Intranasal Topical Application of Tranexamic Acid in Atraumatic Anterior Epistaxis: A Double-Blind Randomized Clinical Trial

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Study objective: To determine the effectiveness of intranasal topical application of tranexamic acid in reducing the need for anterior nasal packing and determine the number of episodes of rebleeding in adult patients presenting with spontaneous atraumatic anterior epistaxis.

Methods: This study was a double-blind randomized trial conducted from September to November 2021 in the ears, nose, and throat (ENT) emergency department (ED), Khalili Hospital, Shiraz, Iran. Cotton pledgets soaked in either phenylephrine and lidocaine (control group) or tranexamic acid with phenylephrine and lidocaine (intervention group) were inserted into the patients' nostrils for 15 minutes. The primary outcome was the need for anterior nasal packing. The secondary outcomes were staying in the ED for more than 2 hours, needing electrical cauterization, and rebleeding within 24 hours and 1 to 7 days of the first referral to the ED. The trial was registered with the Iranian Registry of Clinical Trials (IRCT20210403050815N1).

Results: A total of 240 patients (120 in each group) were enrolled in this study. Tranexamic acid was associated with a lower rate of need for anterior nasal packing (50.0% versus 64.2%; odds ratio [OR], 0.56; 95% confidence interval [CI], 0.33 to 0.94). There were no significant differences between the 2 groups in terms of the need for electrical cauterization and the rate of rebleeding within 1 to 7 days. Tranexamic acid was associated with a lower rate of stay in the ED for more than 2 hours (9.2% versus 20.8%; OR, 0.38; 95% CI, 0.18 to 0.82) and rebleeding in 24 hours (15.0% versus 30%; OR, 0.41; 95% CI, 0.22 to 0.78) compared with the rates in the control group.

Conclusion: Intranasal topical application of tranexamic acid is associated with a lower rate of need for anterior nasal packing and a shortened stay in the ED; it may be considered a part of the treatment for atraumatic anterior epistaxis. [Ann Emerg Med. 2022;■:1-7.]

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INTRODUCTION

Background

Epistaxis is a common emergency department (ED) presentation, accounting for approximately 1 of every 200 visits to the ED in the United States.[1] The main etiologies of epistaxis include surgery, trauma, coagulopathy, and drugs.[2,3] Although epistaxis is commonly self-limited, it may need medical attention.[4] Thus, finding an effective and affordable treatment is of high priority, especially in the ED setting.

Simple procedures,[5] including squeezing the soft area of the nose or using an ice pack, can stop most bleeding episodes. However, some cases may require further management such as the application of topical vasoconstrictors. Chemical cauterization with silver nitrate or electrical cauterization may be necessary. However, the identification of the bleeding site and correct application of cautery might be challenging in patients with profuse bleeding.[6] If these do not work, anterior nasal packing may be needed; it is an effective treatment, and it controls bleeding in up to 85% of cases.[7] Anterior nasal packing is used with or without a topical vasoconstrictor or a local anesthetic and may be associated with a number of complications, including irritation of the posterior nasal mucosa when the pack is inserted and removed, rebleeding after the pack is removed, infection, and tissue necrosis.[8,9] As a result, the search for a more efficient approach continues.

For less systemic absorption of a drug, its topical administration is preferrable.[10] Thus, topical application of tranexamic acid for the treatment of acute epistaxis is gaining popularity in the acute care setting.[11-13] Different main outcomes have been measured in various studies: the need for anterior nasal packing, mean time of cessation of

Editor's Capsule Summary

What is already known on this topic

Early data have suggested a possible benefit to topical tranexamic acid for epistaxis, but more recent data have found no benefit.

What question this study addressed

This was a randomized controlled trial of tranexamic acid for anterior nasal epistaxis used in conjunction with phenylephrine and lidocaine.

What this study adds to our knowledge

Tranexamic acid reduced rates of anterior nasal packing, emergency department stay of more than 2 hours, and rebleeding within 24 hours.

How this is relevant to clinical practice

Tranexamic acid reduces the need for anterior nasal packing and risk of rebleeding in patients not on anticoagulants. Clinicians should consider tranexamic acid as part of the management for anterior epistaxis.

bleeding, rate of discharge within 2 hours of referral, and number of episodes of rebleeding within 7 days of the first referral to the ED.[11-21]

Importance

Several studies, with controversial results, have so far evaluated the efficacy of intranasal topical application of tranexamic acid in patients with persistent epistaxis.[11] Some studies have reported beneficial effects of tranexamic acid,[15-17] whereas others have found no benefit.[13,18,19]

Goals of this Investigation

We conducted this study to determine the effectiveness of intranasal application of topical tranexamic acid in reducing the need for anterior nasal packing in adult patients with spontaneous atraumatic anterior epistaxis. The primary outcome was reduction in the need for anterior nasal packing. The secondary outcomes included staying in the ED for more than 2 hours, needing electrical cauterization, rebleeding within 24 hours after referral to the ENT ED, and rebleeding within 1 to 7 days.

MATERIALS AND METHODS

Trial Design and Setting

We conducted this single-center, double-blind, randomized clinical trial in the ENT ED of a referral academic-teaching otolaryngology center, Khalili Hospital, from September to November 2021. The center is a tertiary ENT specialty hospital (equipped with an electrical cautery device) affiliated to the Shiraz University of Medical Sciences, Shiraz, southern Iran. Our center is the round-the-clock referral center for general EDs in the region for those presenting with severe epistaxis. We have 31 beds (26 ward beds and 5 ED beds) and an operating room for emergency operations. We have approximately 4,500 patient visits monthly, approximately 300 of which are cases of epistaxis. The center has 10 ENT attending physicians, 24 ENT residents, 30 undergraduate medical students, and 10 nurses.

The Shiraz University of Medical Sciences ethics committee approved the study protocol (IR.SUMS.MED.REC.1399.440). The trial was registered with the Iranian Registry of Clinical Trials (IRCT20210403050815N1). All individuals gave informed oral consent before the intervention and subsequently signed an informed written consent form to participate in the study.

Selection of Participants

Adult patients aged 18 years or older with active spontaneous atraumatic anterior epistaxis referred to the ENT ED between 8:00 AM and 8:00 PM were visited by an ENT resident physician who tried to treat them by squeezing the soft area of their nose, applying an ice pack on the back of their neck, and continuously irrigating the mouth with cold water for at least 10 minutes. Patients whose bleeding was not controlled by these procedures were eligible to participate in the current study. Persistent epistaxis was defined as a condition in which blood originating from the nostrils reappears on the upper lip after wiping.

Excluded from the study were patients with an unstable hemodynamic status; a known allergy to tranexamic acid; the lack of capacity or willingness to participate; known nasopharyngeal, nasal cavity, or paranasal malignancy; pregnancy; the experience of out-of-hospital nasal packing; and epistaxis caused by trauma (excluding simple nose picking), any known bleeding disorders (including hemophilia), or any recent use of anticoagulation drugs (heparin, warfarin, rivaroxaban, dabigatran, or enoxaparin) or clopidogrel and patients who were prisoners. Patients with bilateral massive bleeding due to posterior nasal bleeding who were suspected of having posterior epistaxis based on visual inspection were also excluded.

Traumatic epistaxis was defined as a hemorrhage derived from the nasopharynx, sinuses, nasal cavity, or nostrils

caused by either an internal or external injury to the nose, midfacial structures, or central skull base. The baseline data collected comprised data on the patients' sex, age, blood pressure, and history of recent oral use of acetylsalicylic acid (aspirin).

Interventions

We used IBM SPSS Statistics, version 23 (IBM), to randomly assign the eligible patients into 2 study arms—the tranexamic acid arm (treatment arm) or the control arm—using permuted block randomization with a fixed block size of 8. To implement random allocation, a nurse (unaware of the treatment groups) randomized consecutively numbered boxes packed with medication and cotton pledgets in a place away from the ENT ED and unavailable to ENT ED personnel. The numbered boxes were kept at the ENT ED pharmacy and distributed sequentially among otolaryngology resident physicians who were treating patients with epistaxis. The physicians examined the participants after the confirmation of their eligibility and treated them with the items in the box they received from the pharmacy.

The intervention group received topical (applied intranasally) tranexamic acid. Initially, the physicians assessed and screened the patients according to the local guidelines of Khalili Hospital for the management of epistaxis. Packing was used at the discretion of the visiting physicians; they could use alternate treatments when bleeding was mild. A cotton pledget soaked in 5 mL of an intravenously injectable tranexamic acid solution (100 mg/mL; Tranexip; Caspian Tamin Incorporation) and 10 mL (0.05 g) of phenylephrine hydrochloride (Sina Darou Lab) and sprayed with 5 puffs of a 10% lidocaine spray (10 mg/puff, Iran Darou) was inserted into the patient's affected nostril using a bayonet forceps and nasal speculum. It was gently removed after 15 minutes. All patients were blinded to the treatment they received. The procedures performed for patients in the control arm were exactly similar to those performed for patients in the treatment arm, except that the cotton pledget used lacked tranexamic acid. If bleeding occurred after the removal of the cotton pledget and there was no visible site of bleeding, anterior nasal packing was inserted for the patient. Bipolar cauterization was used when there was a visible bleeding site in the anterior part of the nasal cavity. Patients with postcauterization blood oozing from the site of cauterization received nasal packing. We discharged the patients when they had no bleeding for 30 minutes and were hemodynamically stable.

Measurements

We visited and asked the patients about any episodes of rebleeding during the first 3 days of the treatment. An independent otolaryngology resident performed follow-up for rebleeding and probable side effects of the treatments using a structured questionnaire after either making a phone call or arranging a revisit, depending on the patients' preference, on the seventh day of the treatment. The patients were asked about any minor side effects (eg, headache, nausea, vomiting, and local sensitivity) or major side effects (eg, thrombotic events) of tranexamic acid that they might have experienced. To identify thrombotic events, we asked the patients about the signs and symptoms of deep vein thrombosis, pulmonary embolism, and cerebrovascular events. The ENT resident physician who assessed the outcome was blinded to the study groups.

Outcomes

The primary outcome was the use of anterior nasal packing at any time during attendance in the ENT ED, regardless of other therapies used after the trial therapy. The secondary outcome measures included the need for stay in the ED for more than 2 hours, need for electrical cauterization (based on clinical judgment), rebleeding within 24 hours of admission to the ENT ED, and rebleeding within 1 to 7 days of presentation to the ED.

Analysis

We analyzed data using IBM SPSS Statistics, version 23 (IBM), based on the intention-to-treat principle. The sample size was calculated based on the findings of a pilot study conducted on 30 patients by comparing the proportions of patients who needed anterior nasal packing in the 2 study arms, assuming a proportion of 40% in the treatment arm and 60% in the control arm, a minimum acceptable study power of 80%, and a maximum acceptable type I error of 5%, which resulted in a minimum sample size of 95 patients in each study arm. Taking into account a maximum dropout rate of 20%, the minimum number of patients in each arm was 119. Finally, 120 patients were included in each study arm.

We reported categorical variables as numbers and percentages; the χ^2 and Fisher's exact test, when appropriate, were used to compare the categorical variables. Continuous variables not normally distributed were reported as medians and interquartile ranges; the Mann-Whitney *U* test was used for comparing these between the 2 study groups. Odds ratios (ORs) and their 95% confidence intervals were reported as a measure of risk. The

statistician who analyzed the data was also blinded to the study group.

RESULTS

Characteristics of the Study Subjects

Seventy-five (23.8%) of 315 eligible patients enrolled in the study did not meet the inclusion criteria, withdrew from the study, or did not give consent and were, thus, excluded from the study (Figure). The remaining 240 patients were randomized into the study arms between September 1, 2021, and November 10, 2021. All the enrolled patients completed the study. The last patient completed the study on November 17, 2021. The baseline characteristics measured were similar between the 2 study groups (Table 1).

Main Results

Compared with those in the control arm, the patients treated with tranexamic acid were significantly less likely to need anterior nasal packing (OR, 0.56), stay in the ED for more than 2 hours (OR, 0.38), and develop rebleeding within 24 hours of admission (OR, 0.41; Table 2). The study groups were not significantly different in terms of the need for electrical cauterization or the rate of rebleeding within 1 to 7 days of admission (Table 2). None of the study participants reported any minor or major side effects.

Table 1. Baseline characteristics of participants stratified by study arm.*

Variable	Treatment Group (n=120)	Control Group (n=120)
Male sex	66 (55.0%)	60 (50.0%)
Age, y	52 (43-61)	53 (46-63)
Systolic blood pressure, mmHg	135 (125-140)	130 (125-140)
Diastolic blood pressure, mmHg	75 (75-84)	75 (75-80)
Aspirin consumption	33 (27.5%)	40 (33.3%)

*Values are presented as either n (%) or median (interquartile range).

LIMITATIONS

One of the limitations of the current study was that the patient population might have differed from that of other studies in terms of certain variables. This study was conducted in a specialty (ENT) ED, which is likely to have a patient population different from a general ED; therefore, the results might not be as robust because they could have been obtained in a general ED setting. In addition, the patients were about 10 years younger, on average, than those in the NoPAC study.[17] Only 30% of our participants received aspirin, which was contrary to a study by Zahed et al,[15] in which all patients were on antiplatelet agents, and the NoPAC study,[17] in which the majority of patients were on anticoagulants. Our ENT ED was equipped with an electrical cautery device, whereas

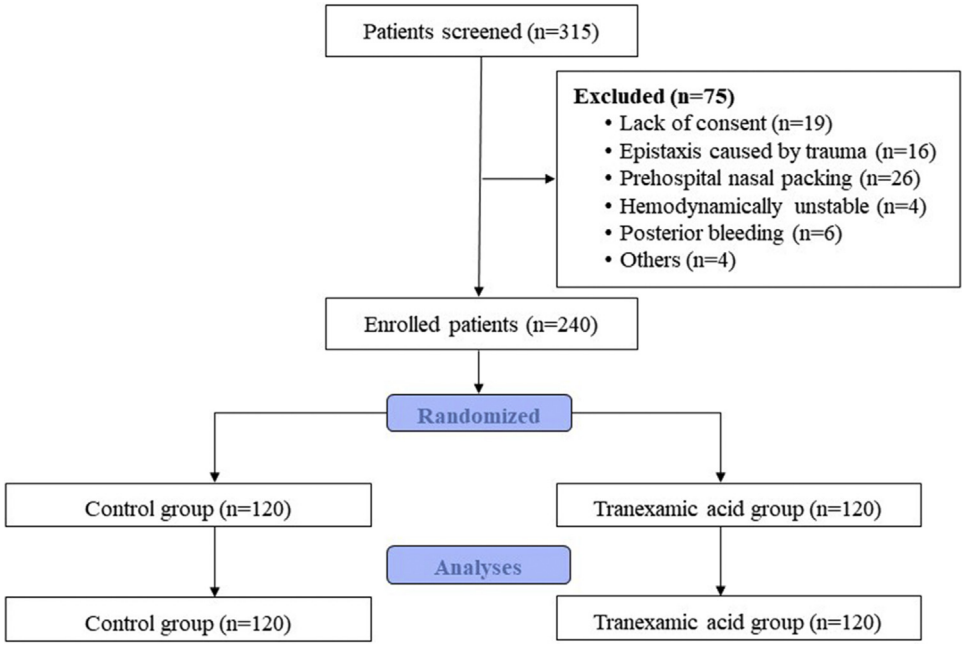

Figure. Consolidated Standards of Reporting Trial flow diagram.

Table 2. Frequency (%) of clinical outcomes in the 2 study arms.

Variable	Tranexamic Acid (n=120)	Control Group (n=120)	Difference, %, (95% CI)	OR (95% CI)
Anterior nasal packing	60 (50.0%)	77 (64.2%)	14.2 (1.8-26.6)	0.56 (0.33-0.94)
More than 2 hours of stay in the ED	11 (9.2%)	25 (20.8%)	11.6 (2.8-20.6)	0.38 (0.18-0.82)
Rebleeding within 24 hours	18 (15.0%)	36 (30.0%)	15 (4.6-25.4)	0.41 (0.22-0.78)
Electrical cauterization	75 (62.5%)	81 (67.5%)	5 (−7.0 to 7.0)	0.80 (0.47-1.36)
Rebleeding within 1-7 days	9 (7.5%)	16 (13.3%)	5.8 (−1.9 to 13.5)	0.53 (0.22-1.25)

CI, Confidence interval; *OR*, odds ratio.

many general EDs in our region were not, leading them to refer patients with severe epistaxis to our center. This may explain why 65% of our patients needed electrical cauterization, which rarely happens in most US EDs. This might also have negatively affected the generalizability of the results. Because there is no global severity scale for spontaneous anterior epistaxis, we could not determine the severity of nosebleeds. However, the randomization used throughout the trial could hopefully account for confounding factors that might have influenced the conclusions. Given that the decision to place anterior nasal packing may be somewhat subjective, a comparison of the need for anterior nasal packing among different studies might not be accurate. Resident physicians may have the tendency to place packing in noses less frequently unless the bleeding is severe. Because the techniques for first aid may have been inconsistent (because they were not protocolized), the rates may have been altered and the effect of tranexamic acid may have been mitigated. Patients with traumatic epistaxis, which can be a concern for emergency physicians in terms of treatment success, were not included in the current study.

DISCUSSION

We found that intranasal topical application of tranexamic acid was significantly beneficial compared with the standard of care in terms of the need for anterior nasal packing, rate of rebleeding within 24 hours, and length of stay in the ED; no difference was observed in the rates of rebleeding or the need for treatment with electrical cauterization between 1 and 7 days of the treatment.

In 1995, Tibbelin et al[18] compared tranexamic acid gel with a placebo in 68 patients with epistaxis (37% of whom had posterior bleeds) treated in an ENT ED, such as that in our center, and found no differences in the rate of rebleeding assessed 30 minutes, 8 days, and 30 days after the treatment. Their study sample size was, however, small. Unlike the study by Tibbelin et al[18] and 2 recent studies,[16,17] we differentiated between anterior and posterior epistaxis. This differentiation helps determine the treatment strategy because hemostasis is more difficult to achieve with posterior bleeding.[22] Patients with posterior epistaxis are more likely to require hospitalization than those with anterior epistaxis; packing is unlikely to work for them.[24]

In their retrospective study, Birmingham et al[21] compared 30 patients treated with tranexamic acid with 92 control patients and found no difference in the length of stay; we found lower rates of ENT consultations (30% versus 65%) and nasal packing (17% versus 24%).

Zahed et al[14,15] performed 2 unblinded, randomized trials comparing tranexamic acid plus lidocaine, epinephrine, and tetracycline with anterior nasal packing. The second trial included patients taking antiplatelet medications. Both the studies found faster control of bleeding, fewer episodes of rebleed, and higher patient satisfaction with tranexamic acid than with anterior nasal packing. An unblinded trial conducted by Akkan et al[16] compared 3 groups of patients—nasal compression with tranexamic acid, nasal compression with a placebo, and anterior nasal packing. Nasal compression plus tranexamic acid and anterior nasal packing had similar initial success; no significant difference was observed in the rates of rebleeding within 24 hours. However, unlike the present study, in which anterior nasal packing was considered an outcome, their trial considered it a study arm.

A nonblinded study conducted by Whitworth et al[23] on 38 patients with anterior epistaxis demonstrated that topical application of tranexamic acid is more effective than the spraying of the vasoconstrictor oxymetazoline applied topically in terms of time to hemostasis.

The largest and most recent study compared tranexamic acid for ED patients with persisting epistaxis after the application of first aid and a vasoconstrictor.[17] The researchers found no differences in the rates of anterior nasal packing or any studied secondary outcomes (hospital admission, blood transfusion, recurrent bleeding, and thrombosis) assessed via a telephone call on the seventh day of the treatment.[17] Their study, however, had several limitations, including a high exclusion rate, which may have resulted in a bias.[17] Unlike the present study, the researchers did not distinguish between anterior and posterior epistaxis. In addition, they excluded patients who were referred for ENT evaluation. In line with the present study, however, they set the need for anterior nasal packing as the primary outcome of their study; however, the current study reached different conclusions in terms of the efficacy of tranexamic acid. The NoPAC study[17] had the outcome decided by the treating clinicians (a diverse group ranging from junior house officers to consultants; it is unclear whether this refers to consultant emergency physicians, consultant ENT surgeons, or some of both), who did not state the number of clinicians who treated the patients at each level. Some clinicians may have been more aggressive or more conservative in deciding to place packing. The current study used ENT residents (a more homogenous group).

A systematic review of randomized controlled trials by Gottlieb et al[12] examining the effects of topical application of tranexamic acid for the treatment of acute epistaxis by comparing it with a control group showed no significant difference in the cessation of bleeding within 30 minutes because of heterogeneity in the control group and primary outcomes; however, it showed that more patients were likely to be discharged within 2 hours of admission and that the reduced rates of rebleeding were linked to the administration of tranexamic acid. They reported 2 critical limitations in those trials. First, only 3 of the included trials assessed the bleeding site, and only patients with anterior epistaxis were involved; the other trials did not indicate the bleeding site. Second, a large number of participants in some of the studies were on antiplatelet agents, which could have contributed to clinical heterogeneity in response to the treatment.[12] The current study assessed the bleeding site and only enrolled patients with anterior epistaxis. Another systematic review by Joseph et al[11] examined 6 clinical trials that compared tranexamic acid in any form (ie, orally, intravenously, or topically) with usual care versus usual care with a placebo, usual care with any other hemostatic drug, and usual care alone.[11] In keeping with the current study, they concluded that the administration of tranexamic acid in addition to usual therapy in adult patients with epistaxis reduces the incidence of rebleeding compared with usual care plus a placebo. However, they presented low-quality evidence exclusively related to topical tranexamic acid (only one study).

The cost of topical administration of tranexamic acid is low, and it is simple to use. This treatment can be performed quickly before more invasive steps are taken; all the necessary means and drugs are readily available in most EDs. Therefore, we suggest the use of topical tranexamic acid for the control of bleeding in adult patients presenting with spontaneous atraumatic anterior epistaxis.

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