Archives of Academic Emergency Medicine. 2021; 9(1): e6
https://doi.org/10.22037/aaem.v9i1.875

OPEN ACCESS

ORIGINAL RESEARCH

Topical Tranexamic Acid versus Phenylephrine-lidocaine for the Treatment of Anterior Epistaxis in Patients Taking Aspirin or Clopidogrel; a Randomized Clinical Trial

Keyvan Amini[1], AmirAhmad Arabzadeh[2]*, Sevda Jahed[3], Payman Amini[3]

1. Department of Emergency Medicine, School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran.
2. Department of surgery, School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran.
3. School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran.

Received: September 2020; Accepted: October 2020; Published online: 19 November 2020

Abstract: **Introduction:** Epistaxis is one of the most prevalent complaints in the emergency department (ED), especially in patients who take antiplatelet agents. This study aimed to compare the effect of topical use of tranexamic acid (TXA) with phenylephrine-lidocaine anterior nasal packing (PANP) in controlling epistaxis of patients who take aspirin or clopidogrel. **Methods:** This prospective, double-blind, parallel-group, randomized clinical trial was conducted to compare the effect of topical use of intravenous (IV) TXA compared with PANP on controlling anterior epistaxis in patients who take aspirin or clopidogrel. **Results:** One hundred patients with the mean age of 59.24 ± 7.75 (45 – 75) years were studied (52% male). Two groups were similar in terms of age (p=0.81) and sex (p=0.23) distribution, diabetes mellitus (p=0.54), and hypertension (p = 0.037). The mean time to stop bleeding was 6.70 ± 2.35 minutes in the TXA group and 11.50±3.64 minutes in the PANP group (p=0.002). Bleeding recurrence occurred in 3 (6%) cases of the TXA group and 10 (20%) cases of the PANP group (p =0.03). Time to discharge from ED in the TXA group was significantly lower than the PANP group (p<0.001). The absolute risk reduction (ARR), relative risk reduction, and number needed to harm of treatment with TXA for anterior nasal bleeding were 14.00% (95%CI: 1.11 – 26.89), 17.50% (95%CI: 0.60 - 37.27), and 7.14 (95%CI: 3.71 -90.43), respectively. **Conclusion:** Topical TXA is an appropriate treatment option in bleeding cessation, and reducing re-bleeding and duration of hospital stay in patients with epistaxis who take antiplatelet agents.

Keywords: Tranexamic Acid; phenylephrine, lidocaine drug combination; Epistaxis; Aspirin; Clopidogrel; Emergency Medical Services

Cite this article as: Amini K, Arabzadeh A, Jahed S, Amini P. Topical Tranexamic Acid versus Phenylephrine-lidocaine for the Treatment of Anterior Epistaxis in Patients Taking Aspirin or Clopidogrel; a Randomized Clinical Trial. Arch Acad Emerg Med. 2021; 9(1): e6.

1. Introduction

Epistaxis is described as bleeding from the nostrils, inner part of the nasal cavity, or nasopharynx, and is one of the most common complaints among patients referring to the emergency department (ED) (1). The lifetime prevalence of epistaxis is about 60% and up to 6% will need medical care (2). Global estimations show that nosebleed mostly occurs in children under 10 and elderly over 60 years old, which results in the bimodal age distribution (3). About 90% of nosebleeds originate from Kiesselbach's plexus in the anterior nasal septum, while the remaining 10% occurs in the posterior nasal septum or the lateral wall of the nasal cavity (4). Many local and systemic conditions such as traumas (physical or medication-induced mucosal traumas), decreased nasal mucosa moisture, septal perforations, viral or bacterial rhinosinusitis, neoplasms, coagulation disorders, and some drugs such as anticoagulant or antiplatelet agents may cause epistaxis (3). Although epistaxis is typically self-limiting; it can be life-threatening in elderly patients, especially those who have underlying diseases and take antiplatelet medications such as aspirin or clopidogrel (5). Various treatment strategies, from compression therapy to nasal packing, are available in ED to control nosebleed (6). Some studies suggest using tranexamic acid (TXA), an antifibrinolytic agent, in oral,

*Corresponding Author: AmirAhmad Arabzadeh; Department of surgery, Fatemi Hospital, Ardabil, Iran. Email: amir.arabzadeh@arums.ac.ir, amir_medico@yahoo.com Fax number: +984533249947, Tel: +984533249947, ORCID: https://orcid.org/0000-0001-9594-5522.

intravenous (IV), or topical forms to control epistaxis; but the clinical evidence of its use is limited, especially in patients who receive antiplatelet aggregation agents (7-9). Since using antiplatelet drugs is common in older ages, it is of great importance to appropriately manage this group of patients. This study aimed to compare the effect of topical use of intravenous (IV) TXA with phenylephrine-lidocaine anterior nasal packing (PANP) in controlling epistaxis of patients who take aspirin or clopidogrel.

2. Methods

2.1. Study design and setting

This prospective, double-blind, parallel-group, randomized clinical trial was conducted in the ED of the Fatemi Hospital, affiliated to Ardabil University of Medical Sciences (ARUMS), to compare the effect of topical use of TXA (intravenous (IV) form) with PANP, in controlling anterior epistaxis. This study was approved by the Ethics Committee of ARUMS (ethics code: IR.ARUMS.REC.1398.249) and was registered on the Iranian Registry of Clinical Trials (IRCT) with the number IRCT20191008045031N1.

Before beginning the study, patients were assured that they were free to participate or not, they would not be charged any additional fees for participating, and the researchers adhered to ethical principles and their personal information is completely confidential and would not be published anywhere. The written informed consent was obtained from all participants before the study.

2.2. Participants

All patients who referred to ED with an episode of epistaxis and were under treatment with antiplatelet drugs (aspirin, clopidogrel, or both) were enrolled in this study. Patients not willing to participate in the study and those with multiple trauma, hereditary hemorrhagic or platelet disorders, hemophilia, renal dysfunction, or obvious bleeding from other parts of the body were excluded.

2.3. Intervention

After diagnosis confirmation by an emergency medicine specialist in the ED, eligible patients were randomly allocated to either receive a single topical application of 1-gram TXA IV form (Tranexip (B: 215)) or PANP (Nasophrin (lot: 902872)) using block randomization method. The triage nurse who was blinded to the intervention, delivered prepacked sequentially numbered boxes, which were not accessible to other ED staff and contained intervention material, in the procedure room. The TXA group received a wad of cotton steeped in the injectable form of TXA (500 mg in 5 mL), which was lodged into the bleeding nostril. The PANP group received a wad of cotton steeped in phenylephrine (1:100,000) + lidocaine (2%) lodged into the bleeding nostril and remained for 10 minutes. Following bleeding cessation, tetracycline ointment-soaked PANP was inserted and left in place for 3 days for both groups. To assess intervention outcomes in both groups, a blinded attending emergency medicine specialist confirmed bleeding cessation and in case of persistent bleeding despite initial intervention, an appropriate second-line treatment e.g., cautery was considered.

2.4. Outcome

The primary outcome was bleeding cessation time defined as the time it took the treatment to stop bleeding. The secondary outcomes were: (a) bleeding recurrence defined as re-bleeding within 72 hours after the initial bleeding episode, (b) the length of hospital stay, and (c) the relationship between bleeding recurrence with sex, hypertension (HTN), and diabetes mellitus (DM) in both treatment arms. Patient's demographic information such as age, sex, duration of aspirin or clopidogrel administration and their dosage were recorded in researcher-developed questionnaires that were filled out by the patients.

2.5. Randomization

The random allocation sequence was generated by our triage nurse, using SPSS software for windows version 16, which was stratified by the center. All patients who met the inclusion criteria were randomly allocated to either the TXA group or the PANP group using a random sampling method. Sequentially numbered boxes containing intervention medications and materials were previously prepared and our nurse used a random allocation sequence to allocate a treatment to each patient. The boxes were completely identical in appearance, size, and weight and were delivered sequentially to the medical intern. The triage nurse was blinded to the intervention and the contents of the boxes. Because of obvious differences in color and smell of the two medications used for our trial, the medical intern who performed the intervention was not blinded to the intervention. However, the attending emergency medicine specialist who evaluated the treatment outcomes and confirmed the bleeding cessation and bleeding recurrence within 72 hours was completely blinded to the intervention. The person who statistically analyzed the data was also blinded to the group assignment.

2.6. Statistical analysis

Based on the data extracted from a previous similar trial, considering the power of 90%, first type error of 0.5%, efficacy in the group p1 = 28.3, and p2 = 66.7%, the sample size was determined as 40 per group using the sample size formula for the intervention. We assigned the sample size of 50 people to each group considering the possibility of sample drop out. All data were analyzed using Statistical Package for the So-

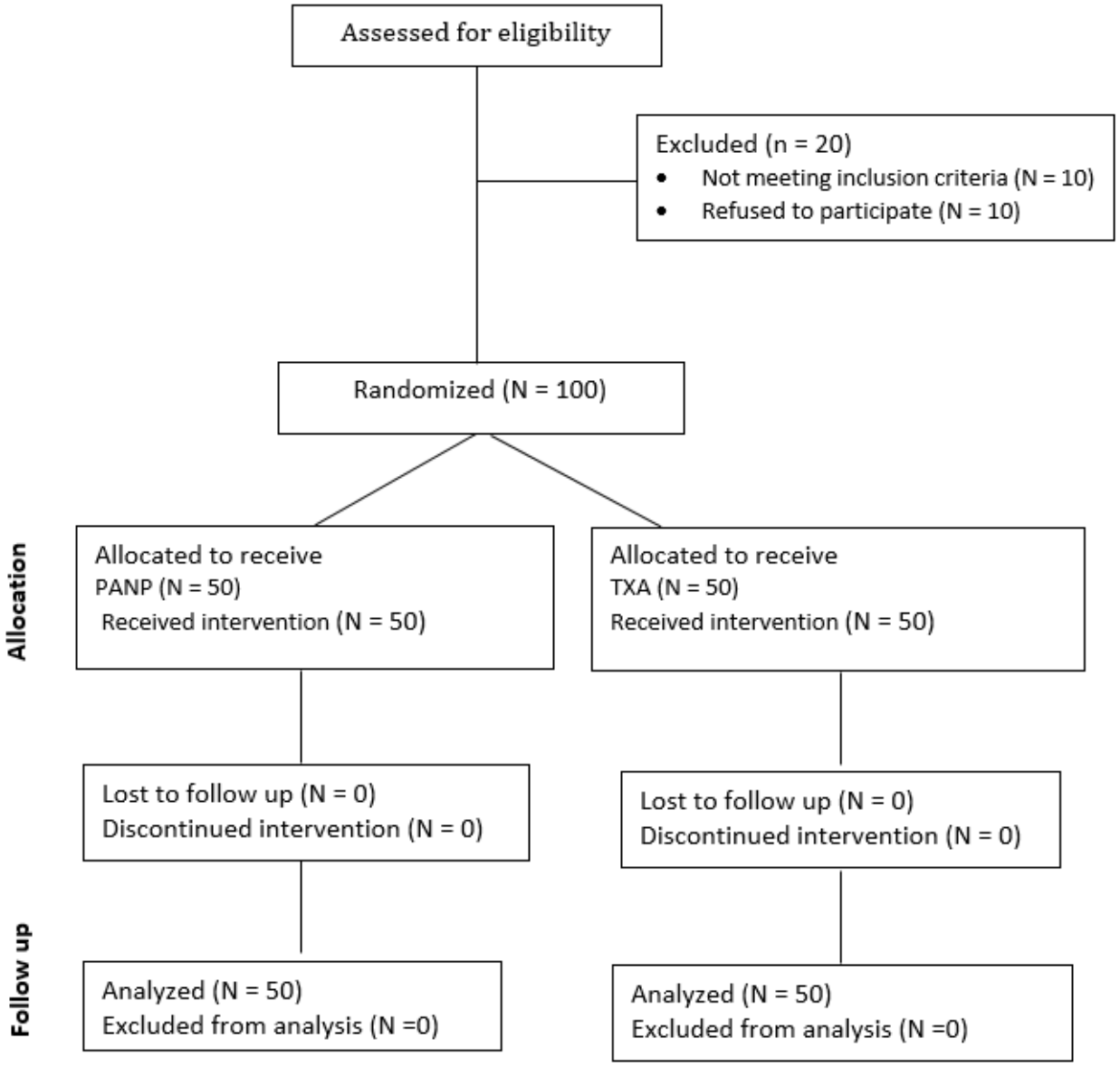

Figure 1: Patient allocation flowchart. PANP: phenylephrine/lidocaine soaked anterior nasal packing; TXA: tranexamic acid.

cial Sciences (SPSS) version16. Descriptive statistical methods (frequency, percentage, mean ± standard deviation [SD]) were used for the presentation of the findings. Independent T-test was used to compare the quantitative findings and Chi-square test was used to compare the qualitative findings. P-values of less than 0.05 were considered significant.

The absolute risk reduction, relative risk reduction, and number needed to harm (uncontrolled bleeding) of treatment with TXA for anterior nasal bleeding were calculated and reported with 95% confidence interval (CI).

3. Results

3.1. Baseline characteristics of the studied cased

One hundred patients with the mean age of 59.24 ± 7.75 (45-75) years were studied (52% male). Figure 1 shows the allocation flowchart of the study. Baseline characteristics of the studied cases were compared between groups in table 1. The two groups were similar in terms of the age (p = 0.81) and sex (p = 0.23) distribution, diabetes mellitus (p = 0.54), hypertension (p= 0.037), and history of bleeding (p = 0.001).

3.2. Treatment outcomes

Table 2 compares the treatment outcomes between the groups. The mean time to stop bleeding was 6.70 ± 2.35 minutes in the TXA group and 11.50 ± 3.64 minutes in the PANP group (p=0.002). Bleeding recurrence occurred in 3 (6%) of the cases who were treated with TXA and 10 (20%) cases treated with PANP (p=0.03). Time to discharge from ED in the TXA group was significantly lower than the PANP group (p<0.001). Patients with a history of HTN had significantly higher rates of bleeding recurrence in the PANP group (p= 0.001).

The absolute risk reduction (ARR), relative risk reduction, and number needed to harm of treatment with TXA for anterior nasal bleeding were 14.00% (95%CI: 1.11 – 26.89), 17.50% (95%CI: 0.60 - 37.27), and 7.14 (95%CI: 3.71 -90.43), respectively.

4. Discussion

The findings of this study indicate that the use of TXA for management of epistaxis is associated with faster bleeding cessation, lower rates of re-bleeding, and a shorter length of hospital stay compared to PANP. Treatment with TXA had 17.5% lower risk of rebleeding. Number needed to harm of treatment with TXA was 7.1, which means that about 7 patients need to be treated with TXA in order for one case to have uncontrolled bleeding.

Local compression is the first step in management of epistaxis with anterior circulation origin (10). The next steps may include the application of a cotton swab soaked in vasoconstrictors, cauterization, and nasal packing. Finally, nasal endoscopy may be considered to find underlying pathogenesis, in cases with recurrent epistaxis (5, 10). Current clinical guidelines suggest using resorbable packing for patients with bleeding disorders or those receiving antiplatelet or anticoagulation agents (10). Packing strategies have shown to lessen the length of hospital stay compared to non-packing ways such as cauterization, embolization, and ligation (11).

Tranexamic acid is a synthetic analogue of lysine amino acid, which binds to plasminogen and plasmin, thereby inhibiting their ability to bind to residual lysine in fibrin, thus preventing fibrinolysis. It is used in heavy menstrual bleedings, postpartum hemorrhage, bleedings following dental procedures, and hematologic disorders (12). This treatment is readily available, inexpensive, and easy to apply (12, 13). Several studies have investigated its effect on controlling epistaxis in patients taking or not taking antiplatelet drugs (9). Interestingly, it has been beneficial in nebulized and atomized intranasal forms in patients with difficult-to-control epistaxis (14, 15). Literature review on TXA efficacy demonstrates its benefits in reducing recurrent bleeding and duration of hospital stay, as well as higher patient satisfaction.

Similar to our findings, Zahed et al. showed that TXA is significantly more efficient in bleeding cessation within 10 minutes of application, compared to PANP, in patients receiving antiplatelet medications such as aspirin and clopidogrel. Moreover, TXA reduced re-bleeding within one week of the first episode and the length of hospital stay (7). In a study by Saeedi et al., 68% of people treated with TXA achieved hemostasis in 5-10 minutes, whereas this measure was 15-20 minutes in patients treated with anterior nasal tampon. They also reported lower re-bleeding rates and hospital length of stay in patients receiving TXA, compared to anterior tampon, which are consistent with our findings (16). Atabaki et al. made a comparison between phenylephrine and TXA in terms of achieving hemostasis after 10 minutes of application in patients with nosebleed, and observed a significant difference between two groups (17). The results of another study by Zahed et al., comparing topical use of the injectable form of TXA with ANP with tetracycline ointment, demonstrated that TXA was more efficient in stopping initial bleeding, which led to shorter hospital stay length, but it showed no superiority in reducing bleeding recurrence (9). Comparison of the effect of topical application of IV form of TXA with topical oxymetazoline spray, a vasoconstrictor medication, revealed the significant advantage of using TXA to control bleeding (18).

A retrospective study of adult patients with epistaxis who were admitted to a general hospital showed that using TXA had considerable results in reducing bleeding. The results of this study specified diabetes and hypertension as strong predictors of re-admission, which is in agreement with our findings (19).

A number of studies have investigated the effect of TXA on some hematologic disorders (20, 21). The results of a placebo-controlled cross-over trial in patients with hereditary hemorrhagic telangiectasia complaining of epistaxis revealed that the administration of TXA significantly reduces the mean duration of epistaxis per month but not the median number of epistaxis episodes per month (20). A similar trial by Geisthoff et al. also suggests that the administration of one gram of TXA, three times daily for three months can reduce epistaxis score by 54% compared to the placebo in patients with hereditary hemorrhagic telangiectasia (21).

Among anticoagulant medications, TXA was considered an effective management option in a patient with underlying atrial fibrillation, receiving rivaroxaban (a factor X inhibitor used for stroke prophylaxis) who was referred to ED due to epistaxis (22). In contrast to our findings, some studies found little or no benefits in using TXA for treating epistaxis. The results of one study, comparing TXA gel with placebo, showed no significant differences in time to control bleeding and its recurrence (23). Using oral TXA for 10 days as adjunct therapy revealed no superiority to placebo regarding re-bleeding

Table 1: Screening performance characteristics of rapid emergency medicine score (REMS) and rapid acute physiology score (RAPS) in prediction of mortality and poor outcome

Variables	Treatments		P value
	TXA (n = 50)	PANP (n = 50)	
Age (year)			
45 - 55	17 (34.0)	18 (36.0)	
55 - 65	27 (54.0)	25 (50.0)	0.91
≥ 65	6 (12.0)	7 (14.0)	
Sex			
Male	29 (58.0)	23 (46.0)	0.2
Female	21 (42.0)	27 (54.0)	
Diabetes mellitus			
Yes	7 (14.0)	5 (10.0)	0.54
No	43 (86.0)	45 (90.0)	
Hypertension			
Yes	5 (10.0)	13 (26.0)	0.037
No	45 (90.0)	37 (74.0)	

Data are presented as mean ± standard deviation (SD) or number (%). TXA: tranexamic acid; PANP: phenylephrine/lidocaine soaked anterior nasal packing.

Table 2: Overall performance of rapid emergency medicine score (REMS) and rapid acute physiology score (RAPS) in prediction of in-hospital mortality and poor outcome

Variables	Treatments		P value
	TXA (n = 50)	PANP (n = 50)	
Successful bleeding control			
Number (%)	47(94.0)	40 (80.0)	0.037
Bleeding Cessation Time (minutes)			
< 5	10 (20.0)	1 (2.0)	
5 – 10	35 (70.0)	6 (12.0)	0.001
10 - 15	5 (10.0)	22 (4.0)	
≥ 15	0 (0.0)	21 (42.0)	
Re-bleeding in 72 hours			
N (%)	3 (6.0)	10 (20.0)	0.03
Duration of hospital stay (Hours)			
<1	19 (38.0)	3 (6.0)	
1 – 2	26 (52.0)	5 (10.0)	<0.001
2 -4	3 (6.0)	24 (48.0)	
>4	2 (4.0)	18 (36.0)	

Data are presented as mean ± standard deviation (SD) or number (%). TXA: tranexamic acid; PANP: phenylephrine/lidocaine soaked anterior nasal packing

and its severity within 10 days of initial epistaxis (24). In the survey of Birmingham et al., topical TXA was not beneficial for reducing ED length of stay; however, it was associated with a significant reduction in otolaryngologist consults and nasal packing rates in management of acute epistaxis (25). Topical use of the IV form of TXA seems to provide a better treatment option for anterior epistaxis compared with PANP in patients, taking antiplatelet drugs. The advantages of topical TXA treatment demonstrated in our study included quick bleeding cessation, and reducing re-bleeding and duration of hospital stay in patients. The technique is also relatively simple and is easy to teach and learn.

5. Limitation

The main limitation of this study was the small sample size. Another limitation was the lack of an objective measurement index for the bleeding cessation in patients with epistaxis; however, we tried to reduce the effect of this limitation by asking for the opinions of an emergency medicine attend for confirming bleeding cessation.

6. Conclusion

Topical TXA is an appropriate treatment option for cessation of bleeding, and reducing re-bleeding and duration of hospital stay in patients with epistaxis who take antiplatelet agents.

7. Declaration

7.1. Acknowledgements

The authors would like to thank Ardabil University of Medical Sciences, Ardabil, Iran for financial support, cooperation, and assistance throughout the study.

7.2. Author contribution

K.A. and A.A.; Designed and performed experiments, analyzed data, and wrote the paper. K.A. and S.J.; Performed experiments. P.A.; Performed bioinformatics analyses. K.A. and A.A.; Supervised the research.

7.3. Funding/Support

None.

7.4. Conflict of interest

The authors declare no conflict of interest.

References

1. Viehweg TL, Roberson JB, Hudson J. Epistaxis: diagnosis and treatment. Journal of oral and maxillofacial surgery. 2006;64(3):511-8.
2. Chaaban MR, Zhang D, Resto V, Goodwin JS. Demographic, seasonal, and geographic differences in emergency department visits for epistaxis. Otolaryngology–Head and Neck Surgery. 2017;156(1):81-6.
3. Bell MD G. Management of Epistaxis. 2016.
4. Tabassom A, Cho JJ. Epistaxis (nose bleed). StatPearls [Internet]. 2020.
5. Svider P, Arianpour K, Mutchnick S. Management of epistaxis in children and adolescents: avoiding a chaotic approach. Pediatric Clinics. 2018;65(3):607-21.
6. Wojak JC, editor Endovascular Treatment of Epistaxis. Seminars in Interventional Radiology; 2020: Thieme Medical Publishers.
7. Runyon MS. Topical tranexamic acid for epistaxis in patients on antiplatelet drugs: a new use for an old drug. Academic Emergency Medicine. 2018;25(3):360-1.
8. Joseph J, Martinez-Devesa P, Bellorini J, Burton MJ. Tranexamic acid for patients with nasal haemorrhage (epistaxis). Cochrane Database of Systematic Reviews. 2018(12).
9. Zahed R, Mousavi Jazayeri MH, Naderi A, Naderpour Z, Saeedi M. Topical tranexamic acid compared with anterior nasal packing for treatment of epistaxis in patients taking antiplatelet drugs: randomized controlled trial. Academic Emergency Medicine. 2018;25(3):261-6.
10. Tunkel DE, Anne S, Payne SC, Ishman SL, Rosenfeld RM, Abramson PJ, et al. Clinical practice guideline: nosebleed (epistaxis). Otolaryngology–Head and Neck Surgery. 2020;162(1_suppl):S1-S38.
11. Zhou AH, Chung SY, Sylvester MJ, Zaki M, Svider PS, Hsueh WD, et al. To pack or not to pack: inpatient management of epistaxis in the elderly. American journal of rhinology & allergy. 2018;32(6):539-45.
12. Sethi RK, Kozin ED, Abt NB, Bergmark R, Gray ST. Treatment disparities in the management of epistaxis in United States emergency departments. The Laryngoscope. 2018;128(2):356-62.
13. Timp JF, Braekkan SK, Lijfering WM, van Hylckama Vlieg A, Hansen J-B, Rosendaal FR, et al. Prediction of recurrent venous thrombosis in all patients with a first venous thrombotic event: The Leiden Thrombosis Recurrence Risk Prediction model (L-TRRiP). PLoS medicine. 2019;16(10):e1002883.
14. McGrath ER, Go AS, Chang Y, Borowsky LH, Fang MC, Reynolds K, et al. Use of oral anticoagulant therapy in older adults with atrial fibrillation after acute ischemic stroke. Journal of the American Geriatrics Society. 2017;65(2):241-8.
15. Cai J, Ribkoff J, Olson S, Raghunathan V, Al-Samkari H, DeLoughery TG, et al. The many roles of tranexamic acid: An overview of the clinical indications for TXA in medical and surgical patients. European journal of haematology. 2020;104(2):79-87.
16. Abootalebi Ghahnavieh A, Tashayoie A, Nasr Esfahani M, Golshani K. Comparative Study of the Efficacy of Topical Tranexamic Acid with Nasal Tampon in Management of Epistaxis: A Randomized Clinical Trial. Scientific Journal of Kurdistan University of Medical Sciences. 2020;25(4):140-9.
17. Atabaki P, Soheili A, Aribi MS, Samarei R, Mehryar HR. A comparative study on the effect of topical phenylephrine with topical tranexamic acid in management of epistaxis. The J Urmia Nurs Midwifery Fac. 2017;15(7):488-96.
18. Whitworth K, Johnson J, Wisniewski S, Schrader M. Comparative Effectiveness of Topically Administered Tranexamic Acid Versus Topical Oxymetazoline Spray for Achieving Hemostasis in Epistaxis. The Journal of emergency medicine. 2020;58(2):211-6.
19. Jervis S, Saunders T, Belcher J, Skinner D. Evaluating three hundred and fifty-two admissions and predictors of re-admissions for epistaxis–is it time to re-evaluate tranexamic acid in epistaxis? Clinical Otolaryngology. 2017;42(2):439-42.
20. Gaillard S, Dupuis-Girod S, Boutitie F, Rivière S, Morinière S, Hatron PY, et al. Tranexamic acid for epistaxis in hereditary hemorrhagic telangiectasia patients: a European cross-over controlled trial in a rare disease. Journal of Thrombosis and Haemostasis. 2014;12(9):1494-502.

21. Geisthoff UW, Seyfert UT, Kübler M, Bieg B, Plinkert PK, König J. Treatment of epistaxis in hereditary hemorrhagic telangiectasia with tranexamic acid-a double-blind placebo-controlled cross-over phase IIIB study. Thrombosis Research. 2014;134(3):565-71.
22. Utkewicz MD, Brunetti L, Awad NI. Epistaxis complicated by rivaroxaban managed with topical tranexamic acid. The American journal of emergency medicine. 2015;33(9):1329. e5-. e7.
23. Tibbelin A, Aust R, Bende M, Holgersson M, Petruson B, Rundcrantz H, et al. Effect of local tranexamic acid gel in the treatment of epistaxis. ORL. 1995;57(4):207-9.
24. White A, O'reilly B. Oral tranexamic acid in the management of epistaxis. Clinical Otolaryngology & Allied Sciences. 1988;13(1):11-6.
25. Birmingham AR, Mah ND, Ran R, Hansen M. Topical tranexamic acid for the treatment of acute epistaxis in the emergency department. The American journal of emergency medicine. 2018;36(7):1242-5.