

Original Contribution

A new and rapid method for epistaxis treatment using injectable form of tranexamic acid topically: a randomized controlled trial[☆]

Reza Zahed MD^a, Payman Moharamzadeh MD^b, Saeid AlizadehArasi MD^b,
Asghar Ghasemi PhD^c, Morteza Saeedi MD^{d,*}

^a Department of Emergency Medicine, Imam Khomeini Hospital Complex, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran

^b Department of Emergency Medicine, Imam Reza Hospital, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

^c Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

^d Department of Emergency Medicine, Shariati Hospital, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Article history:

Received 19 May 2013

Received in revised form 25 June 2013

Accepted 26 June 2013

ABSTRACT

Objective: Epistaxis is a common problem in the emergency department (ED). Sixty percent of people experience it at least once in their life. There are different kinds of treatment for epistaxis. This study intended to evaluate the topical use of injectable form of tranexamic acid vs anterior nasal packing with pledgets coated with tetracycline ointment.

Methods: Topical application of injectable form of tranexamic acid (500 mg in 5 mL) was compared with anterior nasal packing in 216 patients with anterior epistaxis presented to an ED in a randomized clinical trial. The time needed to arrest initial bleeding, hours needed to stay in hospital, and any rebleeding during 24 hours and 1 week later were recorded, and finally, the patient satisfaction was rated by a 0–10 scale.

Results: Within 10 minutes of treatment, bleedings were arrested in 71% of the patients in the tranexamic acid group, compared with 31.2% in the anterior nasal packing group (odds ratio, 2.28; 95% confidence interval, 1.68–3.09; $P < .001$). In addition, 95.3% in the tranexamic acid group were discharged in 2 hours or less vs 6.4% in the anterior nasal packing group ($P < .001$). Rebleeding was reported in 4.7% and 11% of patients during first 24 hours in the tranexamic acid and the anterior nasal packing groups, respectively ($P = .128$). Satisfaction rate was higher in the tranexamic acid compared with the anterior nasal packing group (8.5 ± 1.7 vs 4.4 ± 1.8 , $P < .001$).

Conclusions: Topical application of injectable form of tranexamic acid was better than anterior nasal packing in the initial treatment of idiopathic anterior epistaxis.

© 2013 Elsevier Inc. All rights reserved.

1. Introduction

Epistaxis, a common condition in all age groups, has a bimodal distribution with 2 peaks: under the age of 10 years and in the 60s [1]. Sixty percent of people probably experience epistaxis once in their life [2]. Although epistaxis may occur secondary to surgery, trauma, hypertension, bleeding disorders, hereditary hemorrhagic telangiectasia, and antiplatelet and anticoagulation drug use, its etiology is unknown in 70% to 80% of cases [3]. Epistaxis is usually self-limiting but can be life threatening, especially in elder patients or those with underlying conditions [4].

Currently, treatment of epistaxis includes squeezing the nose, using vasoconstrictor agents, chemical (silver nitrate) or electrical cauterization, and nasal packing with ribbon gauze or nasal tampon [5]. Nasal packing is usually performed after application of an anesthetic agent such as lidocaine and a vasoconstrictor such as epinephrine [6]; this

may cause mucosal shrinkage and ease of insertion of the pledgets covered with petroleum jelly or ointments such as tetracycline and inflatable balloon or packs [4]. Anterior nasal packing, as one of the most routine management for epistaxis, has some limitations including long stay of the pack, need for prophylactic antibiotics, and need for analgesics [4]; these warrant assessing a more simple method.

Several locally applied hemostatic agents including tranexamic acid [7] and aminocaproic acid [8] have been used for epistaxis treatment. Among them, tranexamic acid has been applied orally [9], topically [7], and as local gels [10]; however, systemic tranexamic acid is contraindicated in thromboembolic patients. The aim of this study was to determine the efficacy of the topical application of the injectable form of tranexamic acid in the treatment of epistaxis.

2. Materials and methods

2.1. Study design

This study was a randomized, single-center, parallel group clinical trial, comparing treatment efficacy of local application of injectable

[☆] The authors declare that there is no conflict of interest with this manuscript.

* Corresponding author. Tel.: +98 2184902717; fax: +98 2184902397.

E-mail address: m_saeedi@tums.ac.ir (M. Saeedi).

form of tranexamic acid (500 mg in 5 mL) in the nasal cavity with that of usual anterior nasal packing. Postgraduate year 3 emergency medicine residents participated in a 2-hour workshop for unifying the ability and skill of the anterior nasal packing and introducing with the process we meant to do.

2.2. Setting and selection of participants

Patients of this study were randomly selected from those with ongoing epistaxis presented to our emergency department (ED) in a large city. Patients with epistaxis following major trauma; posterior epistaxis; known history of bleeding disorder such as thrombocytopenia, hemophilia, and platelet disorders; international normalized ratio greater than 1.5; shock; and visible bleeding vessel were excluded. Finally, patients with idiopathic etiology and recurrent anterior epistaxis even with recurrent previous intervention entered in this study. Two hundred twenty-four patients were randomized and included in the intention-to-treat analysis, 107 in the tranexamic acid group and 109 in the anterior nasal packing group (Fig.). The patients participated in this study for 7 days. This study was approved by ethics committee of our institute and was registered at IRCT.Ir (no. IRCT201201308872N1); informed consent was obtained from all patients before entry to trial.

2.3. Randomization and blinding

Treatment allocation was according to a previously determined randomization code by SPSS software as simple randomization. Our research nurse generated a randomization list using computer-generated random numbers by SPSS program. The nurse randomized and blinded the boxes filled by medication and cotton pledgets required for management in a location removed from the ED and inaccessible to the ED personnel. The ED physicians were presented with the unmarked boxes, which were applied for patients in the order determined by randomization according to the protocol they were learned before.

Because of the nature of the study, using different medications differing in consistency, color, and smell for soaking or coating the pledgets and discrepancy in the number of pledgets used, our physicians and patients were not blinded truly. However, data sets analyzed while analysts were blinded. The investigators doing the analysis were not the same as those performing the nasal packing.

2.4. Interventions

In the tranexamic acid group, a 15-cm piece of cotton pledget soaked in injectable form of tranexamic acid (500 mg in 5 mL) was inserted in the nostril of the bleeding side. It was removed after bleeding arrest was determined by examining the blood-soaked pledgets and the oropharynx. In the anterior nasal packing group, usual shrinkage, with a cotton pledget soaked in epinephrine (1:100000) + lidocaine (2%) for 10 minutes, and packing, with several cotton pledgets covered with tetracycline, were performed in the nostril of the bleeding side. Nasal packing was removed after 3 days. Routine anterior nasal packing and cautery, if needed, were considered as rescue treatment for the tranexamic acid group and cautery for the anterior nasal packing group.

2.5. Methods of measurement

The taken time to arrest bleeding was evaluated and recorded in every 5-minute intervals and before leaving the ED. Efficacy variables recorded were (1) the frequency of patients with epistaxis arrested within 10 minutes from treatment onset, (2) the frequency of patients with rebleeding within 24 hours and 7 days after treatment, (3) the hours a patient should stay in the ED, and (4) the patient satisfaction rate evaluated by a 0-10 scale.

Emergency medicine residents did the follow-up for rebleeding occurrence and possible complications by telephone call or revisiting schedule depending on feasibility for patients. At discharge time, the patient satisfaction was rated on a visual analog scale presented by our research nurse.

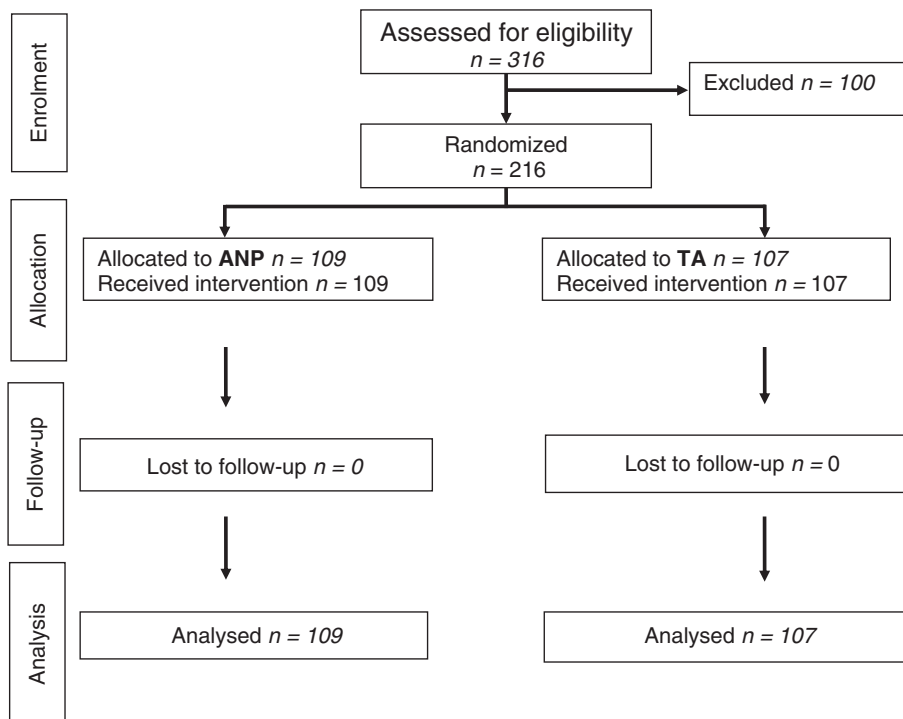


Fig. CONSORT Standards of Reporting Trials flow diagram.

Table 1
Patient characteristics

	Anterior nasal packing (n = 109)	Tranexamic acid (n = 107)	P
Age (y)	54 ± 15.5	50.4 ± 19	.129
Sex (%) (male/female)	52.3/47.7	62.6/37.4	.125
PLT × 10 ³ /μL	293 ± 76	294 ± 80	.935
PT (s)	12.4 ± 1.4	12.4 ± 0.7	.959
INR	1.08 ± 0.16	1.08 ± 0.16	.962
PTT (s)	33.1 ± 3.6	33 ± 2.6	.838
History of epistaxis (% of yes)	13.6	58.1	<.001

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

2.6. Sample size calculation

Based on our experience, in 30% of patients with epistaxis treated with anterior nasal packing, bleeding stopped less than 10 minutes. In the current study, we aimed whether a new treatment (injectable form of tranexamic acid) could achieve 50% success ($\Delta = 20\%$). We set 2-sided α of .05 and power of 80%, and sample size in each group was calculated to be 91 according to the formula:

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} - Z_{1-\beta} \right)^2 \times [\pi_1(1-\pi_1) + \pi_2(1-\pi_2)]}{\Delta^2} = \frac{(1.96 + 0.842)^2 \times [0.3(1-0.3) + (1-0.5)]}{0.2^2} = 91;$$

we added 20% to this value, and final sample size was about 110 in each group [11].

2.7. Analysis

IBM SPSS statistics 20 was used for statistical analyses. The primary and secondary efficacy variables were compared between 2 groups by χ^2 test, and risk estimate and effect size were calculated; ϕ coefficient was considered as effect size statistics. Mann-Whitney *U* test was used for comparing satisfaction rate between groups. For comparing basic characteristics between 2 groups, independent-sample *t* test and χ^2 test were used for continuous and categorical variables, respectively.

3. Results

3.1. Characteristics of study subjects

This randomized clinical trial study was conducted on 216 subjects (124 men and 92 women). Basic characteristics of the patients are presented in Table 1. Two groups were comparable regarding these variables except for epistaxis history, which was significantly higher in the tranexamic acid group.

3.2. Outcomes

Within 10 minutes of treatment, bleedings were arrested in 76 (71%) of 107 patients in the tranexamic acid group, compared with 34 (31.2%) of 109 patients in the anterior nasal packing group (odds ratio, 2.27; 95% confidence interval, 1.68–3.06; $P < .001$). In addition, 102 (95.3%) of 107 patients in the tranexamic acid group were discharged in 2 hours or less vs 7 (6.4%) of 109 patients in the anterior nasal packing group.

There was no statistically significant difference between both groups in complications (nausea/vomiting and intolerance) reported

by patients or observed by physicians. In addition, there was no patient who cannot tolerate this soaked cotton pledget in the tranexamic acid group, and no serious adverse event was observed in the study (Table 2).

Rebleeding was reported in 5 (4.7%) of 107 and 14 (12.8%) of 109 patients during the first 24 hours in the tranexamic acid and the anterior nasal packing groups, respectively ($P = .034$). After 1 week, rebleeding in the tranexamic acid and the anterior nasal packing groups were 2.8% and 11%, respectively ($P = .018$) (Table 2). Satisfaction rate was higher in tranexamic acid (8.5 ± 1.7) compared with anterior nasal packing (4.4 ± 1.8) ($P < .001$).

3.3. Limitations of the study

Our study has some limitations. We excluded posterior epistaxis, so we have no data on this group of patients. In addition, in our study, the patients referred to our ED were included and considered severe enough to need medical attention, so severity of epistaxis was not classified, and the 2 groups were not analyzed regarding this variable. The fact that providers and patients were not blinded to treatment is another limitation.

4. Discussion

Epistaxis treatments are divided into conservative and surgical treatments; in the former, in addition to the routine packing by gauze or cotton pledgets, there are some commercially available products such as Surgicel, Gelfoam, and Merocel.

The results of this trial showed that treating anterior epistaxis with the topical use of injectable form of tranexamic acid is better than usual nasal packing. In our study, nasal bleeding in $\approx 70\%$ of patients in the tranexamic acid group was arrested within 10 minutes compared with $\approx 30\%$ in the anterior nasal packing group, results similar to Petruson [12] using oral tranexamic acid. Unlike our results, Tibbelin et al [10], studying the effect of local tranexamic acid gel in the treatment of epistaxis in 68 patients, have reported that bleeding was arrested in 60% of patients compared with 76% in the placebo group within 30 minutes; however, it should be noted that we used injectable form of tranexamic acid with just a piece of cotton pledget. In the current study, only $\approx 3\%$ of patients in the tranexamic acid group had rebleeding during 1 week compared with 11% in the anterior nasal packing group. Corresponding values in the study of Tibbelin et al are 11% and 31%. Klepfish et al [13] reported a marked decline in the intensity of epistaxis controlling within minutes after using tranexamic acid in a patient with hereditary hemorrhagic telangiectasia, and after years, he almost stopped using iron supplement and blood transfusions almost concomitantly. Sabba et al [7] reported an improvement in treating 3 cases of intractable epistaxis in patients with hereditary hemorrhagic telangiectasia with high doses of tranexamic acid administered orally.

These results indicate that using tranexamic acid for epistaxis treatment could reduce rebleeding. One possible explanation for lower rebleeding rate in the tranexamic acid group observed in our study is that tranexamic acid, as an antifibrinolytic agent, could reduce increased fibrinolytic activity reported in patients with epistaxis [9]. Tranexamic acid such as aminocaproic acid is an antifibrinolytic agent;

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

	Anterior nasal packing	Tranexamic acid	Odds ratio (95% confidence interval)	Effect size ^a	P
Bleeding stop time ≤ 10 min (%)	31.2	71	2.28 (1.68–3.09)	0.398	<.001
Discharge time ≤ 2 h (%)	6.4	95.3	14.8 (7.2–30.4)	0.889	<.001
Complications in the ED (%)	11	4.7	0.42 (0.16–1.16)	–0.118	.128
Rebleeding in the first 24 h (%)	12.8	4.7	0.36 (0.14–0.98)	–0.144	.034
Rebleeding in 1 wk (%)	11	2.8	0.26 (0.07–0.88)	–0.161	.018

^a Based on ϕ coefficient.

however, it is nearly 10 times more potent and has a longer half-life; both drugs exert their effects by reversibly binding to plasminogen and inhibiting its binding to fibrin, which, in turn, prevented plasminogen activation and transformation into plasmin [14,15].

More than 95% of our patients in the tranexamic acid group were discharged within only 2 hours after admission compared with only 6.4% in the anterior nasal packing group. Similarly, it has been reported that using tranexamic acid for epistaxis treatment reduced hospitalization time.

In our study, patient satisfaction was greater in the tranexamic acid group. Convenience is an important factor in each treatment regarding simplicity for providers and patients' pain and discomfort. In addition, this technique may be used by a novice physician or a nurse. Tibbelin et al [10] showed the simplicity and convenience of use in application of an anterior nasal packing with tranexamic acid gel.

In conclusion, it seems that using injectable form of tranexamic acid topically could provide a better treatment for idiopathic anterior epistaxis compared with usual anterior nasal packing. Shorter time to stop bleeding, shorter hospital stay, fewer rebleeding cases, more convenient for patients, and simplicity for health care providers are advantages of this new method.

Acknowledgment

The authors thank Ms Asieh Naderi, BSc of Nursing, PhD student of Physiology.

References

- [1] Viehweg TL, Roberson JB, Hudson JW. Epistaxis: diagnosis and treatment. *J Oral Maxillofac Surg* 2006;64(3):511–8.
- [2] Doyle DE. Anterior epistaxis: a new nasal tampon for fast, effective control. *Laryngoscope* 1986;96(3):279–81.
- [3] Stell PM. Epistaxis. *Clin Otolaryngol Allied Sci* 1977;2(3):263–73.
- [4] Bertrand B, Eloy P, Rombaux P, et al. Guidelines to the management of epistaxis. *B-ent* 2005;1(1):27–43.
- [5] Aejumjaturapat S, Supanakorn S, Cutchavaree A. Toxic shock syndrome after anterior-posterior nasal packing. *J Med Assoc Thai* 2001;84(3):453–8.
- [6] Burton MJ, Doree CJ. Interventions for recurrent idiopathic epistaxis (nosebleeds) in children. *Cochrane Database Syst Rev* 2004;1:CD004461.
- [7] Sabbà C, Gallitelli M, Palasciano G. Efficacy of unusually high doses of tranexamic acid for the treatment of epistaxis in hereditary hemorrhagic telangiectasia. *N Engl J Med* 2001;345(12):926.
- [8] Jash D. Epistaxis—topical use of epsilonaminocaproic acid in its management. *J Laryngol Otol* 1973;87(9):895–8.
- [9] White A, O'reilly B. Oral tranexamic acid in the management of epistaxis. *Clin Otolaryngol Allied Sci* 2007;13(1):11–6.
- [10] Tibbelin A, Aust R, Bende M, et al. Effect of local tranexamic acid gel in the treatment of epistaxis. *ORL J Otorhinolaryngol Relat Spec* 1995;57(4):207–9.
- [11] Daly LE, Bourke GJ. Interpretation and uses of medical statistics. 5th ed. Oxford: Blackwell Science Ltd; 2000.
- [12] Petruson B. Epistaxis. A clinical study with special reference to fibrinolysis. *Acta Otolaryngol Suppl* 1974;317:1–73.
- [13] Klepfish A, Berrebi A, Schattner A. Intranasal tranexamic acid treatment for severe epistaxis in hereditary hemorrhagic telangiectasia. *Arch Intern Med* 2001; 161(5):767.
- [14] Thorsen S. Differences in the binding to fibrin of native plasminogen and plasminogen modified by proteolytic degradation. Influence of omega-aminocarboxylic acids. *Biochim Biophys Acta* 1975;393(1):55–65.
- [15] Hoylaerts M, Lijnen HR, Collen DS. Studies on the mechanism of the anti-fibrinolytic action of tranexamic acid. *Biochimica et Biophysica Acta* 1981;673: 75–85.