

Evaluating Effectiveness of Nasal Compression With Tranexamic Acid Compared With Simple Nasal Compression and Merocel Packing: A Randomized Controlled Trial

Sedat Akkan, MD; Şeref K. Çorbacıoğlu, MD*; Halit Aytar, MD; Emine Emektar, MD; Seda Dağar, MD; Yunsur Çevik, MD

*Corresponding Author. E-mail: serefkeremcorbacioglu@gmail.com, Twitter: [@drserferkem](https://twitter.com/drserferkem).

Study objective: The primary objective of this study is to compare the effectiveness of 3 treatment protocols to stop anterior epistaxis: classic compression, nasal packing, and local application of tranexamic acid. It also aims to determine the frequency of rebleeding after each of these protocols.

Methods: This single-center, prospective, randomized controlled study was conducted with patients who had spontaneous anterior epistaxis. The study compared the effect of 3 treatment options, tranexamic acid with compression but without nasal packing, nasal packing (Merocel), and simple nasal external compression, on the primary outcome of stopping anterior epistaxis bleeding within 15 minutes.

Results: Among the 135 patients enrolled, the median age was 60 years (interquartile range 25% to 75%: 48 to 72 years) and 70 patients (51.9%) were women. The success rate in the compression with tranexamic acid group was 91.1% (41 of 45 patients); in the nasal packing group, 93.3% (42 of 45 patients); and in the compression with saline solution group, 71.1% (32 of 45 patients). There was an overall statistically significant difference among the 3 treatment groups but no significant difference in pairwise comparison between the compression with tranexamic acid and nasal packing groups. In regard to rebleeding within 24 hours, the study found rates of 86.7% in the tranexamic acid group, 74% in the nasal packing group, and 60% in the compression with saline solution group.

Conclusion: Applying external compression after administering tranexamic acid through the nostrils by atomizer stops bleeding as effectively as anterior nasal packing using Merocel. In addition, the tranexamic acid approach is superior to Merocel in terms of decreasing rebleeding rates. [Ann Emerg Med. 2019;■:1-7.]

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INTRODUCTION

Background

Anterior epistaxis is a frequent complaint and one of the most common causes of bleeding in the emergency department (ED).¹ It is self-limited in the majority of cases, but the remaining cases need intervention to stop the bleeding. Although several methods are used to manage anterior epistaxis, including topical vasoconstrictors with nasal compression, silver nitrate sticks, cauterization, and surgical ligation, one of the most common methods used in EDs is anterior nasal packing.²⁻⁵

However, anterior nasal packing, either with or without a topical vasoconstrictor or a local anesthetic, has several complications, including discomfort during placement and removal of the packing, rebleeding after removal of the packing, infection, and tissue necrosis.^{3,6} Therefore, the

search for another effective method continues. Tranexamic acid is an antifibrinolytic agent used to increase hemostasis in major trauma and surgical interventions.^{7,8} A limited number of studies have addressed the topical use of tranexamic acid without nasal packing to manage anterior epistaxis.⁹

Importance

The literature contains many studies of the clinical use of tranexamic acid, including studies of its efficacy for use in anterior epistaxis patients. However, despite the number of studies, it appears to contain no standard for tranexamic acid use in epistaxis management. Instead, it demonstrates that there are many different methods for managing anterior epistaxis and that a significant proportion of them are effective. What is lacking is identification of not only

Editor's Capsule Summary*What is already known on this topic*

Tranexamic acid, an antifibrinolytic agent, has been used to treat anterior epistaxis, but no clear standard for use exists.

What question this study addressed

Is topical tranexamic acid delivered by an atomizer and external nasal compression (without packing) an alternative to traditional nasal packing?

What this study adds to our knowledge

Investigators in this 135-patient randomized trial found no difference in atomized tranexamic acid with nasal compression compared with nasal packing on the outcome of stopping anterior epistaxis bleeding. Rebleeding rates were also lower in the tranexamic acid group.

How this is relevant to clinical practice

Topical tranexamic acid with nasal compression is an effective alternative for stopping anterior epistaxis bleeding and is more comfortable for patients compared with nasal packing.

the most effective method but also the most comfortable one. Some methods, particularly nasal packing, are distressing interventions for patients. Many studies in the literature used the procedure of soaking nasal packing materials with tranexamic acid. This continued use of nasal packing causes patients discomfort, which is why the present study used external compression after administration of tranexamic acid by atomizer in an effort to use tranexamic acid in the most comfortable manner. This innovative feature of our study is its most important contribution to the literature.⁹⁻¹⁴

Goals of This Investigation

Our randomized controlled study aimed to compare the effectiveness of 3 treatment protocols to stop bleeding: classic compression, nasal packing, and local application of tranexamic acid. It also aimed to determine the frequency of rebleeding after each of these protocols.

MATERIALS AND METHODS**Study Design**

This single-center, prospective, randomized controlled study was conducted in the ED of a training and research

hospital that serves 450,000 patients per year and included patients who had spontaneous anterior epistaxis between May and August 2018. Before being enrolled in the study, all participants provided verbal consent before the interventions, and then written informed consent afterward. In addition, the local ethics committee and the national medicines and medical devices agency approved the protocol used in the study.

Outcome Measures

The primary outcome was the success rates of the 3 treatment options in terms of stopping bleeding within 15 minutes. The secondary outcome was a comparison of the rebleeding rate within 24 hours in the 3 treatments groups.

According to the literature, the success rate of nasal packing in stopping bleeding in patients who have anterior epistaxis is 30%.⁹ In the present study, we aimed to achieve a 45% success rate ($\Delta=15\%$) with the tranexamic acid treatment. Hypothesis was set to be 2 sided, with $\alpha=.05$ and a power of 80%, and the sample size in each group was calculated to be 42 patients according to the following formula:

a: $Z\alpha\sqrt{P(1-P)(1/q1+1/q0)}$, b: $Z\beta\sqrt{P1(1-P1)(1/q1)+P0(1-P0)(1/q0)}$, c: $(P1-P0)^2$. The total group size was calculated to be $(a+b)^2/c$. To account for potential protocol violations, the researchers included an additional 3 patients in each group.

Selection of Participants

All patients older than 18 years who presented to the ED with active, spontaneous anterior epistaxis and who did not have any of the exclusion criteria were included in the study, into which patients were enrolled consecutively and continuously. The exclusion criteria were use of current anticoagulation therapy (not antiplatelet therapy) and the presence of hemodynamic instability, defined as patients who had arterial pressure less than 90/60 mm Hg and who had tachycardia (>100 beats/min), or who had altered mental status, traumatic epistaxis, resolved epistaxis on admission, or a known bleeding disorder. All patients who were admitted to triage with nose bleeding complaints and who had received a preliminary diagnosis of anterior epistaxis were evaluated by research assistants. After the first evaluation and examination with a nasal speculum to confirm active anterior epistaxis, patients who did not have any exclusion criteria were included to randomization.

Interventions

Three treatment groups were defined to compare the effectiveness of nasal compression with tranexamic acid,

simple nasal external compression, and nasal packing (Merocel) as treatments for anterior epistaxis. In 3 treatment groups, all patients were asked to blow their nose with tap water, and then an examination was performed with a nasal speculum to visualize the actively bleeding vessel. Before the interventions, all patients were asked to perform external self-compression.

The first treatment group received nasal compression with tranexamic acid; 500 mg of tranexamic acid (Transamine 10% ampoule; Actavis İlaçları AŞ, Istanbul, Turkey) diluted in 5 mL of 0.9% normal saline solution was sprayed with an atomizer into both nostrils of each patient, and then external nasal compression was performed manually for 15 minutes. The second treatment group received compression with saline solution; 5 mL of 0.9% normal saline solution without tranexamic acid was sprayed with an atomizer into both nostrils of each patient, and then external nasal compression was performed manually for 15 minutes. To blind the treating physician and the patients in these 2 groups to the treatment type, the 5 mL of normal saline solution placebo was prepared by another physician before the interventions. All the drugs used had similar colors and amounts. The third treatment group received nasal packing with Merocel (Merocel 2000; Medtronic Xomed, Heerlen, Netherlands) (nasal packing group); nasal packing with Merocel and 2% lidocaine was placed in patients' bleeding nostrils for 24 hours. In all the groups, after 15 minutes, all patients were reexamined to check whether the bleeding had stopped. For the nasal packing group, treatment failure was defined as blood flow over the packing or bleeding into the patient's mouth. In the compression with tranexamic acid and saline solution groups, if bleeding had not stopped, nasal packing was performed. Furthermore, patients whose bleeding continued despite nasal packing were referred to an otolaryngologist for other specific treatment. For purposes of the study, these patients were considered as having treatment failures. All patients were reexamined in the hospital after 24 hours for rebleeding.

All products (tranexamic acid and the Merocel kit) were bought by researchers with their self-budget during the study period.

Three-dimensional permutation blocks that included opaque, sealed envelopes were used to randomly assign (1:1:1) eligible patients to the compression with tranexamic acid, compression with saline solution, or nasal packing groups as their first treatment. The envelopes were prepared by an independent researcher before the study period began.

Although the present study was designed to be double-blind (in regard to both the performing/evaluating physicians and the patients), in the compression with tranexamic acid and compression with saline solution groups, neither the physician nor the patients were blind to the nasal packing in the nasal packing group because of the nature of nasal packing. Therefore, this study cannot be considered blinded.

Primary Data Analysis

All statistical analyses were performed with IBM SPSS (version 20.0; IBM, Chicago, IL). The Shapiro-Wilk test was used to evaluate the normal distribution of continuous variables. The categorical data related to patients were expressed as numbers and percentages and were analyzed with the Pearson χ^2 test. The Kruskal-Wallis test was used to compare the groups' nonparametric data, which were expressed as median values and interquartile ranges (25% to 75%). To compare 2 groups, the Mann-Whitney *U* test was used as a post hoc test after Bonferroni's correction. The median and proportion differences between groups are presented with 95% confidence intervals. The difference of medians was calculated with the method proposed by Bonett and Price.¹⁵

RESULTS

Characteristics of Study Subjects

During the study period, 157 patients who presented to the ED with anterior epistaxis were evaluated. Of these, 22 patients were excluded from the study for various reasons, leaving 135 enrolled in the randomization. The [Figure](#) shows a flowchart of the patients. The median age was 60 years (interquartile range 25% to 75%: 48 to 72 years), and 70 patients (51.9%) were women. All patients' demographic and clinical characteristics are presented in [Table 1](#).

For stopping anterior epistaxis within 15 minutes, the success rate in the compression with tranexamic acid group was 91.1% (41 of 45 patients); in the nasal packing group, 93.3% (42 of 45 patients); and in the compression with saline solution group, 71.1% (32 of 45 patients). The Kruskal-Wallis test found a statistically significant difference among the groups. Comparisons between pairs of groups conducted with the Mann-Whitney *U* test after Bonferroni's correction found no statistically significant difference between the tranexamic acid and nasal packing groups. There was, however, a statistically significant difference between the placebo group and each of the other 2 groups ([Table 2](#)).

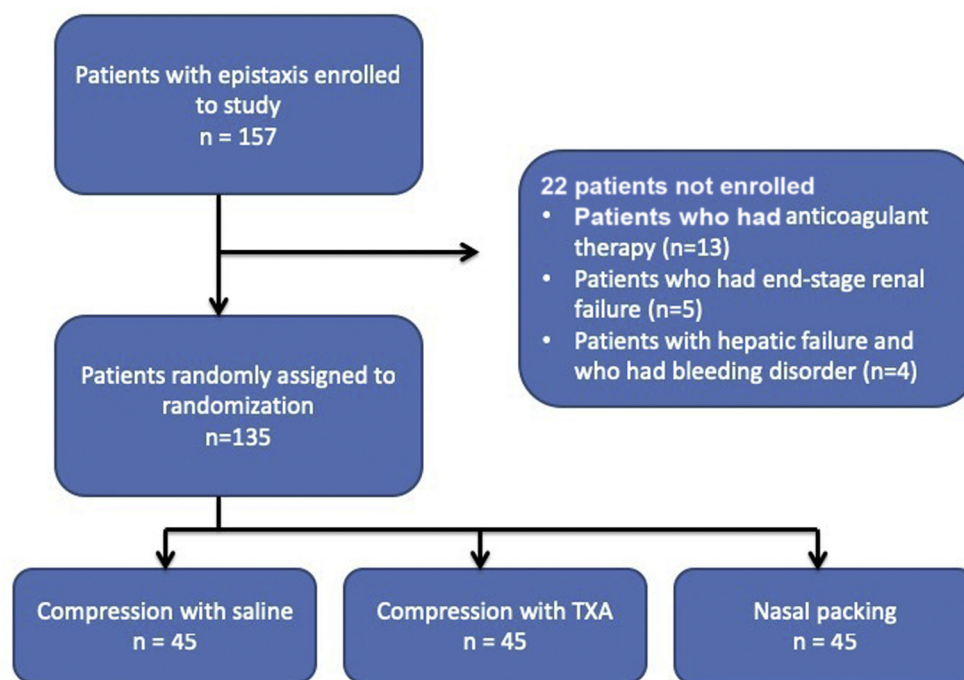


Figure. Flowchart of the patients. TXA, Tranexamic acid.

When rebleeding was considered, it was found that 86.7% of patients in tranexamic acid group (39 of 45 patients), 74% in the nasal packing group (33 of 45 patients), and 60% in the compression with saline solution group (27 of 45 patients) did not exhibit rebleeding at any time up to the defined 24-hour point. A statistically significant difference was found among the groups, and pairwise comparisons between groups (Mann-Whitney *U* with Bonferroni's correction) found that this difference was caused by the tranexamic acid group and there was no significant difference between the nasal packing and compression with saline solution groups (Table 2).

Finally, 7 of the 45 patients in the nasal packing group mentioned severe pain and requested that the procedure be terminated. The procedure actually was terminated in one of these patients, who was considered as having treatment failure according to the intention-to-treat principle. Except for this one case, there were no missing data or protocol violations during the study period.

LIMITATIONS

The present study has 3 main limitations. First, as mentioned in the “Materials and Methods” section, both the physicians and patients in both the tranexamic acid and compression with saline solution groups were blinded to the size of the syringe, the color and amount of its content, and the method of administration, but they were not

blinded to the treatment options because of the nature of nasal packing. Second, the present study did not classify nosebleeds in terms of severity because there is no universal severity scale for spontaneous anterior epistaxis. The Epistaxis Severity Score was originally developed for hemorrhage caused by telangiectasia. Nevertheless, to decrease the effect of this limitation, randomization was performed during the study to provide homogeneity among the groups. Third, although there are many approaches to managing anterior epistaxis, the present study used only anterior nasal tampons and the classic compression method. Therefore, studies using other treatments for anterior epistaxis may reach different results that are based on the approaches used.

We used only Merocel as a commercial packing material. However, there are several studies that reported that other types of commercial packing materials are better tolerated than Merocel. Therefore, if a different type of packing had been used in the present study, the success and adverse effects ratio of the packing group might have changed according to the types chosen.

Although randomization was performed after confirmation of the active anterior epistaxis, before the admission and intervention period the participants could not be standardized in terms of self-treating or first responders treating with external compression.

Finally, we did not include either patients who used anticoagulation therapy or those with traumatic epistaxis,

Table 1. Patients' demographic and clinical characteristics.

	Groups			Differences Between Groups (95% CI)		
	Compression With Saline Solution	Compression With TXA	Nasal Packing	TXA and Saline Solution	Nasal Packing and Saline Solution	Nasal Packing and TXA
Sex, No. (%)						
Women	28 (62.3)	21 (46.6)	21 (46.6)	15.7 (−4.7 to 34)	15.7 (−4.7 to 34)	0 (−19.7 to 19.7)
Age, y						
Median (25%, 75%)	58 (47, 68)*	58 (48, 73)*	63 (48, 73)*	0 (−7.65 to 7.65) [†]	5 (−12.5 to 2.65) [†]	5 (−13.5 to 3.5) [†]
Comorbidities, No. (%)						
Hypertension	21 (46.6)	24 (53.4)	21 (46.6)	6.8 (−13.3 to 26.2)	0 (−19.7 to 19.7)	6.8 (−13.3 to 26.2)
Coronary artery disease	1 (2.2)	7 (15.5)	3 (6.6)	13.3 (1.1 to 26.6)	4.4 (−5.8 to 15.7)	9 (−4 to 22.9)
Diabetes mellitus	5 (11.1)	7 (15.5)	7 (15.5)	4.4 (−10.2 to 19)	4.4 (−10.2 to 19)	0 (−15.3 to 15.3)
COPD	2 (4.4)	1 (2.2)	1 (2.2)	2.2 (−7.6 to 12.7)	2.2 (−7.6 to 12.7)	0 (−9.5 to 9.5)
Congestive heart failure	1 (2.2)	1 (2.2)	1 (2.2)	0 (−9.5 to 9.5)	0 (−9.5 to 9.5)	0 (−9.5 to 9.5)
Other	2 (4.4)	5 (11.1)	3 (6.6)	6.7 (−5.4 to 19.4)	2.2 (−9 to 13.8)	4.5 (−8.3 to 17.6)
Vital signs on admission, median (interquartile range)						
Systolic blood pressure, mm Hg	150 (131-165)*	146 (130-162)*	145 (126-170)*	−4 (−10.2 to 18.2) [†]	−5 (−9.4 to 19.9) [†]	−1 (−14.5 to 16.8) [†]
Diastolic blood pressure, mm Hg	80 (71-90)*	83 (70-94)*	80 (72-92)*	3 (−10.9 to 4.9) [†]	0 (−8.2 to 8.2) [†]	3 (−5.2 to 11.2) [†]
Pulse rate, beats/min	86 (76-96)*	88 (79-96)*	86 (78-95)*	2 (−8.6 to 4.6) [†]	0 (−5.4 to 5.4) [†]	2 (−3.4 to 7.4) [†]
Temperature, °C	36.3 (36-36.7)*	36.3 (36-36.6)*	36.3 (36-36.5)*	0 (−0.6 to 0.6) [†]	0 (−0.6 to 0.6) [†]	0 (−0.6 to 0.6) [†]
Oxygen saturation, %	96 (94-98)*	96 (94-97)*	96 (94-97)*	0 (−1 to 1) [†]	0 (−1 to 1) [†]	0 (−1 to 1) [†]
Respiratory rate, breaths/min	15 (14-16)*	14 (13-16)*	14 (13-16)*	1 (−0.3 to 2.3) [†]	−1 (−2.3 to 0.3) [†]	0 (−1.3 to 1.3) [†]

CI, Confidence interval; COPD, chronic obstructive pulmonary disease.

*Values are presented as median (interquartile range 25%, 75%).

[†]Values are presented as median differences with 95% CI.

groups that are a potential challenge in terms of treatment success for emergency physicians.

DISCUSSION

Our study, which evaluated the effectiveness of topical tranexamic acid as an alternative approach to the standard

treatment of anterior nasal packing in patients with anterior epistaxis, had 3 important findings. First, the success rate of tranexamic acid applied with external compression was not demonstrated to be different from that of standard anterior nasal packing with Merocel in stopping bleeding. Second, the topical tranexamic acid treatment was apparently more

Table 2. Comparison of outcomes according the treatment groups.

	Groups			Differences of Proportions, % (95% CI)		
	Compression With Saline Solution, No. (%)	Compression With TXA, No. (%)	Nasal Packing, No. (%)	TXA and Saline Solution	Nasal Packing and Saline Solution	Nasal Packing and TXA
Stop bleeding within 15 min	32 (71.1)	41 (91.1)	42 (93.3)	20 (3.6 to 35.4)	22.2 (6.3 to 37.3)	2.2 (−10.2 to 14.8)
Rescue treatment	13 (28.9)*	4 (8.9) [†]	3 (6.7) [‡]	20 (3.6 to 35.4)	22.2 (6.3 to 37.3)	2.2 (−10.2 to 14.8)
No bleeding at 24 h	27 (60)	39 (86.7)	33 (73.3)	26.7 (8.4 to 42.8)	14 (−5 to 31.9)	13.4 (−3.3 to 29.4)

*Nasal packing was performed for all patients (13 patients), and bleeding stopped in 10 of the 13 patients. For the remaining 3 patients, cauterization was performed to stopped bleeding.

[†]Nasal packing was performed for all patients (4 patients) and bleeding stopped in all of them.

[‡]Cauterization was performed for all patients (3 patients) and bleeding stopped in all of them.

comfortable because none of the patients receiving it complained of pain, which suggests that tranexamic acid applied with external compression can be preferable to standard anterior nasal packing. Third, the rate of rebleeding within 24 hours was lower in the tranexamic acid group than in both the standard anterior packing group and the classic external compression group. Therefore, given that tranexamic acid application was as good as standard nasal packing at stopping bleeding, better at preventing rebleeding within 24 hours, and more comfortable than both anterior nasal packing and classic external compression, it appears to be very useful in managing anterior epistaxis. Furthermore, tranexamic acid application appears to be cost-effective compared with ready-made products for anterior packing.

The current literature reveals different applications of tranexamic acid for stopping bleeding in anterior epistaxis patients. For example, in a randomized controlled trial, Zahed *et al*⁹ compared nasal packing with tranexamic acid and nasal packing with epinephrine in patients with anterior epistaxis. They found tranexamic acid was more successful in stopping bleeding within 10 minutes than epinephrine (success rates were 71% and 31.6%, respectively). Likewise, tranexamic acid was more successful than epinephrine in terms of the following: the duration of hospitalization, rebleeding within both 24 hours and 7 days, and patient satisfaction. Similarly, in another randomized controlled trial, Clinkard and Barbic¹⁰ compared the use of tranexamic acid-coated and tetracycline-coated anterior nasal tampons in patients with anterior epistaxis. Tranexamic acid was more successful than non-tranexamic acid in bleeding stopped within 10 minutes and rebleeding rates: 71% and 31%, and 4.7% and 12.8%, respectively. Like the results of our study, those of the studies cited above indicate that tranexamic acid may be more effective than anterior nasal packing in managing anterior epistaxis. However, the studies have 2 important differences from our study. First, the researchers applied tranexamic acid to the nostrils by soaking cotton pledgets with it. Second, they did not use ready-made, commercial nasal packing (Merocel, etc). However, in clinical routine, the material used in standard care of anterior epistaxis is just such ready-made packing. Therefore, we believe that the effectiveness of tranexamic acid as a potential new agent must be evaluated against the efficacy of such commercial products. Given this, it is important that our study showed that local administration of tranexamic acid by atomizer without nasal packing was as effective as Merocel, the efficacy of which has been proven.

The difference between past studies and the results of our study is the success rate of stopping bleeding. In each

group, success rates were higher than in previous studies. One of the causes of this high rate might be the differences in the duration of the primary outcome, which was defined as stopping bleeding within 15 minutes rather than 10 minutes. Likewise, in a randomized controlled trial, Tibbelin *et al*¹² compared the abilities of a gel containing tranexamic acid and a placebo in patients with nasal bleeding; the primary outcome was defined as stopping bleeding within 30 minutes, longer than in previous studies. They also reported that the success rate even in the placebo group was 76%.

Heymer *et al*¹³ also described a method of applying tranexamic acid locally to manage epistaxis. Patients were first treated with 2 mL of a solution of tranexamic acid containing 100 mg/mL, administered with a Luer-lock syringe and a mucosal atomizer device, and then soft pressure was applied to the affected nostril. The authors recommended the use of atomizers with drugs to be dispensed over a large surface area because they have greater bioavailability and absorption compared with pipettes or syringe droppers. They also characterized the mucosal atomizer device as ideal for applying injectable tranexamic acid to epistaxis patients in the ICU unless direct pressure or soaked cotton pledgets could be applied. Finally, they recommended that studies with larger sample sizes apply tranexamic acid with atomizers. To our knowledge, our study is the first to evaluate the application of tranexamic acid with an atomizer, thus contributing to filling a significant gap in the literature.

Recently, Zahed *et al*¹⁴ studied patients admitted to the ED with nosebleeds that were associated with antiplatelet therapy. The authors compared the efficacy of topical tranexamic acid and anterior nasal packing and found that patients in the tranexamic acid group had higher cessation of bleeding within 10 minutes and higher patient satisfaction, lower rates of rebleeding within 1 week, and shorter stays in the ED. The number of patients who used antiplatelet therapy was only a small part of our study's population. Therefore, we believe that the study by Zahed *et al*¹⁴ and our study are complementary in terms of the universes they represent.

Another important goal is to determine the optimal dosage of tranexamic acid in treatment of anterior epistaxis. Recently, a systematic review was published by Gottlieb *et al*.¹⁶ Although it has been reported that pledgets soaked in 5 mL (500 mg) of tranexamic acid were used in most studies, a different dosage of tranexamic acid was used in other studies.^{12,13} Overall, we believe that to define optimal dosage and the optimal method of using topical tranexamic acid, novel studies conducted with a standardized dosage regimen and method are required.

Applying external compression after administering tranexamic acid through the nostrils by atomizer stops

bleeding as effectively as anterior nasal packing using Merocel. In addition, the tranexamic acid approach is superior to Merocel in terms of decreasing rebleeding rates. Therefore, we conclude that it may be more logical to manage anterior epistaxis with topical tranexamic acid, which is simple, effective, and comfortable, instead of the relatively uncomfortable anterior nasal packing.

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Author affiliations: From the Department of Emergency Medicine, Kecioren Training and Research Hospital, Ankara, Turkey.

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