Tranexamic Acid for Treatment of Residual Subdural Hematoma after Bedside Twist-Drill Evacuation


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Title: Tranexamic Acid for Treatment of Residual Subdural Hematoma after Bedside Twist-Drill Evacuation

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Running title: TXA for subdural hematoma

Abbreviations:

Abstract

Management of non-emergent, non-acute subdural hematomas (SDHs) ranges from observation to burr-hole evacuation or craniotomy, but recurrence rates are high. We evaluated the safety and efficacy of tranexamic acid (TXA) for the treatment of residual SDHs following bedside twist-drill evacuation.

We performed a retrospective analysis of a prospectively maintained database from November 2013 to November 2014 for all patients who underwent placement of a bedside Subdural Evacuating Port System (SEPS) followed by treatment with oral TXA (650 mg daily). All demographics, evidence of VTE and volumes of pertinent CTs were obtained.

Twenty subdural hematomas in 14 patients met the inclusion criteria for this study. The majority of SDHs were mixed density. Mean SDH volume on presentation was 145.96 cm$^3$ +/- 40.22 with a mean midline shift of 9.44 mm +/- 4.84. Mean volumes decreased to 80.00 cm$^3$ +/- 31.96, and midline shift improved to 4.44 mm +/- 3.29, after SEPS placement (p < 0.0001 and p = 0.0046). All patients were placed on TXA after their procedure. Mean follow-up with CT was 92.1 days +/- 27.5, and mean SDH volume at last follow-up was 7.41 cm$^3$ +/- 15.54 with a mean midline shift of 0.19 mm +/- 0.69 (p < 0.0001 and p = 0.0002). Percent volume reduction was significantly higher after TXA than after SEPS (91.31% versus 40.74%, p < 0.0001). No increase or delayed recurrence of the SDH was noted during TXA treatment. All but one clinical presenting symptom improved at follow-up. No venous thromboembolisms were noted amongst the patients.

In our pilot study, chronic SDH volumes were reduced by 40.74% after SEPS drainage. The residual volume was reduced by an additional 91.31% during oral TXA treatment. No patients developed delayed recurrence or expansion of their SDHs. Further prospective studies are needed to evaluate the role of TXA for adjunctive treatment of chronic SDHs.

Keywords: tranexamic acid, subdural hematoma, bedside evacuation, fibrinolysis, traumatic brain injury, venous thromboembolism
**Introduction**

Non-acute subdural hematomas can cause significant morbidity and mortality. Previous studies have cited an incidence of 8-58 per 100,000 individuals.\textsuperscript{1,2} With an aging population, the incidence of SDHs is likely to increase significantly.

These are several options for treatment, ranging from observation to burr hole drainage at the bedside or in the operative room, to craniotomy. No clear consensus exists amongst practitioners concerning the best mode of treatment, although there has been an increasing trend toward bedside procedures, especially for poor surgical candidates.\textsuperscript{2} Furthermore, most studies have analyzed outcomes with pure chronic SDHs; less information is available for mixed density hematomas.

All current treatments have associated risks and significant recurrence rates. In a systematic review of chronic SDHs treated by various modalities, 11.7% to 28% of patients develop a recurrence.\textsuperscript{2} Multiple factors contribute to recurrence after evacuation. Hyperfibrinolytic activity may play a major role in the liquefaction and enlargement of chronic SDHs, and elevated fibrinogen levels in the subdural fluid are associated with the presence of layering and mixed density subdural hematomas with membranes.\textsuperscript{3}

Theoretically, medications targeting hyperfibrinolytic activity may reduce the incidence of recurrence. Recently, the use of tranexamic acid (TXA), an antifibrinolytic agent, was shown to resolve small chronic SDHs managed non-operatively.\textsuperscript{4} The purpose of this pilot study was to examine the role of TXA as an adjunct to bedside evacuation of large mixed density SDHs.
Material and Methods

After obtaining Institutional Review Board approval, we performed a retrospective search of a prospectively collected database for all patients at Bellevue Hospital Center undergoing bedside twist-drill evacuation of SDHs with SEPS from November 2013 to November 2014. In general, patients who had symptomatic subacute or chronic SDHs were candidates for SEPS. Those with mixed density acute and chronic components were candidates if the acute component was < 50% of the overall hematoma volume. Multiple loculations were not a contraindication for SEPS. Patients who were non-compliant with their medications, or did not have a follow-up CT scan at a minimum of 3 months after treatment, were excluded from analysis. Demographics, diagnosis, clinical presentation, use of oral anticoagulants, platelets and INR were recorded for each patient. All CT images were analyzed by a physician blinded to patient identifiers and time to imaging. SDH dimensions were measured from the CT scans, and hematoma volumes were calculated using the “modified a x b x c/2” method.5

The SEPS placement procedure was performed in an intensive care unit setting and coagulopathies were corrected prior to the procedure. In all cases, conscious sedation with local anesthetic was used. The procedure details have been outlined previously in the literature.6,7 After the procedure, the patients were monitored in an ICU setting. An immediate post-procedure Head CT was obtained if there was a concern for a complication. Otherwise, a CT was obtained immediately prior to removal of the SEPS.

Patients were started on oral TXA at 650 mg daily after the SEPS was removed and were continued on the medication as an outpatient for 6 months or until SDH
resolution was demonstrated on follow-up CT. All patients were seen in the clinic at 2 weeks, 1 month and 3 months with additional visits up to 6 months if there was a persistent residual on the 3 month scan. Lower extremity ultrasonography or contrast CT scans were obtained at the discretion of the treating physicians during the patients’ hospital course and outpatient follow-up if there was a clinical suspicion for a deep vein thrombosis or pulmonary embolus.

The data was entered into a spreadsheet and analyzed using XLSTAT version 2015.1.01 (Addinsoft SARL) Statistical differences between groups were assessed using the Mann-Whitney U test. A p value of ≤ 0.05 was deemed to be significant.
Results

Fourteen patients met the inclusion criteria for this study. Six patients harbored bilateral chronic subdural hematomas which were treated as separate units, so the analysis encompasses 20 subdural hematomas. Three patients were excluded: 2 patients lacked follow-up imaging, and 1 patient was non-compliant with his medication. The average age was 56.4 +/- 16 with the majority being male (86%).

All patients were symptomatic on presentation. The most common symptoms were altered mental status, headache and gait disturbance (Table 1). The majority of SDHs were mixed-density (Table 2). The average volume of the SDH was 145.96 cm³ +/- 40.22 with a mean midline shift of 9.44 +/- 4.84. SEPS was performed on all patients. One patient required a craniotomy due to expansion of SDH following SEPS. After the initial bedside evacuation, SDH volume was reduced by 40.74% to a mean volume of 80.00 cm³ +/- 31.96 (p < 0.0001, Mann-Whitney), and mean midline shift decreased to 4.44 mm +/- 3.29 (p = 0.0046, Mann-Whitney, Figure 1). TXA was started immediately in all patients after SEPS removal except in one patient where TXA was initially deferred due to a history of atrial fibrillation. TXA was started after a recurrence of the SDH was seen on follow-up CT at 2 weeks post-SEPS. Mean and median duration of TXA treatment was 90.3 +/- 27 days and 87 days respectively. Mean time to last radiographic follow-up was 92.1 +/- 27 days after initiation of TXA. Mean SDH volume at last follow-up was 7.41 cm³ +/- 15.54, representing an additional 91.3% reduction from post-SEPS volumes (p < 0.0001, Mann-Whitney, Figure 2). Midline shift also continued to improve (0.19 mm +/- 0.69, p = 0.0002, Mann-Whitney).
Tranexamic acid was discontinued once the follow-up CT scan showed significant resolution of the SDH. The majority of patients experienced rapid clinical improvement after the SEPS treatment, and this was maintained during the TXA treatment period. Ten of 14 patients (71%) had complete resolution of their presenting symptoms at last follow-up. Three patients reported persistent but improved symptoms, and 1 patient had baseline dementia which persisted.

One patient had clinical suspicion for a venous thromboembolism (VTE), but lower extremity ultrasonography showed no evidence of deep vein thrombosis (DVT). The remainder of the patients were asymptomatic and further investigation was not pursued.

**Discussion**

In our cohort of patients who underwent bedside evacuation of moderate to large mixed density SDHs followed by an oral TXA regimen, we achieved a 95% reduction of the initial SDH. SDH volumes were reduced by 40.74% after the initial SEPS drainage, and TXA treatment reduced the residual volumes by an additional 91.3%. More importantly, we noted no increase in the size of the residual SDH during the TXA treatment period, and no patients required additional procedures in the follow-up period after discharge. Most patients experienced improvement in their pre-SEPS symptomatology with the majority achieving complete resolution.

**Management of SDHs**

There is no consensus on the optimal treatment of SDHs and options include observation, burr hole or twist drill craniostomy (TDC) and craniotomy. Bedside
evacuation of SDHs with a twist-drill craniostomy has gained favor in patients who are poor surgical candidates. In a recent review, Ducruet et al., showed that bedside TDC drainage of SDHs had a lower rate of complications and mortality but a higher recurrence rate when compared to a craniotomy for evacuation of SDHs (28.1% vs 19.4%). Recurrence was defined as a re-admission and repeat procedure to evacuate the recurrent SDH. Given the presence of multiple loculated membranes in many chronic SDH, recurrence after either twist drill, burr hole or craniotomy evacuation is not surprising.

The Subdural Evacuating Port System involves inserting a threaded hollow screw through a twist-drill hole. Unlike traditional TDCs, a catheter is not inserted into the subdural space. Instead, low negative pressure is applied to a closed drainage system to promote drainage. Numerous studies have evaluated the complications and success rates of this system, and recurrence rates vary from 12.5 to 34.6%. However, end-points in each of the studies were quite variable and included both clinical (symptomatic improvement, complications, recurrence) and radiological (reduction or expansion in volume) outcomes. There was also significant heterogeneity in the studies’ definition of success, making comparisons difficult.

Chari et al. performed an extensive review and meta-analysis of twist-drill craniostomies with hollow screws. They defined successful outcome as “symptomatic improvement on the same admission with one or more hollow screw/SEPS device,” and recurrence as “readmission and reoperation with any technique, or reoperation with BHC/craniotomy during the same admission.” By applying these definitions uniformly to the raw data from their review, they calculated a recurrence rate of 22.4% after hollow screw twist-drill craniostomies. Of the 796 patients included in their analysis, 390
underwent drainage with the SEPS, which relies on low negative pressure, while the remaining 406 patients were drained using a hollow screw system incorporating intraoperative and postoperative irrigation.

In our current study, 13 of 14 patients (93%) experienced symptomatic relief after SEPS + TXA, and the one remaining patient showed radiographic improvement without further progression in his symptoms. One patient required an immediate craniotomy following a SEPS complication (1 of 20 SDHs, or 5%). Using the definition of recurrence as defined by Chari et al., this SDH was counted as a recurrence for statistical purposes. We observed no additional recurrences during the follow-up period. Despite the small size of our cohort, the recurrence rate is significantly reduced when compared to the 390 patients undergoing SEPS in Chari et al.s. review (p = 0.0485, Mann-Whitney). Although our mean follow-up period was 3 months, the majority of recurrences usually occur within the first 3-month period.

Role of fibrinogen in the pathophysiology of SDH

The pathogenesis of chronic SDHs involves many complex pathways. There have been many proposed overlapping hypotheses including 1) osmotic gradient mechanism; 2) inflammatory process; 3) recurrent hemorrhage model with hyperfibrinolytic activity. The pathway starts with a breakdown of the acute hematoma into products that spark an inflammatory process (hypothesis #2). This results in formation of a membrane comprised of fragile neovascular tissue, enveloping the clot. The clot may expand as the blood products break down and an osmotic gradient is created causing ingress of fluid into the hematoma (hypothesis #1). As the clot expands, the neovascular
membranes stretch, resulting in micro-hemorrhages and recurrence of the above cycles (hypothesis #3).  

Plasminogen plays a critical role in the pathogenesis of SDHs. Traumatic brain injury releases tissue plasminogen activator. The subsequent increase in plasmin activates the fibrinolytic system which promotes the liquefaction of the SDH and propagates the cycles discussed above. Plasmin simultaneously activates the kallikrein system which induces inflammation and increases vascular permeability of the subdural membranes. TXA decreases plasmin activity by reversibly binding to lysine sites on plasminogen, thereby reducing both fibrinolysis and inflammation. In theory, TXA should break the cycle of membrane formation, rehemorrhage, inflammation, and elevated vascular permeability, thus allowing eventual reabsorption of clot over time without expansion.

**Tranexamic Acid**

TXA has been used extensively in orthopedic joint, spinal, cranial vault surgeries, and trauma cases to reduce significant hemorrhage. These studies have all shown a significant trend in the reduction of perioperative blood loss and transfusion requirements. To date, there is only one other report of use of TXA in conservatively managed smaller chronic SDHs with promising outcomes.

As an anti-fibrinolytic agent, TXA is potentially pro-thrombotic; however, in large systematic reviews in the orthopedic and spinal surgery literature, TXA does not seem to increase the rate of thromboembolic events. In these studies, however, intravenous boluses are often given at the time of surgery and continued post-operatively as needed.
for limited amounts of time. Oral treatment, as used in our study, may continue for several months. No patients in our study experienced a VTE. However, given the small number of patients, our study is likely underpowered to demonstrate small increases in the risk of VTEs.

**Limitations**

Our conclusions are limited by a small sample size and lack of a control group, although the results appear promising when compared to historical controls. The data was reviewed retrospectively and thus may exhibit all of the biases that are routinely found in retrospective studies. Furthermore, although no VTEs were observed in our cohort of patients, our study is likely underpowered to detect small increases in the rate of VTEs.

**Conclusion**

In this preliminary pilot study, oral TXA treatment after bedside evacuation of large mixed density SDH appears to be a safe and effective in preventing recurrence. A larger prospective trial comparing TXA to observation with longer follow-up is still required.

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**Author Disclosure Statement:** All authors (OT, FF, CB, GH, DP, DK and PH) have no disclosures to report.
References


12. Safain M, Roguski M, Antoniou A, C.M. S, Malek AM, Riesenburger R. A single center’s experience with the bedside subdural evacuating port system: a


Table 1: Symptoms on presentation and at 3-month follow up.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Presentation</th>
<th>Improvement?</th>
<th>%</th>
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<tbody>
<tr>
<td>Altered mental status</td>
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<td>5</td>
<td>83</td>
</tr>
<tr>
<td>Headache</td>
<td>4</td>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>2</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Focal neurological deficit (speech, motor)</td>
<td>2</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>13</td>
<td>93</td>
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Table 2: Demographics of cohort treated with TXA after SEPS placement for SDH.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>56.4 +/- 16.3</th>
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<tr>
<td>n (%)</td>
<td></td>
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<tr>
<td>Gender</td>
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</tr>
<tr>
<td>Male</td>
<td>12 (86)</td>
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<tr>
<td>Female</td>
<td>2 (14)</td>
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<tr>
<td>Symptoms</td>
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<tr>
<td>Altered mental status</td>
<td>6 (43)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (28)</td>
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<tr>
<td>Gait disturbance</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Focal deficit</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Laterality</td>
<td></td>
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<tr>
<td>Right</td>
<td>4 (28)</td>
</tr>
<tr>
<td>Left</td>
<td>4 (28)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>6 (43)</td>
</tr>
<tr>
<td>Category of SDH</td>
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<tr>
<td>Chronic</td>
<td>2 (10)</td>
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<tr>
<td>Subacute</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Mixed</td>
<td>14 (70)</td>
</tr>
<tr>
<td>Subacute on chronic</td>
<td>8 (57)</td>
</tr>
<tr>
<td>Acute on chronic</td>
<td>6 (42)</td>
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</tbody>
</table>
Figure Legend

Figure 1. A) Volumes of Subdural hematoma at presentation, post-SEPS and at 3 month follow-up after TXA treatment. B) Midline shift on CT at presentation, post-SEPS and at 3 month follow-up after TXA treatment.

Figure 2. Case Example. Patient presented with a right hemiparesis. A) CT reveals a large mixed density subdural hematoma causing midline shift. B) CT immediately after removal of SEPS shows evacuation of a significant portion of the SDH and reduction in the midline shift. A notable residual remains. C) Complete resolution of SDH at 3-month follow-up on TXA treatment.

Figure 3. Case Example. A) Elderly gentleman on anticoagulation for atrial fibrillation with bilateral acute on chronic SDH. B) CT scan post-SEPS. TXA was deferred due to underlying atrial fibrillation. C) Two weeks later, mild confusion was noted and follow-up CT showed recurrence of SDH. After discussion with family regarding risks of a craniotomy versus TXA treatment, TXA was started. D) Patient demonstrated good clinical outcome and complete resolution of SDH on 3 month follow-up.
B  

Midline Shift on CT

<table>
<thead>
<tr>
<th></th>
<th>Midline Shift (mm)</th>
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<tbody>
<tr>
<td>Presentation</td>
<td>12</td>
</tr>
<tr>
<td>After SEPS</td>
<td>4</td>
</tr>
<tr>
<td>After TXA</td>
<td>1</td>
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On behalf of my co-authors, I, Fabio Frisoli, pledge that there are no conflicts of interest and no financial disclosures to report. I certify that this manuscript is a unique submission and is not being considered for publication with any other source in any medium.
Highlights

- Chronic subdural hematoma has a high rate of recurrence after evacuation
- Tranexamic acid greatly reduces the volume of subdural hematoma after bedside evacuation
- Fibrinolysis and activation of the kallikrein pathway are involved in the pathogenesis of chronic subdural hematoma