Original Article

Sedation Quality of Low–Dose Ketamine Combined with Dexmedetomidine versus Propofol in Phacoemulsification under Local Anesthesia

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ABSTRACT

Purpose: To compare the hemodynamic effects of low-dose ketamine combined with dexmedetomidine versus propofol in phacoemulsification under local anesthesia.

Place and Duration of Study: School of Medicine, Isfahan University of Medical Sciences during 2020 – 2021.

Methods: Sixty patients admitted for cataract surgery were included. Those with history of systemic diseases, insufficient pupil dilation, sensitivity to drugs and uncooperative patients were excluded. Participants were randomly allocated to two groups; group which was administered ketamine with dexmedetomidine (Ketodex) and group which was given ketamine with propofol (Ketofel). Effect on blood pressure, pulse and sedation was recorded.

Results: Mean age was 65 ± 9.9 years. Sixty-five percent of patients were females. Ketodex increased the risk of hemodynamic disorders compared to Ketofel (P = 0.04). The risk of nausea and vomiting was higher in the Ketodex group although not significant. The effect of drug course on heart rate, blood pressure and sedation was significant in both groups (P < 0.05). Neither at baseline, nor in the 1st and 5th minutes of surgery, was the mean arterial pressure (MAP) significantly different between the two groups. From 10th minute of surgery until the end of surgery and from the beginning of recovery until the 30th minute of recovery, the MAP and pulse rate were higher in Ketofol group. Sedation effect during surgery was higher in the Ketodex group compared to the Ketofol group, and the difference was statistically significant at minutes 10, 20 and 30 of surgery.

Conclusion: There is higher effect of sedation and fewer side effects of ketamine-dexmedetomidine combination compared to the ketamine-propofol combination.

Key Words: Ketamine; Dexmedetomidine; Propofol; Phacoemulsification; Cataract.

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INTRODUCTION

Cataract is one of the most common eye disorders, with an estimated prevalence of 17.2%.[1] The standard treatment for cataract is surgical, which is performed when the patient's visual symptoms are causing disturbance in performing daily tasks.[2]Given the high prevalence of this disorder, cataract surgery is one of the most commonly performed surgeries around the world. The natural lens of the eye is replaced with a clear artificial lens. Today, phacoemulsification is the most commonly performed cataract surgery, which utilizes ultrasound waves.[3]

Due to significant progress in medical science, anesthesia has shifted from general to topical in cataract surgery.[4] Currently, topical anesthesia and sedation are commonly used for many procedures.[5] General anesthesia is used for pediatric population or uncooperative patients. This protocol is also commonly applied in developing countries.[6] Goal of anesthesia for patients undergoing cataract surgery is

to achieve sedation and the desired outcomes while maintaining safety. In the past, general anesthesia was used for cataract surgery. However, since elderly persons are main candidates for this surgery, general anesthesia can increase health risks, such as permanent brain damage, etc.[7]

Each anesthetic drug produces a combination of anxiolytic, hypotonic, amnesic, and analgesic effects. To select the best agent for anesthesia, many factors must be considered. In other words, it is important to consider the pharmacokinetics and pharmacodynamics of drugs.[8v]Several medicines, such as ketamine, propofol, fentanyl, benzodiazepines, and dexmedetomidine, alone or in combination, have been used to relax patients or reduce anxiety for cataract surgery.[9]

Propofol is a short-acting injectable anesthetic with hypotonic and amnesic effects, which is administered for the induction and maintenance of anesthesia. Depending on its dose, propofol causes greatest decline in systemic blood pressure and its effects on blood pressure become more evident with advancing age or rapid injection.[10] Moreover, dexmedetomidine, as an α2-agonist with a central sympatholytic effect, has analgesic activities that can lead to hemodynamic stability. However, owing to its anesthetic effect, the possibility of delayed recovery following its infusion administration remains unknown. This drug is about eight times more selective than clonidine. It is known to provide adequate sedation for patients undergoing surgical procedures and lead to patient satisfaction, reduced need for opioids and reduced incidence of respiratory depression.[11]

Ketamine is a derivative of phencyclidine which is a selective and non-competitive antagonist of N-methyl-D-aspartate receptor. It can be used alone or in combination with other medications for sedation and analgesia during surgery. It is one of the most widely used drugs in cataract surgery, which is associated with complications, such as hallucination, necessitating its careful administration.[12-14]

Since in previous studies, the efficacy of the mentioned anesthetics has not been compared, the present study aimed to compare the effects of drug combinations in cataract surgery.

METHODS

After obtaining ethical approval from the Medical Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1401.047), this study (IRCT20160307026950N43) was registered in the Iranian Registry of Clinical Trials. In this triple-blinded, randomized clinical trial, the study population consisted of patients who were admitted to ----------for cataract surgery using phacoemulsification during 2020-2021.

The inclusion criteria comprised of patients providing an informed consent, age over 18 years and a candidate for cataract surgery for the first time. On the other hand, patients with a history of obstructive sleep apnea, diabetes, mental disorders, autoimmune disease, nystagmus, leukemia, epilepsy, deafness, drug allergies, or high blood pressure were not included in the study.

Patients with severe hemodynamic disorder following drug injection, insufficient pupil dilation after anesthesia, sensitivity to drugs during the study, occurrence of any complications leading to a change in the anesthesia method uncooperative patients and patients withdrawing from the study at a later stage were excluded.

Sample size was calculated using STATA program, setting the type-1 error (α) at 0.05 and the power (1-β) at 0.8. The results from the previous study[15] showed that in terms of Ramsay sedation scores, there was no statistically significant difference between the two studied groups but the dexmedetomidine/ketamine combination was as effective as the propofol/ketamine combination in terms of sedation efficacy with a p-value less than 0.05. Sample size was 35 cases per group. After coordination with relevant authorities of ----------and accessing the study population, a total of 77 patients were included in the primary evaluation. However, nine patients were excluded as they did not meet the inclusion criteria and eight patients were removed due to lack of consent. The remaining 60 patients were equally assigned to two groups (30 patients per group). Finally, 60 patients who met the inclusion criteria were selected by convenience sampling. After recruitment, each patient was randomly allocated to a group using the Random Allocation Software. The first group was administered ketamine with dexmedetomidine (Ketodex), while the second group was administered ketamine with propofol (Ketofol).

RESULTS

A total of 60 patients, with a mean age of 65 years (SD = 9.9), were included in this study, 39 (65%) of whom were females. The relationship between the type of anesthetic and changes in heart rate and systolic and diastolic blood pressure was investigated using univariate and multivariate (adjusted for age, sex, duration of surgery, duration of anesthesia, and initial values of studied variables) logistic regression methods (Table 1).

As shown in Table 1, in all cases, the ketamine-dexmedetomidine combination (Ketodex) increased the risk of hemodynamic disorders compared to the ketamine-propofol combination (Ketofel). However, only in the univariate test, the relationship between the drug type and systolic hypotension was significant (P = 0.04). The risk of nausea and vomiting was higher in the Ketodex group, although this relationship was

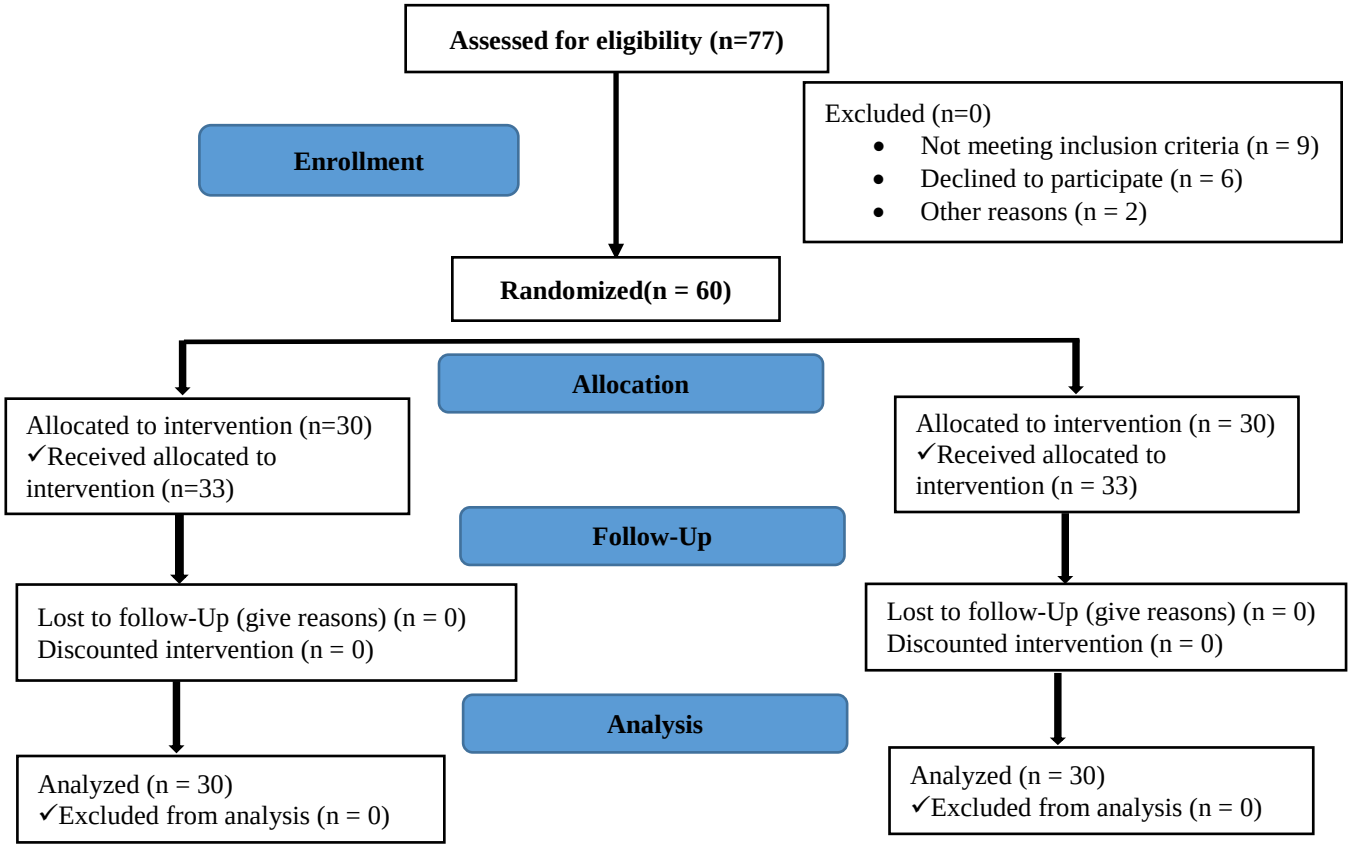

Fig. 1: Study flow diagram.

Table 1: *Comparison and relationship between the type of drug used and the investigated variables groups.*

Variable	Group	Frequency		Univariate		Multivariate	
		No	Yes	Sig.	Odds-Ratio	Sig.	Odds-Ratio
Heart Rate	Ketodex	12	22	0.11	0.44	0.31	0.56
	Ketofol	18	14				
Systolic Blood Pressure	Ketodex	19	24	0.04	0.33	0.05	0.31
	Ketofol	20	12				
Diastolic Blood Pressure	Ketodex	15	19	0.99	0.99	0.76	0.83
	Ketofol	16	16				
Mean Arterial Pressures	Ketodex	21	13	0.46	0.65	0.43	0.58
	Ketofol	25	7				
Vomiting & Nausea	Ketodex	20	10	0.24	0.5	0.34	0.72
	Ketofol	24	6				

significant neither in the univariate analysis (P = 0.24), nor in the multivariate analysis (P = 0.34).

Considering the confounding effects of age, sex, duration of surgery, duration of anesthesia, and the initial values of variables, the effect of drug course on the heart rate per minute was significant in the two groups (P = 0.001). It was also found that the effect of drug course on systolic blood pressure was significant in both groups (P = 0.001). Similarly, in the two groups, the effect on diastolic blood pressure was significant (P = 0.001). Besides, the effect of drug on sedation was significant in both groups (P = 0.01); the results are presented in Figure 2.

The type of analgesic used during surgery and anesthesia had no significant effects based on the univariate linear regression analysis (P = 0.74 and 0.08, respectively) and the multivariate linear regression analysis adjusted for age and sex (P = 0.69 and 0.98, respectively).

According to the results presented in Table 2, neither at baseline, nor in the 1st and 5th minutes of surgery, the mean arterial pressure (MAP) was significantly different between the two groups. However, from the 10th minute of surgery until the end of surgery and also from the beginning of recovery until the 30th minute of recovery, the MAP was higher

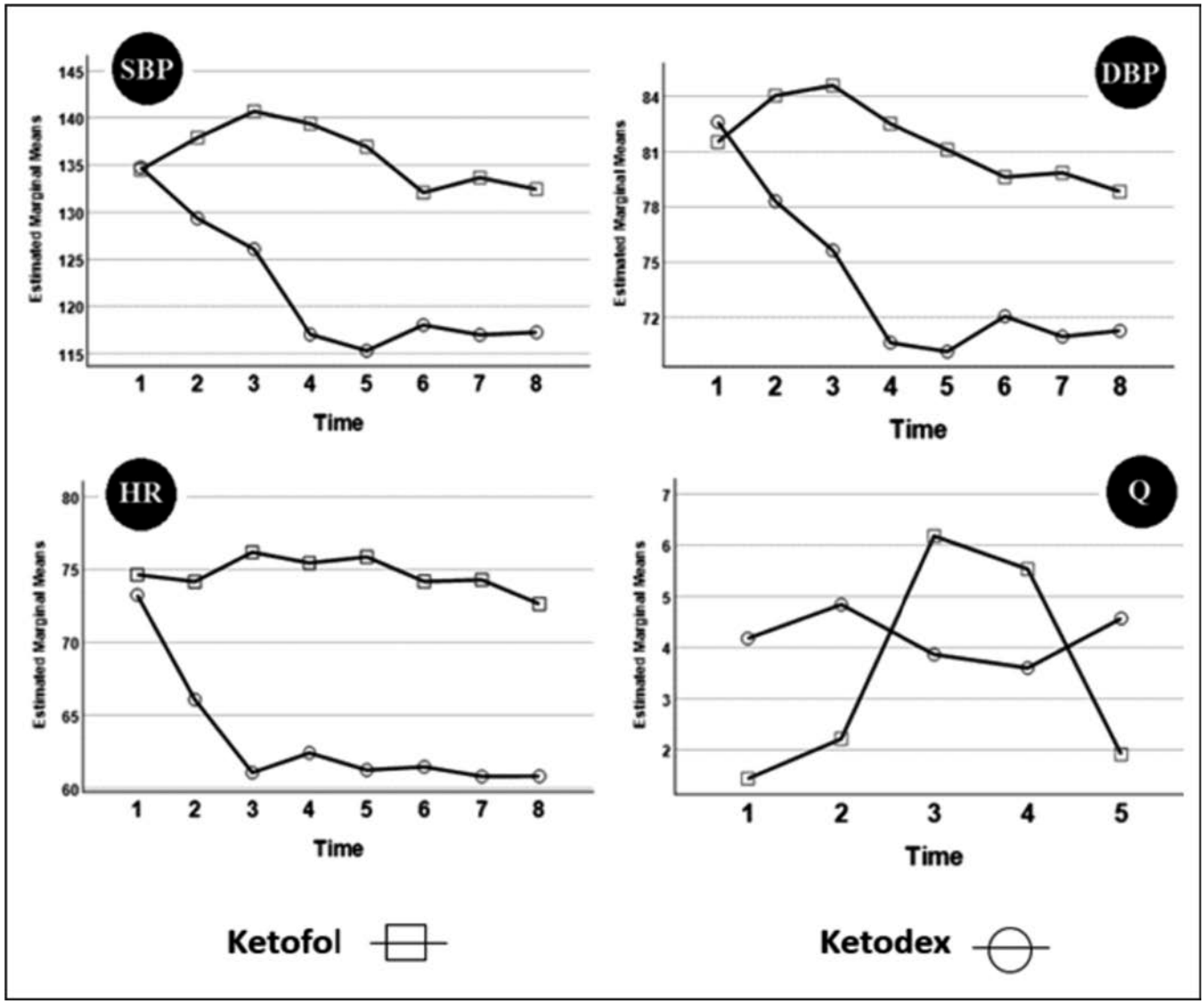

Figure 2: Effect of drugs over time. SBP (systolic blood pressure), DBP (diastolic blood pressure), HR (heart rate), Q (sedation).

Table 2: *Mean pulse rate and sedation in two groups.*

Variable	Time	Ketodex		Ketofol		P-Value*
		Mean	SD	Mean	SD	
Mean Arterial Pressure	Before Surgery	108	2.1	105	2.1	0.29
	1st Min	101	2.2	99	1.9	0.48
	5th Min	97	2.2	100	1.9	0.31
	10th Min	92	1.9	103	1.5	0.001
	20th Min	87	2.7	101	2.6	0.001
	Recovery	86	2.3	99	1.7	0.001
Pulse Rate	10th Min	88	1.8	96	1.8	0.002
	20th Min	87	1.8	97	1.7	0.001
	30th Min	88	1.8	95	1.7	0.006
	Before Surgery	77	2.6	85	2.3	0.024
	1st Min	72	2.0	79	2.5	0.024
	5th Min	64	1.6	80	2.3	0.001
	10th Min	60	1.8	82	2.4	0.001
	20th Min	60	2.0	77	2.8	0.001
	Recovery	61	1.8	80	2.2	0.001
	10th Min	61	1.8	77	2.0	0.001
	20th Min	60	1.8	77	2.0	0.001
	30th Min	60	1.7	75	2.0	0.001
Sedation	Before Surgery	-	-	-	-	-
	1st Min	-	-	-	-	-
	5th Min	-	-	-	-	-
	10th Min	-	-	-	-	-
	20th Min	-	-	-	-	-
	Recovery	3.5	0.19	3.1	0.21	0.15
	10th Min	3.9	0.16	3.3	0.2	0.028
	20th Min	4.2	0.17	3.5	0.25	0.019
	30th Min	4.5	0.45	3.2	0.31	0.018

*Independent t-test

in the Ketofol group compared to the Ketodex group, and the difference was statistically significant. Regarding the pulse rate (PR), in all intervals, the mean PR was significantly higher in the Ketofol group compared to the Ketodex group. Based on the results, the mean sedation effect during surgery was higher in the Ketodex group compared to the Ketofol group, and the difference was statistically significant at minutes 10, 20 and 30 of surgery.

DISCUSSION

The present study aimed to compare the effects of two drug combinations, that is, ketamine-dexmedetomidine (Ketodex) and ketamine-propofol (Ketofol), on the hemodynamics and sedation of patients during cataract surgery. In terms of all the evaluated variables, patients in the Ketodex group had a higher risk of hemodynamic disorders, although only the relationship with systolic blood pressure was significant in the univariate analysis. Regarding the drug course, it was found that the effect of drug course was significant on four variables, including heart rate, systolic blood pressure, diastolic blood pressure, and relaxation effect. In all cases, hemodynamic changes were greater in the Ketodex group compared to the Ketofol group. The difference between the two groups started from the first minute of anesthesia and reached its maximum by the 20th minute. The results indicated the higher sedative effect of Ketodex.

In this regard, a clinical trial was conducted to compare Ketodex with Ketofol during endoscopy for liver patients.[15] Similar to the present study, the background variables were adjusted. Their findings revealed a drop in heart rate in both groups in the first minutes after injection, which was significantly greater in the Ketodex group; this finding was in line with the results of the current study. However, there was no significant difference between the two groups during the study in terms of sedation scores according to the Ramsay Sedation Scale. This finding is inconsistent with the current results, which might be related to the anesthesia protocol and different types of intervention for the two groups.

Moreover, in a clinical trial by Wang et al,

comparing the effects of propofol and dexmedetomidine, a significantly lower heart rate was found in the dexmedetomidine group, which is consistent with the present findings.[16] To explain the cause of this effect, the pharmacodynamic properties of the two drugs should be considered. It is known that activation of postsynaptic α2 receptors by dexmedetomidine results in sympatholysis, which is associated with bradycardia and hypotension. Besides, stimulation of presynaptic α2 receptors reduces the release of noradrenaline, leading to an even greater reduction in blood pressure.[15]

A systematic review of eight clinical trials in 2016, examining more than 600 candidates for cardiac surgery, showed that the prevalence of bradycardia was lower in patients receiving propofol compared to patients receiving dexmedetomidine, which is consistent with the results of the present study.[5] However, this relationship was not statistically significant in the current study, which might be attributed to factors, such as the shorter duration of surgery, smaller sample size, and lower intensity of the intervention in our study. Also, in our study, ketamine was used in combination with two other drugs that can have mild to moderate effects on increasing blood pressure and heart rate.[17]

In a meta-analysis of 341 cases in 2017, although dexmedetomidine was significantly associated with a lower heart rate compared to propofol, the heart rate reduction was not in the bradycardia range,[18] which is in line with our result. This finding can be explained by the short duration of surgery and the lower intensity of interventions in the mentioned research, as well as the present study. According to another meta-analysis, reason for this finding can be attributed to increase in the mean heart rate through stimulation of gag reflex in endoscopy.[19] In our study, the simultaneous use of dexmedetomidine with ketamine, which could increase the heart rate, can be one of the reasons for the lower incidence of bradycardia.

Additionally, a meta-analysis of five clinical trials in 2021showed higher anesthesia quality and less failure in the propofol group compared to the dexmedetomidine group. The study population consisted of patients who underwent endoscopy, and the sample size was estimated at 270.[20] In the current study, it was also found that patients in the propofol-ketamine group had a higher anesthesia quality and higher Ramsay scores. Chang et al., aimed to compare dexmedetomidine with propofol in the surgical operation of patients with a high disease severity. Significantly lower MAP and heart rate were reported in the dexmedetomidinegroup.[21]A similar finding was also reported by Wang and colleagues. Although the results of these two studies were consistent with our findings, there are some differences, as they examined critically ill patients.[19]

Moreover, in a study by Alizadehasl et al, comparing the effects of dexmedetomidine and propofol in transesophageal echocardiography candidates, the dexmedetomidine group had lower blood pressure and heart rate compared to the propofol group 20 minutes after surgery and during recovery, which is consistent with the current findings.[22] This study was similar to the present research in terms of the short surgery time.

The authors recommended the use of Ketofel following to fewer hemodynamic changes and higher sedative effects compared to Ketodex. However, despite the apparent positive effects of ketamine elimination from these two compounds (due to the unknown interfering effects and pharmacokinetic and pharmacodynamic synergism), superiority of propofol to dexmedetomidine cannot be confirmed.

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Conflict of Interest: Authors declared no conflict of interest.

Ethical Approval: The study was approved by the Institutional review board/Ethical review board **(IR.MUI.MED.REC.1401.047)**

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