CLINICAL STUDY PROTOCOL

Tranexamic Acid for The Management of Bleeding Intestinal Angioectasias: A Randomized, Placebo Controlled Trial

Principal Investigator
Daniel Raines

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Study Personnel

Principal Investigator	Daniel Raines Ochsner Health Systems Email: draine@lsuhsc.edu
	Munraj Singh LSU Health Sciences Center - New Orleans Email: msin10@lsuhsc.edu

SYNOPSIS

Primary Objective To determine whether oral therapy with TXA results in improvement in serum hemoglobin concentration and/or requirement for PRBC transfusion compared to placebo in patients treated with standard endoscopic ablation, ocreatide and iron supplementation
Secondary Objectives (if applicable) To determine the need for hospitalization for symptomatic anemia or acute gastrointestinal bleed To determine the need for additional endoscopic interventions To determine the rate of clinically significant side effects associated with TXA therapy leading to drug withdrawal
Study Duration The interventional portion of the study will be conducted over a 3 month period
Study Design In the RCT portion of the study, we will enroll approximately 50 patients with diagnosed intestinal AEs through VCE and/or endoscopy who experience symptomatic anemia despite standard therapy including endoscopic ablation, octreotide and iron supplementation. Subjects will be randomized to either the TXA treatment group versus the placebo treatment group for 3 months. Patients will have initial complete blood counts (CBC) measured as a baseline then subsequent CBCs measured at 1, 2 and 3 months. Patients will be monitored for drug side effects, symptoms related to anemia, the need for blood transfusions and hospitalizations related to GI bleeding/anemia.
Study Population All newly diagnosed adult patients with intestinal angioectasias following at the LSU Health Network GI Clinic who meet screening criteria will be considered for inclusion. Existing patients with intestinal angioectasias that are currently not using TXA may also be approached for study participation.
Number of Participants The study design includes 50 participants enrolled in the study
Number of Study Sites The study site includes the LSU Health Network GI Clinic at Ochsner Kenner Hospital
Primary Outcome Variables Primary outcome variables include hemoglobin concentration and the requirement of packed RBC transfusion.
Secondary and Exploratory Outcome Variables (if applicable) Secondary outcome variables include number of hospitalizations, endoscopic interventions and experienced side effects

Table of Contents

1 - Introduction

1.1 Introductory Statement

Intestinal angioectasias are the most common source of small bowel bleeding in the U.S. Over 50% of patients with bleeding angioectasias develop multiple lesions which recur over time. Current medical therapy for angioectasias is suboptimal as many patients continue to experience significant GI blood loss despite currently available standard therapies such as endoscopic ablation and somatostatin analogue therapy (Octreotide). Our goal is to evaluate the efficacy of tranexamic acid as medical therapy for bleeding intestinal angioectasias in a subpopulation of patients who have failed standard therapy or in whom standard therapy is contraindicated.

2 - Background

2.1 Background/prevalence of research topic

Suspected small bowel bleeding (SSBB) is defined as iron deficiency anemia attributed to chronic gastrointestinal (GI) blood loss or overt GI bleeding which remains undefined in etiology after standard upper and lower endoscopy. SSBB accounts for 5% of all GI bleeding cases.[1] Although missed lesions in the upper GI tract and colon should be considered, up to 75% of patients with SSBB are confirmed to have bleeding sources in the small bowel.[2] Small bowel angioectasias (AE), which are also referred to as angiodysplasias or arterio-venous malformations, are identified as the source of bleeding in 30-40% of all SSBB cases and are the most common small bowel bleeding source in patients older than 50.[3] While AEs can be found throughout the entire GI tract, they are most commonly found in the small bowel specifically in the jejunum, followed by duodenum, stomach and right colon.[4] The prevalence of gastrointestinal AE is estimated to be 0.9-3.0% in non-bleeding patients and up to 6% in patients with evidence of blood loss.[5]

AE's are a collection of dilated submucosal vessels composed of thin tortuous capillaries accompanied by ectasia of the overlying mucosal venules and capillaries.[6] Per Yano-Yamamoto's accepted endoscopic classification system, small bowel AE are classified as type 1 lesions. These lesions are further subclassified as type 1a which are characterized by punctate erythema (<1mm) with or without oozing and type 1b which are classified as patchy erythema (2-3 mm) with or without oozing.[7] Histopathologically, AE consist of thin, dilated and tortuous veins that lack a smooth muscle layer, which is thought to explain their weakness and tendency to bleed.[8]

Pathophysiology and Risk Factors
While the pathogenesis and etiology of gastrointestinal AE remains unclear, two developmental theories exist. The first by Regula et al. suggests that chronic intermittent obstruction of veins as they pass through the muscular layers of the bowel wall may cause dilation and increased pressure within the vessels. Due to chronic hypoperfusion, sympathetic nerve stimulation leads to relaxation of intestinal vascular smooth muscle, causing local vascular overload, dilation, and eventually, permanent AE.[9] Dysregulated angiogenesis termed the "angiogenic theory" is an alternative theory which was first suggested by Junquera et al. They found that the expression of basic fibroblast growth factor and vascular endothelia growth factor (VEGF), both central mediators in angiogenesis, were significantly increased in patients with gastrointestinal AEs.[10,11]

Angioectasias are rarely seen in patients younger than age 50 except in cases of hereditary hemorrhagic telangiectasia (HHT). Patient age is the primary risk factor for AE but these lesions have been associated with additional risk factors. Chronic renal failure, particularly end-stage renal disease, has been shown to predispose patients to the development of AEs due to uremic and metabolically driven platelet dysfunction.[12—14] Aortic stenosis (AS) has also been studied extensively in association with development of AEs, an association known as Heyde syndrome, which may be related to an acquired form of von Willebrand disease.[15] Bleeding due to AEs has also been associated with left ventricular assist device (LVAD) placement.[16] Additional risk factors include tobacco use, obesity, use of antithrombotic agents, use of non-steroidal anti-inflammatory drugs and chronic liver disease.[4,17,18]

Diagnosis of AEs

With the introduction of video capsule endoscopy (VCE) and device-assisted enteroscopy (DAE) in 2001, previous studies for SSBB including small bowel follow through, angiography, cross sectional imaging and nuclear scans are less commonly employed.[19] Due to the anatomic features of the small bowel, conventional endoscopy provides limited evaluation of the deep small bowel.[2,20] VCE is a simple noninvasive procedure which is well tolerated by patients. Per the American Gastrointestinal Associate (AGA) guidelines, VCE is the first line investigation for small bowel evaluation in hemodynamically stable patients with no evidence of obstruction.[21] DAE is usually reserved to pursue positive VCE findings that require intervention or in the setting of high clinical suspicion for small bowel lesions despite negative VCE study. A large meta-analysis study by Pasha et al. found the diagnostic accuracy of VCE (60%) was similar to that of BE (57%).[22]

Interventional Management

Endoscopic management of AEs is difficult and only made possible through the relatively recent advent and development of BE. Endoscopic ablation using argon plasma coagulation (APC) is the most common technique used to treat gastrointestinal AE.[23] Other endoscopic techniques include bipolar electrocautery, sclerotherapy injection and mechanical hemostasis using hemo clips or banding, which may be beneficial in larger lesions.[24] A number of studies report an improvement in Hb, a reduction in transfusions and an improvement in overt bleeding following APC therapy for AE's.[25] However, retrospective studies suggest a high re-bleeding rate of up to 60% for small bowel AEs with or without thermal intervention using double balloon enteroscopy, especially in those patients who required large amount of transfusion before DAE and those with multiple vascular lesions.[2,26]

Radiological embolization is a treatment technique considered for patients with active GI bleeding who are hemodynamically unstable or on which endoscopic therapy has failed. Mesenteric angiography is used to identity bleeding vessels which are subsequently embolized with micro-coils.[27] Although the rate of hemostasis achieved by embolization is high, early recurrent bleeding was found to occur in an estimated 20% of patients.[28] Moreover, severe complications such as arterial dissection and bowel infarction occurring in up to 17% of patients is a major limitation of embolization techniques.[29]

If the above therapies have been exhausted and medical management has been unsuccessful, surgical management is sometimes required. Small bowel surgical resection is reserved for situations when all other forms of management have failed or in an emergent setting due to massive blood loss. Surgery is not commonly seen for the management of small bowel AEs secondary to the high mortality and morbidity as many patients are elderly with significant comorbidities.

Medical therapies

Medical therapy is an important adjunct to endoscopic ablation in patients with AE's as the majority of patients have multiple lesion which may be difficult to completely ablate with new lesions developing over time. Pharmacological treatments including iron supplementation, somatostatin analogues, hormonal therapies and thalidomide have be considered for patients who have not responded well to endoscopic intervention with APC or in whom endoscopy is contraindicated. Conservative management with iron supplementation given orally or intravenously is a mainstay of treatment for mild intestinal AE bleeding.[30] This not only helps maintain an adequate level of hemoglobin but helps reduce the frequency of transfusion. In

more severe bleeding, transfusion of packed RBCs is an essential element of treatment, particularly when mechanistic and medical methods fail.

Somatostatin analogues including octreotide and lanreotide have been used to treat AE. Hypothesized mechanisms include decreased duodenal and splanchnic blood flow, improved platelet aggregation, increased vascular resistance and inhibition of angiogenesis.[31—33] Through a meta-analysis, Brown et al. report a clinical response rate of 76% compared to the natural progression of the disease and reduced blood product requirements.[32] More recently, Nardone et al. performed a retrospective analysis and found that 40% of patients had a reduction of transfusion requirements over a 6-year mean follow up period.[34] There have been no randomized control trials performed to prove the efficacy and safety of somatostatin analogues compared to other treatment options.

Hormonal therapies, predominantly estrogen and progesterone, were initially thought to be useful in the management of intestinal AE in historical studies during the pre-VCE era.[35] However, due to the inability to visual the small bowel the precise nature of what was treated was unknown. The proposed mechanism of action includes stabilization of the vessels through keratinization, increase in the number of circulating activated platelets, inhibition of angiogenesis and decreased mesenteric blood flow.[31,36] While early small scale studies were promising, Junquera et al. reported the only controlled randomized control trial which found there was no reduction in transfusion or iron therapy needs in the patients on hormone therapy vs placebo therapy. The frequency of side effects and limitations for use in patients at risk for thromboembolic events, have resulted in hormonal therapy having only a limited role in the treatment of small bowel bleeding.[10,31]

Therapies utilized to inhibit angiogenesis in cancer patients have been studied due to their potential for inhibition of angiogenesis in the development of new AE's. Thalidomide, an immunomodulatory drug with antiangiogenic properties, has been used to treat small bowel AEs when conventional therapies have been unsuccessful.[37,38] These studies have shown a significant reduction in bleeding episodes and an increase in mean hemoglobin concentration after treatment with thalidomide. However, the use of thalidomide is limited by severe side effects including thromboembolism, hematological abnormalities and teratogenicity.[39—41]

As previously discussed, gastrointestinal AE's are known to strongly express vascular endothelial growth factor (VEGF).[11] Bevacizumab is a known anti-VEGF monoclonal antibody that has shown to be effective in decreasing bleeding events and the need for blood tranfusions in patients with HHT.[42,43] Although effective, bevacizumab therapy is complicated by serious adverse events which include arterial thrombosis, thromboembolic events, heart failure and nephrotic syndrome in up to 10% of patients.[44] Further, another barrier to utilization is securing financial coverage through insurance as most plans do not cover the mono-clonal antibody. Aminocaproic acid is a closely related fibrinolytic inhibitor, similar to our trial drug tranexamic acid. It is a lysine analog that inhibits plasminogen activators to promote hemostasis. Few case reports have shown therapeutic success in treating upper GI bleeds secondary to radiation gastritis and gastric cancer.[45,46] Further research is needed to understand appropriate dosing regimens and the side effect profile.

Tranexamic Acid

Tranexamic acid (TXA) is a hemostatic agent that is a synthetic reversible competitive inhibitor to the lysine receptor found on plasminogen. TXA works by forming a reversible complex that displaces plasminogen from fibrin resulting in the halting of fibrinolysis. TXA has been approved by the FDA for the treatment of heavy cyclic menstrual bleeding and tooth extraction in patients with hemophilia. The antifibrinolytic agent has been further studied in the management of major bleeding in multiple clinical settings including trauma, obstetrics and neurosurgery.[47,48] TXA has been considered a potential adjunctive treatment for GIB with the earliest RCT conducted in 1973.[49] With the recent publication of the large HALT-IT trial, which explored the use of high dose TXA over 24 hours in the setting of acute GI bleed, there has been an increasing interest in the possible applications of TXA.[50]

The literature contains a few case reports commenting on the successful use of TXA in patients with AE's, without increasing the risk of thromboembolic events.[51,52] Of note, there does exist a randomized placebo-controlled trial examining the use of oral TXA for acute lower GI bleeds requiring hospitalization. Smith et al. found no improvement in average hemoglobin and transfusion rates following a four-day treatment regimen with oral TXA, however, the bleeding source for approximately 50% of the study population was diverticular in nature.[53] Moreover, there are no current case series or randomized control trials examining the use of TXA in patients with persistent or progressive anemia due to chronic GI blood loss from AEs despite standard treatment with endoscopic ablation and iron supplementation.

The common side effects of TXA include nausea, vomiting, diarrhea, rash, itching, hypotension, and thromboembolic events as reported by the FDA. Contraindications include a history of venous or arterial thromboembolism, intracranial bleeding or active thromboembolic disease. TXA is not well studied in the renally impaired patient however it is 95% excreted in urine so renal dosing is recommended.[54] Dionne et al. recently published the largest systemic review and meta-analysis examining TXA in GIB and found that the absolute risk of thromboembolic events to be <1%. This presents a small but statistically significant risk of DVT/PTE with high dose IV TXA but cannot be extrapolated to lower dose oral TXA regimens. Further, the safety profile of TXA has been confirmed and well-studied in the fields of trauma and orthopedics.[55,56]

2.2 Prior clinical experience

The principal investigator for this study has been using TXA in his clinic as an off-label drug for the treatment of small bowel AEs. Those who were treated with TXA were those patients that have failed standard therapy. Failure of standard therapy is defined as continued GI bleeding and need for blood transfusions despite endoscopic ablation, octreotide therapy and iron supplementation for at least 3-6 months. Thus far, 9 patients have been treated with TXA therapy consisting or 650 mg oral tablets taken three times per day for 3 months. In 8 of those patients there was an observed clinical response defined as stabilization of hemoglobin which was not previously achieved with prior therapy. Although this sample size of patients was not a controlled study accounting for confounding variables, it does strongly highlight the potential beneficial therapeutic effects of TXA. Of note, there were no side effects observed by the 9 patients.

3 - Rationale/Significance

3.1 Problem Statement

The current management of small bowel AE's is suboptimal as the majority of patients with symptomatic bleeding experience continued or recurrent bleeding despite standard of care therapy including endoscopic ablation, octreotide and iron supplementation. In these cases, patients may require repeated transfusion of PRBC's as palliative treatment which is a source of morbidity including repeated hospitalization and is often complicated over time by transfusion reactions, iron overload, and volume overload. Patients with severe disease may develop antibodies to all blood products over time such that they can no longer tolerated PRBC transfusion.

3.2 Purpose of Study/Potential Impact

Currently, the mainstay of treatment for intestinal AEs includes endoscopic ablation combined with octreotide and iron supplementation. However, many patients continue to suffer from persistent or recurrent symptomatic anemia and often require repeated hospitalizations for blood transfusions. TXA is a hemostatic agent that has the potential to be beneficial in patients with small bowel GI bleeding. Through our literature review multiple case reports have highlighted the impact TXA treatment can have on patients with intestinal AEs. Our study would help determine the potential additive effect of TXA in patients with symptomatic anemia due to GI AE's. Further, we seek to expand our knowledge of the applications of TXA with the goal of decreasing morbidity and mortality.

3.3 Potential Risks and Benefits

3.3.1 Potential Risks

Adverse events will include medication side effects including nausea, vomiting, diarrhea, rash, itching, hypotension, and thromboembolic events. These side effects will be closely monitored through monthly in person or virtual interviews with patients for the entirety of the study period.

Thromboembolic events have the largest potential impact to patient’s health and include deep vein thrombosis (DVT), pulmonary embolism (PE) and stroke. Dionne et al. recently published the largest systemic review and meta-analysis examining TXA in GIB and found that the absolute risk of thromboembolic events to be <2%. This presents a small but statistically significant risk of DVT/PTE with high dose IV TXA but cannot be extrapolated to lower dose oral TXA regimens. Further, the safety profile of oral TXA has been confirmed and well-studied in the fields of trauma and orthopedics. Specifically, a large meta-analysis looking at the 5 RCTs comprising approximately 600 patients found no statistically significance increasing in thromboembolic complications between patients undergoing a total knee replacement who received oral TXA for intra/post-operative bleeding vs control patients. [55,56] We do appreciate that certain populations of patients are at increased risk for thromboembolic events. These include comorbidities such as liver disease and malignancy. On literature review, specific rates of thromboembolic events in these populations with the use of TXA has not yet been studied. Importantly, a group of patients who may not know they would be at an increased risk are those with undiagnosed prothrombotic states. While it would not be possible to screen for all prothrombotic diseases, factor 5 Leiden and prothrombin mutation make up a large portion of hypercoagulable disorders. In order to screen out these patients, lab markers testing for the aforementioned disorders will be ordered in all patients during initial laboratory lab work.

3.3.2 Potential Benefits

If TXA is shown to decrease the need for further blood transfusions and hospital admissions, it becomes a viable option for patients affected by intestinal AEs. Specifically, for patients who experience recurrent blood loss despite current standard medical therapy.

4 - Study Objectives

4.1 Hypothesis

We expect 75% of patients on TXA to have a 2 gm/dl improvement in overall hemoglobin while only 25% in placebo group see a 2gm/dl improvement. We expect 75% of TXA patients to require zero blood transfusions compared to placebo group requiring 1 blood transfusion on average per patient over 3 months.

4.2 Primary Objective

To determine whether oral therapy with TXA results in improvement in serum hemoglobin concentration and/or requirement for PRBC transfusion compared to placebo in patients treated with standard endoscopic ablation and iron supplementation

4.3 Secondary Objectives (if applicable)

To determine the need for hospitalization for symptomatic anemia or acute gastrointestinal bleed
To determine the need for additional endoscopic interventions
To determine the rate of clinically significant side effects associated with TXA therapy leading to drug withdrawal

5 - Study Design

5.1 General Design Description

In the RCT portion of the study, we will enroll approximately 50 patients with diagnosed intestinal AEs through VCE and/or endoscopy who experience symptomatic anemia despite standard therapy including endoscopic ablation and iron supplementation. Subjects will be randomized to either the TXA treatment group versus the placebo treatment group for 3 months. Patients will have initial complete blood counts (CBC) measured as a baseline then subsequent CBCs measured at 1, 2 and 3 months. Patients will be monitored for drug side effects, symptoms related to anemia, the need for blood transfusions and hospitalizations related to GI bleeding/anemia.

5.1.1 Study Date Range and Duration

The interventional portion of the study will be conducted over a 3-month period from March 2023 — May 2023. We will spend the months of December 2022 — February 2023 recruiting patients for the study and collecting demographic data on patients that meet inclusion and exclusion criteria. Following the interventional period of the study we will collect, interpret, analyze and summarize data from June — July 2023.

5.1.2 Number of Study Sites

The study site includes the LSU Health Network GI Clinic at Ochsner Kenner Hospital

5.2 Outcome Variables

5.2.1 Primary Outcome Variables

Primary outcome variables include hemoglobin concentration and the requirement of packed RBC transfusion.

5.2.2 Secondary and Exploratory Outcome Variables (if applicable)

Secondary outcome variables include number of hospitalizations, endoscopic interventions (EGD, Colonoscopy, enterosocopy, video capsule endoscopy) and experienced side effects.

5.3 Study Population

All newly diagnosed Adult patients with intestinal angioectasias following at the LSU Health Network GI Clinic who meet screening criteria will be considered for inclusion. Existing patients with intestinal angioectasias that are currently not using TXA may also be approached for study participation.

5.3.1 Number of Participants

The study design includes 50 participants enrolled in the study that meet inclusion/exclusion criteria.

5.3.2 Eligibility Criteria/Vulnerable Populations

Inclusion Criteria

- Male, female, non-gender conforming patients aged >18 years with symptomatic anemia attributed to chronic GI blood loss from GI AEs despite endoscopic ablation and iron therapy
- Stated willingness to comply with all study procedures and availability for the duration of the study

Exclusion Criteria

- Contraindications to TXA therapy
    - Allergy to TXA, intracranial bleed, history of venous or arterial thromboembolism, active thromboembolic disease, ischemic retinopathy
- Bleeding/Coagulopathy disorder and/or on anticoagulation regimen
- Ulcerative colitis or Crohn's disease
- End stage renal disease
- Decompensated cirrhosis
- Pregnancy or intention to become pregnant
- Patient refusal of blood products because the secondary outcome is pre-determined
- Unable to give formal consent
- Participation in another interventional study where primary outcome includes hemoglobin/hematocrit values
- Inability to adhere to treatment regimen for 3 months
- Non-English speaking
- Patients < 18 years old

6 - Methods

6.1 Treatment - Drug

Tranexamic acid (TXA) is a hemostatic prescription medication available in the US and internationally. TXA is a synthetic reversible competitive inhibitor to the lysine receptor found on plasminogen. The binding of this receptor prevents plasmin from binding to and ultimately stabilizing the fibrin matrix. It is available in intravenous and oral formulations, however for this study we will focus on the oral regimen. Oral TXA has a half-life of up to 10 hours and a bioavailability of 50% resulting in the TID dosing regimen chosen for this study.[57] TXA is currently FDA approved for menorrhagia and short-term prevention following tooth extraction in patients with hemophilia.

6.1.1 Dosage, Admin, Schedule (if applicable)

Patients in the intervention group will be treated with TXA 650 mg three times per day for 3 months. This dosing regimen has been studied in patients with heavy menstrual bleeding and found to be beneficial with limited side effects.[58]

6.1.2 Method of Assignment/Randomization (if applicable)

Allocation concealment will be used to make sure the individual enrolling the trial subjects into the study has no bias towards group assignment. A statistician not directly involved in the analysis of the study will use simple randomization to create the two arms of the study (TXA vs placebo). Randomization will be carried out by using an online random number generating software, excluding the number zero. If an even number is generated, the patient will be placed in the TXA treatment arm, and if an odd number is generated the patient will be placed in the control (placebo) arm. This process will be repeated until there are 25 patients in each group.

6.1.3 Packaging/Labelling

Both TXA and placebo will be packaged in identical bottles with similar labeling so participants and the research team will not be affected by bias.

6.1.4 Storage Conditions

Both TXA and placebo will be stored at the Ochsner Kenner inpatient pharmacy prior to the start of the interventional portion of the study. Participants will pick up their medication from the pharmacy upon start of the trial.

6.2 Assessments

6.2.1 Safety/Pregnancy-related policy

Pregnancy is included in the exclusion criteria for this study. If female identifying participants were to consent to be part of the study, they will undergo a serum pregnancy testing prior to the start of the study

6.2.2. Adverse Events Definition and Reporting

Medical Monitoring
Data will be collected by monthly clinic appointments for the first 3 months. All study patients will have direct access to study personnel via a dedicated cellular phone.
Definition and Classification of Adverse Events
Adverse events will include medication side effects including nausea, vomiting, diarrhea, rash, itching, hypotension, and thromboembolic events.

Data Collection for Adverse Events
Adverse events will be noted in each participant's file. Their responses to the biweekly phone calls and monthly clinic visits about new symptoms related to the study medication will be reviewed and followed up promptly.
Adverse events will be grading according to the following scale:

- Mild: An experience that is transient and requires no special treatment or intervention. The experience does not generally interfere with usual daily activities.
- Moderate: An experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities.
- Severe: An experience that require therapeutic intervention. The experience interrupts usual daily activities. If hospitalization (or prolongation of hospitalization) is required for treatment, it becomes a severe adverse event.

Each adverse event will be assessed and determine to be related or not related to the study medication.

6.2.3 Pharmacokinetics (if applicable)

The bioavailability of oral TXA is 30-50% of the ingested dose and is not affected by food intake. Urinary excretion is the primary means of TXA elimination with 95% of an administered dose being processed by the renal system. The half-life of IV TXA was found to be 2 hours with the mean terminal half-life as approximately 11 hours

6.3 Study Procedures

6.3.1 Informed Consent

Each patient that meets inclusion/exclusion criteria will be asked to fill out and sign the informed consent statement. A copy is attached for reference.

6.3.2 Screening

All newly diagnosed Adult patients with intestinal angioectasias following at the LSU Health Network GI Clinic who meet screening criteria will be considered for inclusion. Existing patients with intestinal angioectasias that are currently not using TXA may also be approached for study participation.

6.3.3 Recruitment, Enrollment and Retention

The patients who meet screening protocol will be called via telephone or video call and asked to participate in the study. Patients will have an initial meeting with research study staff where all questions will be answered. Demographics will be obtained, informed consent will be signed and patient will be enrolled in study. Once enrolled, baseline lab work as previously stated will be collected for the study.

6.3.4 On Study Visits

Research study participants will meet for a screening and consent visit. At this time, inclusion/exclusion criteria will be review and if meet then they will be consented for the study. Following, demographic information will be collected, and baseline lab work will be done prior to the start of the interventional portion of the study.

6.3.5 End of Study and Follow-up

At the end of the interventional 3-month period of the study, patients will have any exit visit with the research staff. At this time, they will fill out a final patient questionnaire (see appendix).

Patient will have another follow up interview at the 6-month period (3 months following the end of the interventional portion of the study) to conclude the study.

6.3.6 Removal of subjects

- At the time of consent, participants will be informed that their participation in this research study is voluntary and they may discontinue participation without penalty at any time.
- Subjects will be withdrawn from the study by the investigator if they are to have serious adverse reactions to TXA or to protect the subjects from excessive risk due to lack of benefit demonstrated by TXA.
- Data collection prior to participant withdrawal may be retained and used in a manner that is consistent with study design and purpose unless participant expresses that their information to not used in the study

6.4 Statistical Method

6.4.1 Sample Size Considerations

We based our sample size estimate on assumptions for our primary aim, as this is the most important aim for providing information to support future recommendations with regards to TXA in patients with intestinal AE. A total of 50 subjects will be enrolled with 1:1 randomization to either TXA or placebo. For the primary study endpoint of hemoglobin, we will have 80% power to detect an average increase of 25% from baseline to 3 months between TXA and placebo groups ($\alpha = 0.05$). We expect 75% of patients on TXA to have a 2 gm/dl improvement in overall hemoglobin while only 25% in placebo group see a 2gm/dl improvement. We expect 75% of TXA patients to require zero blood transfusions compared to placebo group requiring 1 blood transfusion on average per patient over 3 months.

6.4.2 Planned Analyses

We will characterize subjects with regard to baseline and follow up hemoglobin/hematocrit (H/H) and other endpoints previously described. We will summarize demographics and other predictors of clinical status. Continuous variables will be summarized by mean, standard deviation and rage as appropriate. The primary analysis will compare the absolute and percent change in hemoglobin with adjustment for baseline in linear regression models. Using multivariable logistic regression models adjusting for baseline hemoglobin, we will assess if the odds of achieving a clinically relevant improvement in hemoglobin differs by treatment assignment. The secondary outcomes will be analyzed similarly using linear regression models adjusting for baseline values.

6.4.3 Handling of Missing Data

Every effort will be made to secure data and account for all data points. If missing data was to occur, it would be noted during the statistical analysis and clearly outlined in the discussion portion of future manuscripts.

7 - Trial Administration

7.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization

Please find the informed consent statement and HIPAA Authorization attached.

7.2 Subject Confidentiality

Every precaution will be taken to allow for data confidentiality. Only members of the research team will have access to the patient information and subsequent study data. Trial participants will be assigned a unique identification number that will be used in future database reporting. All hard copies of data and patient records will be kept in a secure location within Dr. Raines's office in a locked cabinet.

7.3 Deviations/Unanticipated Problems

We will attempt to minimize missing data; however, we have planned for its occurrence. For subjects lost to follow-up, we will use all of the information available until the end of follow-up. This protocol will continue to follow subjects and perform lab tests even if a subject drops-out from the treatment portion of the study. If a subject decides that he/she does not wish to continue taking the study drug, the subject will stop the investigational treatment, but will still be strongly encouraged to continue to follow-up with the study personnel for all scheduled study follow ups (e.g., lab draws and symptom reporting), so that missing data will be minimized.

7.4 Data Collection

A majority of data/surveys/questionnaires will be electronically collected and stored on REDCap.

7.5 Data or Specimen Storage/Security

All hard copies of data and patient records will be kept in a secure location within Dr. Raines's office in a locked cabinet. Communication about study data will be strictly conducted via LSUHSC email accounts.

7.6 Study Discontinuation

Reasons for discontinuing the study include futility, adverse events (harm), early evidence of superiority of one intervention (benefit) and insufficient recruitment (a cut-off at 80% of the planned sample size).

7.7 Study Completion

Patients will have a follow up interview at the 6-month period (3 months following the end of the interventional portion of the study) to conclude the study. Data will be analyzed with a plan for publication of a manuscript in a gastroenterology related journal.

7.8 Conflict of Interest Policy

There are no conflicts of interest to disclose.

7.9 Funding Source

This is an investigator initiated and funded study. There are no external funding sources.

7.10 Publication Plan

We plan to use the date from this study to write a manuscript for publication in a respected peer-reviewed journal in an appropriate time frame. Journal choice will depend on study findings but will be relating to the field of gastroenterology

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