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

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Author contributions:

RZ, MHMJ and MS conceived the study, designed the trial. MS, MHMJ, and ZN supervised the conduct of the trial and data collection, undertook recruitment of participants, and managed the data. RZ and AN provided statistical advice on study design and analyzed the data. RZ and AN drafted the article, and all authors contributed substantially to its revision. RZ, AN, and MS had full access to all the study data and final responsibility for the decision to submit for publication. MS takes responsibility for the paper as a whole.

Conflict of Interest:

[RZ] reports no conflict of interest.

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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, Clopidegrol or both) who presented to the emergency department (ED).

Methods: A randomized, parallel group clinical trial was conducted at 2 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 re-bleeding rate at 24 hours and one 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 TXAgroup, compared with 29% in the ANP group (difference 44%, 95% confidence interval, 26%-57%; p<.001). Additionally, re-bleeding 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=.007). Patients in the TXA group reported higher satisfaction scores [(median (IQR), 9 (8-9.25)] compared with the anterior nasal packing group [median (IQR), 4 (3-5)] (p<.001). Discharge from the ED in <2 hours was achieved in 97% of patients in the TXA group vs. 13% in the ANP group (p<.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 re-bleeding at 1week, shorter ED LOS, and higher patient satisfaction as compared with ANP.

Introduction

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 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, a frequently performed procedure in the management of epistaxis, has potential complications, including discomfort during placing and removing the pack and re-bleeding 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 has been shown beneficial for the treatment of idiopathic anterior epistaxis [7]. Additionally, topical use of tranexamic

acid 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 tranexamic acid with anterior nasal packing 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% tranexamic acid (500 mg in 5 ml) with that of anterior nasal packing 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, postgraduate year 2 and 3 emergency medicine resident physicians participated in a 2-hour workshop on anterior nasal packing and topical tranexamic acid 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 (TUMS), 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, INR > 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 tranexamic acid group or the anterior nasal packing group. Our research nurse used IBM SPSS Statistics for Windows, version 24 (Armonk, NY: 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 anterior nasal packing as compared with topical tranexamic acid 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 tranexamic acid group received a 15-cm piece of cotton pledget that had been soaked in the injectable form of tranexamic acid (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 anterior nasal packing 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. Anterior nasal packing 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 anterior nasal packing and cautery (if indicated), and cautery alone for the tranexamic acid group and the anterior nasal packing 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 anterior nasal packing group and following the insertion of the tranexamic acid soaked pledget in the tranexamic acid group. Emergency medicine resident physicians performed follow-up assessments by telephone or in-person to document any re-bleeding or adverse events at 24hours and 1week. Our research nurse evaluated satisfaction rate on a numerical rating scale (NRS) 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 anterior nasal packing for the treatment of epistaxis in which approximately 30 percent of patients had bleeding cessation in ≤10 min7. 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 tranexamic acid preferable to anterior nasal packing. 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 (Armonk, NY: IBM Corp). The $\chi 2$-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 on-line 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 $\chi 2$-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). One hundred twenty-four eligible patients were randomized and included in the intention-to-treat analysis: 62 in the tranexamic acid group and 62 in the anterior nasal packing 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 tranexamic acid 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 tranexamic acid, compared with 18 (29%) of 62 patients in the anterior nasal packing (percent difference 44%, 95% CI, 26% to 57%; $p<.001$). The median time to bleeding cessation in the tranexamic acid group (10; IQR: 10-15 minutes) was significantly lower than the anterior nasal packing group (15; IQR: 10-20 minutes) ($p<.001$).

Re-bleeding at 24hours was documented in 3 (5%) of 62 patients in the tranexamic acid group and 6 (10%) of 62 patients in the anterior nasal packing group (p=.299). Re-bleeding at 1 week was documented in 3 (5%) of 62 patients in the tranexamic acid group and 13 (21%) of 62 patients in the anterior nasal packing group (percent difference -16%, 95% CI, -28% to -4 %; p=.007).

ED LOS was shorter for patients in the tranexamic acid group, with 60 (97%) of 62 patients discharged within 2 hours as compared with 8 (13%) of 62 patients in the anterior nasal packing group (percent difference 84%, 95% CI, 71% to 91%; p<.001). Patient satisfaction was significantly greater in the tranexamic acid group (median 9; IQR: 8-9.25) compared with the anterior nasal packing group (median 4; IQR: 3-5) (p<.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 tranexamic acid as an essential medication [16]. It is an anti-fibrinolytic 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 tranexamic acid administration, including oral, intravenous, and topically have been studied for various types of bleeding, including epistaxis [7,8,20-22]. In one study, patients with HHT who took daily oral tranexamic acid had a significant decrease in the duration of epistaxis each month as compared with those taking placebo [23]. Topical tranexamic acid has also demonstrated success in achieving hemostasis and improving the surgical field in endoscopic sinus surgery [10] and has been shown to decrease post-operative hemorrhage after adenoidectomy [12].

Sindet-Pedersen showed that mouth rinse with 10 ml of a 5% aqueous tranexamic acid 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 tranexamic acid can be beneficial in arresting local hemorrhage without producing significant systemic anti-fibrinolysis effects [24]. Furthermore, the topical hemostatic effect of tranexamic acid 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 tranexamic acid for treatment of epistaxis in patients taking antiplatelet drugs. We found the topical application of the

injectable formulation of tranexamic acid to be more effective than anterior nasal packing with tetracycline impregnated pledgets, with 73% of patients in the former group achieving bleeding cessation within 10 minutes as compared with 29% in the latter group.

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

Patient satisfaction was also greater in the tranexamic acid 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. in a study of tranexamic gel for the treatment of epistaxis [25].

Topical use of the injectable form of tranexamic acid seems to provide a better treatment option for anterior epistaxis compared with anterior nasal packing in patients taking antiplatelet drugs. The advantages of topical tranexamic acid 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 tranexamic acid 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 anti-platelet 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 tranexamic acid treatment. However, the only imbalance documented among the treatment groups was a higher proportion of patients with a history of epistaxis in the tranexamic acid group compared with the anterior nasal packing 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 tranexamic acid as compared to anterior nasal packing. 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 tranexamic acid.

Conclusion

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

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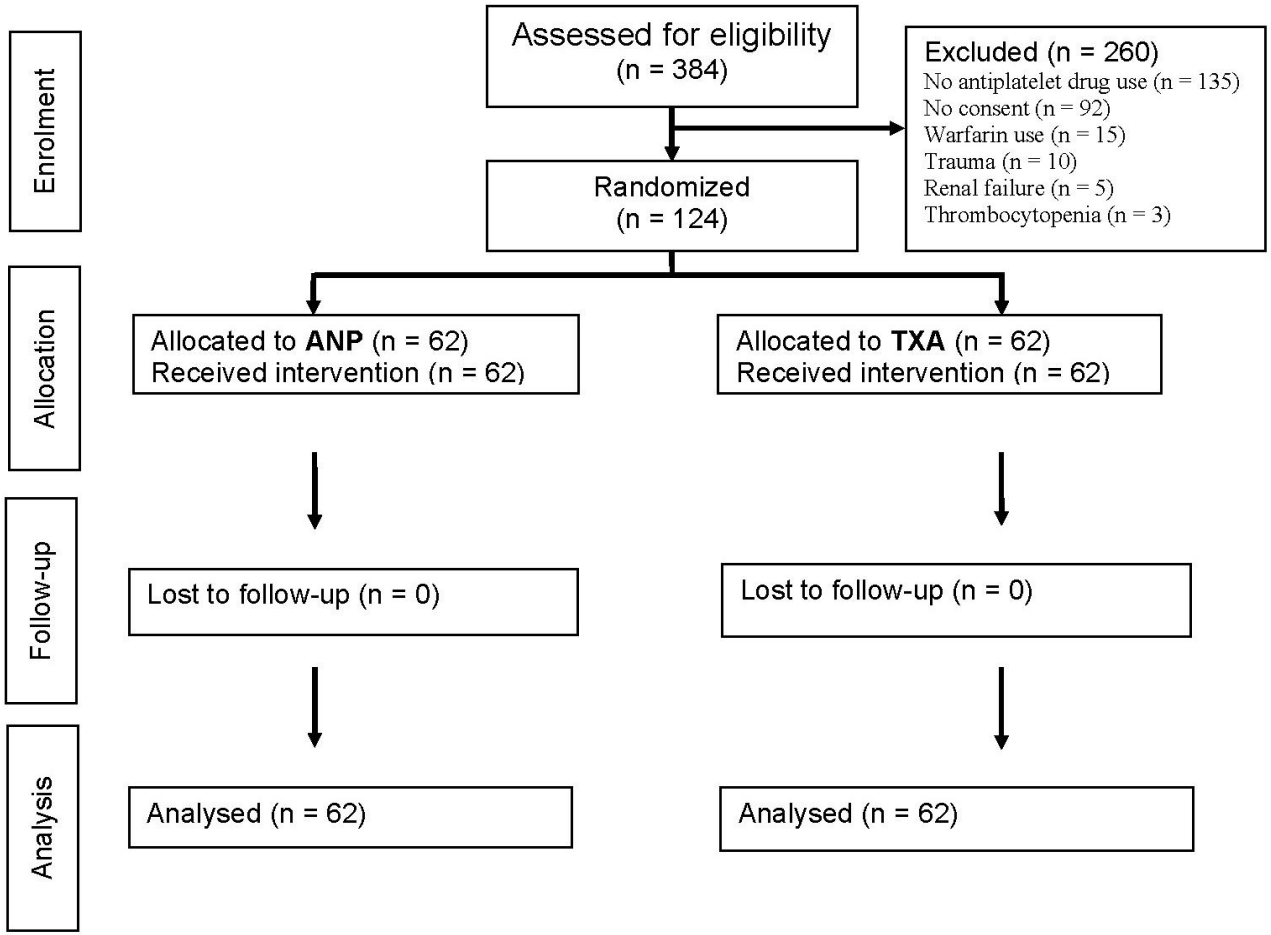
Table 1. Patient Characteristics

	Anterior nasal packing (n=62)	Tranexamic acid (n=62)
Age (year)	60.7±12.2	58.5±16.1
Sex (%) (Male)	52	60
PLT×10^3 /µl	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 (% of yes)	21.0	53
History of drugs (%) (ASA/others)	82/18	81/19

PLT, platelet; PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio.

Table 2. Effects of tranexamic acid compared with anterior nasal packing on efficacy variables

	Anterior nasal packing	Tranexamic acid	Percent difference (95% confidence interval)	P value
Bleeding stop time ≤10 min (%)	29.0	73	44 (26-57)	<0.001
Median of bleeding stop time [IQR] (min)	15 [10-20]	10 [10-15]		<0.001
Discharge time ≤ 2h (%)	13	97	84 (71-91)	<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 till 1 week (%)	21.0	5	-16 (-28 to -4)	0.007



ANP, Anterior Nasal Packing; TXA, Tranexamic Acid.

Figure 1. CONSORT flow diagram.