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Comparison of Different Concentrations of Epinephrine on Hemodynamic Changes and Bleeding after Rhinoplasty in Patients under General Anesthesia

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Abstract

Background The present study was conducted to compare the effects of two different concentrations of epinephrine on hemodynamic changes and bleeding volume in patients undergoing rhinoplasty under general anesthesia.

Materials and Methods: This double-blind randomized clinical trial was conducted on 60 patients undergoing rhinoplasty in affiliated with Kerman University of Medical Sciences in Kerman, Iran, in 2019. The patients were equally divided into two groups administered with lidocaine/epinephrine injection at either dose of 1:100,000 (Group A) or 1:200,000 (Group B). Heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were compared between the two groups. In addition, bleeding and hemodynamic changes were recorded at different time points.

Results: About 90% of the patients were female, and gender distribution was comparable between the two groups (P=0.72). According to the results, the two groups were comparable in terms of demographic variables and the duration of the operation. Group A was found to have a lower level of bleeding (83.16 mL) compared to group B (108.07 mL); however, this difference was not statistically significant (P>0.05). In addition, there was no significant difference between the two groups in heart rate, SBP, DBP, and MAP at different time points (P>0.05).

Conclusion: The results of this study were indicative of the similar effect of the different doses of lidocaine: epinephrine (1:100,000 and 1:200,000) on the level of bleeding, SBP, DBP, and heart rate during rhinoplasty. Moreover, there was no difference between the results of the qualitative and quantitative assessment of bleeding in patients receiving epinephrine at different dosages.

Key Words: Bleeding, Epinephrine; Hemorrhage; Hemodynamic changes; Rhinoplasty.

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1- INTRODUCTION

Cosmetic rhinoplasty under local anesthesia is an accepted approach performed in a small and highly vascularized site (1). Good vasoconstriction is of critical importance for decreasing intraoperative hemorrhage (2, 3). The anatomical limitations of the nasal space complicate proper access to this area. The maintenance of homeostasis during surgery is, therefore, of fundamental importance. Vasoconstrictors are commonly administered through a topical route or subcutaneous injection to maintain better homeostasis during rhinoplasty (4). Moreover, achieving controlled hypotension during anesthesia or hypotensive anesthesia and maintaining sufficient depth of anesthesia are critical for reducing bleeding during rhinoplasty.

Preoperative steroids, intraoperative local anesthetics, and decongestants are commonly used to improve homeostasis and prepare the patient for rhinoplasty surgery. It should be noted that none of the aforementioned agents have any advantages over others, and their choice depends on the clinical perspective and experience of the physician (5). Epinephrine is one of the agents used in preparing patients for rhinoplasty surgery (6). This agent provides good control of bleeding due to its potential to cause vasoconstriction and accelerate blood coagulation, especially in the skin and mucous membranes. Epinephrine can be used both subcutaneously and intradermally. It is normally administered with lidocaine 1-2% as a regulator (7).

However, a rapid intravenous injection of epinephrine may lead to cardiomyopathy, cardiac arrhythmia, cardiac arrest, pulmonary edema, and central retinal artery occlusion (8). Moreover, subcutaneous nasal injection of epinephrine can result in rapid absorption, which may cause severe hemodynamic events in some patients (9). Lidocaine is a widely used agent for anesthesia. The concomitant use of epinephrine with lidocaine increases the duration of anesthesia by reducing the systemic absorption of lidocaine and reduces bleeding during surgery, thereby improving surgical field vision. Pain reduction and decreased need for postoperative analgesics are other advantages of this combination. However, the systemic absorption of epinephrine and lidocaine can be associated with some side effects, such as the dysfunction of the central nervous and cardiovascular systems, hypotension, cardiac arrhythmias, chest pain, and tachycardia (10).

There is no gold standard for the dose of epinephrine to be applied during rhinoplasty. The common administered dose varies from 1:1000 to 1: 200,000 in topical application and from 1: 50,000 to 1: 200,000 in subcutaneous and intramuscular injections. Despite the lack of evidence on the positive effects of epinephrine at high concentrations on homeostasis, most physicians still prefer to use higher concentrations of epinephrine (11). This indicates the fundamental importance of assessing the systemic and side effects of epinephrine administration at different doses.

With this background in mind, the present study was conducted to compare the effects of two different concentrations of epinephrine on hemodynamic changes and bleeding volume in patients undergoing rhinoplasty under general anesthesia. The issues investigated here are whether bleeding increases with decreasing epinephrine concentration, whether hemodynamic changes decrease with decreasing epinephrine concentration, and whether the control group needs more amounts of injectable epinephrine or remifentanil propofol.

2- MATERIALS AND METHODS

2-1. Method

This double-blind randomized clinical trial was conducted on the patients undergoing rhinoplasty in Shafa hospital affiliated with Kerman University of Medical Sciences in Kerman, Iran, in 2019. Sampling of a patient candidate for elective rhinoplasty referred to Shafa Hospital was performed after obtaining informed consent. A rhinoplasty surgeon operated on all patients. Patients were assigned to case or control group according to restricted allocation method and random allocation rule.

Allocation concealment was done with sequentially sealed envelopes and technician who is responsible for checking inclusion and exclusion criteria. For all patients, the same forms were filled out by anesthesia technician in charge of the patient. Epinephrine with a concentration of 1/200,000 or 1/1000,000 was prepared by the surgeon's assistant nurse and was given to the surgeon for injection. At the end of anesthesia and after completing the form, the mark of group A or B was written on the forms by the person in charge of collecting the forms.

2-2. Inclusion and exclusion criteria

The inclusion criteria were the age of 16-45 years and ASA class I and II. Individuals with coagulation disorders, heart disease, hypertension, cerebrovascular disease, or drug allergies were excluded from the study. The American Society of Anesthesiologists (ASA) physical status classification system was developed to offer clinicians a simple categorization of a patient's physiological status to help predict operative risk.

ASA 1: A normal healthy patient. Example: Fit, nonobese (BMI under 30), a nonsmoking patient with good exercise tolerance.

ASA 2: A patient with mild systemic disease. Example: Patient with no functional limitations and a well-controlled disease (e.g., treated hypertension, obesity with BMI under 35, frequent social drinker, or cigarette smoker) (12). In this study patients classified as ASA physical status I or II who were undergoing elective rhinoplasty.

2-3. Study design

A total of 60 patients were divided into two groups, each administered with a different dose of lidocaine/epinephrine injection. The patients were randomly assigned into control and case groups using packets. The sample size was calculated as 60 people in two groups (29 patients in the case group and 31 patients in the control group) considering α of 0.05 and test power of 0.9. Rhinoplasty was performed by one surgeon on all patients. The patients were anesthetized by the total intravenous anesthesia (TIVA) of 0.15 mg/kg midazolam, 2 microgram/kg fentanyl, 2 mg/kg propofol, and 0.5 mg/kg atracurium. After the anesthetic induction, the patients underwent endotracheal intubation and mechanical ventilation. The maintenance phase of general anesthesia was performed by the infusion of 100-200 microgram/kg/min propofol, along with 50% oxygen/50% nitrous oxide.

Controlled hypotension monitoring was established by remifentanil infusion (1-2 microgram/kg/min). In addition, the mean arterial blood pressure (MAP) was maintained between 65-70 mmHg. Patients older than 16-45 years or those who needed other antihypertensive drugs to reduce blood pressure were excluded from the study. Morphine was administered if needed, and its dosage was recorded. The slope of the bed was similar for all patients in both groups. In order to prevent blood from entering the stomach through swallowing during the surgery, a packing was placed in the mouth and throat of the patients. This packing was removed at the

end of the surgery and used as an index for the determination of bleeding amount.

As mentioned, the patients were randomly divided into two groups; one was administered with a high dose of epinephrine and the other was injected with a low dose of this agent. In Group A, after the induction of anesthesia by an anesthesiologist, a 1:100,000 dilution of 2% lidocaine with epinephrine (prepared by a trained assistant surgeon) was injected subcutaneously and intradermally by a surgeon. Group B was injected with a 1: 200,000 dilution of 2% lidocaine: epinephrine. Both the surgeon and the anesthesiologist were unaware of the concentration of the injected substances.

Arterial oxygen saturation was measured by a Finger Pulse Oximeter. Because the volume of epinephrine injection varied depending on the surgeon's discretion and the size of the nose, the amount of injection was determined for each patient separately in mL. In addition, the volumes of the injected propofol and remifentanil applied to maintain anesthesia and MAP (between 65-70 mmHg) were recorded for each patient.

Remifentanil was prepared for all patients at 2% concentration and the volume of infusion was recorded as "mL" for each patient. Without diluting, propofol was also infused at 1% concentration (10 mg/mL). The volume of injected epinephrine to each patient was recorded as "mL".

Systolic blood pressure (SBP), and diastolic blood pressure (DBP), and MAP were measured non-invasively using an automated oscillometric device. In addition, the heart rate and blood pressure were recorded by an anesthetic technician at different stages; before the induction of anesthesia, immediately after intubation, immediately before injection, and then every minute until the third minute, followed by every 5 minutes until the end of the operation. At the end of the operation, the amount of bleeding was quantitatively measured by calculating the exact amount of blood inside the suction and the number of bloody gauzes. Intraoperative bleeding volume was calculated from aspiration. The qualitative measurement of the bleeding rate was performed by asking the surgeon to score bleeding on a six-point scale (from 0 to 5) developed by Fromm and Boezaat.

2-4. Ethical Consideration

The current study was approved by the Research Ethics Committee of Kerman University of Medical Sciences in Kerman, Iran (IR.KMU.REC.1398.572), and registered at Iranian Registry of Clinical Trials (IRCT20190911044743N1). The aims of the study were explained to the patients, and their informed consent was obtained. In addition, the patients were assured about the confidentiality of their information and the possibility of study withdrawal at any time.

2-5. Data analysis

Data were analyzed using SPSS software (version 20.0). Quantitative variables were described through mean and standard deviation, and qualitative variables were explained by frequency and percentage. Chi-square test was used to compare nominal variables between the two groups. A p-value less than 0.05 was considered statistically significant.

3- RESULTS

In the present study, 30 patients in the case group (group B: a 1: 200,000 dilution of 2% lidocaine: epinephrine), and 30 patients in the control group (group A: 1: 100,000 dilution of 2% lidocaine with epinephrine) were assessed. A total of 90% of the patients were female, and gender distribution was comparable between the two groups (P=0.72). The mean ages of groups A and B were 29.8±12.4 and 27.2±7.3 years, respectively, meaning that

the groups were matched in age (P=0.33). The mean weights of the patients were 61.8±9.2 and 64.04±13.1 kg in groups A and B, respectively. The mean lengths of operation were 2.48±0.7 and 2.46±0.98 h in groups A and B, respectively. The patients in the two groups were homogeneous in weight (P=0.58), and operation duration (P=0.93). **Figure.1** shows the comparison of mean heart rate and MAP in the two groups at different time points. Based on the obtained data, groups A and B had the mean heart rates of 77.8 and 75.2 beats per min at different time points, respectively. The mean MAP scores were obtained as 73.9 and 74.7 for groups A and B, respectively. The results revealed no significant difference between the two groups in terms of heart rate and MAP.

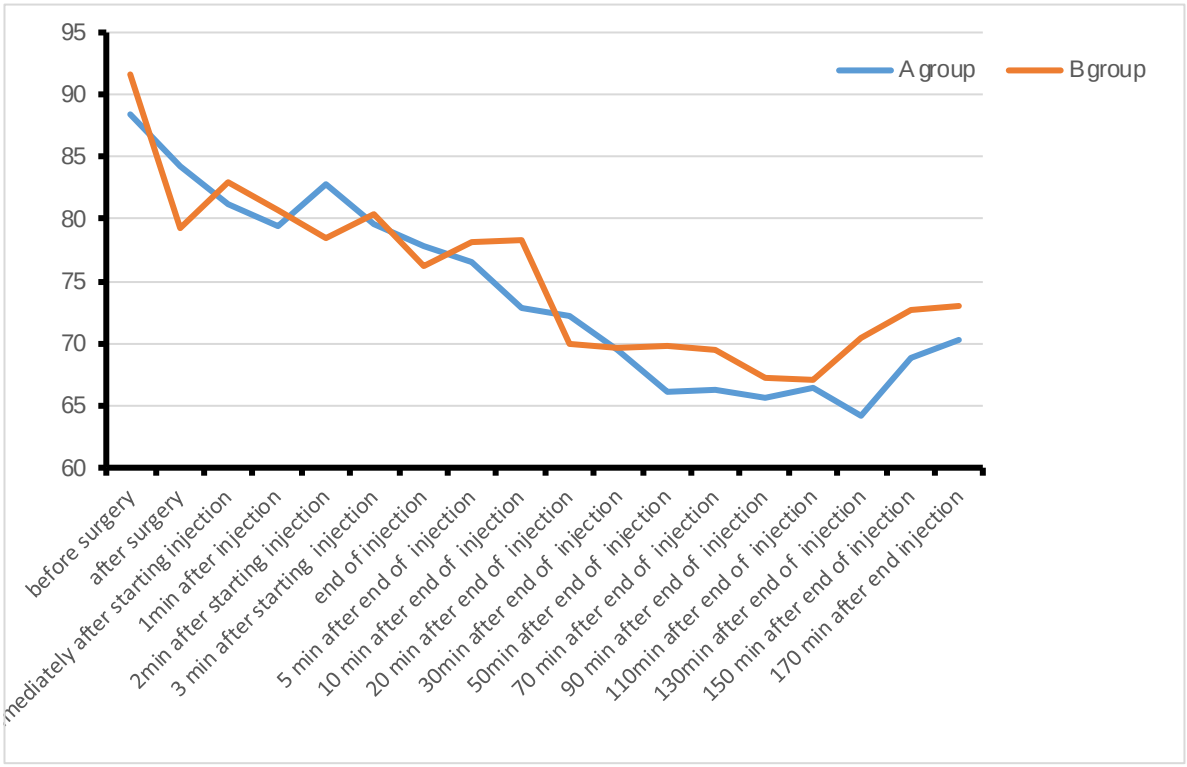

Fig. 1: Comparison of mean heart rate in the two groups at different time points.

Group A: 1: 100,000 dilution of 2% lidocaine with epinephrine and Group B: 1:200,000 dilution of 2% lidocaine: epinephrine.

Figure.2 shows the comparison of mean arterial pressure in the two groups at different time points. There was no significant difference between groups A and B in terms of the mean SBP and DBP (90.9 and 91.1 vs. 63.7 and 57.8, respectively; P>0.05).

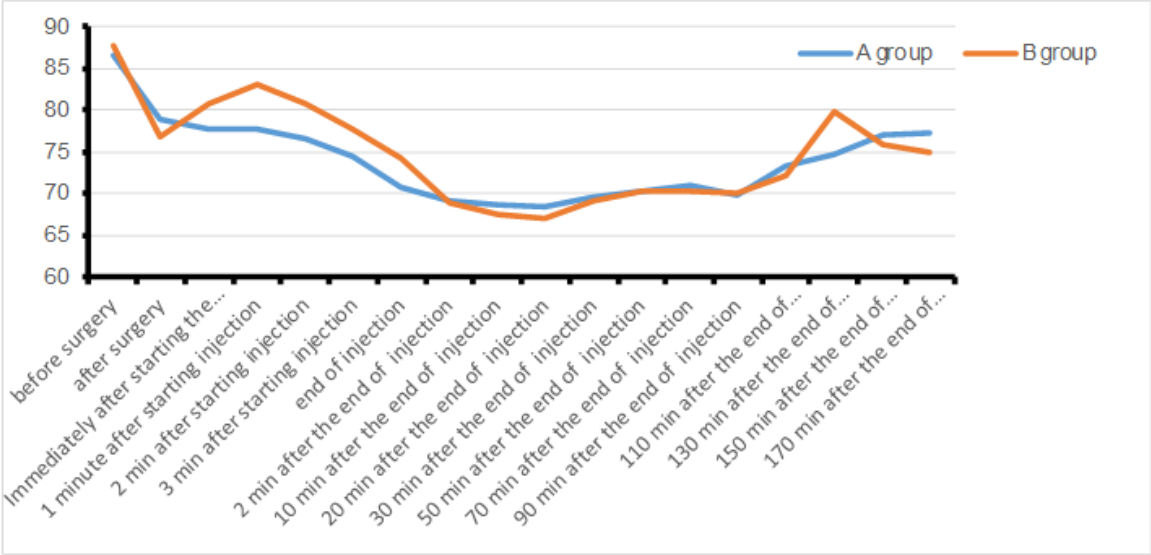

Fig. 2: Comparison of mean of arterial pressure in the two groups at different time points.

Group A: 1: 100,000 dilution of 2% lidocaine with epinephrine, and Group B: 1:200,000 dilution of 2% lidocaine: epinephrine.

Table.1 shows the determination and comparison of remifentanil propofol and epinephrine in the two groups. As seen in **Table.1**, the mean levels of injected remifentanil were 28.52±16.3 mL and 19.39±8.4 mg in groups A and B, respectively (P=0.43). These mean values for propofol were 75.34±10.3 and 98.2±16.7 mL for groups A and B, respectively (P=0.24). Also, the volume of epinephrine injected in the two groups was not statistically significant. **Table.2** displays the mean injection speed in the two research groups. Based on the obtained results, there was no significant difference between the two groups in terms of the injection speed (P=0.702).

Table-1: Determination and comparison of remifentalin, propofol and Epinephrine in the two groups.

Administerd drug	Group A		Group B		P-value
	Mean	Standard deviation	Mean	Standard deviation	
Remifentalin (ml)	28.52	16.30	19.39	8.48	0.437
Propofol (ml)	75.34	10.36	98.26	16.78	0.240
Epinephrine (ml)	13.32	3.44	18.32	8.30	0.240

Group A: 1: 100,000 dilution of 2% lidocaine with epinephrine, and Group B: 1: 200,000 dilution of 2% lidocaine with epinephrine.

Table-2: Mean injection speed in the research groups.

Injection Speed	Group A		Group B		P-value
	Mean	Standard deviation	Mean	Standard deviation	
Very slow	1	3.4	0	0	0.702
Slow	3	10.3	2	7.1	
Moderate	21	72.4	23	82.1	
Fast	4	13.8	3	10.7	

Group A: 1: 100,000 dilution of 2% lidocaine with epinephrine, and Group B: 1: 200,000 dilution of 2% lidocaine with epinephrine.

With regard to the bleeding rate (**Table.3**), the mean bleeding volumes in groups A and B were 83.1±10 and 108±11.6 mL, respectively. The quantitative measurement of the bleeding rate showed no significant difference between the two groups (P=0.97). With regard to the qualitative assessment of bleeding, 3.4%, 50.2%, 31%, and 10.3% of the patients in group A lost 1, 2, 3, and 4 units of blood, respectively. In group B, these rates were 4.8%, 57.1%, 23.8%, and 14.3%, respectively. Similarly, the results of the qualitative assessment of bleeding showed no significant difference between the two groups (P=0.93).

Table-3: The quantitative measurement and qualitative assessment of bleeding.

Bleeding rate	Group A		Group B		P-value
	Mean	SD	Mean	SD	
Bleeding rate (quantitative)	83.16	10.01	108.07	11.68	0.109
Bleeding rate (qualitative)	Frequency	%	Frequency	%	
1	1	3.3	1	3.7	0.931
2	16	53.3	14	51/9	
3	10	33.3	6	22.2	
4	3	10.3	5	18.5	
5	0	0	1	3.7	

Group A: 1: 100,000 dilution of 2% lidocaine with epinephrine, and Group B: 1: 200,000 dilution of 2% lidocaine with epinephrine, SD: Standard deviation..

4- DISCUSSION

The present study aimed to compare the effects of two different doses of epinephrine on hemodynamic changes and bleeding volume in patients undergoing rhinoplasty. The results revealed no difference between the patients receiving epinephrine at the concentrations of 1: 200,000 and 1: 100,000 in terms of hemodynamic parameters, including heart rate, MAP, SBP, and DBP. These findings are in line with the obtained results of similar studies (7, 12). Hemorrhage may occur during rhinoplasty as a result of damage to the large vessels at the site of osteotomy, damage to the small subdermal vessels during osteotomy, or tearing of the periosteal small vessels during osteotomy(13, 14). Epinephrine is a sympathomimetic drug with both α-and b-adrenergic receptors agonist effects. It leads to vasoconstriction and prevents the fast washing and systemic circulation of lidocaine; therefore, the injection of epinephrine in combination with lidocaine has no serious complications (14). Local anesthesia and vasoconstriction occur after the injection of lidocaine in combination with epinephrine and are maintained for at least 60 min and up to 2.5 h. The goal of lidocaine/epinephrine injection during operation is to decrease hemorrhage through the induction of vasoconstriction and reduction of fluid extravasation, decreasing post-operative edema and ecchymosis (15). Based on the literature, the elimination half-life of lidocaine after intravenous bolus injections in combination with epinephrine is approximately 1.5-2 h and the onset of its action is 2-4 min (16). However, in a study performed by Zojajy et al., no decrease was reported in the incidence of postoperative edema and ecchymosis following the local injection of lidocaine/epinephrine solution before rhinoplasty. In this study, the injection of subperiosteal and 1: 100,000 lidocaine/epinephrine was performed immediately before lateral osteotomy (16).

The results of a similar study revealed no difference between the patients using normal saline and those receiving a combination of adrenaline and epinephrine

in terms of bleeding volume, duration of surgery, and the extent of mucosal damage during the surgery (17). Likewise, another study reported no decrease in bleeding rate or post-surgical edema and ecchymosis following the injection of epinephrine (1: 100,000) (15). However, the results of this study may have been affected by the uncontrolled infusion of propofol and remifentanil to maintain controlled hypotension. One of the main advantages of the present study is the systemic recording of the infusion volume of propofol and remifentanil. In this study, there was no difference between the two groups in terms of using propofol, remifentanil, and morphine infusion. The amount of anesthetic agent was not increased to maintain controlled hypotension.

Consistent with our findings, Günel et al. showed the effectiveness of a combination of lidocaine and epinephrine in decreasing bleeding in the patients undergoing rhinoplasty (14). However, they suggested that the topical administration of epinephrine rather than intravenous could facilitate the prevention of some adverse events, including increased bleeding or hemodynamic changes (4).

This discrepancy in research findings may be due to the administration of different dosages in different studies. However, in the present study, the results of both qualitative and quantitative assessments of bleeding in patients receiving epinephrine at the two dosages were similar. The site of injection, characteristics of the samples, or other confounding variables may be the reasons for the contradictory findings. In a study, Ghali et al. compared the impacts of the subdermal injection of 1: 100,000 and 1: 200,000 topical dilutions of lidocaine/epinephrine on cutaneous blood flow in the forearm and face and indicated the site of injection as a confounding factor affecting the cutaneous blood flow (18).

In the present study, there was no significant difference between the patients administered with an epinephrine concentration of 1: 200,000 and those injected with a concentration of 1: 100,000 in terms of SBP, DBP, MAP, and pulse rate. A unit decrease in the blood pressure was observed in both groups 10 minutes after transfusion, which is due to the increase in the anesthetic depth within the interval, following the injection to prep and drape patients in preparation for surgery.

In a study by Demirtas et al., the hemodynamic effects of perioperative stressor events in patients undergoing rhinoplasty under general anesthesia were assessed. A mild to moderate and short-term tachycardia was reported after the infiltration of lidocaine/adrenaline. Also, the changes in blood pressure were not related to perioperative stressors (19). In the present study, there was no evidence of tachycardia, which is probably due to the use of TIVA, the systemic injection of the drug, and the combination of epinephrine and lidocaine.

El-Azzazi et al. also found no difference in SBP after the use of lidocaine:epinephrine (1: 200,000), lidocaine plus dexamethasone, and lidocaine plus ketamine during rhinoplasty (20). However, Goktas et al. observed that lidocaine and epinephrine combination decreased the mean blood pressure in comparison to epinephrine alone. They also reported that the use of this combination increased hemodynamic stability in the patients undergoing rhinoplasty (21).

In another study, Gun et al. examined the effect of a combination of epinephrine and lidocaine on the incidence of edema and ecchymosis after rhinoplasty and showed that this combination decreased hemorrhage in patients. They reported that although lidocaine/epinephrine injection reduced the intraoperative bleeding in

rhinoplasty, it led to an increase in interstitial fluid and pressure[14]. In addition, Junior et al. demonstrated the effectiveness of the application of topical epinephrine at a concentration of 1: 2000 in balancing homeostasis during endoscopic sinus surgery. They showed that the use of adrenaline at higher concentrations could lead to an increase in arterial blood pressure; however, the increase was not above the physiological average (11).

The unexpected entry of drugs into the vein is a main risk factor for intra-nasal injection, which may lead to arrhythmia (9). The administration of adrenalin may lead to cardiac problems even in patients without a history of cardiac disease (8, 22). The results of the present study revealed similar changes in arrhythmia and heart rates in the two groups, which may be due to the maintenance of anesthesia by propofol/remifentanil infusion as the risk of arrhythmia increases with inhalation anesthesia.

Arrhythmia is the most common complication during the injection of anesthetic agents. In this study, bradycardia with unknown reasons was reported in one patient in each group, which was resolved after drug discontinuation. The speed of drug injection and the volume of injected epinephrine were similar in the two groups. The relationship between epinephrine volume and hemodynamic response has not been investigated in the literature.

Epinephrine is one of the most frequently applied topical agents in nasal surgeries, and its benefits and risks largely depend on the infiltration site (15), different uptakes of different mucosal surfaces (23), and duration of the surgery (24). Although epinephrine doses have been determined based on extensive experiments, its absorption and secondary effects cannot be predicted (14). Based on the evidence, the degree of the absorption of topical epinephrine ranges from 5% to 80% (2), and is affected by several factors. It is therefore suggested to perform further studies in this domain to obtain more accurate findings.

As there was no difference between the two groups in terms of anesthetics and quantitative and qualitative bleeding and given the optimal hemodynamic control, it is recommended to use the subcutaneous injection of epinephrine at a dose of 1: 200,000 during rhinoplasty to prevent the incidence of heart problems.

4-1. Study limitation

The present research was performed on a small sample size; therefore, it is suggested to use a larger sample size in future studies to check the reliability of these findings. However, since this study was a double-blind randomized clinical trial, it boasts a high level of evidence and reliability. The patients were randomly assigned into groups, and all procedures were performed by one surgeon. However, the lack of a control group was another limitation of the present study.

5- CONCLUSION

The results of this study were indicative of the similar effects of two concentrations of lidocaine with epinephrine (1: 100000 and 1: 200000) on bleeding volume, SBP, DBP, and heart rate during rhinoplasty. Moreover, no difference was found between the results of the qualitative and quantitative assessments of bleeding in patients receiving epinephrine at different dosages.

6- AUTHORS' CONTRIBUTIONS

Study conception or design: MS, AS, FF, and SS; Data analyzing and draft manuscript preparation: MA and AD, Critical revision of the paper: MS, FF and, SS, Supervision of the research: AS, and MS; Final approval of the version to be published: MS, SS, AS and FF.

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7- CONFLICT OF INTEREST: None.

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