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ORIGINAL RESEARCH NEUROANESTHESIA

Comparison of the effect of low dose ketamine plus dexmedetomidine vs low dose ketamine plus midazolam on hemodynamic changes and pain in electroconvulsive therapy

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ABSTRACT

Background: Currently, electroconvulsive therapy (ECT) is used as an effective treatment method in many psychiatric disorders. The basis of a successful electroshock session is to create a seizure with the precise intensity, quality and duration. In addition to the appropriate method of shock induction, appropriate anesthesia methods should be used to cause such seizures. The present study compared a combination of low-dose ketamine and dexmedetomidine (Ketodex) with a combination of low-dose ketamine and midazolam (Ketomid) on hemodynamic changes in electroshocks applied to patients referred from the psychiatric ward.

Methodology: This study was a randomized triple-blind clinical trial performed after obtaining permission from the Medical Ethics Committee of the Isfahan University of Medical Sciences. For this purpose, 70 patients were selected for electroshock therapy and randomly distributed into two groups of 35 people. In the first group, 0.04 mg/kg midazolam was combined with ketamine 0.1 mg/kg and in the second group, 0.5 µg/kg dexmedetomidine with 0.1 mg/kg ketamine. The patients were placed under complete cardiovascular monitoring. Hemodynamic changes of patients were measured and recorded before injection, after injection, after shock, and at 5 and 10 min after the end of seizures.

Results: In this study, 70 patients who were candidates for receiving ECT were equally divided into two groups of 35: one group received a mixture of Ketodex and the second group a combination of Ketomid. The two study groups showed no significant difference in terms of systolic pressure (P = 0.883), diastolic (P = 0.443), mean arterial pressure (P = 0.443), oxygen saturation (P = 0.018), and heart rate (P = 0.286). Complications such as headache, muscular pain (P = 0.01), bradycardia, nausea and vomiting were reported in the dexmedetomidine and ketamine groups.

Conclusion: Our study showed that although systolic, diastolic and mean arterial blood pressure, heart rate and oxygen saturation were significantly reduced in both study groups, no significant difference was observed between the two groups in terms of hemodynamic changes and neither drug group in our study population was different from the other in terms of these parameters. In addition, neither option was superior to the other. However, due to the fact that complications such as headache, muscular pain, bradycardia, nausea and vomiting were reported in the dexmedetomidine and ketamine groups, the combination of midazolam and ketamine appeared to be a more appropriate combination in patients undergoing electroconvulsive therapy.

Key words: Electroshock therapy; Midazolam; Ketamine; Dexmedetomidine; Hemodynamic changes; Headache pain

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1. INTRODUCTION

Electroconvulsive therapy (ECT) has been used as an effective treatment method in many of the psychiatric disorders, including depression and severe and persistent mania, schizophrenia, mood disorders or suicidal tendencies that are resistant to psychotherapy or medication and other disorders.[1,2] Producing a seizure with the appropriate intensity, quality, and duration is a key element in a successful ECT session. On average, the duration of motor seizures should be at least 20 to 30 sec to be able to provide the desired therapeutic outcomes.[3] Therefore, the important point in this method is the use of an appropriate anesthetic drug that minimizes the complications of seizures,[4] and at the same time does not have a negative effect on the duration and quality of seizures and treatment outcome.[5] In addition, it should maintain the patient's hemodynamic status during seizures,[5,6] have a short half-life, be inexpensive, and have painless injections.[5] Ketamine, a derivative of phencyclidine, is one of the drugs used to induce stable anesthesia and avoid complications in patients undergoing ECT.[7] This drug increases the duration of seizures in ECT, [1,8, 9] and with its antidepressant properties can improve the therapeutic results.[9] But its use has been limited due to the risk of cardiotoxicity and possible overstimulation of the cardiovascular system.[1,5,8]

Midazolam is being used to provide sedation in patients undergoing ECT. It is a relatively short-acting benzodiazepine that has anxiolytic, sedative, anticonvulsant, as well as muscle relaxant effects. It is also used in dental surgeries, induction of sedation before the administration of anesthesia, treatment of epilepsy and seizures, and refractory hiccups.[4] The binding of midazolam with the benzodiazepine receptor is approximately twice that of diazepam, which corresponds to the greater potency of this drug. The most common side effects of midazolam during anesthesia and surgery include hypotension and reduction of respiratory rate.[6]

Dexmedetomidine is an alpha-2 receptor-specific agonist that has been successfully used in recent years as a sedative and analgesic without respiratory depression, shows suppression of postoperative nausea and vomiting in surgeries such as craniotomy, fiberoptic bronchoscopy, and other diagnostic tests. It also helps control hypotension, and maintain stable hemodynamic conditions.[11,12] Respiratory midazolam has been reported to reduce tidal volume, increase respiration rate, and decrease oxygen saturation.[7] It reduces the incidence of delirium and the duration of ventilation compared to other sedatives.[13]

Ketamine is a derivative of phencyclidine. It acts by inhibiting the N-methyl D-aspartate (NMDA) receptor complex and blocking the transmission of pain messages to the limbic system by blocking glutamate receptors in the thalamic region of the brain. Adverse reactions to ketamine which are seen upon awakening, such as hallucinations and lucid dreams and out-of-body experiences, have limited its use.[15] Ketamine also causes an increase in the sympathetic nervous system causing hypertension and increased heart rate (HR). It can increase intracranial and intraocular pressures, and therefore its use is prohibited in situations where such an increase in pressure can be detrimental (head trauma, eye injury, hydrocephalus, or lip and vascular disease).[16] Despite comparative studies of different drugs in the prevention of hemodynamic disorders, an ideal and unified method for controlling blood pressure, HR and respiratory parameters during various procedures, especially ECT, has not yet been presented. Therefore, since ketamine, midazolam and dexmedetomidine appear to have beneficial effects on hemodynamic stability during ECT and the paucity of studies that have examined the effect of different drugs in this regard, this study seemed necessary.

2. METHODOLOGY

This study was a randomized triple-blind clinical trial (IRCT20160307026950N23) which was performed during 2019−2020, in the hospitals of the Isfahan University of Medical Sciences, in patients who were referred to these centers for ECT.

Inclusion criteria

Patients who were candidates for ECT in the age range of 18−70 y, with no history of cardiovascular disease and drug sensitivity, were included. Written consent to enter the study was obtained from all patients.

Exclusion criteria

Participants were excluded from the study in case of unintended complications during the operation, such as a serious hemodynamic disorder requiring medical intervention or voluntary withdrawal from the study.

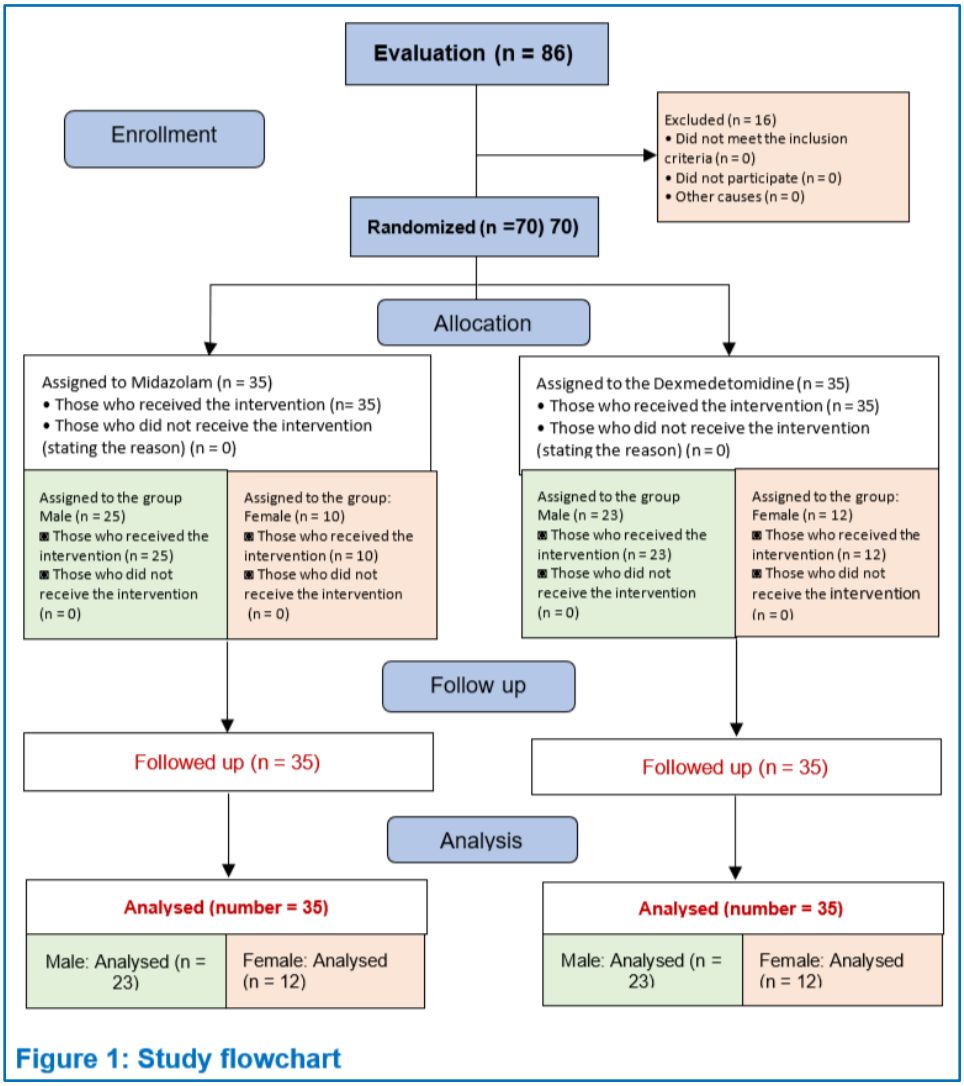

Figure 1: Study flowchart

After obtaining permission from the Medical Ethics Committee of the Isfahan University of Medical Sciences (with ethical code: IR. MUI. MED. REC. 1399. 377), 70 patients were selected by electroconvulsive therapists and randomly distributed into two groups of 35 each. The randomization method was that the first patient was assigned to one of the groups by lottery and the next patients were distributed randomly in two consecutive groups to reach the required number of samples in each group. The blinding method was performed in such a way that patients were unaware of the type of drug received and also the project administrator was unaware of the type of injected drug to the patients. The drugs were prepared and coded in similar syringes by one of the operating room personnel who was not involved in the study and were given to the administrator for injection.

In the first group (Group Ketomid), 0.04 mg/kg midazolam was combined with 0.1 mg/kg ketamine and in the second group (Group Ketodex), 0.5 µg/kg dexmedetomidine was combined with 0.1 mg/kg ketamine and stored in the refrigerator in the operating room. The facilitator, unaware of the contents of the syringes, randomly selected one for each patient. Patients hemodynamic parameters were monitored e.g., systolic (SBP) and diastolic blood pressure (DBP), oxygen saturation (SpO_2) before study drug injection, after shock, and 5 and 10 min after seizure. The incidence of postoperative complications such as nausea, vomiting, and the severity of postoperative pain were also determined and recorded during the stay in recovery. Other factors such as the duration of seizures and the length of stay in the post-anesthesia care unit (PACU) were recorded. Also, the time of discharge after anesthesia was determined.

Statistical analysis

The data were entered into SPSS software version 23 and statistically analyzed. The descriptive data are presented as mean and standard deviation or frequency and percentages. Chi-square test, T-test for normal data, Mann-Whitney U test for abnormal data, and repeated measures tests were used. $P \leq 0.05$ was considered significant.

3. RESULTS

Seventy patients, candidates for ECT, were randomly divided into two groups of 35 each: one group received a mixture of dexmedetomidine and ketamine (Group Ketodex) and the other group received a mixture of midazolam and ketamine (Group Ketomid).

Table 1: Comparative demographic characteristics

Variable		Group Ketodex	Group Ketomid	P-value
Gender	Female	12 (34.3)	10 (28.6)	0.79*
	Male	23 (65.7)	25 (71.4)	
Age (Y)		44.00 ± 13.4	44.71 ± 14.53	0.83**

***T-Test; * Chi square; Data presented as n (%) or mean ± SD*

Table 2: Clinical characteristics of patients after electro-shock therapy

Variable	Group Ketodex	Group Ketomid	*P-value
Seizure duration (sec)	63.97 ± 7.33	65.29 ± 5.68	0.40
Duration of stay in recovery (sec)	54.86 ± 7.90	56.14 ± 5.01	0.42
Charge score from the recovery	8.86 ± 0.81	8.49 ± 0.65	0.057
Complications of laryngospasm	1 (2.9)	–	1.00

**Mann-Whitney U test was applied for comparison; Data presented as mean ± SD*

Table 3: Complications noted during electro-shock therapy

Variable	Group Ketodex	Group Ketomid	**P-value
Headache	5 (14.3)	2 (5.7)	0.42
Muscular pain	10 (11.4)	1 (2.8)	0.01
nausea and vomiting	9 (25.7)	–	0.009
Tachycardia	2 (5.7)	5 (14.3)	0.42
Bradycardia	11 (31.4)	1 (2.9)	0.003
Decreased secretion	2 (5.7)	5 (14.3)	0.42
Complications of laryngospasm	1 (2.9)	–	1.00

*; **Chi square tests were applied for comparisons; Data presented as n (%)*

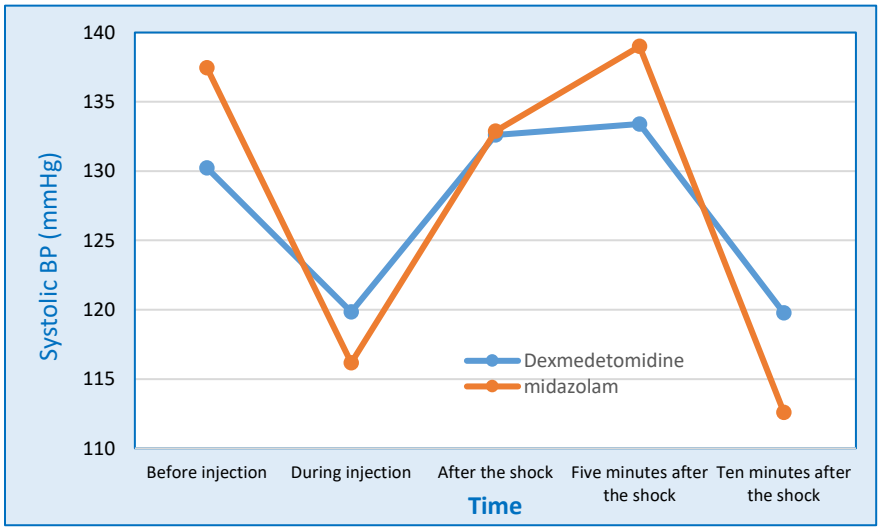

Figure 2: Changes in systolic blood pressure over time in the groups

Out of 70 patients, 48 (68.6%) were male and 22 (31.4%) were female. The mean age of all subjects was 44.36 ± 13.76) y and ranged from 19-68 y. The mean age of women was 42.23 ± 12.79 y and in men it was 45.33 ± 14.20 y. The mean age in the two groups of men and women was not significantly different from each other (P = 0.36) Table 1 shows a comparison of demographic characteristics of the subjects in the groups.

Table 2 shows the clinical information of patients after ECT. According to this table, patients in the Group Ketodex had significantly more bradycardia than patients in the Group Ketomid. All patients with headache, muscular pain and, nausea and vomiting had received Ketodex. Muscular pain was significantly more in Group Ketodex (P < 0.005). However, the duration of seizures, length of stay in recovery, tachycardia, SpO_2, discharge score for discharge from the care unit after anesthesia and the complication of laryngospasm did not show a significant difference between the two groups (Table 3).

As Figure 2 shows, SBP decreased significantly at the time immediately after drug injection, and 10 min after shock compared to the initial reading (P < 0.0001).

Table 4: Mean hemodynamic changes in two groups in the first to 10 min reading

Parameter	Time of assessment	Group Ketomid	Group Ketodex	* P-value
Systolic Blood Pressure (mmHg)	Before injection	130.23 ± 12.5	137.43 ± 15.34	0.0.34
	Immediately after injection	119.83 ± 14.19	116.17 ± 17.96	0.348
	During electro shock	132.60 ± 14.92	132.89 ± 20.72	0.947
	5 min after the shock	133.40 ± 15.21	139.00 ± 17.73	0.161
	10 min after the shock	119.77 ± 15.28	112.06 ± 20.28	0.077
	Comparison of the first to 10 min reading (P)	P < 0.0001	P < 0.0001	0.883
Diastolic Blood Pressure (mmHg)	Before injection	79.89 ± 8.4	86.71 ± 12.01	0.008
	Immediately after injection	74.43 ± 9.76	72.37 ± 12.4	0.443
	During electro shock	81.89 ± 8.9	82.51 ± 10.43	0.787
	5 min after the shock	83.80 ± 9.48	88.63 ± 10.06	0.043
	10 min after the shock	76.31 ± 10.64	71.86 ± 11.51	0.097
	Comparison of the first to 10 min reading (P)	P < 0.0001	P < 0.0001	0.421
Mean Blood Pressure (mmHg)	Before injection	96.67 ± 8.67	103.63 ± 12.02	0.007
	Immediately after injection	89.56 ± 10.25	86.97 ± 13.54	0.370
	During electro shock	98.79 ± 10.2	99.3. ± 12.83	0.853
	5 min after the shock	100.33 ± 10.45	105.42 ± 11.67	0.059
	10 min after the shock	76.31 ± 10.64	71.86 ± 11.51	0.097
	Comparison of the first to 10 min reading (P)	P < 0.0001	P < 0.0001	0.488
Heart Rate (per min)	Before injection	83.74 ± 7.59	86.77 ± 13.62	0.255
	Immediately after injection	74.77 ± 9.22	78.37 ± 12.43	0.173
	During electro shock	80.09 ± 12.55	79.14 ± 11.7	0.746
	5 min after the shock	82.34 ± 10.62	85.69 ± 11.09	0.202
	10 min after the shock	77.49 ± 11.37	77.46 ± 9.11	0.991
	Comparison of the first to 10 min reading (P)	P < 0.0001	P < 0.0001	0.286
SpO_2	Before injection	95.43 ± 4.77	96.51 ± 2.1	0.222
	Immediately after injection	90.91 ± 1.48	91.36 ± 1.5	0.013
	During electro shock	94.94 ± 4.62	96.23 ± 0.97	0.112
	5 min after the shock	95.4 ± 4.76	96.4 ± 1.94	0.254
	10 min after the shock	95.4 ± 4.77	95.71 ± 4.98	0.788
	Comparison of the first to 10 min reading (P)	P < 0.0001	P < 0.0001	0.018

**t-test applied to find out P values. P < 0.05 considered significant*

Table 4 shows that the changes in SBP over time were not significantly different between the two groups (P = 0.883). DBP changed significantly over time (P < 0.0001). However, the results indicated that in general, changes over time did not differ between the two treatment groups (P = 0.443).

The changes in MBP over time did not differ significantly between the two groups (P = 0.488); but MBP showed significant changes over time in both groups (P < 0.0001).

The HR also had significant changes in both groups (P < 0.0001). However, in general, the changes in HR over time and also at all times were not significantly different between the two groups.

The mean SpO2 showed significant changed over time in both groups (P < 0.0001); the difference in changes in the mean SpO2 over time between the two groups was significant (P = 0.018) (Figure 4).

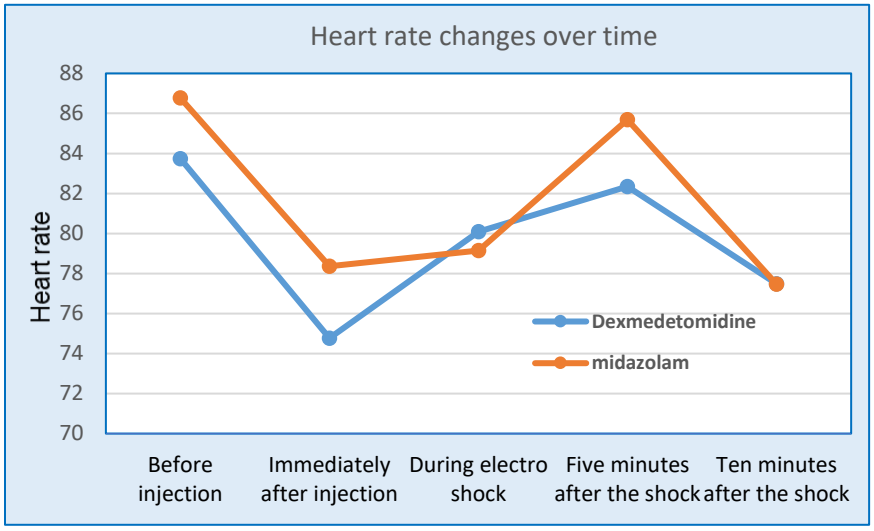

Figure 3: Heart rate changes over time in two groups

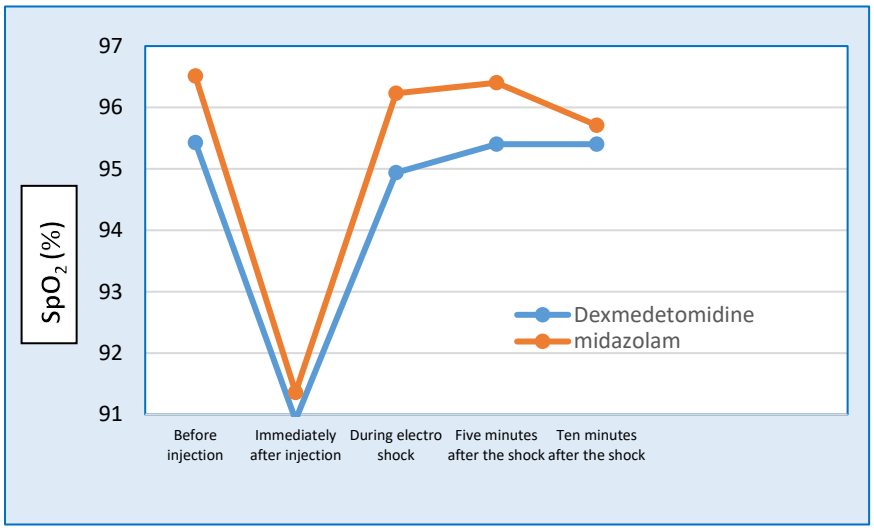

Figure 4: Changes in mean SpO2

4. DISCUSSION

In our study, all studied hemodynamic parameters decreased significantly over time in both of the groups. This finding is consistent with the findings of other studies which show that dexmedetomidine as an alpha 2 receptor antagonist is expected to reduce HR and BP.[17] Although in a number of studies resulted in a greater reduction in BP compared to midazolam,[18–20] but in a meta-analysis by Sun et al. no difference in changes in BP was observed between the two groups. It may be due to differences in age, gender, and race of participants as well as the type and dosage of the medication received. Also, the concomitant administration of these drugs with ketamine may have led to different results in this study. The decrease in SpO_2 over time was significant in both study groups and between the two study groups. This finding is consistent with a study by Nicholas et al., which showed a decrease in SpO_2 levels in children receiving dexmedetomidine.[22]

Regarding the side effects, in our study, bradycardia as well as nausea and vomiting were reported in the ketodex group. Bradycardia has been reported in other studies as a significant complication in cases where dexmedetomidine was used. In a double-blind clinical trial study that looked at the effects of dexmedetomidine and midazolam in intensive care patients, the incidence of bradycardia was almost twice as high in the dexmedetomidine group as in the midazolam group.[23] The incidence of bradycardia in previous studies in children receiving dexmedetomidine for a variety of reasons has differed widely. In some studies no case of bradycardia was observed in the dexmedetomidine group,[24–28] in other cases the rate of bradycardia was reported to be up to 22%.[28,29] Differences in race, age, and the presence or absence of underlying diseases, as well as the dosage and method of drug administration in each group can justify these results in different studies. In a meta-analysis study by Gong et al., the incidence of bradycardia in children treated with dexmedetomidine was estimated to be about 3%.[30] Further clinical trial studies can be useful to investigate this complication.

Nausea and vomiting after ECT were reported more in patients receiving dexmedetomidine and ketamine than in the group receiving midazolam and ketamine. This finding contradicts the preliminary results of the case study of Khasawinah et al., which used dexmedetomidine as a treatment for cyclic vomiting syndrome and obtained acceptable results in three children.[31] Also, in a number of studies performed on the adult population, the frequency of nausea and

vomiting after surgery or anesthesia has been reported less in dexmedetomidine than in other anesthetics and in some cases dexmedetomidine could prevent nausea and vomiting after surgery. It has also been used in a study by Li et al. on children with strabismus who underwent surgery.[32] Postoperative nausea and vomiting decreased in the dexmedetomidine group compared with the control group (normal saline).[33] However, the results observed in these studies are not generalizable, because in a meta-analysis study it was shown that although dexmedetomidine was superior to placebo in preventing nausea and vomiting after surgery, it was not superior to other anesthetics and sedatives.[34] It seems that the study of this complication in the use of Ketodex should be considered more frequently in future clinical trial studies.

5. CONCLUSION

Our study shows that although hemodynamic parameters were significantly reduced in both study groups, there was no significant difference between the two groups and neither of the groups was superior in this respect. However, due to the fact that complications such as bradycardia, nausea and vomiting were reported in the Ketodex group, the combination of Ketomid is a more appropriate combination in patients undergoing electroconvulsive therapy.

6. Data availability

The data related to the study is available with the authors on request.

7. Conflict of interest

The authors reported no potential conflicts of interest.

8. Funding

The study did not involve any funding

9. Authors' contribution

BN: Study concept, analysis, and design, interpretation of the data, critical revision of the manuscript for important

NM: drafting of the manuscript, intellectual content

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