Topical Tranexamic Acid Compared With Anterior Nasal Packing for Treatment of Epistaxis in Patients Taking Antiplatelet Drugs: Randomized Controlled Trial

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ABSTRACT

Objective: We evaluated the efficacy of topical application of the injectable form of tranexamic acid (TXA) compared with anterior nasal packing (ANP) for the treatment of epistaxis in patients taking antiplatelet drugs (aspirin, clopidogrel, or both) who presented to the emergency department (ED).

Methods: A randomized, parallel-group clinical trial was conducted at two EDs. A total of 124 participants were randomized to receive topical TXA (500 mg in 5 mL) or ANP, 62 patients per group. The primary outcome was the proportion of patients in each group whose bleeding had stopped at 10 minutes. Secondary outcomes were the rebleeding rate at 24 hours and 1 week, ED length of stay (LOS), and patient satisfaction.

Results: Within 10 minutes of treatment, bleeding was stopped in 73% of the patients in the TXA group, compared with 29% in the ANP group (difference = 44%, 95% confidence interval, 26% to 57%; $p < 0.001$). Additionally, rebleeding was reported in 5 and 10% of patients during the first 24 hours in the TXA and the ANP groups, respectively. At 1 week, 5% of patients in the TXA group and 21% of patients in the ANP group had experienced recurrent bleeding ($p = 0.007$). Patients in the TXA group reported higher satisfaction scores (median [interquartile range {IQR}], 9 [8–9.25]) compared with the ANP group (median [IQR] = 4 [3–5]; $p < 0.001$). Discharge from the ED in <2 hours was achieved in 97% of patients in the TXA group versus 13% in the ANP group ($p < 0.001$). There were no adverse events reported in either group.

Conclusions: In our study population, epistaxis treatment with topical application of TXA resulted in faster bleeding cessation, less rebleeding at 1 week, shorter ED LOS, and higher patient satisfaction compared with ANP.

Epistaxis is a common complaint in the emergency department (ED).[1] About 60% of population experience epistaxis at least once during their lifetime and 6% require medical attention.[2] The cause of epistaxis is unknown in the majority of cases. Etiologic factors can be divided into local and systemic causes.[3] Of all

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systemic factors, the use of anticoagulants and antiplatelet drugs appear to have a significant correlation with more severe and recurrent epistaxis.[4]

Antiplatelet medications, specifically aspirin and clopidogrel, are widely prescribed for treatment or preventions of various forms of cardiovascular disease.[3] While there is no significant difference in the risk of epistaxis in patients taking aspirin or clopidogrel,[5] epistaxis management is more difficult in patients taking antiplatelet drugs.[4]

Anterior nasal packing (ANP), a frequently performed procedure in the management of epistaxis, has potential complications, including discomfort during placing and removing the pack and rebleeding following removal owing to mucosal injury and synechia formation.[6] As such, more optimal treatment strategies are needed for the management of epistaxis, especially for patients taking antiplatelet drugs.

The efficacy of topical application of the injectable form of tranexamic acid (TXA) has been shown beneficial for the treatment of idiopathic anterior epistaxis.[7] Additionally, topical use of TXA during oral,[8] pulmonary,[9] sinus,[10,11] and adenoidectomy[12] procedures results in significantly less mucosal bleeding. In this study, we compared the effect of topical TXA with ANP for treatment of anterior epistaxis in patients taking antiplatelet drugs.

MATERIALS AND METHODS

Study Design and Setting

A randomized, parallel-group clinical trial study was conducted at two EDs and designed to compare treatment efficacy of topical use of the injectable form of 10% TXA (500 mg in 5 mL) with that of ANP for treatment of epistaxis in patients taking antiplatelet drugs (aspirin, clopidogrel, or both). To ensure a standardized approach to epistaxis management at the two study sites, PGY2 and PGY3 emergency medicine resident physicians participated in a 2-hour workshop on ANP and topical TXA administration. Patient recruitment commenced in October 2015 and finished in April 2016.

Population

Patients were enrolled in the EDs of the two large general academic teaching hospitals of Tehran University of Medical Sciences, one with 510 beds and 40,800 annual ED visits and the other with 540 beds and 43,200 annual ED visits. Both centers have residency programs in multiple specialties. Home to 8.7 million people, Tehran is Iran's capital and most populous city.[13,14]

Subjects were eligible for inclusion if they presented to the ED with an acute, new or recurrent, ongoing anterior epistaxis and were currently taking antiplatelet drugs (aspirin, clopidogrel, or both). In the absence of a universally accepted grading system for the severity of epistaxis, save that for hereditary hemorrhagic telangiectasia, we included patients with persistent bleeding requiring further treatment after 20 minutes of compression of both nostrils with the patient's thumb and index finger.[15] We excluded those with traumatic epistaxis, current anticoagulant drug use, inherited bleeding disorders (including hemophilia), inherited platelet disorders, international normalize ratio > 1.5, shock, a visible bleeding vessel, a history of renal disease, and lack of consent. Our institution's ethics review committee approved the study and it was registered at IRCT.Ir (IRCT201509088872N9). Written informed consent was obtained from all patients prior to entry into the trial.

Study Protocol

Eligible patients were randomly allocated to either the TXA group or the ANP group. Our research nurse used IBM SPSS Statistics for Windows, version 24 (IBM Corp) to generate the random allocation sequence, which was stratified by center. Randomization was done in blocks of two, four, and six. To implement the random allocation process, the research nurse randomized the consecutively numbered boxes filled with medication and cotton pledgets in a location removed from the ED and inaccessible to the ED personnel. Each box was identical in size, shape, and weight. The numbered boxes were held in the ED pharmacy and delivered sequentially to resident physicians treating patients with epistaxis who were enrolled in the study. Due to differences in the numbers of pledgets required for ANP compared with topical TXA and in the consistency, color, and smell of the medications used for soaking and impregnating the pledgets, our patients and physicians were not blinded. However, our analysts were not the same investigators who performed the treatment procedures and they analyzed the data set blinded to group assignment.

The TXA group received a 15-cm piece of cotton pledget that had been soaked in the injectable form of TXA (500 mg in 5 mL) and inserted into the affected nostril. It was removed after the attending physician or

a chief resident examined the oropharynx and blood-soaked pledgets to confirm that the bleeding had stopped. The ANP group received a cotton pledget that had been soaked in epinephrine (1:100,000) + lidocaine (2%) inserted into the affected nostril and left in place for 10 minutes. ANP was subsequently performed with several cotton pledgets covered with tetracycline ointment. The packs were left in situ for 3 days before removal. If the allocated treatment failed, we considered ANP and cautery (if indicated) and cautery alone for the TXA group and the ANP group, respectively.

Measurements

Assessment for ongoing bleeding was performed at 5-minute intervals and when the patient left the ED. The timed assessments began at the completion of packing with the ointment-impregnated pledgets in the ANP group and following the insertion of the TXA soaked pledget in the TXA group. Emergency medicine resident physicians performed follow-up assessments by telephone or in person to document any rebleeding or adverse events at 24 hours and 1 week. Our research nurse evaluated satisfaction rate on a numerical rating scale at the time of ED discharge.

Outcomes

The primary outcome was the proportion of patients in each group whose bleeding had stopped at 10 minutes. Secondary outcomes were: 1) frequency of epistaxis recurrence at 24 hours and 7 days after treatment, 2) ED length of stay (LOS), and 3) patient satisfaction on a 0–10 numeric rating scale, with a higher score indicating greater satisfaction.

Data Analysis

Our sample size calculation was based on the results of a previous study of ANP for the treatment of epistaxis in which approximately 30% of patients had bleeding cessation in ≤10 min.[7] We considered a minimum clinically important difference of 25% (i.e., 55% bleeding cessation at 10 minutes) necessary to make the topical use of the injectable form of TXA preferable to ANP. We calculated that a sample size of 57 per group would give 80% power to detect this difference with an alpha of 0.05. We increased the sample size by 10% in each group to account for patients lost to follow-up, giving a final sample size of 62 per group.

Statistical analyses were performed with IBM SPSS Statistics for Windows, version 24 (IBM Corp). The chi-square test was used to compare the primary and secondary efficacy variables between two groups. Because of their skewed distribution Mann-Whitney U-test was used for comparison of satisfaction rate and median time to stop bleeding between two groups and results are expressed as median and interquartile range (IQR). The 95% confidence intervals (CIs) of the differences in proportions were calculated using VassarStats, an online calculator accessible at http://vassarstats.net/prop2_ind.html. Baseline characteristic comparisons between the two groups were done using the independent sample t-test and chi-square test for continuous and categorical variables, respectively. We considered two-sided p-values < 0.05 to be statistically significant.

RESULTS

Characteristics of Study Subjects

A total of 384 patients were assessed for eligibility, 260 patients were excluded, and 124 subjects (69 men and 55 women) were enrolled in this randomized clinical trial (Figure 1). A total of 124 eligible patients were randomized and included in the intention-to-treat analysis: 62 in the TXA group and 62 in the ANP group. The patients were followed for 7 days. Baseline characteristics of each group are shown in Table 1. Except for prior epistaxis history, which was significantly higher in the TXA group, the baseline variables were comparable between the two groups.

Main Results

The outcomes of each treatment are summarized in Table 2. Bleeding stopped within 10 minutes in 45 (73%) of 62 patients in the TXA, compared with 18 (29%) of 62 patients in the ANP (percent difference = 44%; 95% CI = 26% to 57%; $p < 0.001$). The median time to bleeding cessation in the TXA group (10 minutes; IQR = 10–15 minutes) was significantly lower than the ANP group (15 minutes; IQR = 10–20 minutes; $p < 0.001$).

Rebleeding at 24 hours was documented in three (5%) of 62 patients in the TXA group and six (10%) of 62 patients in the ANP group ($p = 0.299$). Rebleeding at 1 week was documented in three (5%) of 62 patients in the TXA group and 13 (21%) of 62 patients in the ANP group (percent difference = –16%; 95% CI = –28% to –4%; $p = 0.007$).

ED LOS was shorter for patients in the TXA group, with 60 (97%) of 62 patients discharged within

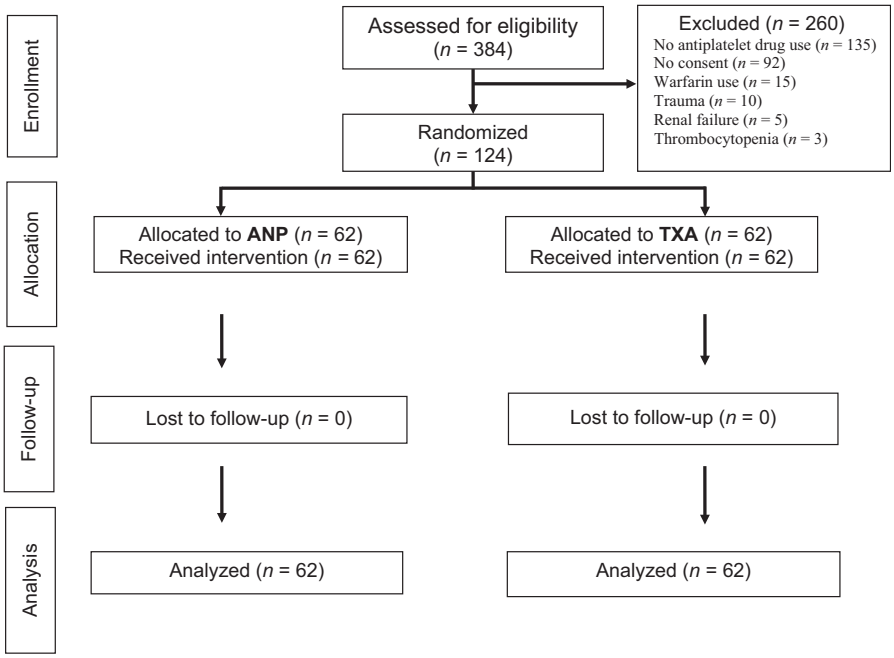

Figure 1. CONSORT flow diagram. ANP = anterior nasal packing; TXA = tranexamic acid.

Table 1
Patient Characteristics

	Anterior Nasal Packing (*n* = 62)	Tranexamic Acid (*n* = 62)
Age (y)	60.7 ± 12.2	58.5 ± 16.1
Sex (% male)	52	60
PLTs $\times 10^9$/l	302 ± 80	298 ± 83
PT (sec)	12.6 ± 0.9	12.5 ± 1.1
INR	1.07 ± 0.10	1.05 ± 0.08
PTT (sec)	32.7 ± 4.6	31.5 ± 3.8
History of epistaxis (% yes)	21	53
History of drugs (%) (ASA/others)	82/18	81/19

ASA = acetylsalicylic acid; INR = international normalized ratio; PLTs = platelets; PT = prothrombin time; PTT = partial thromboplastin time.

2 hours compared with eight (13%) of 62 patients in the ANP group (percent difference = 84%; 95% CI = 71% to 91%; p < 0.001). Patient satisfaction was significantly greater in the TXA group (median = 9; IQR = 8–9.25) compared with the ANP group (median = 4; IQR = 3–5; p < 0.001).

No serious adverse events were detected during the study. There was no statistically significant difference in the incidence of complications (nausea/vomiting and treatment intolerance) between two groups.

DISCUSSION

The World Health Organization lists TXA as an essential medication.[16] It is an antifibrinolytic drug and a synthetic derivative of the amino acid lysine that reduces plasmin concentration by blocking the lysine-binding sites of plasminogen, which in turn inhibits the binding of plasminogen to fibrin and then conversion of plasminogen to plasmin.[17] Plasmin via the complement system may interfere with platelet function[18] and reduce platelet adhesion and aggregation.[19]

Multiple routes of TXA administration, including oral, intravenous, and topically have been studied for

Table 2
Effects of Tranexamic Acid Compared With Anterior Nasal Packing on Efficacy Variables

	Anterior Nasal Packing	Tranexamic Acid	Percent Difference (95% CI)	p-value
Bleeding stop time ≤ 10 min (%)	29	73	44 (26 to 57)	<0.001
Bleeding stop time (min), median [IQR]	15 [10–20]	10 [10–15]		<0.001
Discharge time ≤ 2 h (%)	13	97	84 (71 to 91)	<0.001
Complications in the ED (%)	5	10	5 (–5 to 15)	0.299
Rebleeding in the first 24 h (%)	10	5	–5 (–15 to 5)	0.299
Rebleeding from procedure until 1 week (%)	21	5	–16 (–28 to –4)	0.007

various types of bleeding, including epistaxis.[7,8,20–22] In one study, patients with hereditary hemorrhagic telangiectasia who took daily oral TXA had a significant decrease in the duration of epistaxis each month compared with those taking placebo.[23] Topical TXA has also demonstrated success in achieving hemostasis and improving the surgical field in endoscopic sinus surgery[10] and has been shown to decrease postoperative hemorrhage after adenoidectomy.[12]

Sindet-Pedersen[24] showed that mouth rinse with 10 mL of a 5% aqueous TXA solution achieved very high salivary drug levels and low plasma levels compared with oral administration of 1 g of the drug. These data suggest that topical administration of TXA can be beneficial in arresting local hemorrhage without producing significant systemic antifibrinolysis effects. Furthermore, the topical hemostatic effect of TXA has been shown in the treatment of gingival bleeding in hemophilic patients[20] and in pulmonary hemorrhage from various etiologies.[9]

To the best of our knowledge, this is the first trial investigating the effects of TXA for treatment of epistaxis in patients taking antiplatelet drugs. We found the topical application of the injectable formulation of TXA to be more effective than ANP with tetracycline-impregnated pledgets, with 73% of patients in the former group achieving bleeding cessation within 10 minutes compared with 29% in the latter group.

Moreover, the rate of recurrent bleeding during the first week after treatment among patients in the TXA group was significantly lower than in the ANP group. ED LOS was significantly decreased in the TXA group. This is consistent with findings from a prior study by our group that examined topical TXA treatment of idiopathic epistaxis.[7] As such, adoption of this treatment strategy may improve patient flow through the ED at centers where ANP is commonly employed in the treatment of epistaxis.

Patient satisfaction was also greater in the TXA group. Treatments that are more comfortable for patients and simpler for physicians to perform are more pleasant and more likely to be integrated into clinical practice. This simplicity and convenience has been demonstrated in our prior work[7] and that of Tibbelin et al.[25] in a study of tranexamic gel for the treatment of epistaxis.

Topical use of the injectable form of TXA seems to provide a better treatment option for anterior epistaxis compared with ANP in patients taking antiplatelet drugs. The advantages of topical TXA treatment demonstrated in our study population include quicker hemostasis, shorter ED LOS, lower recurrence rate, and increased patient satisfaction. The technique is also relatively simple and is easy to teach and learn.

LIMITATIONS

This study has several limitations. One key limitation is that patients with posterior epistaxis were not included in this trial and so we cannot comment on the role of TXA in the management of these patients. Another limitation is that the physicians and patients were not blinded to treatment allocation. Moreover, we did not stratify treatment assignment by the specific antiplatelet drug the patient was taking and so we cannot make any conclusions about the relative benefit of the study treatment on the basis of either antiplatelet agent or a combination of the agents. Also, in the absence of consensus on an epistaxis severity grading system, save that for patients with hereditary hemorrhagic telangiectasia, we chose to include those patients with persistent bleeding after 20 minutes of manual compression of both nostrils. While we feel that this is reasonable, clinically relevant population, it is possible that there was an imbalance of epistaxis severity among the groups that could have favored the TXA treatment. However, the only imbalance documented among the treatment groups was a higher proportion of patients with a history of epistaxis in the TXA group compared with the ANP group. Since a history of epistaxis may be a marker for more severe epistaxis (as noted in the Epistaxis Severity Score for Hereditary Hemorrhagic Telangiectasia) it is possible our findings may actually underestimate the beneficial effects of TXA compared to ANP. Finally, although there are commercially available nasal sponges, tampons, and balloon tamponade devices that are designed for epistaxis treatment, we did not compare them in this trial and so cannot comment on their relative efficacy or tolerability as compared with TXA.

CONCLUSION

In our study population of patients taking antiplatelet drugs who presented to the ED with epistaxis, those randomized to topical application of tranexamic acid demonstrated faster bleeding cessation, less rebleeding at 1week, shorter ED length of stay, and higher patient satisfaction than those treated with anterior nasal packing.

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