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Original Article

Use of Tranexamic Acid for Controlling Epistaxis in the Patients Referring to the Emergency Department: Single-blind Randomized Clinical Trial

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Abstract

Introduction: Use of tampons is one of the most common ways to treat epistaxis. This single Randomized clinical trial aimed to assess the efficiency of tranexamic acid (TA) in controlling different types of bleeding.

Methods: From 2019 to 2020, 120 patients with epistaxis, referred to the Imam Reza Hospital(Tabriz-Iran) emergency department, and were treated. The patients were randomly divided into control (tampon) and intervention (TA) groups. The control group received tetracycline-impregnated tampon, while TA-impregnated gauze was used for the intervention group.

Results: The mean time needed to stop bleeding was significantly higher (p=0.011) in the control group (18.59±2.33 Min) than in the intervention group (09.33±1.47 Min). In most patients in the intervention group bleeding stopped in less than 10 minutes; while in the control group. Bleeding in the majority of patients ceased within 10 to 20 minutes (p=0.01).

Conclusion: The results indicate the beneficial effects of TA, as a drug with relatively low side effects in reducing bleeding time in patients with epistaxis. Thus, it can be used as a complementary drug, along with packing to stop bleeding.

Keywords: Bleeding, Tranexamic Acid, Epistaxis, Emergency.

Introduction

Epistaxis or nosebleed is defined as active bleeding from the nose and is one of the most common reasons for referral to the emergency department [1-3]. The condition is most common in children < 10 years and the elderly over 60 years, showing an increasing trend by age [4]. In addition, its incidence is lower among women than men and higher in cold and dry weather (i.e., winter). Despite the high prevalence of this phenomenon, there are still no detailed and standard therapeutic guidelines for rapid management of the emergency department epistaxis [5, 6]

Topical treatments using vasoconstrictor drugs, electrical nasal catheterization, and nasal packs are among the first-line therapy for epistaxis [7, 8]. Applying tampons seems to be an easier and faster way to manage epistaxis compared to other nasal packing tools. However, the packing method has some disadvantages such as causing discomfort to the patient during applying the pack, middle-ear infections, sinus obstruction, nasal mucosal, cartilage necrosis (due to the tampon pressure), toxic shock syndrome, and hypoventilation (which may lead to arterial hypoxia and apnea). Therefore, it seems necessary to provide a relatively simple and cheap therapeutic method to treat epistaxis in a short time and subsequently avoid the complications of tampons [9, 10] .

Tranexamic acid (TA), which acts as a fibrinolysis inhibitor, was first introduced to the market in the 1960s to control blood loss and reduce the need for blood transfusions, and it soon acquired many applications [11] . The drug reversibly and competitively attaches to and blocks the lysine binding sites on plasminogen. In this way, it deactivates the molecule, prevents its conversion to plasmin, and finally reduces its tendency for fibrin. This drug has been widely used to treat many sorts of bleeding; however, studies on its effectiveness for the treatment of epistaxis have reported contradictory results [12]. Among different treatment methods used in these studies, applying diverse tampons has been one of the most common strategies to manage epistaxis. Nevertheless, this method may be associated with the recurrence of epistaxis in some patients. This study aimed to compare the therapeutic effects of topical TA and tampons in controlling epistaxis.

Methods

Design

It was a randomized single-blind (the data analyzer was unaware of group allocations) clinical trial with a control group performed during 2019-2020 in the emergency department of Imam Reza Hospital (Tabriz, Iran).

Sample Size

Considering a confidence interval of 95%, power of 80% with the minimum difference between the mean bleeding time of 0.6 seconds, the sample size was estimated to be 44 per group. Considering a possible dropout during the study and increasing the power of the study, 60 patients were included in each group, giving a final sample size of 120. Patients were recruited by accessible sampling and randomly allocated to study groups.

Randomization

The block randomization method (blocks of 4) was used in the study. One of the researchers who was not blinded to group allocations assigned the intervention (TA) and control (tampon) groups with "A" and "B" letters, respectively. The researcher then distributed the "A" and "B" packs among the patients referring to the emergency department using the block randomization method. The randomized distribution of the blocks based on a random sequence of numbers continued until reaching the required sample size. The random sequence was created by assigning the blocks (6 blocks) a number from 1 to 6. According to the sample size, any number of 4-blocks that were needed was used. The number of the blocks was extracted from the table of random numbers. The sequence of blocks in each group was determined based on these numbers. Randomization was performed using Randlist software (version 2.1).

Inclusion and Exclusion Criteria

All patients with idiopathic anterior epistaxis or those with the previous epistaxis were enrolled. Only the patients who had bleeding from one nasal passage were included. Exclusion criteria were epistaxis due to trauma, posterior epistaxis, and a history of bleeding disorders such as thrombocytopenia, hemophilia, and platelet disorders. Also, patients with seizures (This drug lowers the seizure threshold), arterial or venous thrombosis, those taking anticoagulants, antiplatelet drugs, and even aspirin, besides patients with leukemia, lymphoma, and polycythemia vera, and pregnant women were excluded from the study.

Interventions

Patients' demographic and clinical information, including age, sex, history of cardiovascular diseases, previous epistaxis, systolic, diastolic, and mean arterial blood pressure and heart rate, were recorded. In the control (tampon) group, patients were treated with a tampon lubricated with tetracycline, which was left in the nasal passage for three days. The size of the tampon was adjusted based on the patient's nasal passage. In this group, the cessation of bleeding was due to the pressure applied on the bleeding vessel by the tampon; tetracycline antibiotic was used to prevent the growth of infectious agents such as *Staphylococcus aureus*. In the intervention (TA) group, a 15-cm-long gas was soaked with injectable TA (500 mg per 5 ml) and placed in the bleeding nasal passage. The gas was removed after the bleeding stopped. In this group, the cessation of bleeding was due to the inhibition of fibrinolysis.

Because different interventions were used in this study, it was impossible to use a double-blind strategy, and only the emergency nurse, the person who was responsible for data collection, and the researcher who

analyzed the data were unaware of the grouping process. After the interventions, patients remained in the emergency department for 30 minutes and were examined every 5 minutes to record the bleeding time. The ceased bleeding criterion was observing no bleeding according to a physician's opinion. In addition, the patient's condition was monitored by phone call during the first 24 hours and also one week after the intervention for recording any possible side effects such as nausea and vomiting (Since epistaxis may recur after one week after treatment or side effects of the drug may occur later, patients were ethically followed up for one week). Also, patients' satisfaction was scored as 0 (no satisfaction at all), 1 (average satisfaction), and 2 (complete satisfaction).

Statistical Analysis

The collected data was entered into SPSS version 22 software. The descriptive statistics of mean ±standard deviation, frequency, and frequency percentage were used along with inferential statistical tests including Chi-square and one-way analysis of variance (ANOVA). The significance level in all analyses was considered a P value of <0.05.

Results

During the mentioned period, 254 patients were referred to the emergency department, of which 134 due to the criteria of exclusion (trauma: 43, aspirin: 20, pregnancy: 15, leukemia: 5, seizures: 3 patients, hemophilia: 17 patients, arterial thrombosis: 5 patients, posterior epistaxis: 25 patients) were excluded from the study and the study started with 120 patients and ended with 120 patients (sample loss was zero). (Figure 1)

The majority of participants in both study groups were men; the patients' mean age was 51.48±6.97 years. A history of cardiovascular diseases or epistaxis was seen in a small number of the patients in both groups. The overall mean values of systolic blood pressure, diastolic blood pressure, and heart rate were 145.22 ± 11.59 mmHg, 87.14 ± 8.47 mmHg, and 91.65 ± 9.19 (beat per minute), respectively, showing no statistically significant difference between the two groups (Table 1).

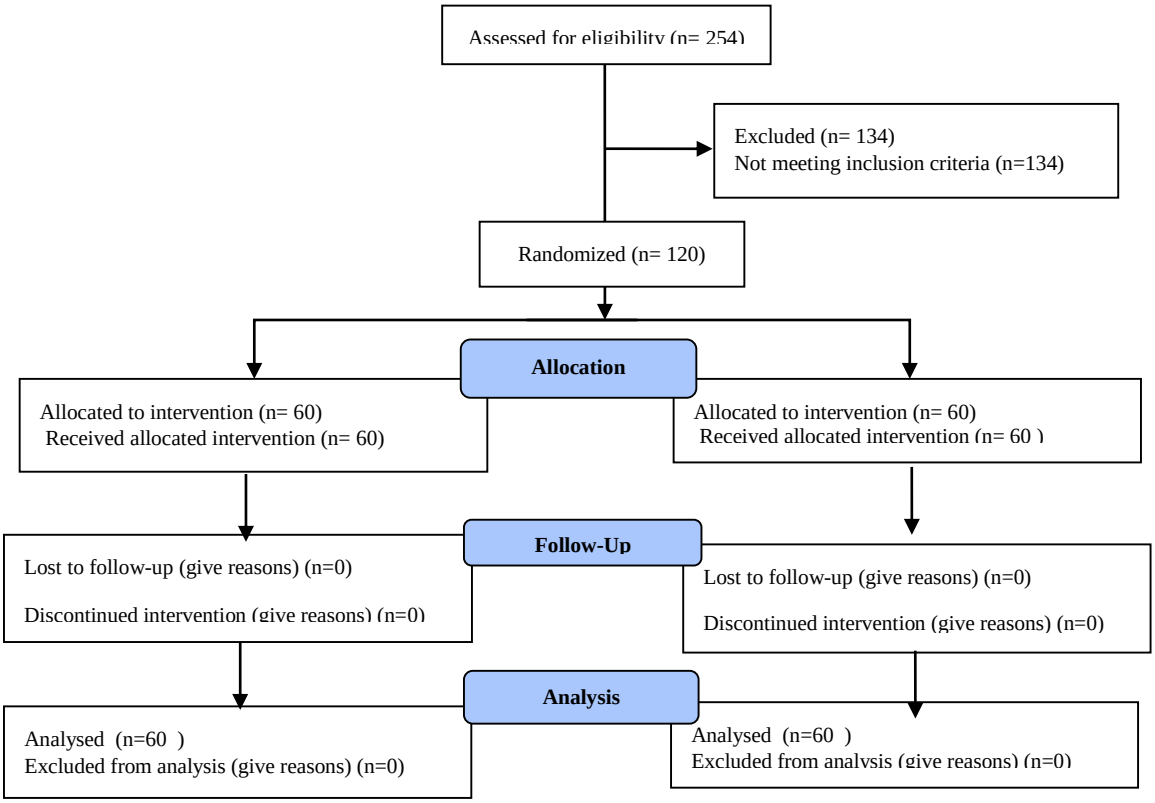

Figure 1: Figure 1: Patients entering and leaving

Table 1. Participants' Demographic and Clinical Information.

Variable		Groups(N=120)		P Value
		TA(N=60)	Control (N=60)	
Sex	Male	40(66.67%)	38(63.33%)	0.514
	Female	20(33.33%)	22(36.67%)	
Age		52.12±7.59	50.39±7.01	0.293
History of cardiovascular disease		11(18.33%)	13(21.67%)	0.201
History of Epistaxis		17(28.33%)	15(25%)	0.245
Systolic blood pressure		141.48±12.59	148.96±12.36	0.315
Diastolic blood pressure		85.40±7.33	89.69±7.67	0.219
Heart Rate		88.74±8.39	94.47±10.25	0.319

The mean time of bleeding to stop was significantly higher in the control group compared with the intervention group (p = 0.011). In most patients in the intervention group, bleeding stopped in less than 10 minutes, while in the control group, the bleeding in the majority of patients ceased within 10 to 20 minutes. Also, no statistically significant differences were observed between the two groups regarding bleeding recurrence during the first 24 hours or the first week after the interventions (Table 2).

Table 2. Comparing Bleeding Time Between the Intervention and Control Groups.

Variable		Groups(N=120)		P Value
		TA(N=60)	Control (N=60)	
Stop the bleeding		09.33±1.47	18.59±2.33	0.011
Bleeding stop time	<10 Min	48(80%)	20(33.33%)	0.01
	10-20Min	9(15%)	26(43.33%)	
	20-30Min	3(05%)	13(21.66%)	
	>30 Min	0(0%)	1(1.67%)	
Re-bleeding	The first 24 hours	5(08.33%)	8(13.33%)	0.319
	The first week	0(0%)	1(1.67%)	

Finally, our results showed that TA administration was associated with fewer side effects than tampon application. In addition, patient satisfaction was higher in the intervention group compared to the control group, indicating the high efficiency of TA in controlling bleeding (Table 3).

Table 3. Comparison of the Complication and Satisfaction Rates Between the Study Groups

Variable		Groups(N=120)		P Value
		TA(N=60)	Control (N=60)	
Satisfaction (First Day)	Low	2(3.3%)	6(10%)	0.008
	Moderate	7(11.6%)	15(25%)	
	High	51(85%)	39(65%)	
Satisfaction (second Day)	Low	0(0%)	6(10%)	0.005
	Moderate	2(3.3%)	6(10%)	
	High	58(96.6%)	48(80%)	
Satisfaction (Third Day)	Low	0(0%)	3(8.3%)	0.001
	Moderate	0(0%)	5(80%)	
	High	60(100%)	52(86.6%)	
Complications	Nausea(First Day)	4(6.6%)	9(15%)	0.009
	Vomit(First Day)	1(1.66%)	3(5%)	
	Nausea(second Day)	0(0%)	5(3.3%)	0.001
	Vomit(second Day)	0(0%)	2(8.3%)	
	Nausea(Third Day)	0(0%)	3(5%)	0.001
	Vomit(Third Day)	0(0%)	1(1.66%)	

Discussion

The present study aimed to evaluate the effects of TA on controlling epistaxis in patients referring to the emergency department. The patients were allocated to two groups, including tetracycline-impregnated tampon (control) and TA-impregnated gas (intervention). The two groups were comparable in terms of baseline characteristics such as age, gender, previous history of nasal bleeding, and other clinical variables, so no confounding variables were assumed to affect the results of the present study. Our results demonstrated

that the time needed for bleeding to stop was significantly longer in the control group than in the intervention group. There were also statistically significant differences between the bleeding times of subsequent episodes (24 hours and one-week post-intervention) between the study groups. Overall, the results of the present study indicated that TA more efficiently prevented bleeding compared to tetracycline-impregnated tampons.

Consistently, Zahed *et al*. (2013) described that the topical use of injectable TA successfully controlled epistaxis in 71% of patients, whereas the nasal packs impregnated with tetracycline prevented bleeding in only 323% of patients. Also, the number of patients discharged in less than 2 hours in the group receiving TA was significantly higher than the group treated with anterior nasal packs. In conclusion, it seems that the treatment of idiopathic anterior epistaxis with the topical application of injectable TA is more effective than using tetracycline-impregnated nasal packs in managing the bleeding [13].

In addition, Logan *et al*. (2016) noted that the topical use of TA might be beneficial in patients with epistaxis [14]. Moreover, in a systematic review by Kamhieh *et al*. (2016), three clinical trials on spontaneous epistaxis were assessed. Of these studies, one declared that oral TA had no effects on acute epistaxis; the other study also described no remarkable effect for topical TA; however, the third study, which had the largest sample size, showed that topical TA treatment was effective in treating acute epistaxis [15].

Nowadays, reaching ideal homeostasis via anti-fibrinolytic agents is one of the principles of treating patients with bleeding, which in turn reduces bleeding and the patient's need for frequent blood transfusions [16]. Because TA inhibits fibrinolysis via blocking a specific lysine residue on plasminogen, it can be used as an effective drug to manage bleeding in many emergencies in which bleeding is potentially or present. Many previous studies have also reported the beneficial effects of this drug in preventing bleeding during various surgeries (ear, pharynx, nose, etc.). For example, Ker *et al*. (2013) confirmed that topical TA reduced bleeding and the need for blood transfusion in the patients undergoing surgery; nevertheless, the effect of this drug on the risk of thromboembolism remains unclear. Moreover, the applicability of topical TA in patients with non-surgical bleeding is not yet verifiable [3].

Unlike the mentioned studies, some other studies did not find conclusive evidence on the effects of TA in controlling bleeding. In contrast to our results, the findings of Hilton *et al*. did not support the use of topical intranasal TA in the management of epistaxis in patients with stable hemodynamics, referring to the emergency department [17]. In addition, Tibbelin *et al*. (1995) observed no significant difference between the control group and the epistaxis patients treated with TA gels [18]. Therefore, although the anti-fibrinolytic effects of this drug are known, different administration methods (e.g., injection, topical, gels, or as impregnated gas) may influence its therapeutic effectiveness. So, the discrepancy between our findings and those of the two mentioned studies may be explained by the different routes of TA administration.

The systemic administration of TA has been associated with complications such as systemic hypercoagulation and the risk of lower extremity vein thrombosis, pulmonary embolism, myocardial infarction, and cerebral stroke. Another study mentioned that although TA might reduce bleeding, its side effects are multiple and understudied. It is noteworthy that in patients referred to the emergency department with epistaxis, TA is administered as a topical, not a systemic, drug, reducing the risk of complications [19].

Limitations and Suggestions

We did not use an objective criterion for detecting the cessation of bleeding, which was tried to be obviated by designing a single-blinded trial and the approval of bleeding cessation by an emergency medicine specialist. Due to the relatively low sample size, it was not applicable to use different doses and methods of TA administration, which was another limitation of the present study. In general, due to the effectiveness of topical TA in managing epistaxis, it is recommended to perform studies with larger sample sizes, applying different TA doses and administration routes.

Conclusion

The results of this study indicated the beneficial effects of TA in reducing bleeding time in patients with epistaxis. Regarding the relatively low side effects of this drug, it can be prescribed as a complementary

treatment along with the standard therapy to better and quickly manage to bleed, especially in patients with severe epistaxis admitted to the emergency department.

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Conflict of Interest Disclosures

None

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Authors' Contributions

NSH: Study Design and Intervention. MMM: Intervention and data collection. AD: Data Collection and Data analysis. RM: Study Design and Manuscript Submission.

Ethical Considerations

This study was approved by the ethics committee of Tabriz University of Medical Sciences and registered in the Iranian Registry for Clinical Trials. No costs were imposed on patients or insurance companies. Written informed consent forms were signed by all participants before the intervention and after explaining the study's goals to them.

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