Original Article

Impact of Topical Tranexamic Acid on Bleeding Control in Rhinoplasty

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ABSTRACT

Background: Hemorrhage during rhinoplasty may impair the surgeon's visibility. Our objective was to examine the impact of subcutaneously administered Tranexamic acid (TXA) on bleeding during rhinoplasty.

Methods: A three-blind randomized clinical trial including 60 patients undergoing nose surgery was conducted to compare the effects of two different anesthetic solutions on surgery results. The control group received a solution consisting of 5 cc of 2% lidocaine and 0.5 cc of epinephrine 1/100000, and the TXA group received a solution containing 5 ml of 2 lidocaine, 0.25 cc of epinephrine 1/100000 and 4.75 cc of 10% TXA. To achieve a total injection volume of 10 ml in both groups, distilled water was added. Bleeding rate, hemodynamic parameters, surgeon satisfaction and overall quality of the surgical field were evaluated.

Results: The hemodynamic parameters exhibited no notable differences between the two groups throughout the study period (P value > 0.05). The volume of bleeding observed in the TXA group was marginally greater than that in the control group (P value=0.061). Additionally, there were no significant variations in the quality of the surgical field or the satisfaction levels of the surgeon between the two groups.

Conclusion: In the TXA group, there was no increase in bleeding despite using a low concentration of epinephrine. Consequently, it is recommended that an injectable formulation of TXA containing a reduced concentration of epinephrine be used in surgical procedures where the use of high-concentration epinephrine is contraindicated, such as in patients with cardiovascular disease.

KEYWORDS
Bleeding; Rhinoplasty; Tranexamic Acid

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INTRODUCTION

Rhinoplasty is one of the most common surgeries in the ear, throat and nose ward and is considered one of the most precise, delicate and difficult plastic surgeries [1].

Intra operative bleeding in this surgery, even in a small amount, can disturb the surgeon's vision and lead to the risk of surgical complications, prolonged bleeding time, postoperative eye problems or cranial base

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bones problems and prolonged operative time. Therefore, paying attention to the management of intraoperative bleeding in rhinoplasty can be of great importance and so far various methods have been used to do [2].

In this regard, some approaches such as using local vasoconstrictors, controlled hypotension, cauterization and packing can be mentioned to control intraoperative bleeding[3]. Each of these methods will lead to complications; for example, controlled hypotension may be associated with administration of higher doses of anesthetic drugs and more side effects, cauterization may be associated with delayed bleeding and tissue damage. Local vasoconstrictors may be associated with hemodynamic instability (especially in patients with hypertension or ischemic heart disease) [3-5].

Generally, none of the mentioned methods can provide a promising surgical field. Intravenous infusion of transoxamic acid (TXA) is another method of intraoperative bleeding management, which has already been approved in endoscopic sinus surgery (4). Until now, TXA has been used to reduce bleeding and need of transfusion in cardiac, gynecological and cesarean sections as well as neurosurgeries and orthopedic surgeries [6, 7]. TXA, a synthetic derivative of the amino acid lysine, is an antifibrinolytic agent that binds to plasminogen and blocks the interaction of plasmin (ogen) with fibrin results to prevent dissolution of the fibrin clot and lysis of blood clots by inhibiting the action of plasmin [4-7]. TXA does not increase thromboembolic complications such as deep vein thrombosis and pulmonary embolism. In addition, previous studies in the field of cardiovascular and orthopedic procedures have shown that TXA reduces bleeding and the need for transfusion; without major complications [8-10].

In addition, study the effect of TXA on the quality of facial plastic surgery, septoplasty and rhinoplasty has been shown that the administration of TXA can be effective in reduction or control of bleeding [11-13].

Although many studies have pointed to the effect of different doses of TXA in reducing postoperative bleeding, but less attention has been paid to the use of this drug in rhinoplasty and comparing the different methods of use (venous, subcutaneous, local). For this purpose, we compared the effect, complications and benefits of subcutaneous TXA on the rate of bleeding in rhinoplasty.

MATERIALS AND METHODS

This clinical trial was conducted in a randomized, triple-blinded, and controlled manner. The participants included individuals who were potential candidates for rhinoplasty and were referred to the educational hospitals affiliated with Isfahan University of Medical Sciences, Iran, between 2022 and 2023. To determine the sample size, previous study [14] were taken into account, which reported the standard deviation of bleeding as 56 and 55 in the TXA and control groups, respectively. With a 95% confidence level, the estimated sample size was 60, with 30 participants in each group.

The Ethics Committee of Isfahan University of Medical Sciences approved the study protocol, with the ethical code: IR.MUI.MED.REC.1400.709. Subsequently, the clinical trial code (IRCT: IRCT20210614051574N14; available at https://irct.ir/trial/66060) was obtained. Informed consent forms were then completed by 60 eligible patients, and their basic and clinical information, including age and weight, was recorded upon study entry.

Inclusion criteria

Included female candidates for rhinoplasty surgery under general anesthesia, aged between 18 and 50 years with ASA class I, with hemoglobin above 10 g/dL and normal INR, PT, and PTT.

In addition, participants provided written informed consent to participate in the study.

Exclusion criteria

Patients with American Society of Anesthesiologists (ASA) class 2 and higher, previous medical history of sensitivity or limitation in the use of study drugs TXA, trinitroglycerin, propofol or lidocaine) history of smoking or drug abuse, use of aspirin, and anti-platelet drugs were not included in the study. Furthermore, if it was not feasible to monitor the patient's condition and measure the necessary parameters until the completion of the intervention due to various reasons, such as the inability to continue the intervention until the end of the surgery or the occurrence of complications that hindered the continuation of the intervention, those patients were also excluded from the study.

Using random allocation software, the 60 patients

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were divided into two groups of 30 each. After positioning the patients on the surgical bed, their mean arterial pressure (MAP), systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were documented. Before anesthesia induction, Ringer's solution was administered at a dosage of 4 mL/kg. A standardized general anesthesia protocol was implemented for all patients using 0.03 mg/kg midazolam, 2 µg/kg fentanyl, 2 mg/kg propofol, and 0.6 mg/kg atracurium. After 3 minutes of mask ventilation, all patients were intubated and were underwent mechanical ventilation.

The maintenance of anesthesia was sustained by infusing propofol at a rate of 100 µg/kg/min using the pump syringe (JMS- SP-500) via Branol 20, which was inserted into the peripheral vein of the left hand. To achieve controlled hypotension within the range of mean arterial pressure (MAP) between 55-65 mmHg, nitroglycerin was infused through the pump syringe (JMS- SP-500) via Branol 20 in the peripheral vein of the right hand, with a dosage range of 0.5-5 µg/kg/minute.

Trinitroglycerin (TNG) can produce hypotension by direct vasodilation, especially in veins. In this study in both groups, the administration of TNG infusion commenced at a rate of 0.1 mcg/kg/minute and was escalated to a maximum of 1 mcg/kg/minute if deemed necessary. Infusion was through the pump syringe (JMS- SP-500) via Branol 20 in the peripheral vein of the right hand.

The TNG utilized in the present study was obtained from Caspian Pharmaceutical Company in Iran and each vial contained 10 mg of the drug in a 2 mL solution. In cases where we did not reach the target blood pressure (MAP=55-65 mmhg) despite prescribing the maximum TNG study dose or excessive bleeding was reported by the surgeon, isoflurane was administered at a concentration of 1-1.5%. If the heart rate during the TNG infusion was more than 100 beats per minute, the TNG dose was reduced to reduce this complication.

To minimize any adverse effects associated with inadequate tissue perfusion, the duration of controlled hypotension was limited to less than 2 hours.

This protocol was followed in both groups. All surgical procedures were conducted by a single surgeon. The intervention medications were administered by a different surgeon who was unaware of the kind of medication and been involved in data collection. Furthermore, the surgeon who performed the rhinoplasty was unaware of the drug grouping of the patients. Additionally, neither the individual responsible for data collection nor the statistician had any knowledge of the intervention assigned to each group.

In both the control and intervention groups, a 10 cc solution was administered locally subcutaneously. The control group received 5 ml of lidocaine 2% and 0.5 ml of epinephrine with a concentration of 1 in 100000, and the total volume of the solution was made up to 10 ml by adding distilled water. On the other hand, the intervention group's solution was prepared by combining 5 ml of lidocaine 2%, 0.25 ml of epinephrine with a concentration of 1 in 100000, and 4.75 ml of TXA 10% (100mg/ml) to reach a total volume of 10 ml. The concentration of epinephrine in the control group was 1 in 200000, while in the intervention group, it was 1in 400000.

In this study, TXA (500 mg/5 ml; Caspian Tamim Pharmaceutical Company; Iran) was used.

For both groups, the local injection site was the midline nasal septum and nasal soft tissue. The incision was performed 10 minutes after the injection.

Outcomes and measurements

During this investigation, various parameters such as HR, SBP, DBP, and MAP were meticulously recorded at 10-minute intervals for one hour during the surgical procedure, as well as for 20 minutes during the recovery phase.

Determining the amount of lost blood loss was done by calculating the volume of blood absorbed by gases (visual guide 1) and the volume of blood collected by suction(which the volume of wash serum was deducted from it). For example, a 10 x 10 cm gas that is 25% saturated with blood is considered to contain 3 cc of blood, and if it is 100% saturated, it is considered to contain 12 mL (Figure 1).

This volume was multiplied by the number of the used gauze. Also, the quality of the surgical field was assessed and scored by the surgeon based on the Boezaart criteria scale, and surgeon satisfaction level was recorded according to a 10-point Likert scale, ranging from 1(lowest satisfaction level) to 10 (highest satisfaction level) (Table 1).

Any complications arising from hemodynamic monitoring, including tachycardia, bradycardia,

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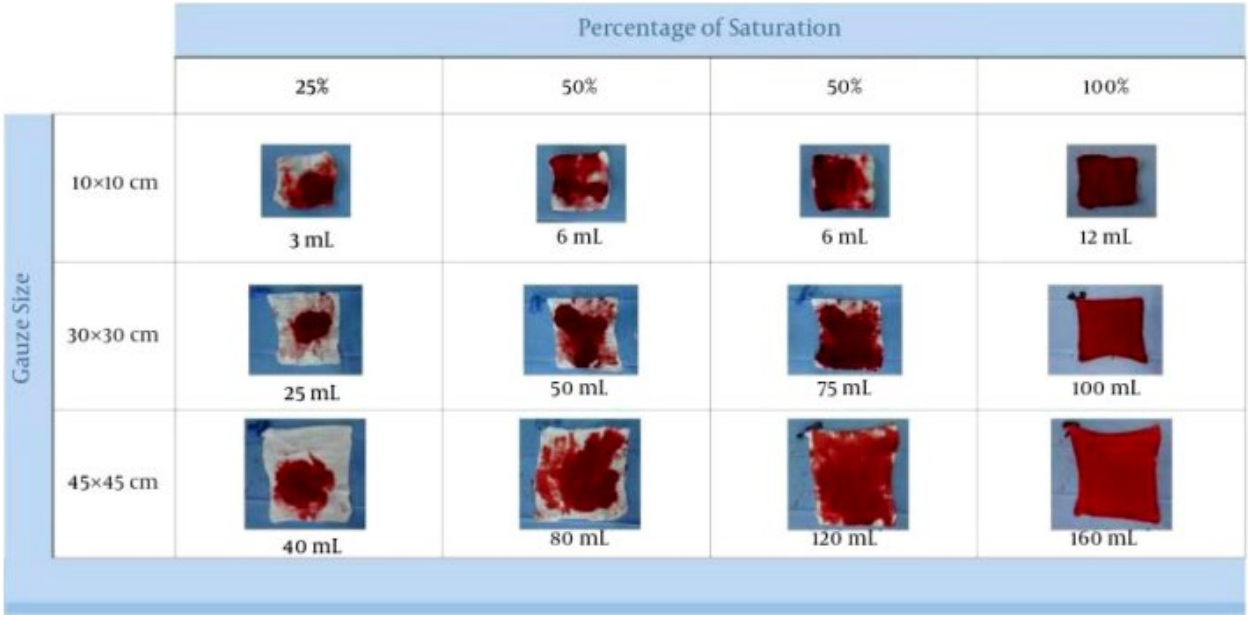

Figure 1: Visual guide for the determination of blood loss for three different sizes of gauze

Table 1: Boezaart criteria grading system for scoring the quality and bleeding of surgical field during surgery

Grade	Surgical field status
0	There is no bleeding - cadaveric conditions
1	Slight bleeding - no need for suction
2	is required Slight Bleeding - sometimes suction
3	Slight bleeding - repeated suction is needed - the bleeding of the surgical site removed for a few seconds after the end of the suction.
4	Moderate bleeding requires frequent suctioning, and bleeding at the surgical site starts immediately after the end of suctioning, but removes during the suctioning.
5	Severe bleeding, continuous suction is needed, bleeding is too fast to remove with suction. The surgical field is heavily involved and surgery is usually not possible.

hypertension, and blood pressure lower than the study target were documented and appropriately managed throughout both the surgical and recovery periods. Additionally, the duration of anesthesia, from the induction to the discontinuation of anesthetics, the duration of extubation, from the discontinuation of medication to the removal of the endotracheal tube (ETT), the duration of the surgical procedure, from the initiation of the incision to the final suture, and the length of stay in the recovery area were all meticulously recorded using a modified Aldrate score.

Data analysis

The statistical analysis was conducted using SPSS version 26 (IBM Corp., Armonk, NY, USA). The data are presented as mean ± standard deviation (SD) or n (%). Based on the results of the Kolmogorov-Smirnov test, the data followed a normal distribution. Therefore, the independent sample *t*-test was employed to compare the mean values of the quantitative variables between the two groups at each follow-up time. Furthermore, repeated measures ANOVA was utilized to assess the changes in the quantitative variables between the two groups at different time points. Additionally, the chi-square test was employed to compare the frequency distribution of qualitative variables between the two groups. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

In this study, one patient in the TXA group was excluded due to uncontrolled blood pressure but

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there was no dropping in the control group (Figure 2). The samples in this study were female and there was no significant difference in the mean of age and weight between the two groups. In addition, both groups had no significant difference in the duration of surgery, duration of extubation time, duration of anesthesia, and length of stay in recovery (Table 2).

The assessment of the hemodynamic parameters in the patients revealed that there was no statistically significant difference in the mean of SBP, DBP, MAP, and HR between the two groups at the start of the study, as well as during the intra and postoperative periods (Table 3).

Finally, although the amount of bleeding in the TXA group was lower than the control group, the significant level was borderline and the difference between the two groups was not considered significant. The quality of the surgical field and the surgeon's satisfaction were not significantly different between the two groups (*P* value<0.05) (Table 4).

DISCUSSION

This study was conducted on 60 patients who were candidates for rhinoplasty and divided into two groups, including a subcutaneous TXA group and a control group. The initial assessment of the patient's conditions demonstrated that the two groups were

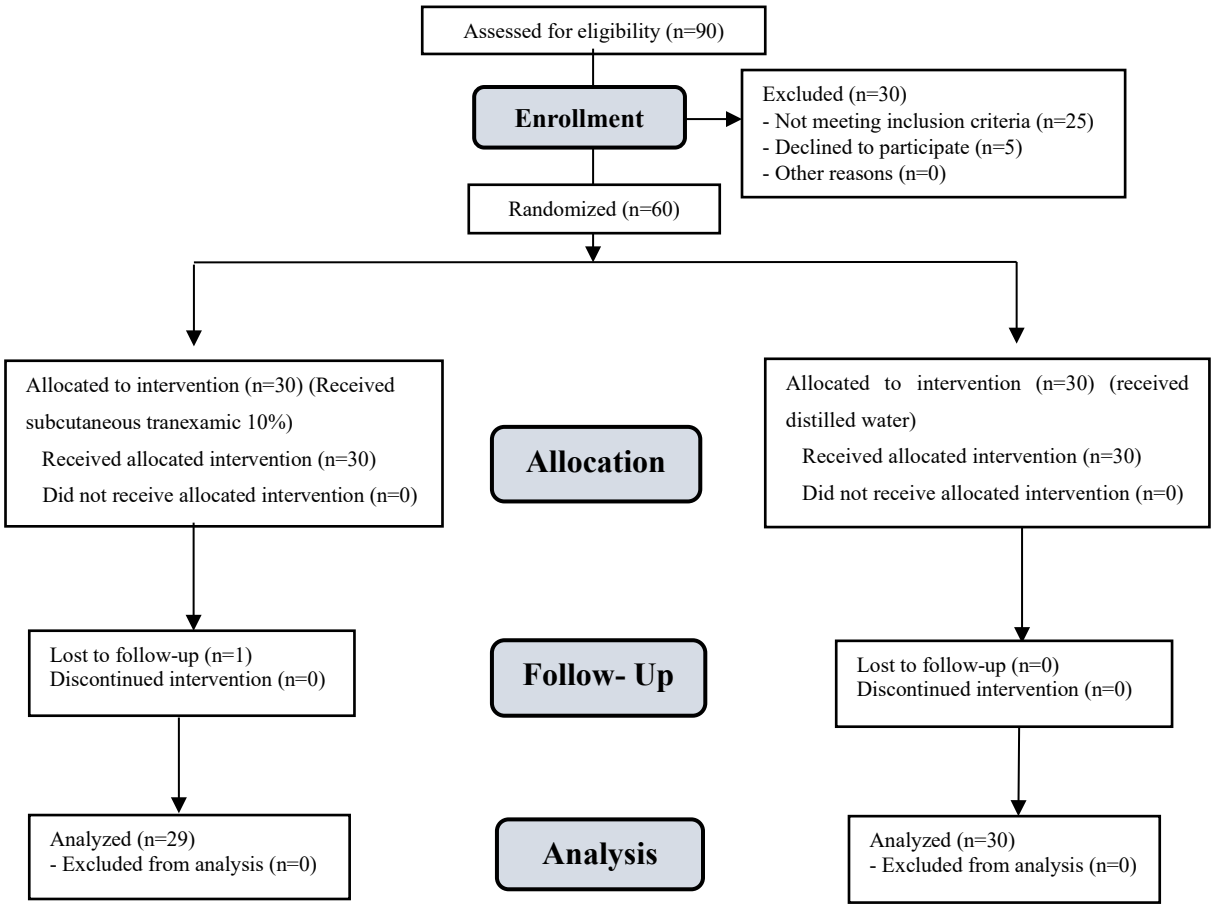

Figure 2: Consort flowchart of patients

Table 2: Comparison of basic and clinical characteristics of patients in the two groups

Characteristics	Control group (N=30)	TXA group (N=29)	*P* value
Weight; kg	61.00±10.74	64.72±9.03	0.155
Age; year	33.13±6.66	30.14±6.58	0.088
Surgical time; min	79.67±17.68	79.21±22.77	0.931
Tim of extubation; min	10.47±2.16	11.72±2.87	0.070
Time of anesthia; min	102.57±17.04	102.17±24.50	0.943
Time of recovery; min	33.67±2.2	33.10±2.47	0.363

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Table 3: Comparison the mean of hemodynamic parameters in the follow-up times in the two groups

Parameters	Follow-up Time	Control group (N=30)	TXA group (N=29)	*P* value[1]
SBP; mmHg	Baseline	120.14±9.07	119.80±10.24	0.894
	T10	103.76±10.83	101.47±10.67	0.416
	T20	82.52±8.92	87.97±12.98	0.066
	T30	79.97±10.62	78.77±8.05	0.626
	T40	78.07±6.46	77.73±8.84	0.866
	T50	77.45±5.75	76.00±7.01	0.743
	T60	79.97±6.50	78.13±6.74	0.293
	R10	88.13±8.74	85.31±10.25	0.259
	R20	90.13±9.74	88.98±11.74	0.683
	P value[2]	<0.001	<0.001	
DBP; mmHg	Baseline	74.07±9.29	75.27±8.42	0.128
	T10	65.76±15.31	64.43±11.80	0.305
	T20	63.79±8.69	60.37±10.52	0.178
	T30	62.90±11.38	62.40±8.01	0.847
	T40	58.90±11.14	52.77±7.56	0.123
	T50	52.31±8.56	52.27±5.75	0.982
	T60	53.10±8.05	51.83±7.79	0.540
	R10	61.66±9.54	60.13±11.66	0.848
	R20	63.69±9.12	62.57±10.66	0.665
	P value[2]	<0.001	<0.001	
MAP; mmHg	Baseline	92.03±8.66	90.03±13.33	0.496
	T10	79.50±12.20	78.59±13.44	0.785
	T20	66.13±10.09	68.07±8.23	0.423
	T30	58.37±7.69	58.38±9.12	0.995
	T40	58.57±7.85	56.34±5.95	0.225
	T50	57.48±5.90	55.69±4.56	0.196
	T60	59.57±6.33	61.03±7.69	0.426
	R10	77.62±10.99	76.87±10.49	0.789
	R20	78.55±9.97	76.13±10.03	0.357
	P value[2]	<0.001	<0.001	
HR; bpm	Baseline	92.33±13.43	92.24±17.53	0.982
	T10	91.20±14.05	89.34±8.14	0.539
	T20	94.27±7.12	92.10±7.56	0.261
	T30	92.10±7.37	91.17±7.30	0.628
	T40	91.43±10.33	90.97±7.85	0.848
	T50	88.37±8.98	89.24±8.65	0.706
	T60	88.17±8.76	88.66±9.39	0.836
	R10	89.63±9.83	88.79±11.47	0.763
	R20	89.17±9.09	89.12±12.52	0.986
	P value[2]	<0.001	<0.001	

matched for age, sex (all female), and weight. The previous studies conducted in this field have paid attention to matching their study groups in terms of demographic and clinical factors [15-17].

Furthermore, there were no notable disparities observed between the two cohorts in terms of the average values of heart rate HR, SBP, DBP, and MAP at the commencement of the investigation, during the surgical procedure, and the recovery phase. This finding aligns with the research conducted by Eftekhari et al., who examined the impact of oral TXA on intraoperative bleeding in rhinoplasty patients. Their study also revealed no significant distinctions between the TXA and control groups in

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Table 4: Comparison the mean of bleeding amount, surgeon's satisfaction with the surgical field, quality of surgery and complications in the two groups

Grade	Surgical field status
0	There is no bleeding - cadaveric conditions
1	Slight bleeding - no need for suction
2	is required Slight Bleeding - sometimes suction
3	Slight bleeding - repeated suction is needed - the bleeding of the surgical site removed for a few seconds after the end of the suction.
4	Moderate bleeding requires frequent suctioning, and bleeding at the surgical site starts immediately after the end of suctioning, but removes during the suctioning.
5	Severe bleeding, continuous suction is needed, bleeding is too fast to remove with suction. The surgical field is heavily involved and surgery is usually not possible.

terms of pre and intraoperative HR, SBP, DBP, and MAP, as well as in the recovery phase [16].

Previous studies have been conducted to compare the effects of TXA (administered orally and intravenously) at different doses (5 mg/kg or 10 mg/kg) with or without a control group. There were no significant differences between the two groups in terms of heart rate HR, SBP, DBP, and MAP in the intraoperative and recovery periods [11,18].

Additionally, studies comparing TXA with other medications such as dexmedetomidine and aminocaproic acid have shown that TXA can effectively control blood pressure (15, 19). Based on our perspective, reducing the dose of epinephrine (or eliminating it) and using TXA together with lidocaine can be effective in preventing increased heart rate in patients with cardiovascular disorders.

Furthermore, the group receiving local TXA did not exhibit any significant difference in terms of bleeding, the quality of the surgical field, and the surgeon's satisfaction level.

However, contrary to our study, several previous studies have shown that intravenous TXA is effective in controlling bleeding in various surgeries. For instance, it is effective in bilateral mandibular fractures [6], endoscopic sinus surgery [20], and elective cesarean section [21]. A recent systematic review even reported a significant reduction in intraoperative blood loss of 41.6 ml in the TXA group compared to the control group [22].

Moreover, many studies have demonstrated that the surgeon's satisfaction with the quality of the surgical field was significantly higher in the group receiving intravenous TXA in mandibular surgery [23], endoscopic sinus surgery [19,24], and rhinoplasty surgery [14], compared to the control groups. These findings are inconsistent with the results of our study.

This discrepancy may be due to the method of drug prescription in the present study; in fact, local administration between the middle nasal septum and nasal soft tissue could not play a significant role in bleeding control. In addition, in our study; both groups had received epinephrine in a local solution, which was actually a comparison between the effect of TXA with low concentration of epinephrine and higher concentration.

Pre-operative local injection of TXA decreased intraoperative and in recovery bleeding and reduced ecchymosis of skin in upper blepharoplasty [25].

Local infiltration of TXA combined with a lidocaine with epinephrine solution during facelift surgery could reduce rebound bleeding and the time required to obtain the hemostasis [26]. The local injection of TXA could decrease intraoperative bleeding in dermatologic surgery [27].

The local use of TXA along with lidocaine and epinephrine was related to decreased bleeding, higher surgeon satisfaction, lower need of Karpol injection, and better hemodynamic stability in septoplasty surgery [11].

In the current study, only one patient in the TXA group developed hypertension and was excluded. Also, one case in the control group had temporary PVC after local drive nasal injection and it resolved on its own, and no further complications were observed.

Therefore, in the TXA group with lower concentration of epinephrine, the amount of bleeding was similar to the group of higher concentration. Therefore, in patients who are at high risk to receive higher concentrations of epinephrine; it is possible to use the combination of TXA with lower epinephrine concentration to achieve the same result in terms of suitable operation field and less bleeding. On the

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other hand, many previous studies also investigated the complications such as ecchymosis and edema, and in the present study, according to the expertise of the researchers, the main attention was focused on the hemodynamic parameters and bleeding in the patients. In fact, this study intended to manage the anesthesia process intraoperatively and in recovery associated with hemodynamic stability and simultaneously less bleeding. Therefore, no special complications were reported in this study following the local injection of TXA.

One of the limitations of this study was the small sample size and no comparison of TXA at different doses. Moreover, in the current study, other approaches of administration (such as systemic) were not investigated and only the method of local injection was evaluated because few studies employed this approach for TXA administration. It is recommended to do more studies with larger sample size at different doses of TXA.

CONCLUSION

The local injection solution used in the intervention group, which contained TXA, had a similar surgical field quality to the control group, despite having half the concentration of epinephrine. It also did not result in a higher amount of bleeding. Therefore, it is recommended that in patients undergoing rhinoplasty who have limitations on the use of high-concentration local epinephrine injections, such as patients with cardiovascular diseases, a local injection solution containing TXA along with a lower concentration of epinephrine should be used, to achieve the desired outcome in terms of bleeding control and surgical field quality. This study was conducted on patients without any underlying diseases. It is suggested to investigate the effect of a locally injected TXA-containing solution with a lower concentration of epinephrine on patients with cardiovascular diseases who require the use of locally injected solutions containing epinephrine during various surgeries. Additionally, the impact of this solution on their hemodynamic stability should be studied.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests.

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