RESEARCH ARTICLE

The Small Dose of Ketamine Prevents the Hemodynamic Disturbance in Patients Who Underwent Phacoemulsification with Topical Anesthesia and Monitored Anesthesia Care

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Background: Ketamine is the only anesthetic agent that leads to an increase of blood pressure and heart rate by activation of sympathetic nervous system. However, there is a controversy about this effect of ketamine especially if used in small dosage. We proposed to evaluate the hemodynamic effect of small dose of ketamine during Phacoemulsification.

Methods: One hundred patients of ASA physical status I-III were chosen for this prospective, randomized, double-blind placebo-control study. Our patients were assigned randomly to two groups, ketamine group (n=50) and a control group (n=50). After premedication, 0.15 mg/kg ketamine was injected intravenously in ketamine group. After three minutes Phacoemulsification was begun under topical anesthesia. The hemodynamic variables were recorded during the procedure and compared between two groups.

Results: The systolic, diastolic and mean blood pressure were statistically significantly higher in the ketamine group ($p<0.001$) during the procedure. The heart rate during operation was higher in the ketamine group compared to control group ($p<0.001$). 46 (92%) patients in the ketamine group and 38 (76%) patients in the control group were satisfied according to surgeons ($p=0.001$). Nausea and vomiting occurred at similar rates in each group. Also, hallucination and other psychological events did not occur in either of the groups.

Conclusion: We found that systolic, diastolic, mean arterial blood pressure in patients who received small dose of ketamine were higher during the operation.

Keywords: ketamine; blood pressure; Phacoemulsification

Among anesthetic agents ketamine is the only agent that led to increased blood pressure and heart rate by activation of sympathetic nervous system [1]. This hemodynamic change is associated with an increase of catecholamine plasma concentration [2]. It has been suggested that small dose of ketamine when injected into the cerebral circulation in goats, led to increased arterial blood pressure and heart rate and it was assumed to evoke central sympathetic activation [3]. Pharmaceutical research in isolated tissues identified that ketamine inhibits neural norepinephrine uptake. Therefore, norepinephrine accumulates in the synaptic cleft and this justifies an increase of arterial blood pressure and heart rate through thecentral sympathetic drive [4-5]. On the other hand it was suggested that NMDA receptors by activation of NO synthase increase the production of NO from L-arginine in neural tissue. Accordingly, the antagonist effect of ketamine on NMDA receptors may increase arterial blood pressure by the inhibitory effect on NO formation [6]. However, it was shown that the S (+) -isomer of ketamine inhibits both neuronal and extraneuronal uptake of norepinephrine, whereas the racemic isomer of ketamine has no effect on extraneuronal uptake of catecholamines [7]. Moreover, some studies even showed the inhibitory effect of ketamine on sympathetic activity. It is identified that administration of ketamine decreased sympathetic activity [8-9], had no effect on it [10-11] or even induced a biphasic effect on sympathetic activity [12-13]. These different results of ketamine were reported with an anesthetic dose of it and the subject that has been less studied in literature was the effect of small dose of ketamine on the hemodynamic and sympathetic system. This study aimed to evaluate the effects of small dose of ketamine on arterial blood pressure and heart rate in patients who underwent Phacoemulsification.

Methods

One hundred patients of ASA physical status I-III and ranging in age range from 42 to 88 years, were chosen for

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this prospective, randomized, double-blind placebo-control study. All patients were scheduled for elective cataract surgery by Phacoemulsification under topical anesthesia by one surgeon. Approval from the hospital ethics committee and written consent from patients were obtained. Exclusion criteria included patients with clinically significant cardiovascular, respiratory and neurological disease. Intraoperative monitoring included noninvasive blood pressure, pulse oximetry and electrocardiography. Our patients were assigned randomly according to a computer generated random number table to one of two groups, ketamine group (n=50) and a control group (n=50). Number of subjects in each group provided a 90% power for detecting a 30% difference in blood pressure with an alpha level of 0.05. All patients were premedicated with midazolam (0.01mg/kg IV) and fentanyl (0.5µg/kg IV). After premedication 0.15 mg/kg ketamine was injected intravenously in ketamine group. After three minutes Phacoemulsification was begun under topical anesthesia with tetracaine 0.5% eye drop. The outcome variables such as systolic, diastolic and mean arterial blood pressure, heart rate and arterial oxygen saturation were recorded by a nurse of anesthesia who was blinded to the type of groups. The hemodynamic variables were recorded at the following time intervals: D0 (baseline value, immediately before intravenous administration of ketamine), and D3-D21 (3 to 21 minutes after intravenous administration of ketamine). Also, if during procedure, patients felt pain, 0.5µg/kg fentanyl was injected additionally. Statistical analysis of our data was performed with SPSS 16.0. Parametric variables were analyzed with t-test and compared between two groups. Blood pressure and heart rate were analyzed using repeated measures test. Categorical variables were compared between two groups by $\chi 2$ or Fisher's exact test. All data were presented with as mean with standard deviation (SD). The results were considered to be significant at a p-value <0.05.

Results

The demographic characteristics were comparable between two groups (Table 1). The systolic, diastolic and mean blood pressure changes during operation were statistically significant between two groups (p<0.001). (Table 2-4) (Figure 1-3) The heart rate during operation was higher in the ketamine group compared to control group (Table 5) (Figure 4) (p<0.001). Desaturation defined as pulse oximetry <90% was observed in 4 (8%) patients in ketamine group and in 3 (6%) patients in the control group during the procedure (p=0. 64). All of these cases required simple reposition of the airway with head tilt or chin lift and supplemental oxygen and none needed mask ventilation or endotracheal intubation. None of the patients in both groups showed apnea. 46 (92%) of the patients in the ketamine group and 38 (76%) patients in the control group were good as far as surgeon's satisfaction was concerned (p=0. 001). The administration of opioid during operation was necessary for 5 (10%) patients in the ketamine group compared to 14 (28%) patients in the control group (p<0.001). Nausea and vomiting requiring treatment in the postoperative period occurred at similar rates in each group, 3 patients (6%) versus 4 patients (8%), p=0. 32. Also, hallucination, nightmares and other psychological events did not occur either of the groups.

Figure 1- The comparison of systolic blood pressure between ketamine and control groups during procedure (p<0.001)

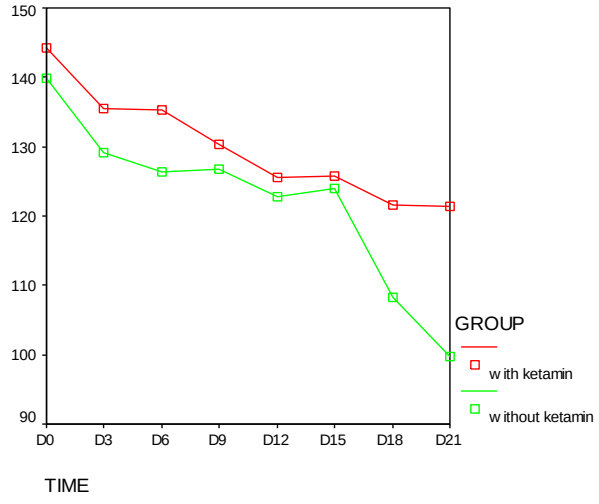

Figure 2- The comparison of diastolic blood pressure between two groups during procedure (p<0.001)

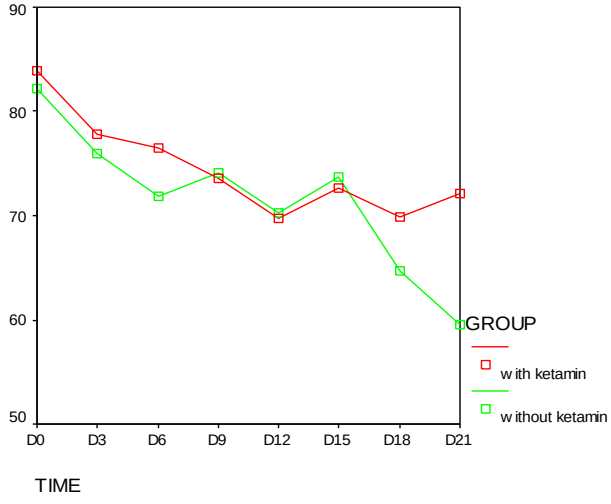

Figure 3- The comparison of mean arterial blood pressure between two groups during procedure (p<0.001)

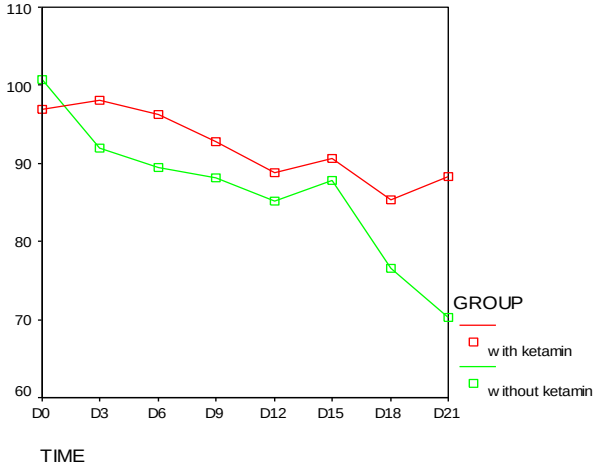

Figure 4- The comparison of heart rate between two groups during procedure (p<0.001)

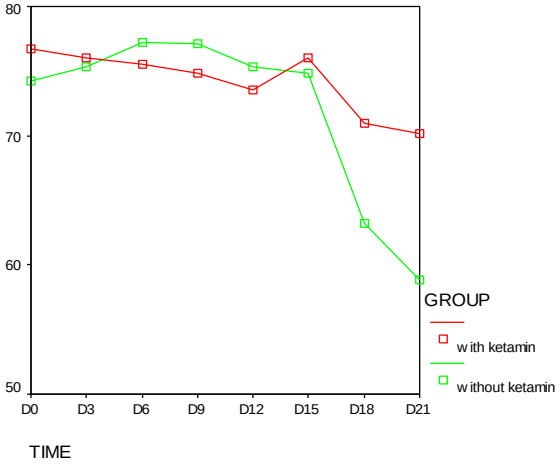

Table 1- The demographic variables of both groups

Variables	Ketamine group	Control group	P-value
Age (y)	67±20	69±22	0.64
Sex (male/female)	2.3	2.1	0.22
ASA Class 3	18 (36%)	16 (32%)	0.92
Diabetes	12 (24%)	11 (22%)	0.63
Hypertension	18 (36%)	20 (40%)	0.38
Ischemic Heart Disease	14 (28%)	12 (24%)	0.63
Smoking	8 (16%)	10 (20%)	0.48
Opium Addiction	8 (16%)	9 (18%)	0.52
Renal Failure	2 (4%)	3 (6%)	0.09
Congestive Heart Failure	4 (8%)	6 (12%)	0.64

Table 2- The comparison of systolic blood pressure between ketamine and control groups during procedure. D0 (baseline value, immediately before intravenous administration of ketamine), and D3-D21 (3 to 21 minutes after intravenous administration of ketamine)

Variables	Ketamine group	Control group	P value
Systolic blood pressure D0	154.1±27.7	158.5±27.7	<0.001
Systolic blood pressure D3	138±23.3	130.8±20.5	<0.001
Systolic blood pressure D6	141.1±28.2	131±23.6	<0.001
Systolic blood pressure D9	148.3±28.3	134.9±23.3	<0.001
Systolic blood pressure D12	148.4±27.9	134.8±21.5	<0.001
Systolic blood pressure D15	147.2±23.6	138.2±20.6	<0.001
Systolic blood pressure D18	150.2±29.3	140.4±22.7	<0.001
Systolic blood pressure D21	149.2±29	139.2±24.2	<0.001

Table 3- The comparison of diastolic blood pressure between two groups during procedure. D0 (baseline value, immediately before intravenous administration of ketamine), and D3-D21 (3 to 21 minutes after intravenous administration of ketamine)

Variables	Ketamine group	Control group	P value
Diastolic blood pressure D0	87.8±12.5	88.9±9.7	<0.001
Diastolic blood pressure D3	81.9±14.1	75.1±8.2	<0.001
Diastolic blood pressure D6	82.8±13.7	76.2±11.9	<0.001
Diastolic blood pressure D9	84.9±16.3	75±10.5	<0.001
Diastolic blood pressure D12	82.1±14	75.3±9	<0.001
Diastolic blood pressure D15	84.5±12.8	79.6±10	<0.001
Diastolic blood pressure D18	86±12.7	79.1±8.6	<0.001
Diastolic blood pressure D21	86±19.9	78.8±12.1	<0.001

Table 4- The comparison of mean arterial blood pressure between two groups during procedure. D0 (baseline value, immediately before intravenous administration of ketamine), and D3-D21 (3 to 21 minutes after intravenous administration of ketamine)

Variables	Ketamine group	Control group	P value
Mean arterial blood pressure D0	109.9±16.6	112.1±14.8	<0.001
Mean arterial blood pressure D3	100.5±16.3	93.5±11.3	<0.001
Mean arterial blood pressure D6	102.3±18	94.4±15.8	<0.001
Mean arterial blood pressure D9	105.9±19.5	95±13.9	<0.001
Mean arterial blood pressure D12	104.1±17.4	95.1±12.5	<0.001
Mean arterial blood pressure D15	105.5±15.5	99.1±12	<0.001
Mean arterial blood pressure D18	107.3±17	99.4±12.5	<0.001
Mean arterial blood pressure D21	108.1±15.5	99.8±17.4	<0.001

Table 5- The comparison of heart rate between two groups during procedure. D0 (baseline value, immediately before intravenous administration of ketamine), and D3-D21 (3 to 21 minutes after intravenous administration of ketamine)

Variables	Ketamine group	Control group	P value
Heart rate D0	76.7±15.9	78.5±14.7	<0.001
Heart rate D3	78±17.2	73.1±13.6	<0.001
Heart rate D6	75.2±16.6	69.2±11.8	<0.001
Heart rate D9	74±15.6	66.2±11	<0.001
Heart rate D12	72.3±15.6	66.4±10.8	<0.001
Heart rate D15	71.3±14	66.8±9	<0.001
Heart rate D18	72±14.2	67.7±11.5	<0.001
Heart rate D21	72.1±15.8	68±14.4	<0.001

Discussion

This study evaluated small dose ketamine affect on hemodynamic variables such as systolic, diastolic and mean arterial blood pressure. Intergroup comparison of heart rate showed the statistically significant difference between two groups because of the administration of ketamine. Previous studies showed that ketamine acts through binding to the receptor of NMDA channel and by noncompetitive manner inhibits glutamate activity of this channel [14]. Moreover, it was shown that ketamine interacts with opioid receptors (μ, k, σ), g-amino butyric acid (GABA) receptor, non NMDA glutamate receptor, nicotinuric and muscarinergic receptors, sodium, potassium and calcium channel [15]. Despite the

wide interaction of ketamine with many different receptors there are controversies about the effect of ketamine on sympathetic outflow. Many previous studies suggested that ketamine increases sympathetic activity by directly stimulating the central nervous system independently of the baroreceptor reflex [16]. The stimulating effect of ketamine on central sympathetic nervous system has been shown by an increase of plasma norepinephrine concentration after ketamine administration [17]. This finding was supported by observation that showed the augmentation effect of ketamine was attenuated with a ganglion blocker [18]. One previous study demonstrated that the cardiovascular augmentation of ketamine was mediated by inhibiting the NMDA receptors in the nucleus tractus solitarius [19]. Also, there was a hypothesis that supports the sypmpathoexcitatory effect of ketamine through suppression of central NO formation [16]. Therefore, the centrally mediated increase in sympathetic drive and inhibition of catecholamine uptake after ketamine administration were two different mechanisms that justified the stimulation of sympathetic nervous system with ketamine [20-21]. In clinical practice it has been reported that shortly after ketamine administration, plasma concentration of norepinephrine and epinephrine raised and to increase arterial pressure and heart rate [22-24]. One study supported the idea of the centrally effect of ketamine on sympathetic drive by injection of a small amount of ketamine into the cerebral circulation in goats and showed that the increase of arterial pressure, heart rate and cardiac output were similar to a larger dose of ketamine when administered intravenously [25]. In addition, it was suggested that ketamine may affect the adrenal medullary system and contribute to the marked increase in epinephrine plasma concentration and lead to an increase of blood pressure and heart rate [9]. However, in contrast to previous reports, vasodilatory and negative inotropic effects of ketamine have been suggested in certain experimental model and in patients with heart failure [26-27]. Indeed, it is reported that these effects of ketamine are observed when the sympathetic nervous system is extensively activated at baseline such as in patients with cardiac failure [28]. Therefore, these studies concluded that ketamine evokes an increase in arterial blood pressure and increase plasma catecholamine concentration, but a baroreflex induced inhibition of muscle sympathetic activity [9,29-30]. Moreover, there is evidence that identified ketamine can decrease central sympathetic outflow and this reduced dose is not related to blockade of NMDA receptors [31]. Another important point that should be mentioned and has been less studied in previous literatures was the effect of small dose of ketamine on the hemodynamic and sympathetic system. Can a small dose of ketamine affect sympathetic outflow in the same fashion as an anesthetic dose of it? It was shown that in rat models, the plasma concentration of ketamine suitable for surgical setting was approximately 50 µM and this study reported that the minimum concentration that effectively attenuated sympathetic outflow was 10 µM [32]. Therefore, it suggested that subanesthetic dose of ketamine similar to the anesthetic dose could induce activation of the sympathetic system. According to this study, we found that small dose of ketamine could attenuate the sympathetic activity. In conclusion, we found that systolic, diastolic and mean arterial blood pressure in patients who received small dose of ketamine before procedure compared to control group were higher during the operation. Moreover, heart rate was statistically significantly higher in the ketamine group compared to another group during the procedure.

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