

Preemptive low-dose of ketamine does not effective on anesthetic consumption, perioperative analgesic requirement and postoperative pain, nausea and vomiting in painful ophthalmic surgery

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Background: Ketamine, a non-competitive NMDA (N-Methyl-D-Aspartate) receptor antagonist, is recognized as an intraoperative anesthetic agent. Increasing interest in the use of low-dose ketamine for postoperative analgesia has developed in part because of its NMDA-antagonistic properties, which may be important in attenuating central sensitization and opioid tolerance. Despite of many trial evaluations which have been done on the effect of low-dose ketamine in postoperative pain, the role of ketamine, as a component of perioperative analgesia, remains unclear. We evaluated the analgesic effect of low-dose ketamine during anesthesia induction in painful ophthalmic surgery. **Materials and Methods:** After institutional approval and written informed consent, 88 patients undergoing retinal detachment, strabismus, and keratoplasty surgery aged 18-80 years old were randomly divided into equal case and control groups. Anesthesia was induced with sodium thiopental, fentanyl, atracurium, and lidocaine, and maintained with N₂O, O₂, and propofol. Ketamine 0.5 mg/kg was administered intravenously to patients in the case group during anesthetic induction. Mean blood pressure and pulse rate were listed in questionnaire every 5 minutes. The consumption of anesthetic, perioperative additional analgesic, extubation time, postoperative pain and nausea scores (based on Visual Analog Scale), vomiting frequency, and the recovery time were recorded. **Results:** There were no differences in the recovery time (17.3 ± 3.4 in the case group vs. 16.3 ± 3 in the control group, $P < 0.05$), postoperative pain scores (5 ± 1 in the case group vs. 5.6 ± 2 in the control group, $P < 0.05$), the consumption of anesthetic (9376.9 ± 1245.8 in the case group vs. 9012.9 ± 1620 in the control group, $P < 0.05$), the analgesic requirements (1000 in the case group vs. 940.9 ± 135.6 in the control group, $P < 0.05$), and perioperative additional analgesic (63.4 ± 26.5 in the case group vs. 69.4 ± 25.6 in the control group, $P < 0.05$) between two groups. The extubation time in the case group (13.59 ± 4.83) was significantly shorter than in the control group (15.9 ± 3.6) ($P = 0.01$). **Conclusion:** This study demonstrates that a low dose administration of ketamine during anesthesia induction in retinal detachment, strabismus, and keratoplasty surgery improves the extubation time but have no effect on postoperative pain, nausea and vomiting, and perioperative additional analgesic requirements.

Key words: Analgesic requirements, keratoplasty, low-dose ketamine, postoperative pain, retinal detachment, strabismus

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INTRODUCTION

Pain is an unpleasant sensory experience associated with actual or potential tissue damage.^[1] Adequate pain management, ideally resulting in the complete absence of postoperative pain, not only provides comfort to patients, but may also contribute to improved healing and a reduction in the incidence of postoperative complications.^[2] Many options are available for the treatment of postoperative pain, including systematic analgesics (i.e., opioid and nonopioid), and regional analgesic.^[3]

It seems that certain receptors (e.g., N-Methyl-D-Aspartate) may be especially important for the development of chronic pain after an acute injury.^[3]

The role of the NMDA receptor in the processing of nociceptive input has led naturally to renewed clinical interest in NMDA receptor antagonists such as ketamine.^[4]

Ketamine is traditionally recognized as an intraoperative anesthetic agent.^[5] Ketamine differs from most other drugs used to induce anesthesia because it has a significant analgesia effect.

There are some evidence that ketamine occupies opiate receptors in the brain and spinal cord, and this property could account for some of the analgesic effects.^[6]

Low-dose ketamine (defined as a bolus dose of less than 2 mg/kg when given intramuscularly or less than 1 mg/kg

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when administered via the intravenous or epidural route) as an adjuvant to opioids or local anesthetics may play an important role in the treatment of acute postoperative pain.^[7]

Increasing interest in the use of low-dose ketamine for postoperative analgesia has developed in part because of its NMDA antagonistic properties, which may be important in attenuating central sensitization and opioid tolerance.^[5]

Postoperative pain management with opiate is often limited by adverse effects such as nausea and vomiting. Ketamine may be of value in giving better analgesia with fewer adverse effects.

A literature review concludes that the role of ketamine, as a component of perioperative analgesia, remains controversial.^[7]

Patients undergoing the surgery of posterior segment (Retinal detachment), eye muscles (Strabismus), or cornea (Keratoplasty), especially if performed under general anesthesia, are more likely to experience serious postoperative pain.^[2]

As there are currently no published data studying the effect of low-dose ketamine on painful ophthalmic surgery (Strabismus, Retinal detachment, Keratoplasty), we aimed to study the effect of low-dose ketamine during anesthesia induction in painful ophthalmic surgery and evaluate anesthetic consumption, perioperative analgesic requirement, and postoperative nausea, vomiting, and pain.

MATERIALS AND METHODS

The study was registered on IRCT.ir (number Irct ID: IRCT201102235889N). After institutional ethical committee approval and the nature of the trial was explained to the patient, each patient signed an informed consent. In this randomized double-blind clinical trial, we studied 88 patients with ASA physical status I or II, and aged 18-80 years old, that were undergoing strabismus, retinal detachment, and keratoplasty surgery in Fayz Hospital. Exclusion criteria included had addiction to opium and drugs and had contraindications to ketamine (increased ICP, intracranial mass lesions, open eye injury, ischemic heart disease, vascular aneurysms, and psychiatric disease^[6]).

Patients were randomly assigned to one of the following two groups, according to a computer-generated random numbers table: The case group ($n = 44$) and the control group ($n = 44$). The three types of surgeries were divided equally in two groups. Sample size was estimated according to the following formula:

$$n = \frac{(z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2 (\delta_1^2 + \delta_2^2)}{d^2}$$

Significant level $\alpha = 0.05 \rightarrow z_{1-\frac{\alpha}{2}} = 1.961 - \beta = 0.80 \rightarrow z_{1-\beta} = 0.84$

The duration of preoperative NPO and serum therapy of all patients was the same. All patients received standard monitors including electrocardiography, noninvasive arterial pressure, end tidal CO₂ pressure, and pulse oximetry. Preoperative blood pressure and heart rate were recorded before anesthetic administration. Age, gender, weight, and underlying disease of patients were noted.

After preoxygenation, anesthesia was induced intravenously using sodium thiopental 4-6 mg/kg, fentanyl 12 µg/kg, atracurium 0.6 mg/kg, and lidocaine 1.5 mg/kg. After ventilation with mask and oxygen, patients were intubated. In the case group, ketamine 0.5 mg/kg was given intravenously during anesthesia induction. Patients allocated to the control group were given an identical volume of saline. Investigator involved in data collection was not aware of the group assignment. Anesthesia was maintained using intravenous infusion of 100 µg/kg/min propofol (propofol 10%, 0.6 cc/kg/h). Patients were ventilated mechanically with oxygen (50%) and N₂O (50%).

Ringer's solution (7 cc/kg) was infused before anesthesia induction and at a rate of 2 cc/kg/h during surgery.

For maintaining 80-100% of the baseline preoperative systolic blood pressure value, propofol was increased at the rate of 16.6 µg/kg/min (0.1 cc/kg/h) to the maximum rate of 150 µg/kg/min (0.9 cc/kg/h) every 5 minutes. If the preoperative basal blood pressure was not reached, fentanyl 0.5 µg/kg every 10 min would be administered until the 80-100% basal blood pressure would be obtained.

At the end of the surgery, muscle relaxation was reversed using atropine (0.02 mg/kg) and prostigmin (0.04 mg/kg) intravenously in all patients.

When spontaneous breathing resumed with at least 2/3 of the normal tidal volume and the end expiratory CO₂ pressure of less than 45 mmHg, patients were extubated and transferred to the recovery room.

Mean atrial blood pressure and heart rate values were recorded at 5 min intervals. The amount of anesthetic consumption and analgesic requirements during surgery were recorded. The duration of surgery (from surgical incision till the end of operation) was also noted. The duration of extubation was recorded from discontinuation

of anesthetics till extubation. In the recovery room, when the patient was awake and oriented, the evaluation of postoperative pain was performed using Visual Analogue Scale (VAS). All patients were informed from VAS before operation started, VAS graded from 0 = no pain to 10 = severe pain. 15 mg/kg paracetamol was given intravenously within 20 min to the patients who had VAS \geq 4. If patient had VAS \geq 4, 20 min after infusion of paracetamol, 0.5 mg/kg pethidine was given intravenously. If postoperative vomiting happened, it would be noted. Postoperative nausea was evaluated during recovery time via VAS that scored from 0 to 10.

The amount of analgesic requirements in the recovery was noted. Recovery time was recorded as the time from entering the patient in recovery room to achievement conditions of discharge, based on the criteria in the following table.

Criteria score

Level of consciousness

Awake and oriented 2

Arousable with minimal stimulation 1

Responsive only to tactile stimulation 0.

Physical activity

Able to move all extremities on command 2

Some weakness in movement of the extremities 1

Unable to voluntarily move the extremities 0.

Hemodynamic stability

Blood pressure <15% of the baseline MAP value 2

Blood pressure between 15% and 30% of the baseline MAP value 1

Blood pressure >30% below the baseline MAP value 0.

Respiratory stability

Able to breathe deeply 2

Tachypnea with good cough 1

Dyspneic with weak cough 0.

Oxygen saturation status

Maintains value >90% on room air 2

Requires supplemental oxygen (nasal prongs) 1

Saturation <90% with supplemental oxygen 0.

Postoperative pain assessment

None or mild discomfort 2

Moderate to severe pain controlled with IV analgesics 1

Persistent severe pain 0.

Postoperative emetic symptoms

None or mild nausea with no active vomiting 2

Transient vomiting or retching 1

Persistent moderate to severe nausea and vomiting 0

Total score 14

A score over 12 with no individual less than 1 is required for fast-tracking.

MAP = mean atrial pressure.^[8]

Statistical analysis

The result of the study was evaluated using the SPSS statistical analysis package. Characteristics such as age, weight, recovery time, duration of surgery, perioperative additional narcotic, the maximum consumption of anesthetic, the amount of postoperative analgesic requirements, postoperative pain scores, and the duration of extubation were compared among the groups using the independent sample *t*-test. Gender and underlying disease were compared using the Chi-square test. Data are presented as mean value \pm SD, number (n), percentage *P*<0.05 was considered as statistically significant differences between the case and control groups.

RESULTS

Eighty-eight patients were enrolled in this study. The demographic characteristics (age, body weight, gender), duration of surgery, recovery time, and postoperative pain scores in the recovery were similar between the groups [Table 1]. The minimum age of the patients in the study was 18 and the maximum age was 70. The consumption of anesthetic and the analgesic requirements (μ g/kg/min, μ g/kg) were similar between the groups [Table 1].

Nausea in the recovery was observed in one patient with VAS=3 in the control group that was undergoing strabismus

Table 1: Patients demographic data, intraoperative consumption of anesthetic and additional narcotic, postoperative analgesic requirements, postoperative pain scores, recovery time, duration of extubation, underlying disease

	The case group (n=44)	The control group (n=44)	P value
Age (yr)	34 \pm 13.4	36.3 \pm 17.8	0.49
Gender (M/F)	28/16	24/20	0.38
Weight (kg)	65.2 \pm 7.3	64.2 \pm 9	0.58
Duration of surgery (min)	70.1 \pm 15	69.2 \pm 16.2	0.79
Underlying disease (n) (%)	1 (2.3)	2 (4.5)	0.5
The consumption of anesthetic (μ g/min)	9376.9 \pm 1245.8	9012.9 \pm 1620	0.24
Perioperative additional analgesic (μ g/min)	63.4 \pm 26.5	69.4 \pm 25.6	0.51
Postoperative analgesic requirements (mg)	1000 \pm 120	940.9 \pm 135.6	0.17
Postoperative pain score during recovery time (VAS)	5 \pm 1.5	5.6 \pm 2	0.49
Recovery time (min)	17.3 \pm 3.4	16.3 \pm 3	0.17
Extubation time (min)	13.5 \pm 4.8	15.9 \pm 3.6	0.01

Notes: Data are presented as mean \pm SD or n (%), n=44

surgery. Vomiting was not observed in 88 patients in the recovery in this study. The extubation time in the case group was significantly shorter than in the control group ($P = 0.01$, Table 1). Underlying disease did not differ significantly between the groups [Table 1]. Adverse effects of ketamine did not seen in any patients.

DISCUSSION

The objective of this study was to assess the effect of low-dose ketamine during anesthesia induction in strabismus, retinal detachment, and keratoplasty surgeries. Identifying perioperative analgesia requirements and postoperative nausea, vomiting, and pain were other objectives of this study. There are some undesired effects of the surgery such as postoperative pain, nausea, and vomiting. Since serious pain was not infrequently found despite pain monitoring, the need for anesthetic techniques that reduce or even prevent postoperative pain is obvious.

The present study demonstrates that low-dose ketamine during anesthetic induction does not improve postoperative pain scores of patients undergoing strabismus, retinal detachment, and keratoplasty surgery. Our finding is consistent with those of some other studies about postoperative pain scores.^[9-14]

Contrary to our study, Mizrak *et al.*^[11] reported that infusion of ketamine is more effective than intravenous infusion of propofol in decreasing postoperative pain scores of children undergoing strabismus surgery. This may be due to the dose-dependent effect on pain processing of ketamine.^[6] In a study by Mizrak *et al.*, ketamine was administrated in anesthetic dose (1-3 mg/kg) that is two times higher than our dosage. Another reason could be the duration of surgery that was less than the present study. Aydin *et al.*^[15] reported that ketamine decreases postoperative pain of children undergoing tonsillectomy and adenotomy. Because of continuous intravenous infusion of ketamine during surgery and different surgical procedures, our finding is inconsistent with Aydin's study in postoperative pain scores.

The present study indicates that a low dose administration of ketamine does not decrease analgesic requirements in the recovery. A number of previous studies demonstrate that a low dose of ketamine has no preemptive analgesic effect.^[10-13,16,17] In contrast to our findings, Menigaux *et al.*^[18] found that patients received small dose of ketamine (0.15 mg/kg) at the end of the surgery (intraoperative), reduced postoperative morphine requirements and improve pain scores, and mobilization 24 h after arthroscopic anterior ligament repair. In the current study, patients received IV ketamine (0.5 mg/kg) during induction of anesthesia. The plasma half-life of ketamine is <17 minutes. Analgesia produced by ketamine 125-250 µg/kg IV lasts approximately

5 min when the plasma ketamine concentration is >100 ng/ml.^[14] The negative findings of postoperative pain scores and analgesic requirements can be explained by different surgical procedures and the time of ketamine administration during surgery.

Suzuki *et al.*^[14] found that small dose of ketamine reduced VAS and morphine-induced analgesia after outpatient surgery. Shorter duration of the surgery and simultaneous use of small dose of ketamine with morphine, 15 min before the end of operation, could be the reasons of this inconsistency with our negative finding. Nesher and colleagues^[16] concluded that ketamine 5 mg IV spares morphine consumption after transthoracic lung and heart surgery. The reason for our negative finding of analgesic requirements may be different surgical procedures and different dose of ketamine administration. In contrary to our study, Remrand *et al.*^[19] reported that 24 h ketamine infusion decreased morphine consumption at 24 h after total hip arthroplasty that may be due to different surgical procedures and 24 h ketamine infusion.

In this study, no difference was found between ketamine and control groups with respect to intraoperative additional narcotic. To the best of our knowledge, the present study is the first investigation to examine the effect of low dose of ketamine on intraoperative additional narcotic.

Small dose of ketamine does not seem to be a useful adjunct to anesthetic and does not decrease the consumption of anesthetic during surgery. In this case, our finding is consistent with a number of previous studies.^[11,12] In contrast to our finding, Mizrak *et al.*^[11] indicated that infusion of ketamine is effective on decreasing the consumption of anesthetic. The duration of ketamine anesthesia is determined by the dose; larger doses produce more prolonged anesthesia.^[6] In the study by Mizrak *et al.*,^[11] patients in group K were infused ketamine 1-3 mg/kg/h but in the present study, patients in group 1 received ketamine 0.5 mg/kg. This contrast may be due to larger dose of ketamine administration in Mizrak's study that causes the lower consumption of anesthetic.

In the current study, recoveries from anesthesia and discharge parameters were similar among the groups. Our finding is consistent with a study by Aydin *et al.*^[15]

The finding of this study indicates that low dose of ketamine during anesthesia induction can improve extubation time in painful ophthalmic surgery. To the best of our knowledge, the present study is the first investigation to evaluate the effect of low dose ketamine on extubation.

In strabismus surgery, postoperative nausea and vomiting (PONV) frequency are 50% to 80% without

treatment.^[20] In adults, although the incidence of PONV decrease with age, it has not always been a strong risk factor. In children, however, Eberhart and coworkers have shown that an age of 3 years or older is associated with an increased risk for PONV.^[17]

In the present study, the incidence of PONV is lower than a study by Mizrak *et al.*^[11] This may be due to patients aged 4-11 years undergoing strabismus surgery who enrolled for Mizrak's study. We came to the conclusion that age and strabismus surgery cause a high incidence of PONV.

CONCLUSION

This study demonstrates that administration of low-dose of ketamine during induction of anesthesia for retinal detachment, strabismus, and keratoplasty surgeries decrease extubation time and improve it, but failed to show any benefit on postoperative pain, PONV, consumption of anesthetic drug, intraoperative additional narcotic, and postoperative analgesia requirements.

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