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Original Article

Comparative Study of the Effects of Clonidine and Tranexamic Acid on Intraoperative Bleeding in Rhinoplasty: A Clinical Trial

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ABSTRACT

Introduction: The present study was conducted to compare the effects of clonidine and tranexamic acid on the volume of bleeding and quality of the surgical field in terms of bleeding in candidates who underwent rhinoplasty.
Methods: In this two-sided clinical trial, candidates eligible for rhinoplasty were randomly assigned to two treatment groups: tranexamic acid and clonidine. The first group received tranexamic acid at a dose of 700 µg/kg of body weight 2 hours before the surgical procedure, whereas the second group received clonidine orally at a dose of 2 mg/kg of body weight, 90 minutes before surgery. Subsequently, the volume of bleeding was calculated based on the amount of blood collected via suction and in blood-soaked gauze, which was previously weighed.
Results: Among the 92 patients who underwent rhinoplasty, 82% were women. The mean age and standard deviation (SD) of individuals who underwent rhinoplasty were 29.22 ± 8.50 years. There were no significant differences between the two treatment groups

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in terms of age, gender, and body mass index. The volume of blood collected via suction during rhinoplasty, categorized into surgery duration <63 minutes and ≤63 minutes, showed a significant difference between the 2 treatment groups.

Conclusion: The use of tranexamic acid, compared with clonidine, resulted in lesser intraoperative bleeding and better surgical field quality. Considering the superior effectiveness of tranexamic acid in reducing intraoperative bleeding, it is recommended to use tranexamic acid instead of clonidine in rhinoplasty.

Introduction

Rhinoplasty, a common ENT surgery, faces challenges due to intraoperative bleeding.[1] Surgeons require a clear field for this delicate procedure, whereas anesthesiologists aim to maintain hemodynamic stability.[2] Medications and deliberate hypotension are common strategies to reduce bleeding. Clonidine, an alpha-2 agonist, reduces bleeding by lowering the heart rate and blood pressure.[3] This study compares the effectiveness of clonidine and tranexamic acid in reducing intraoperative bleeding during rhinoplasty.[4]

Various surgical techniques have been used to mitigate complications in rhinoplasty; however, complete prevention remains elusive.[5] Controlled reduction of blood pressure during surgery has proven effective in reducing blood loss, shortening surgical duration, and enhancing the surgical site.[6] Among the strategies used to minimize bleeding, antifibrinolytic agents such as tranexamic acid (TXA) play a crucial role.[7] TXA functions by inhibiting the conversion of plasminogen to plasmin, thereby reducing bleeding.[8] Numerous studies have affirmed its efficacy in diminishing bleeding and the necessity for blood transfusion.[9,10]

Several studies have addressed concerns regarding the risk of thrombosis following TXA administration.[11] These studies have highlighted the need to strike a delicate balance between antifibrinolysis and anticoagulation, indicating that earlier anticoagulation may be necessary after TXA administration. Although there is robust evidence supporting the effectiveness of TXA in reducing blood transfusions during surgery, further trials focusing on its impact on transfusion outcomes are unlikely to yield significant new insights. However, the potential effects of TXA on thromboembolic events and mortality remain areas of interest and ongoing research. Our investigation revealed a positive association between the use of oral TXA and venous thromboembolism (VTE), albeit with a relatively higher dose needed to adversely affect the patient after 5 days of treatment.[12] This suggests that TXA may act as an independent risk factor for VTE, underscoring the importance of future studies aimed at identifying the patient subgroups that may benefit the most from TXA treatment. Such research endeavors are crucial for developing a more personalized approach to treatment that maximizes the benefits while minimizing the potential adverse effects associated with TXA administration.[13]

Both cocaine and epinephrine, at the concentrations used in this study, are suitable as topical vasoconstrictive agents in aesthetic rhinoplasty. Another method of reducing bleeding during surgery involves applying cocaine pledgets containing 4% cocaine solution before the procedure. This preparation helps constrict blood vessels in the surgical area. Additionally, administering local anesthesia containing epinephrine further minimizes bleeding by inducing vasoconstriction. Together, these approaches effectively reduce intraoperative bleeding, ensuring a clearer surgical field for the medical team. This enhancement in visibility enhances the overall safety and success of the surgery.[14]

In rare cases, local application of TXA could potentially cause irritation or damage to the nasal mucosa, leading to mucus necrosis.[15] This risk may be influenced by various factors, including the

concentration of the TXA solution, duration of exposure, and individual patient factors such as pre-existing nasal conditions or allergies.[16]

Bleeding is a common issue in nasal surgeries, prompting the use of methods such as antifibrinolytic agents including TXA and clonidine for control.[17] TXA has shown notable effectiveness in reducing bleeding during ENT surgeries.[18] Although various methods exist to mitigate bleeding, comparative studies on drugs that reduce bleeding during rhinoplasty are limited, with most research focusing on single-agent approaches.[19,20]

This study aimed to compare the effects of clonidine and TXA on bleeding volume and surgical field quality in rhinoplasty candidates. The findings are likely to offer practical insights into optimizing the efficacy of these medications for rhinoplasty procedures.

Materials And Methods

The study is a double-blind, randomized clinical trial (patient and surgeon). Patients in this study were selected through convenience sampling, and they were completely randomized into 2 equal groups of 46 individuals each using a four-block design, with the drug type assigned to each group by a knowledgeable person. In total, 92 patients were enrolled in this study, and their details were recorded in their medical files by a trained nurse in the prescription department.

Before surgery, all patients underwent intravenous access establishment and routine operating room monitoring, including noninvasive blood pressure measurement, electrocardiography monitoring, and pulse oximetry, were performed. Patients received 5 ml/kg of Ringer's lactate or normal saline as preanesthetic fluid before induction of anesthesia. As pre-anesthetic medications, midazolam at a dose of 25 µg/kg and fentanyl at a dose of 3 µg/kg were administered to the patients.

Anesthesia was induced using 2 ml/kg of propofol and 0.5 ml/kg of atracurium. To maintain anesthesia, patients also received 100 µg/kg/min propofol and 10 mg atracurium every 20-30 minutes. In the first group, TXA was administered orally at a dose of 700 mg/kg of body weight 2 hours before surgery, and in the second group, clonidine was administered orally at a dose of two 2 µg/kg of body weight 90 minutes before surgery by a trained nurse in the prescription department, and the information was recorded in the patient's file. In this study, the volume of bleeding was calculated based on the weight of blood collected via suction and in blood-soaked gauze.

In this study, the evaluator (ear, nose, and throat surgeon) was unaware of the patient groups and the use of medications, and the patients were also unaware of their treatment group. Only the responsible study executor, who carried out the patient allocation, was aware of the patient group assignments. If the mean arterial blood pressure was not <70-65 mm of mercury, nitroglycerin infusion at a dose of 0.1-0.5 µg/kg was administered. In case of a decrease in the mean arterial blood pressure to <60 mm of mercury, the anesthetic drug dose was initially reduced, and blood pressure was adjusted using intravenous fluids during the surgery. However, if it was not controlled, intravenous epinephrine at a dose of 0.5 mg was used, and in case of a severe heart rate drop to <50 beats per minute (BPM) for 60 s, 0.5 mg of intravenous atropine was administered.

The volume of bleeding was calculated based on the weight of blood collected via suction and in blood-soaked gauze, which was previously weighed. The data were recorded by the second investigator and a trained nurse in an information form, which included variables such as age, gender, other demographic factors, bleeding volume, blood pressure, arterial oxygen pressure, heart rate every 30 minutes, duration of surgery, and recovery time. After completing the questionnaire, the data were entered into SPSS version 22 software for final analysis.

Inclusion Criteria: individuals' willingness to participate in the study, age between 18 and 60 years.

Exclusion Criteria: addiction to various drugs and benzodiazepines, liver and kidney insufficiency, diabetes, respiratory and cardiac diseases, coagulation disorders (conditions that affect blood clotting), history of sensitivity to clonidine and TXA, and pregnancy.

Sampling Method and Sample Size: According to the study by Berenjian et al.,[21] the minimum sample size in each group was calculated to be 46 patients.

The data were collected and analyzed using a researcher-made checklist based on the study's objectives, which included variables such as age, gender, other demographic factors, bleeding volume,

blood pressure, arterial oxygen pressure, heart rate every 30 minutes, duration of surgery, and recovery time.

Data Analysis

For data analysis, summarizing, and describing the variables, descriptive statistical methods were used, including the construction of one-dimensional and two-dimensional frequency distribution tables, calculation of numerical indices such as mean and standard deviation for quantitative variables, and percentages for qualitative variables.

To conduct the independent *t*-test and confirm the normality of the data, the Kolmogorov–Smirnov test was used. For inferential data analysis, initially, analytical statistical methods, including the chi-squared test, were used to assess the homogeneity of the two groups after random assignment, based on several important and influential intervention variables in this study. An independent *t*-test (along with Levene's test to examine the homogeneity of variances between the groups) was used to compare the means of the quantitative variable of interest in the two treatment groups. Data analysis was performed using SPSS version 25, and a significance level of <0.05 was considered for all tests.

The study was approved by the board of ethical committee of Kermanshah University of Medical Sciences, Kermanshah, Iran (IR.KUMS.MED.REC.1402.172).

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Results

In this rhinoplasty study involving 92 patients, 81.5% were women, and 18.5% were men. The overall mean age was 28.22 ± 8.50 years, with a range of 17-52 years. The clonidine and TXA treatment groups had mean ages of 28.17 ± 8.78 years and 30.26 ± 8.17 years, respectively.

The Kolmogorov–Smirnov test showed normal distribution for age, body mass index, diastolic and systolic blood pressure, heart rate, and blood coagulation factor prothrombin time (PT) in clonidine (P=0.327, 0.166, 0.604, 0.871, 0.205, and 0.075, respectively) and TXA groups (P=0.453, 0.405, 0.474, 0.811, 0.420, and 0.096, respectively). However, surgery duration and blood coagulation factor activated partial thromboplastin time (PTT) had a non-normal distribution in both groups (clonidine: P=0.000 and 0.011; TXA: P=0.000 and 0.009, respectively).

Additionally, the Kolmogorov–Smirnov test indicated normal distribution for blood volume collected via suction device and the weight of blood gases in clonidine (P=0.369 and 0.147, respectively) and TXA groups (P=0.341 and 0.087, respectively).

In the clonidine group, approximately 76% were women and 24% were men. In the TXA group, approximately 87% were women and 13% were men.

In the clonidine group, 65% were <29 years old, and in the TXA group, 57% were <29 years old.

In the clonidine group, 57% had a BMI <24 kg/m^2, and in the TXA group, 39% had a BMI <24 kg/m^2.

In the clonidine group, 59% had diastolic blood pressure <80 mmHg, whereas in the TXA group, 44% had diastolic blood pressure <80 mmHg.

In the clonidine group, 46% had systolic blood pressure <111 mmHg, and in the TXA group, 48% had systolic blood pressure <111 mmHg.

In the clonidine group, 52% had a heart rate <89 BPM, and in the TXA group, 44% had a heart rate <89 BPM.

In the clonidine group, 91% had a surgical duration of <63 minutes, whereas in the TXA group, 76% had a surgical duration of <63 minutes.

In the clonidine group, 57% had PT of <34 s, and in the TXA group, 52% had PT <34 s.

In the clonidine group, 46% had PTT of <12 s, whereas in the TXA group, 50% had PTT <12 s.

The independent *t*-test revealed no significant differences between the clonidine and TXA groups in terms of age, BMI, diastolic and systolic blood pressure, heart rate, and blood coagulation factor PT. Mean values of age, BMI, diastolic blood pressure, heart rate, and PT were higher in the TXA group, whereas systolic blood pressure was higher in the clonidine group (Table 1).

Table 1
Comparison of characteristics of individuals undergoing rhinoplasty in the clonidine and tranexamic acid treatment groups.

Factors	Group				P-value
	Tranexamic acid (n=46)		Clonidinen (n=46)		
	SD	Mean	SD	Mean	
Age (yr)	17/8	26/30	78/8	17/28	0.241
BMI (kg/m^2)	71/2	27/24	61/2	41/23	0.127
DBP (mmHg)	65/8	93/79	94/5	11/79	0.595
SBP (mmHg)	29/12	89/110	10/10	39/111	0.832
Heartbeat (BPM)	34/7	48/90	38/7	43/89	0.498
PT (mm Hg)	27/3	35/34	31/3	04/34	0.658

DBP, diastolic blood pressure; SBP, systolic blood pressure; PT, prothrombin time

Table 2
Comparison of characteristics of people undergoing rhinoplasty surgery in clonidine and tranexamic acid treatment groups.

Factors	Group		P-value
	Mean rank		
	Tranexamic acid (n=46)	Clonidine (n = 46)	
Duration of surgery (min)	17/8	26/30	0.148
BMI(Kg/m^2)	71/2	27/24	0.669

Table 3
Comparison of bleeding rate (volume of blood collected via suction) during rhinoplasty according to age, gender, and body mass index in two treatment groups of clonidine and tranexamic acid.

Factors		Group				P-value
		Tranexamic acid (n = 46)		Clonidine (n = 46)		
		SD	Mean	SD	Mean	
Age (yr)	29<yr	17.13	71.23	14.11	77.13	0.163
	29>yr	12.18	71.45	15.50	70.81	0.891
Gender	Female	15.60	71.15	15.44	75.20	0.263
	Male	11.48	72.50	12.95	74.09	0.805
BMI(Kg/m^2)	24<	12.71	70.11	16.14	71.35	0.787
	24≥	16.52	72.11	11.50	79.60	0.088
DBP (mmHg)	80<	15.33	72.65	15.39	75.63	0.514
	80≥	15.01	70.31	14.16	73.95	0.415
SBP (mmHg)	111<	18.02	71.77	15.07	77.76	0.245
	111≥	12.04	70.92	14.36	72.56	0.667
Heartbeat (BPM)	89<	18.03	74.00	15.73	73.54	0.929
	89≥	12.22	69.27	13.82	76.45	0.062
PT (mm Hg)	34<	17.20	72.42	15.48	77.19	0.307
	34≥	12.53	70.14	13.58	72.00	0.646

DBP, diastolic blood pressure; SBP, systolic blood pressure; PT, prothrombin time.

The Mann–Whitney test indicates no significant differences in the surgical duration and blood coagulation factor PTT between the clonidine and TXA groups. The mean PTT was higher in the clonidine group, whereas the mean surgical duration was higher in the TXA group.

Additionally, the independent *t*-test showed no differences in the effect of clonidine and TXA on blood volume during rhinoplasty based on age or gender.

The independent *t*-test showed no significant difference in the effect of clonidine and TXA on blood volume or blood gases during rhinoplasty based on BMI, diastolic blood pressure, systolic blood pressure, heart rate, or blood coagulation factors (Tables 2 and 3). Similarly, the test indicates no differences based on age, gender, or surgery duration (Tables 4 and 5).

Table 4
Comparison of the amount of bleeding (weight of blood gases) during rhinoplasty according to age, gender, and body mass index in the two treatment groups of clonidine and tranexamic acid.

Factors		Group				P-value
		Tranexamic acid (n = 46)		Clonidine (n = 46)		
		SD	Mean	SD	Mean	
Age (yr)	29<yr	13.32	58.46	13.75	60.87	0.510
	29>yr	11.67	62.30	11.76	56.13	0.125
Gender	Female	12.46	61.58	14.45	60.23	0.666
	Male	9.91	50.50	7.35	56.00	0.211
BMI(Kg/m^2)	24<	12.68	61.00	12.61	61.15	0.969
	24≥	12.81	59.57	13.75	56.70	0.461
DBP (mmHg)	80<	11.26	56.15	15.08	58.85	0.504
	80≥	12.99	63.19	10.19	59.74	0.341
SBP (mmHg)	111<	11.46	59.09	12.92	57.05	0.586
	111≥	13.81	61.08	13.34	61.04	0.991
Heartbeat (BPM)	89<	12.15	58.40	12.99	60.17	0.646
	89≥	13.08	61.46	13.56	58.18	0.399
PT (mm Hg)	34<	11.50	60.33	12.54	56.35	0.248
	34≥	14.05	59.91	13.31	62.95	0.477

DBP, diastolic blood pressure; SBP, systolic blood pressure; PT, prothrombin time.

Table 5
Comparison of the amount of bleeding (volume of blood collected via suction) during rhinoplasty according to the duration of the surgery and blood coagulation factor PTT in the two treatment groups of clonidine and tranexamic acid.

Factors		Group		P-value
		Mean rank		
		Tranexamic acid (n=46)	Clonidine (n=46)	
Duration of surgery (min)	63<	32.69	44.26	0.023
	63≥	9.82	3.00	0.006
PTT (mm Hg)	12<	19.70	25.57	0.128
	12≥	23.78	25.16	0.733

PTT, partial thromboplastin time

The suctioned blood volume in the clonidine and TXA treatment groups during rhinoplasty was approximately 75 mg and 71 mg, respectively. The independent *t*-test indicates no significant difference between the groups (P=0.248; Figure 1).

The weight of blood gases in the clonidine and TXA groups were approximately 59 and 60 mm Hg, respectively, with no significant difference (P=0.735; Figure 2).

Discussion

The primary objective of this research was to assess the impact of clonidine and TXA on bleeding during rhinoplasty, involving a total of 92 patients who underwent the procedure.

In line with the findings of our study, a previous investigation by Karkhanehei et al.[22,23] discovered no significant age difference between the two treatment groups during rhinoplasty. Our study also revealed no significant variation in BMI between the clonidine and TXA groups. Nevertheless, the average BMI in the TXA group was higher than that in the clonidine group.

When comparing the effects of clonidine and TXA based on age, our study contrasted with the research by Karkhanehei et al.,[23] as we found no significant difference in blood volume collected in the nasal area during surgery. The TXA group exhibited lower bleeding levels compared to the saline group.

Upon analyzing the impact of gender on bleeding during rhinoplasty, our study uncovered no significant gender-based differences in blood volume between the clonidine and TXA groups, contra-

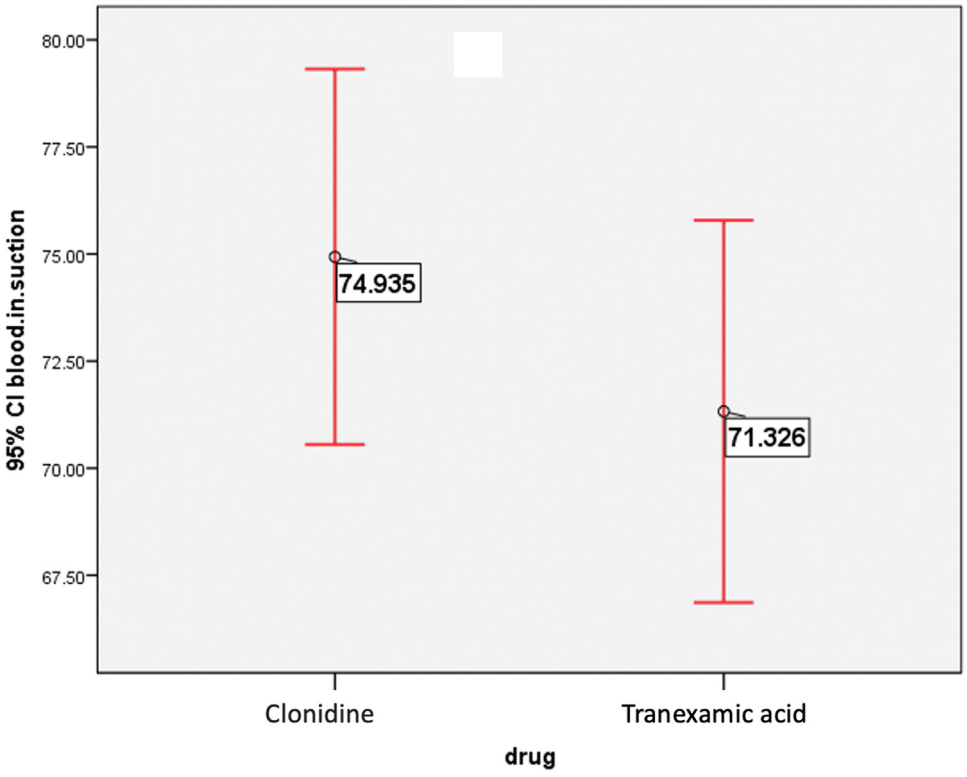

Figure 1. Blood volume by therapeutic groups of clonidine and tranexamic acid.

dicting the findings of Ahmadi et al.,[33] who reported higher bleeding in the dexmedetomidine group compared to the TXA group.

When assessing the influence of BMI on bleeding, our study's results were consistent with those of Morgan et al.,[23-28,34] who reported reduced bleeding with TXA in surgeries. In the case of rhinoplasty, where bleeding levels are not excessively high, dexmedetomidine might be a more suitable option, as indicated by Berenjian et al.[21,29,30]

Regarding surgery duration, similar to our findings, Karkhanehei et al.[23] noted a significant difference in bleeding levels between the TXA and saline groups, thereby favoring TXA.[31-34]

Contrary to our study, Modir et al.[35] investigated the effectiveness and safety of various treatments and found no significant differences in bleeding during septorhinoplasty. Nonetheless, TXA significantly reduced bleeding compared to dexmedetomidine.

In line with our results, Fuzi et al.[36] and Locketz et al.[29] suggested that TXA can reduce surgery duration in various contexts. However, Ahmadi et al.[33] found no significant differences between surgery duration and bleeding.

Ghorbani et al.[37] found that clonidine reduced surgery duration during nasal sinusitis procedures, whereas Tugrul et al.[38] reported the same for endoscopic sinus surgery. Additionally, Mohammadi et al.[39] found that preoperative clonidine improved bleeding control in orthognathic surgery.

In a comparison of premedication options, clonidine was found to be effective in reducing bleeding, similar to the results of Puthenveettil et al.[40] and Wawrzyniak et al.[41] Moreover, Mohseni and Ebneshahidi[42] noted the effectiveness of oral clonidine in reducing bleeding before surgery. Meanwhile, TXA, as demonstrated by Alimian et al.,[43] effectively reduced bleeding during surgery.

Considering mean arterial blood pressure, Ahmadi et al.[33] observed no significant differences between dexmedetomidine and TXA. In contrast, Jabel Aameli found significantly lower bleeding in the TXA group during endoscopic sinus surgery, while maintaining stable blood pressure.

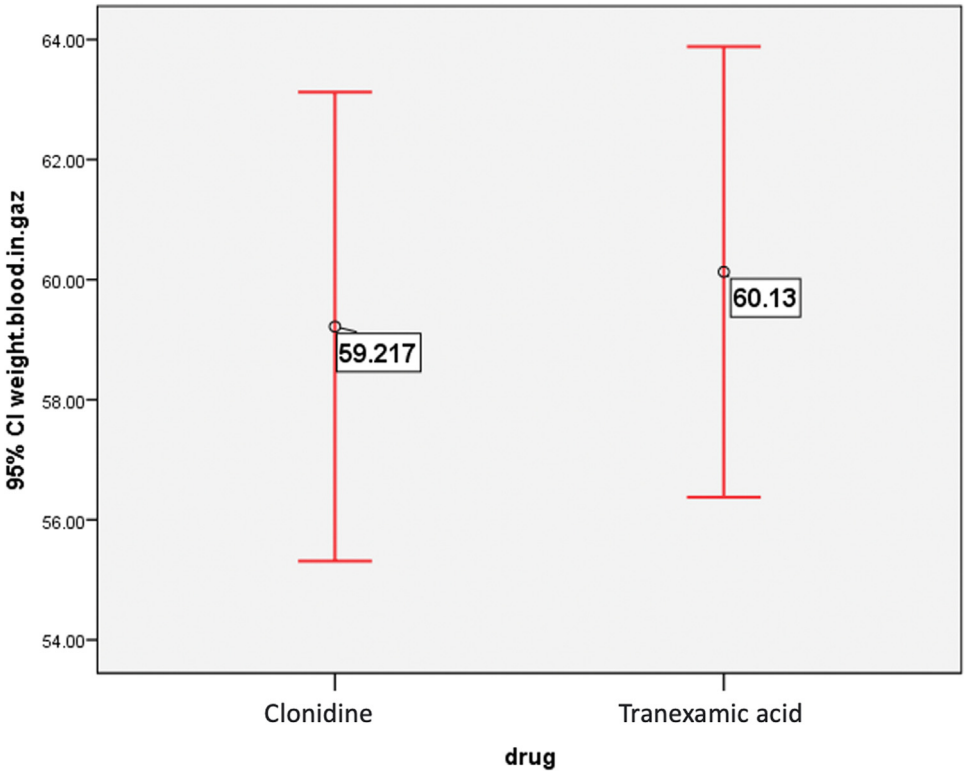

Figure 2. Blood gas weight by therapeutic groups of clonidine and tranexamic acid.

Another study[43] compared TXA and dexmedetomidine, with results being consistent with our study in terms of effectiveness. However, they noted a lower decrease in arterial blood pressure with dexmedetomidine.

In contrast to our findings, Khandelwal et al.[44] reported that oral clonidine reduced surgical bleeding during endoscopic sinus surgery for rhinosinusitis while maintaining stable blood pressure. A prior study[45] found that prostaglandin and clonidine reduced blood loss without affecting blood pressure.

Regarding heart rate, Ghorbani et al.[37] reported no differences in bleeding reduction during surgery, regardless of the heart rate.

In terms of blood coagulation factors, Morgan et al.[34] found significantly lower bleeding in the TXA group in pelvic fracture surgery, irrespective of patient characteristics. Eftekharian et al.[46] observed that TXA significantly reduced bleeding during orthognathic surgery.

Conclusion

In general, no study has been conducted to date for a simultaneous comparison of the effects of clonidine and TXA on reducing bleeding during surgery and creating a better surgical field. Our findings showed a statistically significant difference between these two drugs. To control bleeding during the surgery in patients undergoing rhinoplasty, TXA use resulted in reduced blood loss and a better surgical field quality compared to clonidine use. Owing to the superior effectiveness of TXA over clonidine in reducing intraoperative bleeding, the use of TXA instead of clonidine is recommended in rhinoplasty.

Declaration of competing interest

The authors deny any conflict of interest in any terms or by any means during the study.

Human and animal rights

No animals were used in this research. All human research procedures followed were by the ethical standards of the committee responsible for human experimentation (Kermanshah University of Medical Sciences, Kermanshah, Iran (IR.KUMS.MED.REC.1402.172) and with the Helsinki Declaration of 1975, as revised in 2013.

Approval of the research protocol: The study was approved by the board of ethical committee of Kermanshah University of Medical Sciences, Kermanshah, Iran (IR.KUMS.MED.REC.1402.172).

Informed Consent: Informed consent was obtained from each participant.

Consent for publication

Informed consent was obtained from each participant.

Availability of data and materials

All relevant data and materials are provided in manuscript.

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Contributors' Statement Page: Dr. Mohammad Bagher Heydari: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr. Behzad Hemmatpour: Designed the data collection instruments, collected data, conducted the initial analyses, and reviewed and revised the manuscript.

Dr. Maryam Safdari: Coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

Consent for publication: Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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