Statistical Analysis Plan (SAP)

Atomized Intranasal Tranexamic Acid for Epistaxis in the Emergency Department:

A Pilot Study (EpisTXA Trial)

Principal investigator	Aimee Moulin, MD Professor of Emergency Medicine University of California Davis School of Medicine Sacramento, CA
Author	Brian Dang, PharmD University of California Davis Medical Center Sacramento, CA

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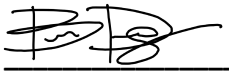
Principal Investigator: 

Aimee Moulin, MD

Author: 

Brian Dang, PharmD

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Introduction

The aim of this study is to test the efficacy and safety of nasal atomization of tranexamic acid (TXA) for epistaxis at a single centered academic tertiary hospital. This is a randomized controlled trial with a primary outcome of time to control of bleeding and secondary outcome of length of stay in the ED, rebleeding within 24 hours & one week, and adverse events.

This statistical analysis plan (SAP) will give a more detailed description of the outcomes and analysis performed.

Study Design

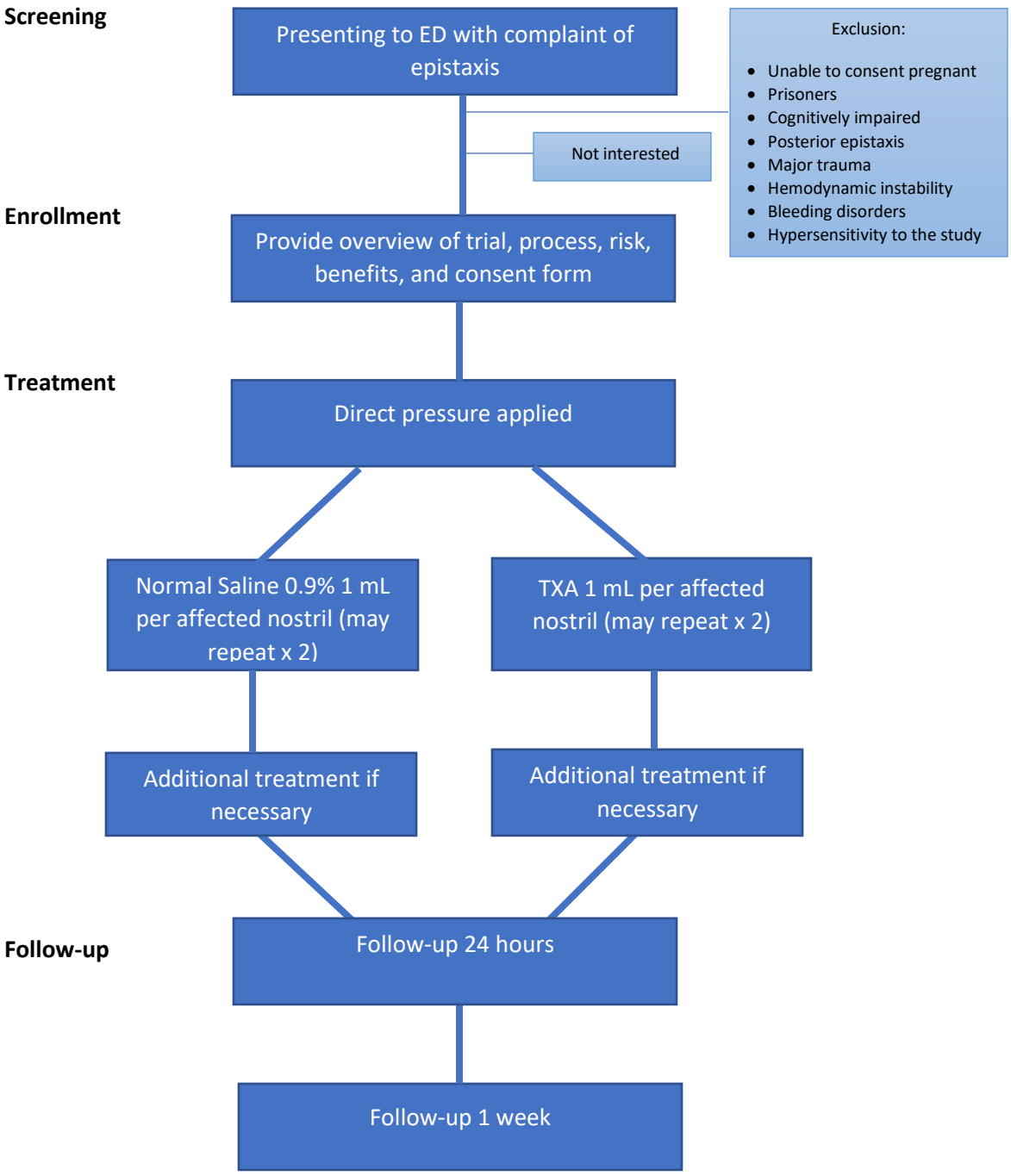
This study is a prospective, double-blinded, placebo-controlled pilot study conducted at an academic tertiary care medical center with 24-hour emergency medical services. The study will be performed at the University of California Davis Medical Center (UCDMC) between February 18, 2016 and December 31, 2019. The Emergency Department at UCDMC has approximately 80,000 annual ED visits and is located in Sacramento, California.

Inclusion criteria will be patients greater than or equal to 18 years of age and diagnosed with anterior epistaxis. Patients will be excluded if they were unable to consent, pregnant, prisoners, cognitively impaired, diagnosed with posterior epistaxis, major trauma, hemodynamic instability, bleeding disorders, and hypersensitivity to the study drug. Patients will be screened for inclusion and exclusion criteria once they had been assigned a room/location. The Emergency Medicine Research Associate Program (EMRAP), medical staff, and study investigators conducted screening for eligible patients.

Randomization will be conducted by the Investigational Drug Services (IDS) using a web-based computerized randomization program (randomizer.org[1]). Randomization will be performed in blocks of four. IDS will perform sterile compounding for all study medications. TXA or normal saline 6 mL will be placed into a clear 10 mL vial with white labels containing only study information. Vials will be placed into a locked refrigerator within the emergency department. After obtaining consent, the study kit, which includes a nasal atomizer, syringe, and vials, is removed from the fridge in sequential order and delivered to the treating provider.

Following the enrollment of patients, both groups will receive direct pressure to the nares applied by a medical professional. In addition to direct pressure, patients will receive either tranexamic acid 100 mg/1 mL or placebo (normal saline 1 mL) to each affected nostril(s) via a nasal atomization device. Additional doses may be repeated up to two times to each affected nostril at the discretion of the treating providers. Following 20 minutes from the administration of the medications, the provider will be allowed to provide any standard of care medical

intervention. Prior to discharge, patients will be informed that they would be contacted at 24 hours and one week to inquire about incidences of rebleeding and any complications.



Sample size calculation

Data from a previous trial using topical TXA for epistaxis were used to calculate sample size. Zahed and colleagues conducted a prospective randomized control trial using a cotton pledget soaked with TXA 500 mg/5 mL and inserted into the bleeding nostril (Am J Emerg Med. 2013;31(9):1389-92.). This was compared to anterior nasal packing group who were treated with a cotton pledget soaked with lidocaine-epinephrine 2% and 1:100,000. Nasal packing was removed after three days. The primary end point of the study was bleeding control within 10 minutes. Bleeding was controlled within 10 mins for 71% (76 of 107) in the TXA group compared to 31.2% (34 of 109) in the nasal packing group (OR 2.27; 95% CI 1.68-3.06; P<0.001).

Based off this study, we assumed that the mean or median time to control of bleeding would be 10 minutes and assumed that 68% of patients will fall within 5 minutes of that control of bleeding time. Previous studies have not reported time to resolution of bleeding. Based on the effectiveness of TXA in the Zahed study, we expected to see a 50% difference in time to resolution of bleeding between the two groups. In order to detect at 50% (5 minutes) difference between groups with a standard deviation of 5 minutes, we will need 16 patients in each group to achieve 80% power with a 2-sided α set to 0.05. A total number of 32 patients would be need to meet power.

Aims and objectives

The study is testing to see if atomized tranexamic acid is effective and safe for the treatment of anterior epistaxis.

Outcomes

Primary outcome: Time to resolution of bleeding (minutes). Time of resolution of bleeding was started after the application of the study drugs.

Secondary outcomes:

i. Length of stay in the ED (minutes)
ii. Rebleeding at 24 hours. Study investigators conducted a phone call follow-up 24 hours after study enrollment. Patients reported any rebleeding episodes since treatment with study drug.
iii. Rebleeding at 1 week. Study investigators conducted a phone call follow-up 1 week after study enrollment. Patients reported any rebleeding episodes since treatment with study drug.

Safety outcomes

iv. Any reported events during ED visit, 24-hour phone call follow-up, and 1 week phone call follow-up.

Population and subgroup to be analyzed

Populations:

Intention-to-treat (ITT) for all randomized study subjects.

Per Protocol (PP) will be used for patients that are missing primary outcomes.

Subgroups: Due to small sample size, no subgroup analysis will be performed.

Analyses

Data that is normally distributed will be reported by mean and standard deviation; whereas, skewed data will be reported as median and interquartile range. Descriptive statistics will be used for secondary outcomes. SAS® software version 9.4 for Windows®[3] will be used for all statistical analysis

Primary outcome

The primary outcome will compare time to resolution of bleeding in minutes between the treatment and control group.

Secondary outcome

Length of stay in the ED in minutes will be compared between treatment and control group. Rebleeding within 24 hours and one week will be reported as percentage of patients reported bleeding during those time periods in each group. Adverse effects during the treatment period and at follow-up will also be reported as percentage reporting a specific adverse event.

Missing data

No imputations will be made for missing data.

References

1. "Research Randomizer." Research Randomizer. N.p., n.d. Web. 1 Feb. 2016.
2. Zahed R, Moharamzadeh P, Alizadeharasi S, Ghasemi A, Saeedi M. A new and rapid method for epistaxis treatment using injectable form of tranexamic acid topically: a randomized controlled trial. Am J Emerg Med. 2013;31(9):1389-92.
3. SAS Institute Inc 2013. SAS/ACCESS® 9.4 Interface to ADABAS: Reference. Cary, NC: SAS Institute Inc.