs) will be completed by the St. Jude Clinical Research Associates (CRAs). Data from the participant's medical record will be entered directly into a secure Trial Master database developed and maintained by St. Jude Clinical Research Informatics.

Data collection will be performed by the CRA working in the Department of Surgery. Protocol-specific data and adverse events will be recorded by the CRA in the Trial Master database. All questions will be directed to the attending physician and/or PI and will be reviewed at regularly scheduled working meetings. Adverse event/toxicity data to be collected and entered into the Trial Master database include: Time point; AE category; Grade; Onset date; Is AE permanent (yes or no); Resolved date; Relationship; Action; Outcome; Was AE serious as defined by the protocol (yes or no); AE expected (yes or

no); AE result in off treatment (yes or no); Was this an unanticipated problem (yes or no); Comments.

Regular summaries of toxicity and protocol events will be generated for the PI and the Department of Biostatistics to review. Participants will be followed for up to 6 months post-op.

10.2 Study Monitoring

This study is considered high risk (HR-3) for monitoring purposes. Protocol and regulatory compliance, including essential regulatory documentation, will be assessed as well as the accuracy and completeness of all data points relating to the primary and secondary objectives semi-annually. If the study design has strata, accrual will be tracked continuously. The first two enrollees will be monitored and 15 % of the study enrollees thereafter, semi-annually.

The PI and study team are responsible for protocol and regulatory compliance, and for data accuracy and completeness. The study team will meet at appropriate intervals to review case histories or quality summaries on participants and retain copies of the minutes which are signed by the PI.

Clinical Trials Operations (CTO) will verify informed consent documentation and eligibility status on 100% of St. Jude participants within 5 working days of enrollment completion.

Overall study conduct, compliance with primary and secondary objectives, age of majority consenting, safety assessments and reporting, and the timeliness and accuracy of database entries are monitored routinely.

Study documents routinely monitored on selected participants include medical records, database entries, study worksheets, and case report forms. Study documents are monitored for participant status, demographics, staging, subgroup assignment, treatments, investigational drug accountability, evaluations, responses, participant protocol status, off-study and off-therapy criteria, and for all other specifics as detailed in a separate study-specific monitoring plan. The study-specific monitoring plan may be revised over time, to adapt monitoring frequency and/ or intensity to a changing environment when appropriate (for example: new safety signals; positive history of compliance; all participants are in long term follow-up; or the enrollment period has ended).

The recording and reporting of Adverse Events, Serious Adverse Events (SAEs), and Unanticipated Problems (UPs) to include type, grade, attribution, duration, timeliness and

appropriateness will be reviewed by the Monitor/ CRM. The CRM will generate a formal report which is shared with the Principal Investigator (PI), study team and the Internal Monitoring Committee (IMC).

Continuing reviews by the Institutional Review Board (IRB) and Clinical Trials-Scientific Review Committee (CT-SRC) will occur at least annually. In addition, unanticipated problems are reviewed in a timely manner by the IRB.

10.3 Confidentiality

Subjects' information will be kept in secure files on secure, password protected computers. Only investigators and study staff will have access to PHI. PHI will not be shared with anyone outside SJCRH. When the data are published, no identifiers will be used that can possibly link the reported information to a given subject.

The medical records of study participants may be reviewed by the St. Jude IRB, FDA, clinical research monitors, etc.

11. STATISTICAL CONSIDERATIONS

11.1 Sample Size Consideration and Randomization

This study will be conducted as a randomized, placebo-controlled double-blind trial of the administration of TXA vs. placebo prior to a limb salvage procedure. The primary objective will be to evaluate if TXA will reduce the proportional blood transfusion volume and EBL. The sample size is calculated based on the hypothesis that the TXA administration will reduce the average total volume of red blood cell transfused per kilogram of body weight by 40% relative to the average total volume of red blood cells transfused of the placebo group. Our historical data should be representative of our proposed placebo group, and historically, the average total red blood cell volume transfused per kilogram of body weight is 19.78 mL/kg $\pm$ 11.38. The distribution of the intra-or post-operatively transfused blood volume is normally distributed after log(1+x) transformation (mean=2.906, sd = 0.507). We use the two-sample t-test with unequal variances to access the primary objective through the log(1+x) transformation of proportional blood transfusion volume.

We calculate the sample size with the two-sided two-sample t-test with unequal variances for the log(1+x) transformation proportional blood transfusion volume. Nineteen patients in each group are sufficient to detect a 40% decrease of log(1+x) transformation of proportional blood transfusion volume (mean=2.435, sd = 0.488) with 0.8 power and type I error 0.05. It can be safely assumed that the number of patients who

do not require blood transfusion is less than 5%. Given the sample size, we do not anticipate the blood transfusion volume will have substantial ties at 0.

Randomization will be performed in the SJCRH Pharmaceutical Services Department by a pharmacist using the randomization program developed by the Department of Biostatistics.[26] The drug is clear and will be given IV. The people who would determine the transfusion volume are blinded to the treatment. The randomization is stratified by the variable pre-operative weight that leads to two strata: pre-operative weight > 45.2 kg and pre-operative weight <=45.2 kg, where 45.2 kg is the median of pre-operative weight in the historical control data underwent limb-sparing tumor resections of the proximal tibia or distal femur. The assignment ratio of the TXA group to the placebo group is 1:1.

The patients who receive only one dose due to anaphylaxis (grade 3 or 4) or seizure will be removed from the evaluation of all objectives. The anticipated rate of each toxicity is about 1%. However, the descriptive statistics will be calculated for these patients who receive only one dose, e.g., adverse events and endpoints in all the objectives. The expected accrual number for our study will be 39 patients (to yield 38 evaluable subjects).

Unacceptable toxicities consist of acute kidney injury (defined by doubling of creatinine) or anaphylaxis (grade 3 or 4) or thrombotic event or seizure. The anticipated rate of each toxicity is about 1%. Thrombotic events occurring six weeks beyond the time of surgery will not be considered related to TXA administration. A heuristic approach is used to monitor each of the three toxicities in the TXA group. For each toxicity, starting from the 3rd patient, if the number of patients with any toxicity is equal to or larger than 3, the study accrual will be paused and amendments to the protocol will be discussed with the IRB. This monitoring rule yields the largest type-I error rate 0.044 when the 20^{th} (one patient is removed due to not receiving the 2^{nd} dose) patient show the toxicity (the 20^{th} patient and any two previous patients in the TXA group).

11.2 Primary Objective

11.2.1. To evaluate the difference in intra-or post-operatively transfused blood volume (mL/kg) for patients undergoing limb salvage procedures who are randomized to receive perioperative tranexamic acid (TXA) versus placebo.

The intra-or post-operative volumes of transfused blood for both the TXA treated group and placebo group will be estimated with a two-sided 95% confidence interval. The blood volumes transfused per kilogram of body weight of the two groups (TXA vs. Placebo) will be evaluated using a two-sided student's t-test after log(1+x) transformation.

11.2.2. Accrual and study duration

This study will be conducted solely at St. Jude Children's Research Hospital (SJCRH). According to the historical data, during January of 2014 through December of 2017 (48 months), 39 patients underwent limb-sparing tumor resections of the proximal tibia or distal femur that met the inclusion criteria for our proposed study. These preliminary data suggest that the randomized controlled trial with 39 patients (TXA vs. Placebo) would be feasible in a 48 months period of time.

11.3 Secondary Objectives

11.3.1. To evaluate changes in platelets and hemoglobin from pre-op to post-op level for patients randomized to receive perioperative TXA versus placebo.

Summary statistics will be provided for the changes in platelet level and decline in hemoglobin from pre-op to post-op level, for both the TXA and placebo group. Two sample t-test or Wilcoxon rank sum test will be used to compare the differences between the two groups. Multiple comparison correction might be used for p-values to address the multiple testing issues due to measurements at multiple time points.

11.3.2. To evaluate differences in post-operative daily surgical drain output for patients randomized to receive perioperative TXA versus placebo.

Summary statistics will be provided for postoperative daily surgical drain output (in milliliters per 24 hour period for the duration of the drain) for each group. The group difference will be compared using two-sample t-test or Wilcoxon rank sum test depending on the distribution of the observed data. Multiple comparison correction might be used for p-values to address the multiple testing issues due to measurements at multiple time points.

11.3.3. To evaluate changes in estimated blood loss (EBL) for patients randomized to receive perioperative TXA versus placebo.

The EBL for pre-op to post-op level, for both the TXA treated group and placebo group will be estimated with a two-sided 95% confidence interval. The EBL of the two groups (TXA vs. Placebo) will be evaluated using a two-sample t-test or Wilcoxon rank sum test depending on the distribution of the observed data.

11.3.4. To evaluate the association between the intra-or post-operatively transfused blood volume and estimated blood loss (EBL) for patients randomized to receive perioperative TXA and placebo, respectively.

Regression model will be used to access the correlation between the log transformed intra-or post-operatively transfused blood volume and EBL.

11.4 Exploratory Objectives

11.4.1. To evaluate differences in functional outcomes post-operatively for patients randomized to receive perioperative TXA versus placebo.

Summary statistics will be provided for postoperative functional assessment scores (at each physical therapy session and at timepoints 6, 12, and 24 weeks) for each group. The group difference will be compared using two-sample t-test or Wilcoxon rank sum test, depending on the distribution of the observed data. Multiple comparison correction might be used for p-values to address the multiple testing issues due to measurements at multiple time points. We will calculate the missing proportions of the functional outcomes at every follow-up.

11.4.2. To explore if significant correlations are observed between parameters reported with rotational thromboelastometry (ROTEM®) and EBL and transfusion requirements in pediatric and young adult patients undergoing limb salvage procedure who are randomized to perioperative TXA versus placebo.

Multiple regression model is used to analyze the association between each measurement of rotational thromboelastometry (ROTEM®) and EBL and transfusion requirements while accounting for possible covariates. Multiple comparison correction might be used for p-values to address the multiple testing issues due to multiple measurements of ROTEM. Multivariate regression model may be used to study the associations between multiple measurements of ROTEM and EBL and transfusion requirements jointly. We will calculate the missing proportions of ROTEM at every follow-up.

11.4.3. To evaluate differences in the prevalence and management of wound complications such as superficial or periprosthetic infections, wound dehiscence, contact dermatitis, post-operative hematomas, or any other clinically significant wound complication between patients randomized to receive perioperative TXA versus placebo.

The proportions of observed wound complications and proportions of observed interventions will be estimated for both the TXA group and placebo group with 95% confidence intervals and compared between these two groups using Fisher's Exact Test. We will calculate the missing proportions of wound complications at

every follow-up. Multiple comparison correction might be used for p-values to address the multiple testing issues due to measurements at multiple time points.

11.5 Anticipated Completion Dates

Anticipated Primary Completion Date: 09/2024
Anticipated Study Completion Date 03/2025

12 OBTAINING INFORMED CONSENT

12.1 Informed Consent Prior to Research Interventions

Informed consent must be obtained from the participant family prior to performing any non-standard of care research tests for this study.

12.2 Consent at Age of Majority

The age of majority in the state of Tennessee is 18 years old. Research participants must be consented at the next clinic visit after their 18th birthday.

12.3 Consent When English is Not the Primary Language

When English is not the patient, parent, or legally authorized representative's primary language, the Social Work department will determine the need for an interpreter. This information will be documented in the participant's medical record. Either a certified interpreter or the telephone interpreter's service will be used to translate the consent information. The process for obtaining an interpreter and for the appropriate use of an interpreter is outlined on the Interpreter Services, OHSP, and CTO websites.

Additionally, the study participant family will be given a written short form consent in their native language during the initial consenting process which clarifies that the study is research. The study team will request a summary of the protocol in the participant's native language (long-form consent) and obtain re-consent when the more detailed native language information is available.

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APPENDIX I: SCHEDULE OF EVALUATIONS

Schedule of Study Evaluations										
Event	Pre-OP	PACU	1-6 days (if inpt)	1 week	2 weeks	4 weeks	6 weeks	2 months	3 months	6 months
CBC, Differentials, Platelets	x	x	x	x						x
ROTEM		x								
Drain Output		x	x	x						
Wound f/u		x	x	x	x	x	x	x	x	x
Physical Therapy Attendance	x		x	x	x	x	x	x	x	x
CMP	x		x	x						x
PT, PTT, INR, Fibrinogen	x	x	x	x						x
History	x		x	x	x	x	x	x	x	x
Physical (Ht, Wt, BSa, VS, BMI)	x		x	x	x	x	x	x	x	x
Type and Screen	x									
Urinalysis	x									
Pregnancy Test	x									
FMA							x		x	x
PROMIS	x						x		x	x
ROM	x						x		x	x
EBL		x								
Evaluation for Adverse Events		x	x	x	x	x	x	x	x	x

APPENDIX II IND DETERMINATION TABLE 1/3

Agent	FDA Indication	Pediatric Indications	Pediatric Trials	Pediatric Dosing	FDA Label Dose	Additional Safety Info	Reference (clinicaltrials.gov)
Tranexamic Acid	Immediately before tooth extraction and following for 2 to 8 days in patients with hemophilia.	Limited use in pediatric patients with hemophilia, principally in connection with tooth extraction. The limited data suggest that dosing instructions for adults can be used for pediatric patients needing CYKLOKAPRON therapy.		Same as adult dosing	FDA approved dose = 10 mg/kg IV Following tooth extraction, 10 mg/kg IV body three to four times daily, may be used for 2 to 8 days.		FDA Approved Labeling
Tranexamic Acid			NCT01141127 Prospective, randomized parallel assignment of two dosing regimens of tranexamic acid in pediatric cardiac surgery (n=18 from 12 mo-12 yrs)	10 mg/kg IV at beginning, middle and end of surgery -or- Loading Dose=10 mg/kg IV followed by maintenance dose = 1mg/kg/hr until end of surgery			Couturier R, Rubatti M, Credico C, Louvain-Quintard V, Anerkian V, Doubine S, Vasse M, Grassin-Delyle S. Continuous or discontinuous tranexamic acid effectively inhibits fibrinolysis in children undergoing cardiac surgery with cardiopulmonary bypass. Blood Coagul Fibrinolysis. 2014 Apr;25(3):259-65. doi: 10.1097/MBC.0000000000000051.
Tranexamic Acid, Placebo (NS)			NCT01228136 Prospective, randomized, double-blind comparison of tranexamic acid or placebo in pediatric adenotonsillectomy	10 mg/kg IV, 30 min before surgery then q 8 hrs x 2 doses		Drug Intolerance or adverse effects were not observed.	Brum MR, Miura MS, Castro SF, Machado GM, Lima LH, Lubianca Neto JF. Tranexamic acid in adenotonsillectomy in children: a double-blind randomized clinical trial. Int J Pediatr Otorhinolaryngol. 2012 Oct;76(10):1401-5. doi: 10.1016/j.ijporl.2012.04.028. Epub 2012 Jun 16.
Tranexamic Acid			NCT02188576 Prospective, Phase 4, randomized, parallel assignment of two dosing regimens in pediatric (3 mo-6 yrs) craniosynostosis surgery	Loading Dose = 50 mg/kg IV or 10 mg/kg IV with maintenance of 5 mg/kg/h IV during surgery			

APPENDIX II IND DETERMINATION TABLE 1/3

Agent	FDA Indication	Pediatric Indications	Pediatric Trials	Pediatric Dosing	FDA Label Dose	Additional Safety Info	Reference (clinicaltrials.gov)
Tranexamic Acid, Epsilon-Aminocaproic Acid, Placebo (NS)			NCT00958581 Prospective, randomized, double-blind comparison of tranexamic acid, epsilon-aminocaproic acid, and placebo used intraoperatively in patients with adolescent idiopathic scoliosis in 125 pt. (36 TXA, 42 Aminocaproic acid, 47 NS Placebo	Loading Dose=10 mg/kg IV infused over 15 min Maintenance Dose= 1 mg/kg/hr IV		Ongoing bleeding in one participant resulted in unblinding (placebo group). In four partipants, a drain was not placed during the skin closure due to unfamiliarity with protocol and they were excluded from drain output analysis. One participant was readmitted for persistent wound drainage that resolved with antibiotic treatment. There were no renal, thromboembolic or other major complications observed in study.	Verma K, Errico T, Diefenbach C, Hoelscher C, Peters A, Dryer J, et al. The relative efficacy of antifibrinolytics in adolescent idiopathic scoliosis: a prospective randomized trial. The Journal of bone and joint surgery American volume. 2014 May 21;96(10):e80. Epub 2014/05/31.
Tranexamic Acid, Placebo (NS)			NCT01813058 Efficacy of IV Tranexamic Acid in decreasing blood loss in pediatric idiopathic scoliosis surgery?	Loading Dose=50 mg/kg IV infused over 15 min Maintenance Dose= 10 mg/kg/hr IV during surgery or Placebo (NS)		No patient in either group had clinical evidence of thromboembolic or neurologic complications. Analysis confirmed that the PK of TXA in craniosynostosis paediatric surgical patients is well described by a structural two-compartmental open model. Incorporating bodyweight and age significantly influenced individual pharmacokinetic parameters and improved TXA predicted concentrations. Of particular clinical significance, CL was determined to be related to bodyweight and age. Patients weighing ≤10 kg or age ≤12 months have significantly lower CL than the others.	1.) Goobie SM, Meier PM, Sethna NF, et al. Population pharmacokinetics of tranexamic acid in paediatric patients undergoing craniosynostosis surgery. Clinical pharmacokinetics 2013; 52:267-76. 2.)Goobie SM, Meier PM, Pereira LM, McGowan FX, Prescilla RP, Scharp LA, Rogers GF, Proctor MR, Meara JG, Soriano SG, Zurakowski D, Sethna NF. Efficacy of tranexamic acid in pediatric craniosynostosis surgery: a double-blind, placebo-controlled trial. Anesthesiology. 2011 Apr;114(4):862-71. 3.) Sethna NF, Zurakowski D, Brustowicz RM, Bacsik J, Sullivan LJ, Shapiro F. Tranexamic acid reduces intraoperative blood loss in pediatric patients undergoing scoliosis surgery. Anesthesiology. 2005 Apr;102(4):727-32.
Tranexamic Acid, Placebo (NS)			NCT02840097 Prospective, Phase 2, Randomized, Triple Blind, Parallel Assignment in pediatric trauma (n= 40 < 18 years)	Loading Dose = 15 mg/kg over 10 min followed by 2 mg/kg/hr over 8 hrs -or- Loading Dose = 30 mg/kg over 10 min followed by 4 mg/kg/h over 8 hrs or- Placebo (NS)			

APPENDIX II IND DETERMINATION TABLE 3/3

Agent	FDA Indication	Pediatric Indications	Pediatric Trials	Pediatric Dosing	FDA Label Dose	Additional Safety Info	Reference (clinicaltrials.gov)
Tranexamic Acid, Placebo (NS)			NCT02180321 Prospective, Randomized, Triple Blind, Parallel Assignment in pediatric patients undergoing craniosynostosis surgery (n=50 < 6 yrs)	Loading Dose=10 mg/kg IV infused over 15 min Maintenance Dose= 5 mg/kg/hr IV of Placebo (NS)			
Tranexamic Acid, Placebo (NS)			NCT00994994 Prospective, randomized parallel assigned single-blind study to determine if tranexamic acid reduces blood loss in pediatric cardiac surgery (n=160 2 mo to 18 years)	Loading Dose =50 mg/kg IV of tranexamic acid was given as a bolus at the induction of anesthesia, followed by 15 mg/kg of continuous infusion and another 50 mg/kg into the bypass circuit in TXA group. same volume of normal saline was given in Placebo group		One patient in the TXA group suffered from cerebral infarction at ~ 2 weeks post-surgery. The neurological status gradually improved on an outpatient clinic basis. There were no significant differences in pre- and postop creatinine values between the TXA and placebo groups.	Shimizu K, Toda Y, Iwasaki T, Takeuchi M, Morimatsu H, Egi M, Suemori T, Suzuki S, Morita K, Sano S. Effect of tranexamic acid on blood loss in pediatric cardiac surgery: a randomized trial. J Anesth. 2011 Dec;25(6):823-30. doi: 10.1007/s00540-011-1235-z. Epub 2011 Sep 24.
Tranexamic Acid or No Intervention			NCT03128866 Prospective, randomized parallel assignment open label study reducing blood loss in hemipelvectomy surgery with use tranexamic acid	1. Adult patients and pediatric patients > 40 kg given a loading dose of 15 mg/kg 30 min prior to skin incision over 15 minutes followed by a 10 mg/kg/hour maintenance infusion during the surgical procedure. TXA infusion discontinued after wound closure. 2. Pediatric patients (age < 12 and weight 5 - 40 kg) given a loading dose of 6.4 mg/kg (maximum 1 gram) dose 30 minutes prior to skin incision over 15 minutes, followed by 2 - 3.1 mg/kg/hr maintenance infusion until skin closure			
Tranexamic Acid, Placebo (NS)			NCT03714360 Prospective, Phase 4 randomized double-blind placebo-controlled, parallel-group study of tranexamic acid during minor lumbar spinal surgery (ASA grades 1 or 2) (n=250 pediatric and adult)	Single dose of 10mg/kg IV (max= 1 g) of TXA or equivalent volume of NS (placebo) prior to incision		No safety listed in clinicaltrials.gov, but brief summary stated mean postoperative blood loss in patients who received tranexamic acid was statistically significantly lower than placebo.	

APPENDIX III: TESTS PERFORMED FOR GOOD CLINICAL CARE

All tests and evaluations mentioned in the protocol are considered Standard of Care except for those listed in APPENDIX IV.

APPENDIX IV: RESEARCH TESTS

Research Test	Pre-Study	During Study	End of Study
ROTEM	No	In PACU, required	No
Tranexamic acid (TXA)	**No**	1 IV dose over 5 to 15 minutes; second IV dose over 5 to 15 minutes to be given 6 hours later if serum creatinine level has not doubled	No

APPENDIX V: FUNCTIONAL ASSESSMENT

Functional Mobility Assessment (FMA) is a tool that was developed to measure functional mobility in children and adolescents with lower-extremity sarcoma. It is comprised of well-established outcome measures that examine various domains of function. The six categories tested by the FMA include pain, functional mobility, use of assistive devices, satisfaction with quality of gait, participation in the community, and endurance. 1.) Pain is measured by using a numeric scale requiring patients to rate any pain experienced in the prior week on a 0 (no pain) to 10 (worst pain imaginable) scale. 2.) Functional mobility will be measured by using the Timed Up and Down Stairs (TUDS) and Timed Up and Go (TUG). TUDS assesses the time required for a patient to walk up and down 12 stairs to measure functional mobility, balance, and motor skills. TUG measures the time needed to stand from a seated position, ambulate 3 meters, turn around, return to chair and resume sitting. This will provide a measure of dynamic balance and mobility. 3-5.) The use of supports, patient satisfaction, and participation in the community will be measured by patient provided responses to questions pertaining to the use of supports (brace, cane, crutches), satisfaction with walking quality, and participation in school, work, and/or sports. The responses will be scored on a 0-5 scale, with 0 demonstrating the least preferred outcome. 6.) A modification for the FMA will be implemented to measure endurance, which will be assessed using the 9-Minute Run-Walk Test. The patient will be instructed to walk or run for 9 minutes while trying to cover as much distance as possible. Heart rate (HR) and rate of perceived exertion (RPE) data will be collected during the walk/run. RPE measures the level of the patient's exertion using a likert scale of numbers (6-20) and adjectives describing effort. A wheeled feet counter will measure distance and a stopwatch will track time. Upon completion of the 9-minute run-walk, the physiological cost index (PCI) will be calculated by dividing the difference in the patient's heart rate (HR while walking- HR at rest) by walking speed in meters per minute. Marchese, et al.[20] reported that the FMA demonstrated good internal consistency as well as good construct validity in its ability to discriminate between patients with lower extremity malignancy and healthy controls.

- **Range of Motion** Active and passive ROM will be measured using a goniometer. Measurements for patients with lower extremity surgery will include hip flexion, hip abduction and adduction, hip internal and external rotation, knee flexion and extension, and ankle dorsiflexion. ROM will be attempted on bilateral lower extremities, however if post-operative ROM precautions are implemented, the involved extremity will not be measured. Goniometry is a reliable and valid measure for active and passive ROM when following standardized procedures.

Lower Extremity ROM

ROM Measure	Procedural Description	Patient Position	Pivot Point	Stationary Arm	Moving Arm
Hip flexion	The contralateral LE stabilized with hip and knee flexed	Supine	Greater Trochanter	Parallel to the long axis of the trunk and spine	Parallel to long axis of femur
Hip abduction and adduction	Stabilize the contralateral LE	Supine	Anterior superior iliac spine	Anterior superior iliac spine	Parallel to long axis of femur
Hip internal and external rotation	Stabilize the contralateral LE	Sitting	Tibial tuberosity	Parallel to floor	Parallel to tibial crest
Knee Flexion and Extension	Stabilize the contralateral LE	Supine	Lateral femoral condyle	Parallel to the long axis of femur	Parallel to long axis of fibula
Ankle Dorsiflexion	Stabilize the contralateral LE	Sitting	Posterior and inferior to lateral malleolus	Parallel to long axis of fibula	Parallel to fifth metatarsal

Patient-Reported Outcomes Measurement Information System (PROMIS) is a patient-reported outcome tool created by the National Institutes of Health (NIH), to establish a means of systematic outcome reporting for all patients across the health care spectrum.[21] Due to its efficiency, reliability, and applicability to all patient types, the PROMIS continues to grow in popularity in many fields of medicine, including pediatrics, oncology, and orthopedics.[22-25] It has shown good validity in both adult and pediatric populations, and is available in pediatric (ages 8-17), adult (ages 18 and older), and parent proxy (ages 5-17, or those unable to complete form independently) versions. The physical function domain of the PROMIS is intended to capture a patient's self-reported ability to perform daily activities, self-care, and athletic activities, and are subdivided into the areas of mobility and upper extremity. Additional domains utilized for this study include strength impact and pain interference. PROMIS forms will be provided to all patients enrolled on this study at the time of their functional assessment with adequate, allotted time for completion of questionnaires, and collection of forms at the end of assessment appointment.

APPENDIX VI: RELATION OF STUDY ENDPOINTS TO PROTOCOL OBJECTIVES

Item	Pre-OP	PACU	1-6 d Post-OP	1 wk. Post-OP	2 wks. Post-OP	4 wks. Post-OP	6 wks. Post-OP	2 mos. Post-OP	3 mos. Post-OP	6 mos. Post-OP
Objectives 1.1.1 & 1.2.3 & 1.3.2: Amount of Blood transfused/ placebo arm		X	X							
Objectives 1.1.1 & 1.2.3 & 1.3.2: Amount of Blood transfused/ TXA- treatment arm		X	X							
Objectives 1.2.1: Platelet changes/placebo arm	X	X	X	X						
Objective 1.2.1: Platelet changes/TXA-treatment arm	X	X	X	X						
Objective 1.2.1: Hemoglobin changes/ placebo arm	X	X	X	X						
Objective 1.2.1: Hemoglobin changes/ TXA-treatment arm	X	X	X	X						
Objective 1.2.2: Drain output/placebo arm		X	X	X						
Objective 1.2.2: Drain output/ TXA-treatment arm		X	X	X						
Objectives 1.2.3 & 1.2.4 & 1.3.2: EBL/placebo arm (includes sponge counts + other measures during surgery)		X								
Objectives 1.2.3 & 1.2.4 & 1.3.2: EBL/TXA treatment arm (includes sponge counts + other measures during surgery)		X								
Physical Therapy Attendance (could relate to obj 1.3.1)	X		X	X	X	X	X	X	X	X
Objective 1.3.1: FMA							X		X	X
Objective 1.3.1: PROMIS	X						X		X	X
Objective 1.3.2 ROTEM		X								
Objective 1.3.3 Wound f/u placebo arm (as needed)		X	X	X	X	X	X	X	X	X

Objective 1.3.3 Wound f/u TXA-treatment arm (as needed)		x	x	x	x	x	x	x	x	x