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

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Abstract: Introduction: Epistaxis is one of the most prevalent complaints in the emergency department (ED), especially in patients who take antplatelet 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 antplatelet agents.

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

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 Kiesselebach'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 antplatelet 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 antplatelet 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,
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 Fatemeh 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 IRCT2019100845031N1.

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.

3. Results

3.1. Baseline characteristics of the studied cases

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, cautery, 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 cautery, 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.
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.

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)       |            |         |
| Age (year)         |            |         |
| 45 - 55            | 17 (34.0)  |         |
| 55 - 65            | 27 (54.0)  |         |
| ≥ 65               | 6 (12.0)   |         |
| Sex                |            |         |
| Male               | 29 (58.0)  |         |
| Female             | 21 (42.0)  |         |
| Diabetes mellitus  |            |         |
| Yes                | 7 (14.0)   |         |
| No                 | 43 (86.0)  |         |
| Hypertension       |            |         |
| Yes                | 5 (10.0)   |         |
| No                 | 45 (90.0)  |         |

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)                       |            |         |
| Successful bleeding control        |            |         |
| Number (%)                         | 47 (94.0)  |         |
| Bleeding Cessation Time (minutes)  |            |         |
| < 5                                | 10 (20.0)  |         |
| 5 – 10                             | 35 (70.0)  |         |
| 10 – 15                            | 5 (10.0)   |         |
| ≥ 15                               | 0 (0.0)    |         |
| Re-bleeding in 72 hours            |            |         |
| N (%)                              | 3 (6.0)    |         |
| Duration of hospital stay (Hours)  |            |         |
| <1                                 | 19 (38.0)  |         |
| 1 – 2                              | 26 (52.0)  |         |
| 2 – 4                              | 3 (6.0)    |         |
| ≥4                                 | 2 (4.0)    |         |

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

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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. PA.; 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.

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