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Efficacy of Laryngeal Mask Airway Impregnation with Diltiazem Gel on Hemodynamic Changes in Patients with Hypertension Undergoing Phacoemulsification Surgery: A Randomized Clinical Trial

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Abstract

Background: Airway control problems are among the most prevalent causes of anesthesia-related mortality and morbidity. Some devices provide patients with adequate oxygen supply and ventilation during surgery by creating a safe airway in anesthetized patients. One of these devices is the laryngeal mask airway (LMA). The compression and painful stimuli following the LMA cuff inflation can lead to hemodynamic changes. Diltiazem gel is used in the control and treatment of hypertension (HTN) and heart arrhythmia and is absorbed through the tracheal mucosa.

Objectives: By assuming that diltiazem gel is superior to other drugs used to prevent arrhythmias and hemodynamic changes during surgery, this study aimed to evaluate the effect of LMA impregnation with diltiazem gel, compared to lubricant gel.

Methods: This study was conducted as a double-blind, randomized clinical trial on 80 participants with HTN who were candidates for phacoemulsification (phaco) surgery in Imam Khomeini Hospital, Kermanshah, Iran. The participants were assigned to an intervention (LMA impregnated with diltiazem gel) and a control group (LMA impregnated with lubricant gel) through the block random method in the form of 40 blocks of 2 using a random-numbers table. Hemodynamic changes (systolic and diastolic blood pressure and heart rate) were measured before, immediately after, 5 min, and 15 min after intubation, during surgery every 15 min, upon entering the recovery unit, and 15 and 30 min after entering the recovery unit.

Results: The mean systolic and diastolic blood pressure in the intervention group showed a significant decrease, compared to that in the control group. A significant difference was also observed in the mean heart rate difference between the two study groups, but only at the beginning of the study ($P<0.05$). Additionally, according to the results of repeated measures analysis of variance, the mean of the measured variables showed a significant difference at different measurement times in the intervention group ($P<0.05$).

Conclusion: The findings supported the effectiveness of diltiazem gel in reducing blood pressure, especially in the final stages of surgery, decreasing the number of premature ventricular contractions, and controlling normal breathing. Therefore, specialists and surgeons can use diltiazem gel to control the hemodynamic status of patients.

Keywords: Diltiazem, Hemodynamics, Hypertension, Laryngeal mask, Phacoemulsification

1. Background

In any surgery, airway control is one of the most essential skills of anesthesiologists. Airway control problems are among the most prominent causes of anesthesia-related mortality and morbidity. According to the American Society of Anesthesiologists (ASA), 6% of complaints were related to airway injuries (1). Some devices provide patients with adequate oxygen supply and ventilation during surgery by creating a safe airway in anesthetized patients. One of these devices is the laryngeal mask airway (LMA), which has become very popular among anesthesiologists over recent decades. The LMA is commonly used to create a safe airway and maintain ventilation and spontaneous ventilation in short outpatient surgeries under general anesthesia, such as phacoemulsification (phaco) in patients with cataracts (2-4). However, the compression and painful stimuli following the LMA cuff inflation can lead to hemodynamic changes. Following these stimuli, there is a possibility of increased blood pressure and heart rate in patients, which are likely to be harmless to those with normal blood circulation but can be dangerous for those with a history of hypertension (HTN), coronary artery disease, and cardiac tamponade (5). In addition to being hazardous for patients with cardiovascular disease (CVD), increased stimulation can also be dangerous for patients with intracranial complications. Several methods have been used to prevent these responses, including the use of narcotics, beta-blockers, intravenous lidocaine, and topical medications, such as gels, sprays, and liquids, but the effect of these topical drugs is restricted to a short time after the administration, and they are absorbed through the tracheal mucosa (6). Meanwhile, diltiazem is a drug that inhibits the

intracellular entry and exit of calcium. Therefore, it slows he rate of atrio-ventricular and sinus-atrial conduction and leads to the relaxation of smooth muscles of the heart and arteries wall. This medication is used in the control and treatment of HTN, angina pectoris, Raynaud's syndrome, and heart arrhythmia. Furthermore, it is currently the most widely used medication after thoracotomy for prophylaxis and heart arrhythmia (7). The half-life of diltiazem following a single-dose consumption is 20 to 30 min, and it is about 5-8 h for repeated doses. On the other hand, the half-life of a medication administered by intravenous injection (IV) is about 3-4 h. Diltiazem injection produces its effect within 3 min (8). It is also available as a gel in pharmacies in some countries, which has fewer side effects than the mentioned drugs (9). Diltiazem should not be administered orally in patients undergoing surgery, who must be Nihil Per Os: Nothing by Mouth (NPO) or avoid eating by mouth. Therefore, its IV form is used, which is rapid and short-acting (10), but these patients need continuous absorption of diltiazem during surgery. In such conditions, patients had better use the gel form of this medication, which, in addition to having fewer side effects, compared to other types, is also absorbed through the tracheal mucosa. In this case, the initiation of action is 20-30 min, and its half-life is about 3-4 h (11). On the other hand, by dilating the arteries, it improves the flow of endoderm mucosa, relieves the pain, and heals the wound caused by ischemia (12, 13). In light of the above, by assuming that diltiazem gel is superior to other drugs used to prevent arrhythmias and hemodynamic changes during surgery, we decided to design a clinical trial to evaluate the effect of LMA impregnation with diltiazem gel on the hemodynamic changes of patients with HTN who underwent phaco surgery to treat cataract, given the high frequency, easy accessibility, and the identical type of surgery.

2. Objectives

The findings can open a new way for subsequent similar research and help health planners and policymakers to reduce hemodynamic complications, as well as the use of other medications and anesthetics in surgeries with general anesthesia.

3. Methods

3.1. Study Design and Participants

The study was carried out as a double-blind, randomized clinical trial with parallel groups on hemodynamic changes in patients with HTN who were referred to Imam Khomeini Hospital, Kermanshah, Iran, in 2020 to undergo phaco surgery. The Ethics Committee of Kermanshah University approved the patient information sheet, the study design, and the informed consent given by the participants (IR.KUMS.REC.1399.131). The study was recorded in Iranian clinical trials (IRCT20200516047457N1). The applicable guidelines of Consolidated Standards of Reporting Trials (CONSORT) were implemented, and the participants signed a consent form.

The patients participated in the study after giving informed consent and if they had the given criteria. Those with a history of CVD (such as myocardial infarction, heart arrhythmia, and congestive heart failure), diabetes, and other systemic diseases, as well as pregnant women, were excluded from the study. Additionally, patients whose intubation took more than 30 sec and those who, according to the ASA Physical Status Classification, were arranged as ASAI or ASAII and had difficulty in intubation were not included in the study. To minimize the error rate in the trial results, the main researcher and the patients were kept blind. The number of participants was determined following Attari (14) and using the Pokac formula with a 95% confidence interval and 80% power (15). Considering the sample dropout during the study, 40 was determined as the number of patients in each group.

3.2. Procedure

The participants were assigned to an intervention and a control group through the block random method in the form of 40 blocks of 2 using a random-numbers table (Figure 1). A statistician assigned the participants using a random allocation sequence.

Upon entering the operating room, patients were monitored continuously using a cardiac monitor and a digital fingertip oximeter. The LMA intubation was performed by an anesthesiologist. Midazolam (0.02 mg/kg^{-1}), sufentanil (0.1-0.2 mg/kg^{-1}), propofol (2 mg/kg^{-1}), and atracurium (0.5 mg/kg^{-1}) were used for all patients. After oxygenation by 100% oxygen, the patients with LMA tube cuff were assigned to the two groups. The intervention and control groups whose LMA was impregnated with lubricant gel and diltiazem gel, respectively, were intubated. To ensure consistency, all patients underwent surgery by the same surgeon. In this study, the primary outcome variable was blood pressure, and the secondary outcome variables were heart rate and dysrhythmia. Diastolic and systolic blood pressure and heart rate were measured in eight stages (before, immediately after, 5 min after, and 15 min after inserting the LMA and gel, during surgery every 15 min, upon entering the recovery unit, and 15 and 30 mins following entering the recovery unit) and recorded afterward. Dysrhythmia was also controlled. The pressure within the LMA cuff was maintained between 20-25 mm Hg in all patients using a Gauge measuring device. Throughout the surgery, every half hour, the cuff pressure, hemodynamic changes (heart rate and

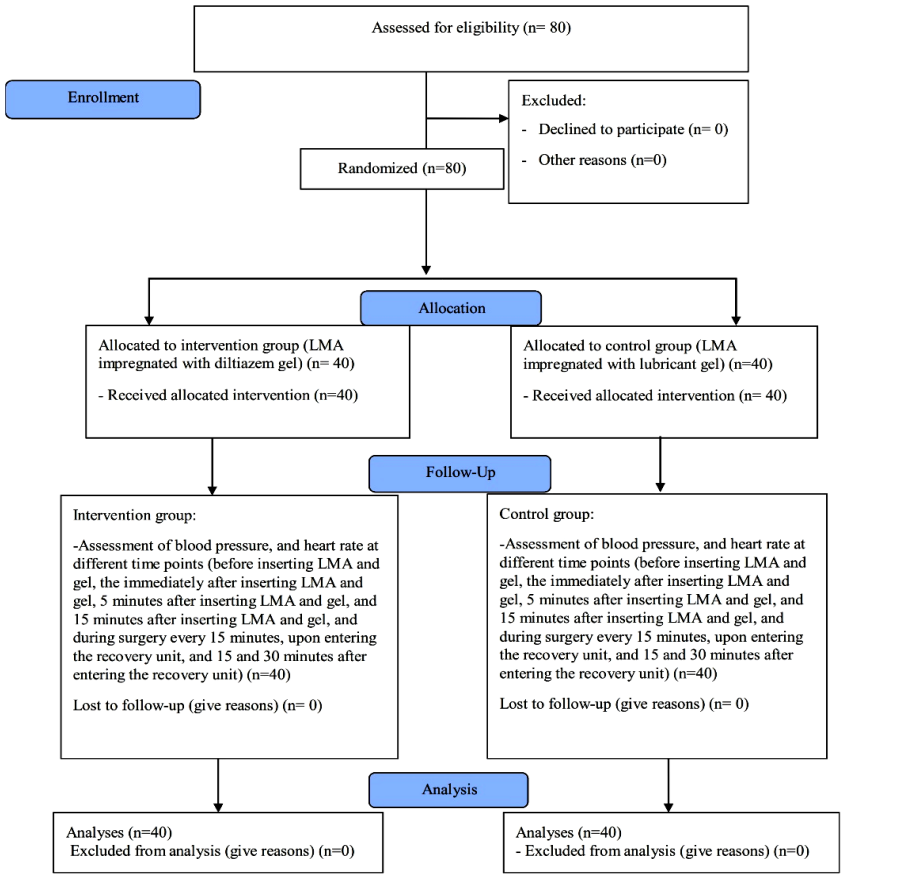

Figure 1. Study flow chart

blood pressure), and dysrhythmia were assessed and recorded in the checklist, along with the demographic characteristics of patients (such as age, gender, and weight).

Diltiazem gel was prepared by the researchers of this study as follows:

1. 4g diltiazem powder was dissolved in the intended solvent at a specified time and temperature.
2. The hydrophilic polymer was dissolved in the aqueous base at a specified time and temperature.
3. The pH was set.
4. Preservatives and sweeteners were added to the remaining amount of solvent and stirred at the appropriate time and speed.
5. The ingredients were added together under 200 rpm stirring speed.
6. The prepared gel was poured into a suitable pump container.
7. The container labeling was done.

3.3. Statistical Analysis

The data were summarized in the SPSS software (version 23), and the results of quantitative variables were reported through the mean score and standard deviation (SD), while qualitative variables results were reported using percentage and frequency. To check the normality of data distribution, the Kolmogorov-Smirnov (K-S) test was employed. The independent sample t-test, Fisher's exact test, and the Mann-Whitney U test were used to compare the intended variables. Before performing the within-group analysis of variance, the homogeneity of variance /covariance of blood pressure and heart rate was evaluated using Mauchly's W test. Considering that the P-Value was less than 0.05, the Greenhouse-Geisser test was utilized. Moreover, Friedman statistical test was used to compare the number of dysrhythmias recorded during the measurement stages between the two groups. The significance of the tests was investigated at the level of 0.05.

4. Results

In total, 80 patients with HTN who were candidates for phaco surgery participated in the study. The participants' age range was 40-55, with mean±SD of 49.28±4.55 years in the control group and 50.42±2.69 years in the intervention group. According to the Mann-Whitney U test results, there was no significant difference between the two groups in age (P=0.451). Moreover, as shown by Fisher's exact test and the independent t-test, the two groups were homogeneous in the underlying variables, including gender distribution, weight, previous medical history, and medication use history, with no significant differences. Additionally, the number of breaths per minute after consciousness was

calculated in both groups, which was reported to be lower and within the normal range (12 breaths per minute) in the intervention group with the mean±SD of 12.75±1.58 breaths per minute, compared to the control group with the mean±SD of 19.40±3.14 breaths per minute (16). The difference was statistically significant (P<0.001) (Table 1).

The results of the repeated measures analysis of variance (ANOVA) test with Greenhouse-Geisser correction (due to the violation of the sphericity assumption according to Mauchly's test of sphericity) showed that for blood pressure and heart rate variables, the mean score of systolic blood pressure in the control group exceeded that of the intervention group, and except for the first stage of the measurement, the difference was significant in all cases (P<0.001 and 0.027). The major difference observed in terms of the mean score of systolic blood pressure was in the sixth measurement (when entering the recovery unit). Pairwise comparisons in the intervention group regarding systolic blood pressure showed that the most profound mean difference of this variable was observed between the fifth and first measurements, the fourth and first measurements, as well as the third and first measurements. The most considerable difference in the mean systolic blood pressure in the control group, on the other hand, was seen between the fifth and sixth, fourth and sixth, second and sixth, and third and sixth measurements.

In addition, the mean score of diastolic blood pressure was higher in the control group than the intervention group in most stages, which was statistically significant in all stages except for the first and second stages of measurement (before and immediately after the LMA impregnation with the gel) (P=0.001 and 0.007). The greatest difference in the mean diastolic blood pressure between the two groups was related to the sixth, fifth, and fourth measurements. In pairwise comparisons in the intervention group, the biggest difference in the mean diastolic blood pressure was related to the fifth and first, fourth and first, and third and first measurements. Additionally, in the control group, the major difference in the mean diastolic blood pressure was reported between the fifth and sixth, fourth and sixth, and eighth and sixth measurements.

The difference in the heart rate of patients was significant between the two groups only in the first and second stages of measurement (P=0.001 and 0.002), with higher values in the intervention group than in the control. The most considerable difference in the mean heart rate between the two groups was related to the first and second measurements. In addition, in pairwise comparisons in the intervention group, the most profound difference in the mean heart rate was related to the fifth and second, eighth and second, and fourth and second measurements. The major difference in the mean heart rate in the control group, on the other hand, was related to the first and sixth, first and fourth, first and third, first and second, and the eighth and sixth measurements. It should be noted that the within-groups P-value was less than 0.001 for diastolic blood pressure, systolic blood pressure, and heart rate in the two groups. The results of the ANOVA showed that the within-group changes and interactions were significant for heart rate and diastolic and systolic blood pressure in the two groups. It means that the effect of diltiazem gel on heart rate and blood pressure was different during the measurement times such that a significant reduction was observed in the diastolic and systolic blood pressure from the beginning to the end of surgery in the intervention group, compared to the control (P<0.001) (Table 2).

Table 1. Characteristics of intervention and control groups

Variables		Intervention group (n=40)	Control group (n=40)	P-value
Age (y)		50.42±2.69	49.28±4.55	0.451$
Gender	Female	16 (40%)	17 (42.5%)	0.500#
	Male	24 (60%)	23 (57.5%)	
Weight (kg)		74±6.85	74.48±9.21	0.794&
Previous medical history	No	27 (67.5%)	28 (70%)	0.809#
	Yes	13 (32.5%)	12 (30%)	
Type of disease	No disease	27 (67.5%)	28 (70%)	0.303#
	CVD	1 (2.5%)	0 (0%)	
	Diabetes	6 (15%)	9 (22.5%)	
	Hypothyroidism	3 (7.5%)	0 (0%)	
	Hyperlipidemia	2 (5%)	0 (0%)	
	COPD	1 (2.5%)	0 (%0)	
	Asthma	0 (0%)	2 (5%)	
	Cancer	0 (0%)	1 (2.5%)	
History of medicine use	Have	14 (35%)	12 (30%)	0.812#
	Do not have	26 (65%)	28 (70%)	
History of drug abuse	Have	5 (12.5%)	4 (10%)	1.000#
	Do not have	35 (87.5%)	36 (90%)	
Number of breaths per minute after consciousness		12.75±1.58	19.40±3.14	0.00$

$ Mann-Whitney U test, # Fisher's exact test, and Independent sample t-test
Values are mean±SD or number (%).
CVD: Cardiovascular disease
COPD: Chronic Obstructive Pulmonary Disease

Table 2. Comparison of the mean systolic and diastolic blood pressure and heart rate in the intervention and control groups during the eight stages

Time	Systolic blood pressure (mm Hg)			Diastolic blood pressure (mm Hg)			Heart rate (beats per minute)		
	Intervention group (n=40)	Control group (n=40)	*P*-value	Intervention group (n=40)	Control group (n=40)	*P*-value	Intervention group (n=40)	Control group (n=40)	*P*-value
Before inserting LMA and gel	157.03±19.83	163.3±12.65	0.136*	92.6±10.51	89.58±7.12	0.137*	76.75±14.11	67.6±8.73	0.001*
Immediately after inserting LMA and gel	142.05±27.15	155.85±27.51	0.027*	83.88±11.2	87.33±13.8	0.224*	82.43±12.84	73.85±10.41	0.002*
5 mins after inserting LMA and gel	134.1±19.13	155.93±28.06	0.001*	80.20±8.1	87.38±14.0	0.007*	76.23±12.38	74.88±9.1	0.583*
15 mins after inserting LMA and gel	130.38±18.2	155.1±21.1	0.001*	78.93±8.79	87.1±10.34	0.001*	72.25±10.42	75.1±9.6	0.220*
During surgery, every 15 mins	129.28±17.41	154.1±17.34	0.001*	77.68±7.81	86.1±7.55	0.001*	69.43±10.62	72.1±7.24	0.201*
Upon entering the recovery unit	142.5±12.26	169.58±15.03	0.001*	83.83±7.1	94.5±7.2	0.001*	76.3±11.42	75.38±7.5	0.682*
15 mins following entering the recovery unit	138.8±12.9	160.63±12.55	0.001*	82.78±9.1	89.53±7.2	0.001*	73.1±10.91	72.1±7.87	0.631*
30 mins following entering the recovery unit	137.63±10.9	159.2±11.93	0.001*	82.55±7.86	89.2±6.86	0.001*	72.18±10.38	69.28±8.5	0.176*
***P*-value within groups**			0.001**			0.001**			0.001**

Values are mean±SD. LMA: laryngeal mask airway, * Independent sample t-test, **Repeated Measures ANOVA test

Additionally, the results of measuring and recording dysrhythmia in the eight stages showed that in the third measurement (5 min after LMA impregnation with the gel) in the intervention group, 36 patients did not have dysrhythmia, and out of the remaining four patients, two had dysrhythmia, and two had premature ventricular contractions (PVCs). In the control group, at this stage of measurement, 30 patients did not have dysrhythmia, and PVC was observed in the remaining 10 patients. In most measurement stages, the number of PVCs observed in the control group was reported to be higher than that of the intervention group. Moreover, in the third measurement, a statistically significant difference (P=0.014) was seen between the frequency of dysrhythmias in both groups; however, there was no significant difference between the frequency of dysrhythmia in the two groups after the first and second measurements and fourth to eighth measurements. Considering the significance of the P-value between groups based on the Friedman test (P=0.019 and 0.001), it can be stated that the changes in the incidence of dysrhythmia in both groups were statistically significant during the eight measurement stages (Table 3).

Table 3. Comparison of the number of patients with dysrhythmia in the intervention and control groups during the eight stages

Time	Intervention group (n=40)			Control group (n=40)			*P*-value between groups
	Do not have	Have	PVC	Do not have	Have	PVC	
Before inserting LMA and gel	38 (95%)	2 (5%)	0 (0%)	40 (100%)	0 (0%)	0 (0%)	0.494*
Immediately after inserting LMA and gel	33 (82.5%)	2 (5%)	5 (12.5%)	28 (70%)	0 (0%)	12 (30%)	0.063*
5 mins after inserting LMA and gel	36 (90%)	2 (5%)	2 (5%)	30 (75%)	0 (0%)	10 (25%)	0.014*
15 mins after inserting LMA and gel	38 (95%)	1 (2.5%)	1 (2.5%)	39 (97.5%)	0 (0%)	1 (2.5%)	1.000*
During surgery, every 15 mins	37 (92.5%)	1 (2.5%)	2 (5%)	40 (100%)	0 (0%)	0 (0%)	0.241*
Upon entering the recovery unit	35 (87.5%)	2 (5%)	3 (7.5%)	36 (90%)	0 (0%)	4 (10%)	0.548*
15 mins following entering the recovery unit	39 (97.5%)	1 (2.5%)	0 (0%)	40 (100%)	0 (0%)	0 (0%)	1.000*
30 mins following entering the recovery unit	39 (97.5%)	1 (2.5%)	0 (0%)	40 (100%)	0 (0%)	0 (0%)	1.000*
P-value within groups		0.019**			0.001**		

Values are number (Percentage) LMA: laryngeal mask airway, PVC: Premature ventricular contractions*Fisher's exact test, **Friedman test

5. Discussion

The findings of this study indicated the effectiveness of diltiazem gel in blood pressure reduction, especially in the final stages of surgery, the reduction of the number of PVCs, and normal breath control.

A study was conducted by Talwar et al. (2018) in India to evaluate the effect and safety of esmolol, diltiazem, and their combination on the hemodynamic response of laryngoscopy and intubation. In their study, 124 adult patients were classified as ASAI and ASAII based on the ASA Physical Status Classification and randomly assigned into four groups of 31 (one control group receiving saline recipient and three intervention groups receiving diltiazem, esmolol, and a combination of diltiazem and esmolol). Unlike our study, in which the mask was impregnated with the gel form of the medication, in their study, the medications were administered by IV injections. In line with our study, their findings indicated a significant increase in heart rate in the control diltiazem groups and a significant reduction in heart rate in the groups receiving esmolol and the combination of diltiazem and esmolol after laryngoscopy. Unlike the control group, a decrease in systolic blood pressure was reported in other groups. This study emphasized the use of a combination drug at appropriate doses to effectively reduce blood pressure and heart rate during surgery (17).

Another study was conducted by Fuji et al. (1995) in Japan to evaluate the effect of calcium channel blockers (CCBs) on blood circulation response to tracheal intubation in patients with hypertension by comparing the effect of nicardipine and diltiazem. Patients aged 39-74 were divided into three groups receiving nicardipine, diltiazem, and placebo. There was no difference in baseline values of hemodynamic variables between the studied groups. However, a significant increase was observed in the mean arterial blood pressure and the heart rate in patients receiving placebo and nicardipine from the beginning of the study and 5 min after laryngoscopy and tracheal intubation, but in the diltiazem receiving group, the heart rate remained high for approximately 1 min. Though the suppressive effect of both drugs on the mean arterial pressure (MAP) change was similar, less reduction was observed in intubation-related heart rate in the diltiazem group, compared to the nicardipine group (18).

In a study in 1985 in America, Bruse et al. stated that in patients with stable angina, short-term and long-term administration of diltiazem significantly reduced the frequency of spontaneous angina attacks and improved exercise tolerance, compared to the placebo. Additionally, unlike propranolol, diltiazem enhanced the function of the left ventricular in ischemic heart disease patients. Diltiazem combined with nifedipine was also an effective compound in patients who did not respond to monotherapy (19).

A study was conducted by GaziParvez et al. (2010) in India to reduce the reaction to tracheal and laryngoscopy intubation with esmolol and intravenous diltiazem in controlled surgical patients with hypertension. In their study, 150 eligible patients aged 40-60 years were divided into three groups: dextrose, diltiazem, and esmolol recipients. Unlike the results of our study, esmolol and diltiazem groups showed a significant increase in diastolic and systolic blood pressure and MAP, compared to the control group. However, consistent with our study, diltiazem failed to alleviate the increase in heart rate (20).

Diltiazem is a benzothiazepine derivative and a CCB whose analgesic and antihypertensive capabilities were studied and compared to other beta-blockers, angiotensin-converting enzymes, diuretics inhibitors, and other CCBs in different demographic groups. Valuable research efforts have also been made worldwide to study the skin penetration, formulation, and reduction of the daily intake of various classes of CCBs as potential drugs for HTN treatment due to their low oral bioavailability and short half-life (21, 22). However, experimental evidence examining the effect of diltiazem and lubricant gel formulations on reducing hemodynamic complications during general anesthesia surgeries in hypertensive patients that must be NPOs and are more vulnerable to hemodynamic complications (18) was not found during our study, which can be among the strengths of this study. However, this prevented the comparison of findings and the complete interpretation of the overall results. On the other hand, according to some studies, IV diltiazem is accompanied by increased nausea, decreased ventricular rate, and reduced blood pressure, and no suppressive effect of diltiazem was observed in the use of doses lower than 0.2% (23, 24). The use of 0.2% diltiazem gel can be thus regarded as an advantage of this study.

In general, the limitation of the conducted studies in this field makes it difficult to interpret the results. One of the constraints of this study is the sample size and the type of disease in the participants. Considering this study was conducted on patients with hypertension and undergoing phaco surgery, the results are not generalizable to other patients. Therefore, it is recommended to conduct further studies on other patients to determine the exact mechanism of the effect of LMA lubrication with diltiazem gel.

6. Conclusion

In addition to reducing complications, such as nausea, especially in the IV types and other forms, diltiazem gel is absorbed through tracheal mucosa (11, 23) due to skin adsorption and its rapid-acting

nature during general anesthesia in hypertensive patients. Therefore, it reduces concern over the incidence of cardiovascular accidents during surgery in this group of patients.

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Footnotes

Conflicts of Interest: None.
Authors' contributions: JAS and SHR developed the concept and design of the study. SHM, YAS, and MY collected and analyzed the data. All authors prepared the first draft of the manuscript. JAS and SHR edited and reviewed the manuscript. All authors reviewed and approved the paper.
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Ethical statements:
Ethical approval (No. IR.KUMS.REC.1399.131) was obtained from the Ethics Committee of Kermanshah University of Medical Sciences, Kermanshah, Iran, on 11/05/2020. The study was recorded in the Iranian Registry of Clinical Trials (IRCT) on 26/05/2020 with the number IRCT20200516047457N1. The date of the first registration was 20/06/2020. The applicable guidelines of Consolidated Standards of Reporting Trials (CONSORT) were followed, and the participants signed a consent form before participating in the study.

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