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The Effects of Ketamine on Cognitive Function in Elderly Patients Undergoing Ophthalmic Surgery: A Pilot Study

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BACKGROUND: Acute postoperative cognitive dysfunction is characterized by neurocognitive dysfunction and confusion. In this study, we compared the cognitive status of a geriatric population undergoing ophthalmic surgery, as assessed by the Short Portable Mental Status Questionnaire (SPMSQ) before and after ketamine administration.

METHODS: Eighty patients were enrolled and randomly assigned in a double-blind study to receive either ketamine (0.3 mg/kg dose) or physiologic solution (control group). Sixty-five (control, n = 32; ketamine, n = 33) patients completed the trial. Cognitive performance was assessed with an abbreviated version of the SPMSQ. Measurements of analgesia, sedation, intraocular pressure, and hemodynamic variables were recorded.

RESULTS: With respect to cognitive performance, the baseline evaluation was similar for the control and ketamine groups. Postoperative evaluation showed an improvement only in the ketamine group. No increase in intraocular pressure or a secondary nystagmus was observed. The average dose of midazolam was higher in the control group, but the difference was not clinically significant. After surgery, analgesic behavior was better in the ketamine group than in the control group. There were no differences between groups in the sedation scale or in hemodynamic variables.

CONCLUSIONS: The administration of 0.3 mg/kg ketamine during ophthalmic surgery in geriatric patients changed their cognitive status as assessed by the SPMSQ, decreased the required dose of anesthetics, and produced no increase in intraocular pressure or in hemodynamic variables. However, because the evaluation only analyzed the immediate effects of the administered drug, further research will be required to examine the impact of ketamine on the postoperative cognitive performance of geriatric patients before the drug can be formally recommended for this purpose. (Anesth Analg 2016;122:969–75)

Aging is the main risk factor for cognitive changes that affect the performance of older patients in the solution of problems and the execution of tasks,[1] as well as their memory and speed of thought.[2] Another significant risk factor is poor vision and the association between age-related degenerative diseases and age-related macular degeneration in older people.[3] Anesthesia and surgery also contribute to cognitive changes[4]; a decline in cognitive status after surgery is called postoperative cognitive dysfunction (POCD).

The incidence of POCD varies in different reports and is attributable to conditions of anesthesia and surgery, the time elapsed after surgery, the population studied, and the type of cognitive test used.[5] Few studies have addressed the issue of POCD in the setting of minor or outpatient surgery; thus, its true incidence is probably underestimated. However, the reported incidence of cognitive dysfunction in the elderly is approximately 6.8% 7 days after minor surgery,[6] and approximately 10% of elderly people subjected to surgery will develop POCD.[7]

Based on the time of onset and the clinical symptoms, acute POCD has been identified during the first few minutes after anesthesia and could be confused with delirium; however, it should be recognized as a distinct clinical entity using screening tools[8] such as the Short Portable Mental Status Questionnaire (SPMSQ).[9] Although POCD is usually not associated with outpatient ophthalmic surgery or cognitive behavior, degenerative eye diseases have been proposed to be associated with decreased cognitive function.[10]

Treatment of POCD remains empirical and unreliable. Research has suggested that ketamine could be an option for the attenuation of POCD in patients undergoing surgery based on the intracellular signaling studies. It has also been proposed as having neuroprotective effects by suppressing the inflammatory response to surgery.[11,12] Ketamine, an antagonist *N*-methyl-D-aspartic acid (NMDA) receptor, reduces neuronal cell loss in the cortex by preventing excitotoxic injury and apoptosis after cerebral ischemia.[13]

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Ketamine may also confer neuroprotection by suppressing the inflammatory response to surgery.[14]

Thus, the purpose of this study was to compare the cognitive status, as assessed by the SPMSQ, of elderly patients undergoing ophthalmologic surgery before and after ketamine administration. We hypothesized that patients receiving ketamine would exhibit better cognitive performance.

METHODS

Setting of the Study

After research ethics board approval, we registered the study protocol at ClinicalTrials.gov. The protocol was accepted on January 29, 2014, and assigned the identifier number: NCT02049411, with Dulce María Rascón, M.D, as the principal investigator. Written informed consent was obtained from all subjects included in the study.

Participants

Participants were patients scheduled for vitrectomy or cataract surgery involving a retrobulbar block. The inclusion criteria were as follows: patients aged 60 years and older, intraocular pressure <20 mm Hg, and ASA physical status I to III. Patients with a history of psychosis, schizophrenia, nephropathy, difficult to control arterial blood pressure, uncontrolled hepatic disorders, or allergy to ketamine were excluded. In addition, patients were excluded if they were found to have moderate to severe depression according to Yesavage abbreviated Geriatric Depression Scale, presented with postoperative delirium or required medications other than study drugs. Ketamine administration was suspended when it was contraindicated.

Study Design and Procedures

Evaluation of patients' cognitive status was conducted with the SPMSQ. Patients were randomly assigned to one of the study groups. Sealed and numbered envelopes (assigned using a table of random numbers) indicated the prepared solution to be applied as follows: ketamine was administered at a dose of 0.3 mg/kg in a physiologic solution at 0.9% (250 mL), whereas the control group received only physiologic solution at 0.9%, with the same physical characteristics of the ketamine solution. Placebo or ketamine was administered IV after initial sedation and throughout surgery. Infusion velocity was calculated using the routine time for a particular type of procedure.

There does not seem to be 1 regimen indicative of standardization of sedation practice in eye surgery.[15] Because advanced age is associated with increased central sensitivity to midazolam combined with fentanyl, initial sedation was induced with minimal doses of 0.01 mg/kg midazolam + 1 μg/kg fentanyl. The dose of ketamine was based on the previous studies, which used approximately 0.21 to 0.25 mg/kg ketamine for sedation/analgesia.[16,17] Because we did not combine ketamine with propofol, we decided to increase the ketamine dose to 0.3 mg/kg. Once sedatives were administered, the ophthalmologist performed a retrobulbar block. Additional sedatives could be administered during the operation according to the judgment of the anesthesiologist, with the aim of keeping patients comfortable and pain free. Two hours after surgery, when patients were ready for discharge, their cognitive statuses were assessed again using the tools described earlier. Because delirium is described as an acute confusional state associated with disturbances in attention and decreased awareness of the environment, and patients are often disoriented after surgery,[18,19] we used the confusion assessment method[20] to exclude postoperative delirium.

Mental Status Test

Pfeiffer designed the SPMSQ in 1975 for the detection of cognitive deterioration in geriatric patients[21]; it was validated and translated into Spanish in 1992 by Gonzalez Montalvo et al.[22] It consists of 10 questions that explore short- and long-term memory, orientation, information about daily events, and the capacity to calculate. Assessed on a scale of 1 to 10, a patient is assigned to 1 of 4 categories according to the number of errors committed: intact cognitive function (0–2 errors), mild cognitive deterioration (3–4 errors), moderate cognitive deterioration (5–7 errors), or severe cognitive deterioration (8–10 errors). The questions are the following: What is the date today? What day of the week is it? What is the name of this place? What is your telephone number? What is your street address? How old are you? When were you born? Who is the President now (we asked about the Mexican president)? Who was the president just before him? What was your mother's maiden name? Subtract 3 from 20, and keep subtracting 3 from the result all the way down to 0. The Spanish version of the SPMSQ has 100% sensitivity and 90% specificity for patients with up to 5 errors. This screening tool has a correction factor for low levels of education.

The most stringent criterion for the diagnosis of POCD is a decline of at least 2 SDs in 2 cognitive domains or a decline of at least 2 SD in a composite cognitive score.[23,24] A liberal criterion has been proposed in several prominent studies when there is at least 1 result below the range of 1 SD in any cognitive domain or in a composite cognitive score.[25]

In our study, postoperative results of the SPMSQ were compared with the baseline evaluation. When fewer errors were found in the postoperative assessment (accounting for SD), we considered that the patient's cognitive behavior had improved.

In addition, we performed an evaluation of analgesia and sedation using the verbal numerical scale and Ramsey test, respectively. We recorded the vital signs of each patient, as well as any signs of nystagmus, respiratory depression, or hallucinations. The intraocular pressure of the nonsurgical eye was measured before and after surgery using a Schiotz tonometer.

Statistical Analysis

The sample size required for the study was estimated assuming a difference of 2 SD in the results of the 2 groups, according to a previous report of the effects of ketamine on cognitive performance after cardiac surgery.[11] In this way, assuming an $\alpha = 0.05$ and a power of 90% ($Z\alpha = 1.96$ and $Z\beta = 1.28$, respectively, for 2-sided tests), at least 21 subjects were required per treatment group. We arbitrarily chose to test at least 10 additional subjects per group, considering that some of them may not complete the study.

Baseline characteristics were compared between groups using the χ^2 analysis of contingency tables for categorical data and the independent sample *t* tests for continuous data. The analysis of changes in hemodynamic variables, respiratory rate, oxygen saturation, and sedation between the baseline and the final assessments (90 minutes into surgery), according to the Ramsey scale, was done using a general linear model. A similar analysis was done for intraocular pressure (assessed before and after surgery). Analgesia was assessed after regional anesthesia (retrobulbar block) and after surgery. A comparison was made between groups with the χ^2 test.

Patients were included in an analysis of mean change of the number of items incorrectly answered in the SPMSQ between the preoperative and the postoperative assessments using an analysis of covariance model, which considered baseline status as covariate and the treatment group as the effect of interest.

RESULTS

Demographic and Clinical Characteristics of the Sample

Eighty patients were recruited and randomly assigned, 10 patients withdrew their consent. Five patients were excluded from analysis: 2 from the ketamine group because of hypertensive crisis (n = 1) and myocardial infarction (n = 1); 3 from the control group because of hypertensive crisis (n = 1), increased intraocular pressure (n = 1), and postoperative emesis (n = 1). The remaining 65 patients were assigned to the control (n = 32) or ketamine (n = 33) groups. Figure 1 is the patient flow diagram.

Demographic and surgical variables were similar between groups. The mean dose of anesthetic medications was higher in the control group; the difference was significant for midazolam, whereas a trend was observed for fentanyl (Table 1).

Cognitive Performance

Before surgery, similar SD in the results of the SPMSQ were reported for the control and ketamine groups (1.9, SD = 1.6, and 2.1, SD = 2.0, respectively) (t = −0.60, df = 63, P = 0.54). Table 2 shows the change in the score of errors in the SPMSQ between baseline and postoperative evaluations (compared with the analysis of covariance model). Significant changes over time were observed only in the ketamine group, in which patients had fewer errors in the postoperative SPMSQ compared with the baseline evaluation.

According to the scoring scale, in the preoperative assessment, 68.8% (n = 22) of patients in the control group and 66.7% (n = 22) in the ketamine group performed within the normal range, whereas the remaining patients performed within the mild/moderately impaired range (χ^2 = 0.03, df = 1, P = 0.85). After surgery, an increased number of patients in the ketamine group performed within the normal range (n = 28, 84.8%; P = 0.03), whereas the percentage of patients in the control group with a normal cognitive performance remained almost unchanged (n = 24, 75%; P = 0.62).

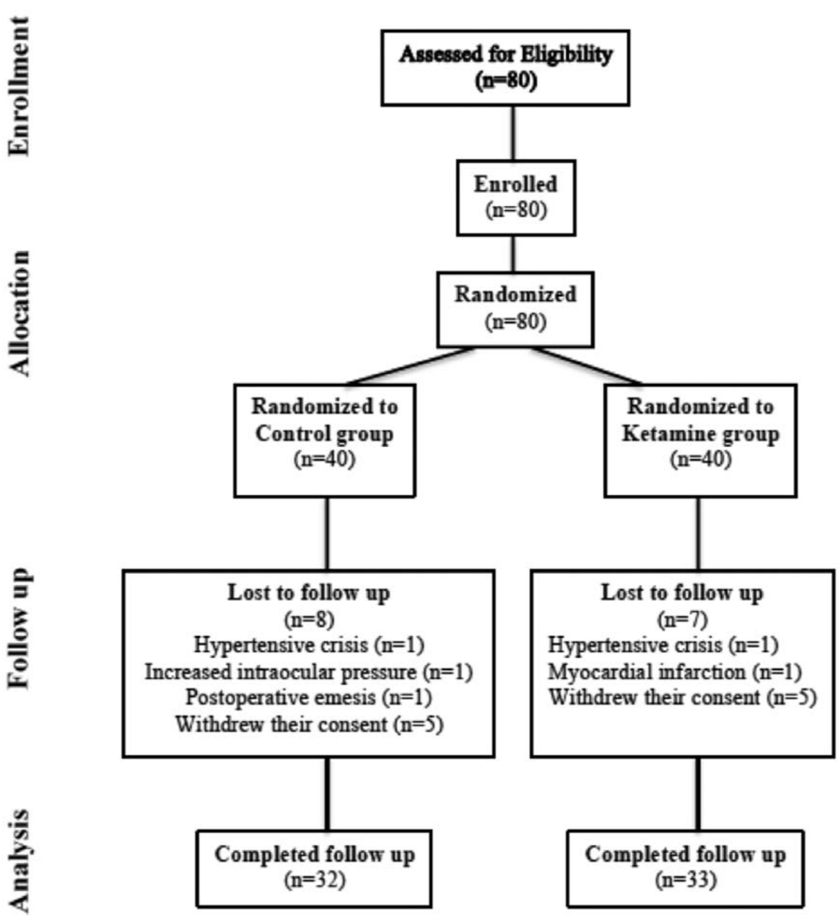

Figure 1. CONSORT flowchart indicating the selection, randomization, and follow-up of the patients included in the study. Fifteen subjects were excluded because of intraoperative complications and personal concerns.

Table 1. Demographic, Surgical, and Anesthetic Variables Between Groups

	Control (n = 32)	Ketamine (n = 33)	Statistics
Sex, n (%)			χ^2 = 0.37, df = 1, P = 0.54
Male	16 (50)	14 (42.4)	
Female	16 (50)	19 (57.6)	
Educational level, n (%)			χ^2 = 2.15, df = 2, P = 0.54
None—elementary school	21 (65.7)	19 (57.6)	
Secondary school	9 (28.1)	8 (24.2)	
High school	2 (6.2)	6 (18.2)	
Comorbid medical conditions, n (%)			
Hypertension	24 (75.0)	19 (57.6)	χ^2 = 2.20, df = 1, P = 0.13
Diabetes	19 (59.4)	22 (66.7)	χ^2 = 0.37, df = 1, P = 0.54
Chronic renal insufficiency	5 (15.6)	6 (18.2)	χ^2 = 0.07, df = 1, P = 0.78
Type of surgery, n (%)			χ^2 = 1.92, df = 4, P = 0.74
ECCE and IOL implantation	15 (46.9)	13 (39.4)	
Vitrectomy	9 (28.1)	9 (27.3)	
Vitrectomy + phacoemulsification	4 (12.5)	4 (12.1)	
Vitrectomy + ECCE + IOL	3 (9.4)	3 (9.1)	
Phacoemulsification	1 (3.1)	4 (12.1)	
Age (y), mean (SD)	70.5 (4.7)	68.7 (7.1)	t = 1.20, df = 63, P = 0.23
Weight (kg), mean (SD)	67.9 (10.5)	68.8 (13.3)	t = −0.29, df = 63, P = 0.70
Height (cm), mean (SD)	158.5 (9.8)	160.6 (10.1)	t = −0.81, df = 63, P = 0.42
Body mass index (kg/m^2), mean (SD)	26.8 (3.4)	26.6 (4.6)	t = 0.20, df = 63, P = 0.83
Midazolam dose (mg), mean (SD)	1.0 (0.5)	0.7 (0.3)	t = 2.33, df = 63, P = 0.02
Fentanyl dose (μg), mean (SD)	118.1 (39.6)	102.4 (33.6)	t = 1.72, df = 63, P = 0.09
Duration of Surgery (min), mean (SD)	94 (28.9)	99 (21.8)	t = 0.81, df = 63, P = 0.41

ECCE = extracapsular cataract extraction; IOL = intraocular lens implantation.

Table 2. Hemodynamic Measurements, Respiratory Rate, and Oxygen Saturation

	Control (n = 32), mean (SD)	Ketamine (n = 33), mean (SD)	Statistics (time × group)
Heart rate (bpm)			F = 2.57, P = 0.11
Baseline	69.5 (12.6)	77.0 (14.2)	
After retrobulbar block	66.1 (10.9)	70.3 (13.3)	
90 min into surgery	64.2 (10.7)	67.9 (12.0)	
Systolic blood pressure (mm Hg)			F = 1.1, P = 0.29
Baseline	166.0 (21.9)	163.7 (17.1)	
After retrobulbar block	154.0 (21.3)	150.9 (22.0)	
90 min into surgery	141.7 (14.1)	141.7 (14.1)	
Diastolic blood pressure (mm Hg)			F = 1.2, P = 0.26
Baseline	79.4 (9.3)	85.2 (19.6)	
After retrobulbar block	77.2 (12.3)	83.2 (17.2)	
90 min into surgery	75.3 (10.5)	77.5 (14.9)	
Arterial blood pressure (mm Hg)			F = 0.94, P = 0.33
Baseline	116.7 (15.2)	118.6 (26.2)	
After retrobulbar block	111.1 (14.4)	110.0 (16.7)	
90 min into surgery	106.1 (12.8)	102.6 (11.8)	
Oxygen saturation (%)			F = 0.20, P = 0.65
Baseline	92.6 (3.5)	93.2 (4.0)	
After retrobulbar block	96.0 (3.7)	95.6 (3.7)	
90 min into surgery	98.0 (1.9)	98.3 (2.0)	
Respiratory rate (bpm)			F = 1.7, P = 0.18
Baseline	18.9 (2.2)	18.6 (2.7)	
After retrobulbar block	14.1 (2.0)	13.6 (2.4)	
90 min into surgery	13.0 (3.0)	13.9 (2.9)	
Ramsey scale total score			F = 0.46, P = 0.49
Baseline	1.26 (0.4)	1.34 (0.5)	
After retrobulbar block	2.32 (0.5)	2.16 (0.4)	
90 min into surgery	2.16 (0.4)	2.00 (0.2)	

Hemodynamic Measurements, Oxygen Saturation, Sedation, Intraocular Pressure, and Analgesia

Significant decreases over time were observed independently in both groups in hemodynamic variables and respiratory rate ($P < 0.001$), whereas oxygen saturation and sedation level increased ($P < 0.001$). No significant changes over time × group were observed in these variables in the general linear model (Table 3). Similarly, the control and the ketamine groups showed similar changes in intraocular pressure between the preoperative (15.9, SD = 2.8 vs 14.4, SD = 3.6 mm Hg, respectively) and the postoperative evaluation (15.0, SD = 3.0 vs 13.2, SD = 3.4 mm Hg, respectively; $F_{time \times group} = 0.20$, $P = 0.65$).

Table 3. Change in SPMSQ Error Scores Between Baseline and Postoperative Assessments in Both Groups

Test	Control (n = 32), mean (SD)	Ketamine (n = 33), mean (SD)	Statistic[a]
SPMSQ error score			
Baseline	1.91 (1.63)	2.18 (2.0)	F = 12.4, df = 1,
Mean change	−0.18 (0.88)	−1.0 (1.06)	P = 0.001

SPMSQ = Short Portable Mental Status Questionnaire.
[a]Based on analysis of covariance adjusted for baseline score.

Conversely, significant changes were observed in analgesia, which was evaluated using a numerical verbal scale, followed by a Likert scale for statistical analysis. After anesthesia, 75% (n = 24) of patients in the control group reported mild/moderate pain, compared with 56.2% (18) of patients in the ketamine group (χ^2 = 4.8, df = 3, P = 0.18). After surgery, a significantly smaller proportion of patients reported mild/moderate pain in both groups, although it was less in ketamine group patients (n = 3, 9.1% vs n = 17, 51.3% of the control group; χ^2= 18.5, df = 3, P < 0.001).

DISCUSSION

In this study, we found statistical differences between the errors committed in the postoperative SPMSQ compared with the baseline evaluation. Previous studies concerning the effect of ketamine on POCD focused on complex surgery involving different levels of anesthesia; the subject of these studies were intracellular signaling[26] and neurologic effects related to attention, working, and semantic memory,[27] but the effect of ketamine on common conditions of geriatric patients, including comorbid conditions and minor surgeries, has not been well studied. More studies should be conducted on ophthalmic surgery, because common age-related eye diseases such as cataracts, as well as age-related macular degeneration, have been proposed to be associated with the changes in cognition,[28] with aging as a major preoperative risk factor.

Some studies suggest that the NMDA receptor has a direct role in short-term and recognition memory[29] through anti-inflammatory mechanisms,[30] whereas other reports assign the effect to increased cerebral blood flow[31] or to the binding of the drug to NMDA receptors. This binding reduces neuronal apoptosis by suppressing the expression of the factor $k\beta^2$ involved in transcription of genes that codify proinflammatory cytokines,[32] such as tumor necrosis factor α and interleukins 6 and 8.[33] Consequently, ketamine attenuates the systemic inflammatory response to tissue injury and maintains cerebral perfusion pressure by activating the sympathetic nervous system.[34]

In the control group, the number of baseline errors recorded in the SPMSQ was 1.91, whereas the number was 1.73 after surgery. In the ketamine group, the number of baseline errors was 2.18, which decreased to 1.18 after surgery. Given the nature of the questions, it is difficult to know with precision if the difference reported really had anything to do with the effect of ketamine on cognitive changes or if it was a difference in learning, but this issue can be answered by comparing the cognitive performance between groups.

Our aim was to detect minor changes in cognitive performance; this is why the baseline evaluation of cognitive function was compared with another evaluation immediately after surgery. By performing the study in this way, we sought to avoid confusion that could be introduced by a postoperative evaluation after a longer period of time.

Unlike other studies, we included patients with mild depression (without treatment), which means that cognitive deterioration could be caused by this depression (an etiologic factor) or by the eye illness (a prodromal clinical manifestation).[35] The former possibility should be explored in future studies.[36]

As in other studies, ketamine reduced the required dose of opioids,[37] which suggests the importance of new research on the relationship between pain and cognitive performance. There is a possible relationship between the cognitive distortion and the degree of pain experienced in the past[38]; to our knowledge, this approach is absent in the literature.

We found that, with the dose used in our study, ketamine did not increase intraocular pressure. Because patients received a retrobulbar block, neither blepharospasm nor nystagmus was observed in eyes before or after surgery. This could be associated with the dose used, regional anesthesia, and the degree of comfort provided by sedative agents, particularly ketamine, which is known as a sedative agent in ophthalmic surgery.[39,40]

Furthermore, patients in the ketamine group required a significantly lower average dose of midazolam. There was a difference in the use of fentanyl, but no significant difference between groups with respect to the sedation required according to the Ramsey scale. This might be explained by the scale used and/or the interobserver variations.

Ketamine was administered throughout the surgical procedure; therefore, the need for midazolam/fentanyl was reduced with potential benefits. It is possible to assume that the evaluation performed in the immediate postoperative period considered only the immediate effects of the administered drugs. Because patients not receiving ketamine received larger amounts of midazolam, it is not possible to exclude that the difference was because of the effect of the drug. However, we do not think it very probable that the statistically significant difference was produced by the effect of midazolam because of the minimally different doses between groups, which does not represent a clinical difference of interest with respect to patients' cognitive function or sedation.

Because of the design of this study, we can provide no evidence of pathophysiologic mechanisms and the neuroprotective effect on POCD attributable to ketamine. Because POCD may last longer than the immediate postoperative periods, further studies should be done to evaluate cognitive performance at least 24 hours after surgery using various validated tests.[41]

The use of only 1 questionnaire has limited benefits, and further research using other instruments is needed. However, our study showed that 0.3 mg/kg ketamine may be useful for inducing better cognitive performance after ophthalmic surgery in elderly patients, enhancing the effect of analgesics with safety improvements in hemodynamics, oxygen saturation, and intraocular pressure. However, these results need to be replicated in future studies.

DISCLOSURES

Name: Dulce M. Rascón-Martínez, MD, MSc.
Contribution: This author helped design the study, conduct the study, and write the manuscript.
Attestation: Dulce M. Rascón-Martínez has seen the original study data and approved the final manuscript.
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Contribution: This author helped analyze the data and write the manuscript.
Attestation: Ana Fresán-Orellana has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
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