TRANEXAMIC ACID FOR cSDH-

A PILOT STUDY ON THE SAFETY OF TRANEXAMIC ACID FOR THE CHRONIC SUDURAL HEMATOMA POPULATION

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Study Objectives

1. Establish the safety of using tranexamic acid in the treatment of chronic subdural hematomas
2. Determine if the use of oral tranexamic acid reduces the rate of ipsilateral recurrence following drainage of chronic subdural hematomas

Background

Chronic subdural hematomas are a common problem faced by neurosurgery with an annual incidence of 13.5/100,000 persons per year and up to 58/100,000 in the over 65 years old population (Kudo). Their treatment is often complicated by recurrence with rates reported as high as 33% (Muzii). Currently there is no good strategy to help avoid this problem, which adds significantly to patient morbidity. The pathogenesis of this problem is believed to be related to the propensity of the associated neo-membranes to bleed (Ito, Weir, Lim, Labadie). Ito et.al. showed with labeled red blood cells that bleeding continues to occur into the hematoma cavity (1976). It has also been shown that there are high levels of tissue plasminogen activator in the outer membrane of chronic subdural hematomas (Ito 78 and Labadie 74). Lim et.al. found that ratio of tissue plasminogen activator to plasminogen activator inhibitor contributed to the pathogenesis (Lim 95). It has also been shown that chronic subdural hematomas have high levels of fibrin degradation products which in addition to marking the breakdown of fibrin are themselves anti-hemostatic by enhancing tissue plasminogen activator activity (Nieuwenhuizen 83), having an anti-thrombin affect (fletcher 62) and inhibiting platelet aggregation (kowalski 64) and fibrin polymerization (Alkjaersig 62). Essentially, a scenario of ongoing hemorrhage and repeated clot formation and hyperfibrinolysis leads to the expansion and recurrence of chronic subdural hematomas.

Given the importance of plasmin and hyperfibrinolysis in the pathophysiology of chronic subdural hematomas, interrupting its action and the vicious cycle it propagates seems an ideal therapeutic target. Tranexamic acid is a synthetic lysine amino acid derivative. It binds to the fibrin binding sites on plasmin or plasminogen and prevents its interaction and degradation of fibrin. This effect on the neo-membranes of chronic subdural hematomas should prevent rebleeding and the re-accumulation of the subdural hematoma.

Supporting Data

Kageyama et.al. showed the safety and potential efficacy of treating chronic subdural hematomas in their retrospective study of 21 patients. There were no recurrences in their 21 patients. Vujkovac et.al. also showed that tranexamic acid could be used safely and effectively in their case report of a hemodialysis patient who begun therapy following another recurrence after the third operation. The hematoma completely resolved and the patient made a complete recovery.

Tranexamic acid has been shown to be safe and effective in reducing blood loss and transfusions in a number of types of surgery, reduced mortality and need for urgent surgery in patients with GI bleeding and reduced bleeding associated with menorrhagia and pregnancy. Adverse effects are generally mild. Thought there is a theoretical increased risk of thromboembolic complications, multiple randomized controlled trials have not shown an increased risk (McCormack, Dunn, Katsaros, Barer, Benon). Furthermore, in a study of over 3000 gynecologic patients using tranexamic acid, Bekassy et.al. had no thromboembolic complications. This is likely because tranexamic acid has been shown to not have an effect on plasminogen in the vein wall (Astedt).

Study Design

This study is a single center single armed study of 50 patients to determine the safety of tranexamic acid in the chronic subdural hematoma population following surgical drainage of chronic subdural hematomas. This will be compared to historical controls. This study intends to be a prerequisite to a large nationally funded randomized control trial.

Selection and Enrollment of subjects

Inclusion Criteria:
-all patients undergoing intervention for cSDH including drainage
-cSDH will be defined as hematoma on CT imaging that is predominantly isodense to hypodense to brain
- 18-85 years of age

Exclusion Criteria
-cSDH not requiring surgical drainage
-patients undergoing bedside twist drill craniostomy
-medically unstable for surgery
-patients requiring long-term anticoagulation- unable to stay off for less than 30 days
-patients not expected to survive to the completion of follow-up
-patients comatose prior to the initiation of treatment
-history of thromboembolic problem including stroke, MI, DVT, PE
-pregnant
-minor
-allergy/sensitivity to tranexamic acid
-irreversible coagulopathy
-known clotting disorder
-bilateral hematomas with both requiring drainage
-incarcerated
-any patient not judged suitable for the study by the investigators
-women who are taking combination oral contraceptive

Study Enrollment

Patients meeting all of the inclusion and exclusion criteria will undergo standard treatment of their chronic subdural hematoma including operative treatment with the addition of preoperative and postoperative oral tranexamic acid treatment. Patients will receive a dose of 1300mg orally three to four hours prior to surgery. They will then take 1300mg orally three times daily for three days or until discharge, whichever occurs first. Tracking and follow-up will be explained to the patients and arranged by the study coordinator.

Study Interventions

All patients will undergo an intervention for the drainage of their subdural hematoma. The type of procedure i.e. burr-hole drainage or craniotomy excluding twist drill craniostomy will be at the discretion of the treating physician

All patients will be followed daily during their hospitalization

All patients will have follow-up CTs on postop days 1, 3, 7 and 30 +/- 7days

All patients will have clinical follow-up on Day 30 +/- 7 days

All patients will be treated using standard ICU protocols
-neurologic status will be assessed at least every four hours for the first 48 hours
-care will be directed toward the goal of normotension and adequate oxygenation

All patients will have DVT prophylaxis with spontaneous compression devices. Pharmacologic prophylaxis will be at the discretion of the treating physician.

Experimental Interventions

Patients will receive tranexamic acid in the following dosing regimen:
1. 1300 mg times one immediately prior to surgery
2. 1300 mg orally three times daily for three days or until discharge- whichever comes first.
   -First postop dosing will start 8 hours after preop dose is given.

All patients will have creatinine monitored daily while on study drug. Patients with creatinine > 1.4 will have dosage adjustments as follows:

Table 1. Dosage of LYSTEDA in Patients with Renal Impairment

LYSTEDA		
Serum Creatinine (mg/dL)	**Adjusted Dose**	**Total Daily Dose**
Cr above 1.4 and ≤ 2.8	1300 mg (two 650 mg tablets) two times a day for a maximum of 5 days during menstruation	2600 mg
Cr above 2.8 and ≤ 5.7	1300 mg (two 650 mg tablets) once a day for a maximum of 5 days during menstruation	1300 mg
Cr above 5.7	650 mg (one 650 mg tablet) once a day for a maximum of 5 days during menstruation	650 mg

Prohibited Interventions

Therapeutic anticoagulation

Clinical and Laboratory Evaluations

Presentation Day 0- CT scan, NIH stroke scale, pregnancy test, informed consent, modified Rankin Score (mRS)

Postop-
Day 1 CT Scan

Day 14 clinical follow-up, CT scan

Follow-up Day 30- CT scan, NIH stroke scale, mRS

Timing of Evaluations

Registration- the start of the screening process when the study team is notified of a potentially eligible subject

Pre-Enrollment- all screening evaluations will be performed prior to enrollment

Enrollment- will occur prior to surgical intervention or receiving experimental medication

Medication period- Patients will continue on medication from immediately preoperatively to three days postoperatively or until discharge

Post Medication period- follow-up will continue until the patient is discharged from the neurosurgeon's care

Management of Adverse Events

All adverse events will be closely monitored and evaluated

Management of recurrent bleeding: recurrent SDHs will be managed according to best practices as determined by the treating physician

Criteria for Intervention Discontinuation

1. patient unable to tolerate side effects
2. thromboembolic complication including stroke, MI, DVT or PE
3. if in the investigator's judgment, withdrawal from the trial will be in the patients best interest
4. consent is withdrawn by the patient or their legal representative

End Points

1* Incidence of medication related complications including stroke, MI, DVT, or PE and other drug related adverse events
2- Return to OR for same sided surgery
2* Postop hematoma expansion, functional outcome (mRS, NIHSS) discharge location, LOS, volume of hematoma at 30 days

Data Points

Age, presenting symptom, admission GCS, language and motor function, preoperative living situation, width of hematoma, visible septations present, extent of MLS, operative approach, drain used, new preoperative deficit, immediate postop hematoma width, LOS, discharge GCS, language and motor function, discharge location, width of hematoma on follow up imaging, medication not tolerated, medication side effects, thromboembolic complications, other complications, blood loss, NIH stroke scale Day 0 and 30, mRS day 0 and 30

Statistical Data Analysis

Frequencies will be reported for ordinal and categorical variables. Descriptive analyses of central tendency (mean) will be used for continuous variables. Nonparametric tests will be used for statistical comparison, including the Kruskal–Wallis rank-sum test for multiple groups and the Mann-Whitney U test for 2 groups. Data tabulation and analysis will be analyzed using R statistical software version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria). Chi-square test, analysis of variance (ANOVA), and multivariate linear and log-linear regression models where appropriate. A P value < 0.05 will be considered statistically significant. P values for difference among time point means (preoperative, postoperative days 3, 7 and 30) to be determined by ANOVA.