Original Article

Comparison of the Cardiovascular Response to Sedation with Dexmedetomidine, Midazolam, and Etomidate in Phacoemulsification under Local Topical Anesthesia; A Double-Blind Randomized Controlled Clinical Trial

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Abstract

Background: The present study aimed to compare the cardiovascular response to sedation with dexmedetomidine, midazolam, and etomidate during phacoemulsification under local Topical anesthesia.

Materials and Methods: In this double-blind randomized clinical trial, a total of 90 cataract surgery candidates undergoing phacoemulsification were selected and divided into three groups. The first group received 1 µg/kg dexmedetomidine over 10 minutes, followed by an infusion of dexmedetomidine at a rate of 0.5 µg/kg/h. The second group received 0.05 mg/kg midazolam, and the third group received 0.2 mg/kg slow IV etomidate. Hemodynamic parameters, sedation level, and adverse effects were recorded before anesthesia, during surgery, and during recovery.

Results: The results of this study showed that in the 10th minute of surgery, the systolic blood pressure (SBP) in the etomidate group was significantly higher than the other groups P value = 0.029). The pulse rate (PR) in the etomidate group at the 15th minute during surgery, 10th, 20th, and 30th minute in the recovery period (mean 70.33 ± 10.34 bpm, 72.10 ± 10.18 bpm, 73.70 ± 10.18 bpm, and 75.03 ± 6.73 bpm, respectively) was significantly higher than the other two groups (P value < 0.05). No adverse effects such as dizziness, restlessness, vomiting, or nausea were observed in the midazolam group. However, decreased heart rate was significantly higher in the dexmedetomidine group (26.7%) compared to the etomidate (3.3%) and midazolam (6.7%) groups (P value = 0.021).

Conclusion: According to the results of this study, the sedation level achieved by dexmedetomidine, midazolam, and etomidate was similar. However, etomidate seemed to have a better effect on maintaining blood pressure and pulse rate compared to the other two drugs.

Keywords: Dexmedetomidine, etomidate, midazolam, phacoemulsification, sedation

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Introduction

Cataract surgery is one of the most common surgical procedures performed worldwide, with approximately 3 million annually in the United States.[1] In most cases, local anesthesia and sedation are used for cataract surgery.[2] The role of sedation in increasing patient comfort and cooperation, especially during procedures under local or regional anesthesia, is crucial. The clinical application of sedation during ocular local anesthesia in various medical settings is often associated with some adverse effects.[3]

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In this regard, various drugs such as propofol, pentazocine, ketamine, fentanyl, midazolam, dexmedetomidine, and etomidate have been used alone or in combination for reducing anxiety and providing sedation.[4]

Dexmedetomidine is a selective alpha-2 receptor agonist that provides sedation and analgesia without causing respiratory depression. It allows patients to respond to verbal commands during sedation.[5,6] Dexmedetomidine has been increasingly used as a sedative for monitored anesthesia care due to its analgesic properties, sedation during surgery, and lack of respiratory depression.[7,8] It has recently been suggested as an alternative to sedation for cataract surgery.[9]

On the other hand, midazolam is a benzodiazepine that induces sedation and amnesia. Its single dose has a rapid onset of action within 30–60 seconds and lasts for 15–80 minutes, but its hemodynamic and respiratory depression effects are observed in combination with opioids.[10]

Another commonly used nonbarbiturate, nonbenzodiazepine drug derivative of midazolam used for eye surgeries is etomidate. It has a rapid onset of action, short duration of sedation, less clinically significant hemodynamic changes, and less respiratory depression. Etomidate has no analgesic effect and is recommended to be used in combination with analgesic drugs such as fentanyl.[11]

In comparative evaluations of anesthesia quality and hemodynamic stability, various studies have been conducted with the three drugs, etomidate, midazolam, and dexmedetomidine, in different surgical procedures. For example, no significant difference has been reported in the quality of anesthesia among these three drugs.[12-14] However, some studies have reported that etomidate compared to other drugs had the minimum changes in blood pressure and heart rate, and reduced risk of apnea, respiratory failure, and cerebral protection.[15] Other studies have shown that midazolam provides a more stable heart rate compared to etomidate. Moreover, midazolam is associated with higher patient satisfaction, less pain, and a shorter recovery time compared to dexmedetomidine.[13,16] Conversely, another study has reported that dexmedetomidine is superior to midazolam in terms of anesthetic quality and hemodynamic changes.[17]

Considering that the majority of patients undergoing these surgeries are elderly and have at least one chronic disease,[18] the choice of less invasive anesthesia methods to maintain hemodynamic stability and achieve desirable cardiovascular responses is of special importance in these patients. Given the contradictory results of previous studies in different surgical procedures and anesthesia types and the lack of studies comparing dexmedetomidine, etomidate, and midazolam, the present study was conducted to investigate and compare the effect of cardiovascular responses to anesthesia with dexmedetomidine, midazolam, and etomidate in phacoemulsification under local anesthesia.

Materials and Methods

The current study is a double-blind randomized controlled clinical trial. The study population includes all patients eligible for eye procedures under local anesthesia who referred to Feiz Hospital in Isfahan in March 2022 to January 2023.

From this population, a sample size of 90 patients (30 in each group) was determined with a confidence level of 95%, a test power of 80%, and considering the results of previous studies[3] on standard deviation of heart rate in the two groups receiving midazolam and dexmedetomidine, which were 8.93 and 9.01, respectively, with the mean difference of 6.5.

This sample was randomly selected from patients over 18 years old, with controlled blood pressure, candidates for phacoemulsification under local anesthesia, and classified as American Society of Anesthesiologists (ASA) class I or II, who gave their consent to participate in the study. Patients with mental disorders, chronic use of sedative, psychotropic, alcohol, or narcotic drugs, allergies to study drugs, obstructive pulmonary disease, asthma, cardiovascular disease (including left ventricular failure with EF less than 30), cardiac block, heart rate less than 50 per minute, systolic blood pressure (SBP) less than 90 mmHg, and use of sedative or analgesic drugs within 24 hours before surgery were excluded from the study. In cases of changes in the surgical procedure, type of anesthesia, or patient's withdrawal from the study, the patient was excluded and replaced with another sample.

After obtaining ethical approval from the Ethics Committee of Isfahan University of Medical Sciences (code: IR.MUI.MED.REC.1400.674) and registration code of clinical trial (IRCT20180416039326N20), and written informed consent from eligible patients to participate in the study, a total of 90 patients were randomly assigned to three groups of 30 individuals. At the beginning of the study, their demographic information, including age, gender, height, weight, and body mass index (BMI), was recorded, and then using the random allocation software, the patients were divided into three groups of 30 individuals [Figure 1].

After entering the operating room, all patients were under standard monitoring (using the SAADAT brand), which included intermittent noninvasive blood pressure, pulse oximetry, electrocardiography, and capnograph. To prevent blood pressure drops during induction of sedation, a lactate ringer's solution of 5 mL/kg was intravenously infused. During the stay in the operating room and the recovery room, oxygen was administered through the nasal cannula with a flow rate of 4 liters per minute. All patients in the three groups received sedatives at the same time. Ten minutes before the start of surgery, two drops of 0.5% tetracaine were instilled 5 minutes apart to create local anesthesia.

In the first group, patients received dexmedetomidine at a dose of μg/kg 1 in 20 mL normal saline over 10 minutes, followed by an infusion of dexmedetomidine at a rate of μg/kg/h 0.5 (dexmedetomidine group). In the second group, patients

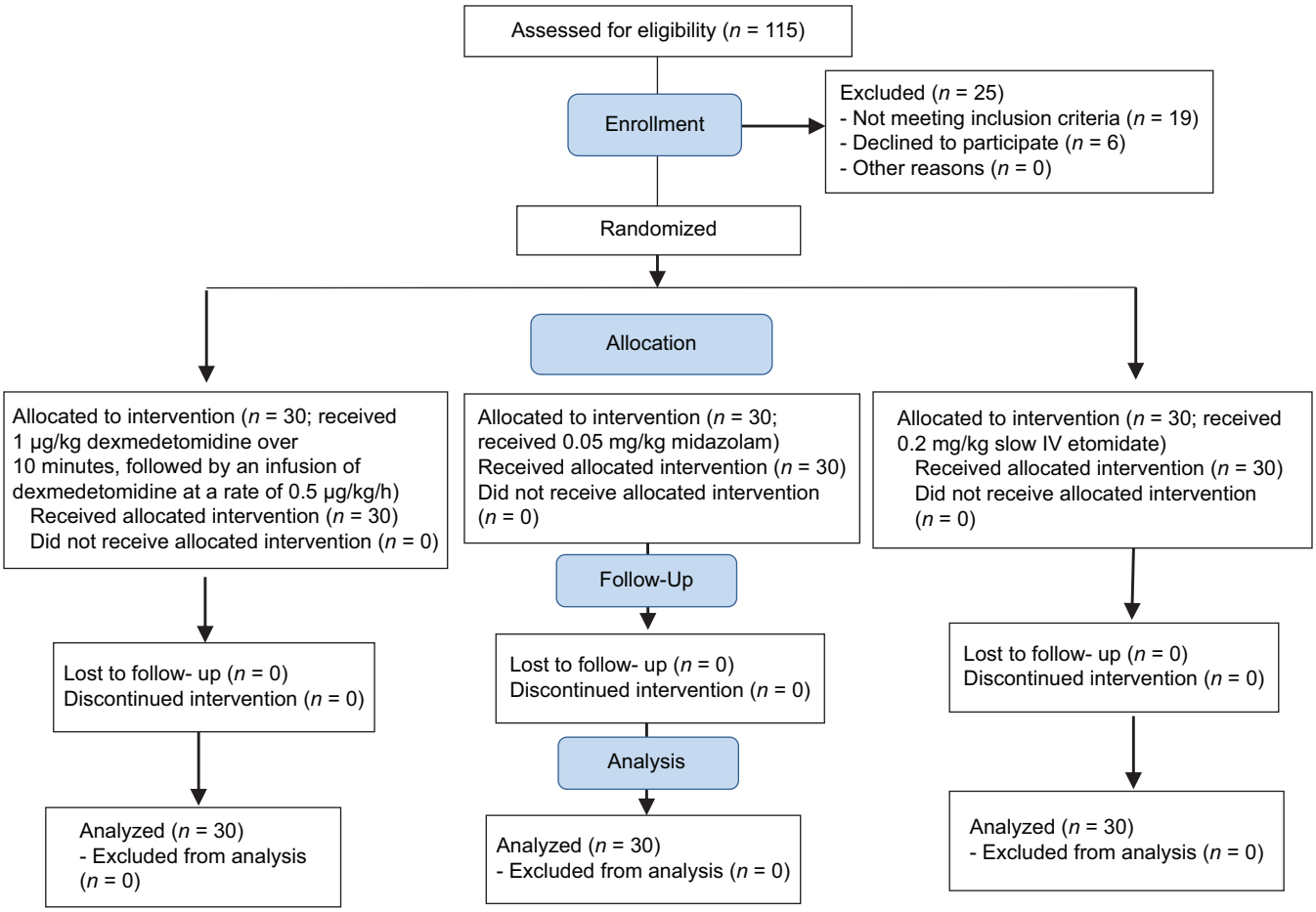

Figure 1: Consort flowchart of patients

received a slow intravenous infusion of midazolam at a dose of mg/kg 0.05 (midazolam group). In the third group, patients received etomidate at a dose of 0.2 mg/kg (etomidate group). In all three groups, for analgesia, fentanyl was administered at a dose of 1.5 mcg/kg, and if more sedation was required, propofol at a dose of 0.5 mg/kg and concentration of 5 mg/mL was administered.

To maintain blinding, the drugs were prepared by the anesthesiologist before the intervention, placed in coded syringes, and stored in the operating room without the investigator's knowledge about the type of drug, and then administered according to the assigned group.

The hemodynamic parameters of the patients, including SBP, diastolic blood pressure (DBP), heart rate, and arterial oxygen saturation (SPO2), were evaluated and recorded before surgery (before anesthesia induction), during surgery at 5, 15, and 30-minute intervals, and in the recovery room at 10, 20, and 30-minute intervals.

The occurrence of any cardiovascular complications during surgery and in the recovery room, including hypertension (an increase of blood pressure more than 20% from baseline), tachycardia (increase of heart rate more than 20% from baseline), hypotension (decrease of blood pressure more than 20% from baseline), decrease of heart rate more than 20% from baseline, and a decrease in SPO2 (environmental SPO2 decrease to less than 92%), was also recorded.

At the end of the surgery or after full recovery, the patients' and surgeons' satisfaction (using sedation level and complications) based on a five-point Likert scale (1 = strongly disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, 5 = strongly agree) were evaluated and recorded.

Statistical analysis

Finally, the collected data were analyzed by SPSS software (ver. 23). The data were presented as mean ± standard deviation or frequency (percentage). Due to the normal distribution of the data based on the Kolmogorov–Smirnov test, one-way analysis of variance (ANOVA) was used to compare the means of quantitative variables among the three groups, and repeated measures analysis of variance was used to compare the means of quantitative variables over time within each group. Additionally, the Chi-square test was used to compare the frequency distributions of qualitative data among the three groups. A significance level of less than 0.05 was considered for all analyses.

Results

In the present study, in the dexmedetomidine group, there were 17 males (46.7%) and 13 females (43.3%) with the mean age of 37.91 ± 9.15 years. In the midazolam group, 14 cases (46.7%) were male and 16 cases (53.3%) were female with the mean age of 39.74 ± 8.90 years. In the etomidate group, 18 cases (60%) were male and 12 cases (40%) were female with the mean age of 37.81 ± 11.24 years (*P* value > 0.05) [Table 1].

Before the operation onset and anesthesia induction, there was no significant difference in mean systolic blood pressure (SBP), pulse rate (PR), and arterial oxygen saturation (SPO2) among the three groups (*P* value > 0.05). However, in the 10th minute during surgery, the SBP in the etomidate group with the mean of 123.03 ± 22.68 mmHg was significantly higher than the dexmedetomidine and midazolam groups with the means of mmHg 118.70 ± 20.09 and 107.03 ± 22.24 mmHg, respectively (*P* value = 0.029). Additionally, although the mean diastolic blood pressure (DBP) was higher in the etomidate group compared to the other two groups, there was no significant difference among the three groups at any of the follow-up times (*P* value > 0.05). The PR in the etomidate group at the 15th minute during surgery, and 10, 20, and 30 minutes in the recovery, was significantly higher than the other two groups (*P* value < 0.05). Furthermore, changes in this parameter were significantly higher in the midazolam group compared to the etomidate group (*P* value < 0.05). In fact, the least changes in PR were observed in the etomidate group (0.94 bpm), followed by the dexmedetomidine group (5.9 bpm) and midazolam group (11.12 bpm) (*P* value < 0.05). The mean SPO2 did not show any significant difference among the three groups at any of the follow-up times (*P* value > 0.05) [Table 2].

Finally, the results of the frequency distribution analysis of complications among the three groups indicated that dizziness, restlessness, vomiting, and nausea were not reported at all in the midazolam group. Additionally, a decrease in heart rate was significantly more prevalent in the dexmedetomidine group (26.7%) compared to the midazolam and etomidate groups with values of 6.7% and 3.3%, respectively (*P* value = 0.021) [Table 3].

Discussion

The results of the current study showed that there was no significant difference in the quality of anesthesia among the three groups. Additionally, in the 10th minute of surgery, the SBP in the etomidate group was significantly higher than the dexmedetomidine and midazolam groups. The pulse rate (PR) was also higher during surgery and recovery in the etomidate group and midazolam than in the group. In other words, the PR changes were less in the etomidate group compared to the other groups, leading to higher mean PR during the follow-up times. The least changes in PR were observed in the etomidate group, followed by the midazolam and dexmedetomidine groups. The mean arterial oxygen saturation (SPO2) did not show any significant difference among the three groups at any of the follow-up times.

In line with our study, Cheung *et al*.[12] showed that heart rate in dexmedetomidine group was significantly lower than the midazolam group at all four period times. Compared to the midazolam group, blood pressure in the dexmedetomidine group was significantly lower during surgery, recovery, and in the ward. Another clinical trial found no significant difference in the quality of anesthesia between the propofol, etomidate, and midazolam groups in combination with fentanyl during facemask ventilation. However, considering other factors such as hemodynamic evaluation, recovery time, sedation side effects, and patient satisfaction, propofol, and midazolam were

Table 1: Baseline and clinical characteristics of patients in the three study groups

Variables	Dexmedetomidine group (*n*=30)	Midazolam group (*n*=30)	Etomidate group (*n*=30)	*P*
Sex				
Male	17 (56.7%)	14 (46.7%)	18 (60.0%)	0.559
Female	13 (43.3%)	16 (53.3%)	12 (40.0%)	
Age; year	37.91±9.15	39.74±8.90	37.81±11.24	0.694
ASA				
I	17 (56.7%)	16 (53.3%)	10 (33.3%)	0.147
II	13 (43.3%)	14 (46.7%)	20 (66.7%)	
Weight; kg	70.69±12.17	66.90±10.94	68.27±11.64	0.454
Height; cm	1.68±0.09	1.65±0.08	1.66±0.10	0.284
BMI; kg/m^2	24.84±3.57	24.73±3.75	24.80±4.01	0.994
Ramsay score				
1	1 (3.3%)	4 (13.3%)	1 (3.3%)	0.821
2	3 (10%)	2 (6.7%)	1 (3.3%)	
3	6 (20%)	5 (16.7%)	11 (36.7%)	
4	20 (66.7%)	19 (63.3%)	17 (56.7%)	
During surgery; min	11.96±6.61	15.80±2.59	15.65±5.01	0.651
Time of Sedation; min	27.58±8.81	24.71±4.07	24.00±2.76	0.792

Table 2: Determination and comparison of mean hemodynamic parameters of patients in the three groups

Variables	Dexmedetomidine group ($n=30$)	Midazolam group ($n=30$)	Etomidate group ($n=30$)	P^1
Systolic BP; mmHg				
Baseline	144.33±15.27	148.30±20.69	142.47±22.83	0.285
T_1	115.77±28.17	121.50±26.37	127.17±23.63	0.245
T_2	107.03±22.24	118.70±20.09	123.03±22.68	0.029
T_3	111.93±20.69	114.83±21.78	118.97±19.23	0.737
T_4	114.34±23.68	114.77±14.55	117.30±15.84	0.982
T_5	112.79±29.02	115.77±14.93	119.44±15.63	0.542
T_6	117.77±27.74	119.33±30.42	121.07±35.29	0.318
Change	19.56	17.97	5.40	0.358
P^2	<0.001	<0.001	<0.001	
Diastolic BP; mmHg				
Baseline	88.07±9.78	87.53±10.65	86.60±12.16	0.871
T_1	75.70±17.74	82.23±14.12	74.73±19.41	0.192
T_2	69.70±14.86	78.17±17.83	72.47±15.78	0.125
T_3	69.03±14.00	73.40±11.68	68.40±15.17	0.311
T_4	70.47±13.23	69.04±12.69	71.45±15.23	0.806
T_5	70.68±13.85	70.18±11.16	72.87±14.97	0.710
T_6	73.47±12.63	74.60±9.51	77.23±12.61	0.443
Change	14.60	12.93	9.37	0.182
P^2	<0.001	<0.001	<0.001	
Pulse rate; bpm				
Baseline	75.93±14.36	80.37±14.96	75.97±14.78	0.409
T_1	76.00±14.51	74.70±11.36	73.83±9.96	0.784
T_2	74.57±11.03	69.07±12.55	70.13±10.39	0.145
T_3	69.80±13.73	67.83±10.52	70.33±10.34	0.005
T_4	64.70±13.37	63.89±8.82	72.10±10.18	0.010
T_5	66.30±13.37	65.49±8.82	73.70±10.18	0.010
T_6	70.03±8.98	69.25±11.75	75.03±6.73	0.039
Change	5.9	11.12	0.94	<0.001
P^2	<0.001	<0.001	<0.001	
SPO_2; %				
Baseline	98.43±1.38	98.67±0.80	98.67±1.03	0.638
T_1	97.57±1.04	97.77±0.77	97.80±0.99	0.587
T_2	97.27±1.66	97.60±1.19	97.20±1.92	0.593
T_3	98.47±1.20	98.67±0.84	98.77±1.07	0.531
T_4	98.17±1.44	98.41±0.97	97.55±2.03	0.566
T_5	98.43±1.37	98.67±0.92	97.79±2.00	0.535
T_6	98.57±1.04	98.77±0.77	98.70±0.99	0.587
Change	0.14	0.10	0.03	0.621
P^2	<0.001	<0.001	<0.001	

Baseline: before injection of anesthetic drugs; T1: 5th minute during surgery; T2: 10th minute during surgery; T3: 15th minutes during surgery; T4: 10th minute in recovery, T5: 15th minute in recovery, T6: 30th minute in recovery

found to be superior to etomidate.[13] Although propofol was not evaluated in the current study, they also reported better hemodynamic stability and heart rate with the administration of midazolam compared to etomidate, which is inconsistent with our study.

In another study, it was demonstrated that the use of etomidate for anesthesia was equally effective as midazolam. However, blood pressure and heart rate were higher in the midazolam group.[19] It is worth noting that in their study, both groups received fentanyl, and in the midazolam group, ketamine was also used in addition to fentanyl. This led to fewer cardiac and respiratory complications and shorter recovery time in the midazolam/fentanyl/ketamine combination group compared to the etomidate/fentanyl group.

The results of the study by Dogan *et al*.,[16] which was conducted prospectively to investigate the effect of dexmedetomidine and midazolam/fentanyl in local anesthesia and peribulbar block, indicated that the combination of midazolam/fentanyl resulted in higher patient satisfaction, less pain, and shorter recovery time. Additionally, both local anesthesia and peribulbar block methods showed similar efficacy. In our study, the percentage of complications was lower in the midazolam group, and there

Table 3: Determination and comparison of the frequency distribution of complications during and after surgery in the three groups

Complication and satisfaction	Dexmedetomidine group ($n=30$)	Midazolam group ($n=30$)	Etomidate group ($n=30$)	P^1
Complication				
Dizziness	1 (3.3%)	0 (0%)	0 (0%)	0.364
Restlessness	2 (6.7%)	0 (0%)	2 (6.7%)	0.117
Vomiting and Nausea	1 (3.3%)	0 (0%)	3 (10%)	0.160
Decrease of heart rate	8 (26.7%)	2 (6.7%)	1 (3.3%)	0.021
Tachycardia	3 (10%)	3 (10%)	2 (6.7%)	0.872
Hypotension	2 (6.7%)	3 (10%)	4 (13.3%)	0.690
Satisfaction				
Surgeons' satisfaction	4.10±0.85	4.50±0.30	4.62±0.17	0.136
Patients' satisfaction	4.60±0.11	4.77±0.21	4.87±0.77	0.147

was no difference in surgeons' and patients' satisfaction among the three groups.

Another study also found that the level of sedation in the two groups of midazolam/fentanyl and dexmedetomidine did not differ significantly, but the surgeon and patient satisfaction was higher in the dexmedetomidine group. This was attributed to the lower heart rate and blood pressure (BP) in the dexmedetomidine group, which resulted in a more desirable surgical field and increased satisfaction for both the surgeon and the patient.[20] Therefore, it is possible that the hemodynamic response to anesthetic drugs and the level of satisfaction with their administration may vary in different types of surgeries, as lower or higher hemodynamic parameters could be considered desirable depending on the surgical procedure.

Furthermore, in the study by Paswan *et al*.,[17] it was observed that the changes in heart rate and mean arterial pressure (MAP) were greater in the midazolam group compared to the dexmedetomidine group. Hence, they reported that dexmedetomidine had better efficacy, safety, and hemodynamic changes compared to midazolam. However, in contrast to their findings, our study did not establish dexmedetomidine as superior to midazolam, but it might be advisable to consider using dexmedetomidine in conjunction with other anesthetic drugs to control some of the anesthesia-related complications. Additionally, in our study, a decrease in heart rate was significantly more frequent in the dexmedetomidine group compared to the other two groups. It should be noted that one of the etomidate complications is myoclonus, but this complication was not reported in our study with the administration of etomidate at 0.2 mg/kg.

On the other hand, in the study by Nishizawa *et al*.,[21] no significant difference was observed in the reduction of oxygen, bradycardia, and hypotension between the midazolam and dexmedetomidine groups. In fact, the appropriate dose of dexmedetomidine reduced preoperative stress-induced tachycardia and hypotension and provided a better surgical field for microsurgical eye procedures.[22,23] Although, in our study, patients' and surgeons' satisfaction in the etomidate and midazolam groups was slightly higher than the dexmedetomidine group.

Vinson and Bradbury also reported that the occurrence of nausea and vomiting due to etomidate was very rare.[24] In another study, bradycardia (decrease of heart rate), tachycardia, and hypoxemia were more common in the etomidate group compared to the midazolam group.[25] Similarly, in our study, a decrease in heart rate was more common in the dexmedetomidine group compared to the other two groups. In fact, it can be said that etomidate can have better effects, and its use is preferable to midazolam or dexmedetomidine in patients with cardiovascular diseases.

Contrary to the present study, Adinehmehr *et al*.[13] also reported a higher incidence of bradycardia, tachycardia, and hypotension in the etomidate group compared to the midazolam group. In their study, propofol was introduced as more stable in hemodynamics and with fewer complications, followed by midazolam, and then etomidate.

It should be noted that in our study, the effects of propofol and fentanyl as common anesthetic drugs, in combination with etomidate, dexmedetomidine, or midazolam, were not evaluated, which could be considered a limitation of this study. Additionally, the small sample size, not evaluating different doses of the mentioned drugs, and not assessing the patient's and surgeon's satisfaction could also be considered as other weaknesses. However, regarding the few comparative studies on the effectiveness of these three drugs in cataract surgery, and more definitive results in this area could aid in selecting the best anesthetic drug with the least cardiovascular and respiratory complications and the most desirable sedation, it is recommended that other researchers in similar studies investigate the effectiveness of these three drugs at different doses and follow-up times to provide more reliable results for the community.

Conclusion

Based on the results of this study, the effectiveness of the three drugs, dexmedetomidine, midazolam, and etomidate, did not show a significant difference in the patient's sedation.

Additionally, etomidate demonstrated more stable blood pressure with fewer PR decreases compared to the other two drugs. Furthermore, the most common complication in this study was a decrease in heart rate in the dexmedetomidine group, while no dizziness, restlessness, vomiting, or nausea were observed in the midazolam group. It seems that etomidate had better cardiovascular responses with fewer complications than the other two drugs and can be a suitable prescription option for patients with cardiovascular diseases.

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Conflicts of interest
There are no conflicts of interest.

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