ORIGINAL ARTICLE

# Effect of preinduction low-dose ketamine bolus on intra operative and immediate postoperative analgesia requirement in day care surgery: A randomized controlled trial

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## ABSTRACT

**Background:** Availability of narcotics is an issue in developing countries, and low-dose ketamine offers an alternative to these drugs. **Objective:** The objective of this study is to evaluate the effect of a preemptive dose of low-dose ketamine on intra operative and the immediate postoperative analgesic requirements. **Design:** Randomized double-blind control trial. **Settings:** This study has been performed in the operating rooms and postanesthesia care unit at Aga Khan University Hospital, Karachi, Pakistan. **Materials and Methods:** Totally, 60 adult American Society of Anesthesiologists I and II patients undergoing day care surgery were randomly allocated into two groups, Group A (ketamine group) and Group B (saline group). **Intervention:** All patients underwent general anesthesia. Propofol 2 mg/kg was used as an induction agent; laryngeal mask airway (size 3 for females and 4 for males) was inserted. Following induction patients in Group A received ketamine 0.3 mg/kg and Group B saline bolus in a blinded manner. All patients were administered injection fentanyl 1 μg/kg as an analgesic and anesthesia was maintained with oxygen 40%, nitrous oxide 60% and isoflorane 1-2 minimum alveolar concentration. Patients breathed spontaneously on Lack circuit. Postoperatively rescue analgesia was provided with intravenous morphine 0.1 mg/kg when patient complained of pain. **Main Outcome Measures:** We observed analgesic effects of low-dose ketamine intra operatively and narcotic requirements in immediate postoperative period for day care surgeries. **Results:** There was no significant difference in demographic data in between groups. Saline group required more rescue analgesia (morphine) postoperatively ($P < 0.001$). No significant psychotomimetic symptoms were noted in either group. **Conclusion:** Low-dose ketamine 0.3 mg/kg provided adequate co-analgesia with fentanyl 1 μg/kg and was effective in a reduction of morphine requirement in the postoperative phase with minimal adverse effects.

**Key words:** *Day care surgery, low-dose ketamine, postoperative analgesia*

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## INTRODUCTION

The discovery of N-methyl-D-aspartate receptor and its links to processing and spinal neural plasticity has renewed an interest in ketamine as a potential anti-hyperalgesic agent.[1] High-dose ketamine is traditionally used as an intravenous (IV) anesthetic, but in low-dose ketamine acts as an analgesic.[2,3] Availability of narcotics is an issue in many developing countries and use of alternative analgesic drugs or those decreasing the narcotics requirements are needed.[4] Ketamine has been used preemptively in doses of 300-700 μg/kg as a peroperative analgesic without significant adverse effects.[5]

The objective of this study was to evaluate the effect of a preemptive 300 μg/kg single bolus dose of ketamine on intra operative and immediate postoperative analgesic requirements in day care surgery patients.

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## MATERIALS AND METHODS

The study was approved by the Ethical Review Committee, Aga Khan University and written informed consent was

obtained from all patients enrolled in the study. Totally, 60 American Society of Anesthesiologists (ASA) I, II and stable ASA III patients between 18 and 60 years of age and with no history of psychiatric illness, admitted for elective day care surgery were included. Patients with hypertension, ischemic heart disease, raised intracranial pressure, and positive history of hypersensitivity to any study drug were excluded. Patients were randomly divided into two groups by a sealed envelope technique. Group A (study group) patients were administered ketamine 0.3 mg/kg and Group B patients received saline IV (control). All patients received fentanyl 1 μg/kg for analgesia.

Preoperatively the patients were explained the pain assessment scale. Visual analogue scale (VAS) of 0-10 was used as a tool to monitor pain (0-1 no pain, 2-3 mild pain, 4-5 lot of pain, 6-8 almost unbearable pain, and 9-10 unbearable or horrible pain). Oral midazolam 0.1 mg/kg was given 30 min before surgery.

A person not involved in the study prepared the study drugs. The calculated dose and the saline bolus were both prepared in a 10 ml volume. Routine perioperative monitoring included continuous monitoring of oxygen saturation, electrocardiogram, noninvasive blood pressure, and end tidal carbon dioxide. Heart rate and blood pressure (systolic, diastolic and mean) was monitored every 5 min during the surgery (Datex Ohmeda AS, Helsinki, Finland). Following insertion of 20 gauges IV cannula; induction was performed with propofol 2 $mg^{-1}$ followed by, laryngeal mask airway (LMA) insertion (size 3 for females or 4 for males). Following induction all patients received the study drug or a placebo. Both groups received injection fentanyl 1 μg/kg as analgesic and anesthesia was maintained with oxygen 40%, nitrous oxide 60% and isoflorane 1-2 minimum alveolar concentration with patients breathing spontaneously on Lack circuit.

Hemodynamic parameters were maintained at 20% of baseline. For hypotension (systolic blood pressure <90 mm Hg), IV fluid bolus was given, if hypotension persisted IV injection ephedrine 5-10 mg titrating doses or phenylephrine 100 μg was administered. For hypertension (systolic blood pressure >140 mm Hg), IV hydralazine or metoprolol in titrating dose was administered. Fentanyl 0.5 μg/kg was used as rescue analgesia during the perioperative phase. The frequency of use of rescue analgesia was also noted.

Postoperative pain was evaluated 30 min after surgery by VAS.

Intravenous morphine 0.1 mg IV was used when patients complained of pain at VAS score on 4 and above. We also observed for any potential side effects of study drugs, e.g., (hallucination, nausea/vomiting and respiratory depression). For hallucination IV haloperidol 5 mg, for nausea, IV injection metoclopramide 10 mg and for respiratory depression (respiratory rate <8/min), a titrated dose of injection naloxone 0.1 mg was to be given IV. Side effects were observed till 4 h postoperatively, after which the study was terminated.

A sample size of 30 patients in each group was needed to detect a change of 20% in mean hemodynamic parameters (systolic blood pressure) between groups with 80% power and 5% type I error. All statistical analysis was performed using Statistical Packages for Social Science version 19 (SPSS Inc., Chicago, IL, USA). Results are presented as mean (standard deviation [SD]) and number (%). Normality assumption was checked by Kolmogorov-Smirnov test for qualitative data. Hemodynamic data were analyzed using independent sample *t*-test for intergroup comparison and paired *t*-test for intragroup comparison. Categorical data such as side effect and pain severity were analyzed with the Chi-square test. A $P < 0.05$ was considered as statistically significant.

## RESULTS

A total of 60 patients were included in the study [Figure 1]. There were no dropouts. Baseline characteristics and duration of surgery were comparable in both groups [Table 1].

Heart rate was significantly lower compared to baseline at 5 and 35 min following LMA insertion in ketamine fentanyl group, whereas it was significantly lower compared to baseline at 30 min in the saline fentanyl group. A significant difference in heart rate between the two groups was observed at 35 min with values in the saline group being lower than ketamine group [Figure 2].

Systolic blood pressure was significantly different from baseline at 1 and 5 min following LMA insertion in the ketamine fentanyl group whereas it was significantly different from baseline at all-time points post-LMA insertion in saline fentanyl group. A statistically significant

**Table 1: Comparison of demographic variables and duration of surgery between groups**

| Variables | Ketamine group (*n* = 29) | Saline group (*n* = 29) | *P* |
|---|---|---|---|
| Age (years) | 36.13 (10.59) | 36.07 (8.97) | 0.97 |
| Weight (kg) | 75.73 (14.01) | 75.75 (8.97) | 0.42 |
| Height (cm) | 166.36 (9.17) | 164.33 (7.05) | 0.34 |
| Duration of surgery (in min) | 38.5 (17.6) | 38.6 (21.0) | 0.97 |

Data are presented in mean (SD) and analyzed by independent sample *t*-test form normally distributed data and Mann-Whitney test for nonparametric data.
SD: Standard deviation

difference was observed between two groups at pre-LMA insertion, immediately post-LMA insertion and then 20, 30 and 35 min post-LMA insertion [Figure 3].

Diastolic blood pressure was significantly different from baseline at 5 min following LMA insertion in the ketamine fentanyl group, whereas it was significantly different from baseline at all-time points post-LMA insertion in saline fentanyl group. A significant difference was observed in diastolic blood pressure between two groups only at the baseline [Figure 4].

Mean blood pressure was significantly different from baseline at 1 and 5 min following LMA insertion in the ketamine fentanyl group whereas it was significantly lower from baseline at all points of time including pre-and post-LMA insertion in saline fentanyl group. A significant difference was observed in mean blood pressure between two groups at baseline and 10 min post-LMA insertion [Figure 5].

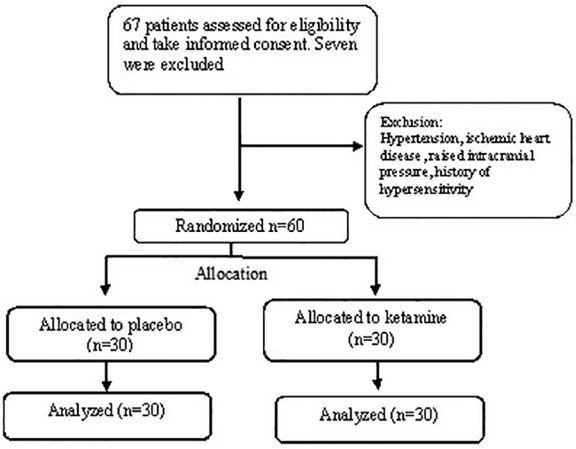


**Figure 1:** Flow diagram of patient distribution

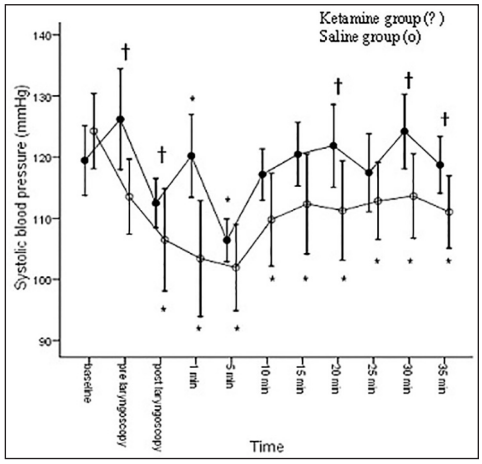


**Figure 3:** Comparison of mean systolic blood pressure between ketamine group (•) and saline group (o). The symbol *indicates a significant difference from baseline and †indicates intergroup significant difference

The VAS scores are shown in Figure 6. Pain assessment was performed every 10 min after arrival of patients in the recovery room until discharge. The total duration of patients stay in the recovery room varied between 30 and 45 min. The difference in the pain assessment was not significant between groups. Four patients (13.3%) in ketamine group needed morphine postoperatively while 16 patients (53.3%) in saline group received morphine and this difference was found to be statistically significant ($P = 0.001$).

The mean morphine consumption in ketamine fentanyl group was 5 mg (SD 0.82) and in saline fentanyl group it was 8 mg (SD 2.46). This difference was significant, $P = 0.02$.

Hallucination ($n = 2$), nystagmus ($n = 2$), and nausea ($n = 4$), were observed postoperatively in four patients in ketamine group while only nausea was observed in eight patients in

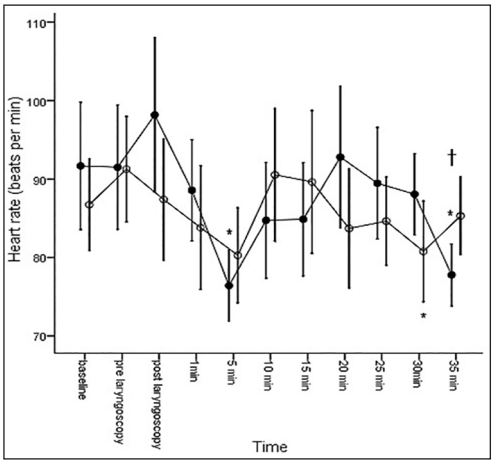


**Figure 2:** Comparison of mean heart rate between ketamine group (•) and saline group (o). The symbol *indicates a significant difference from baseline and †indicates intergroup significant difference

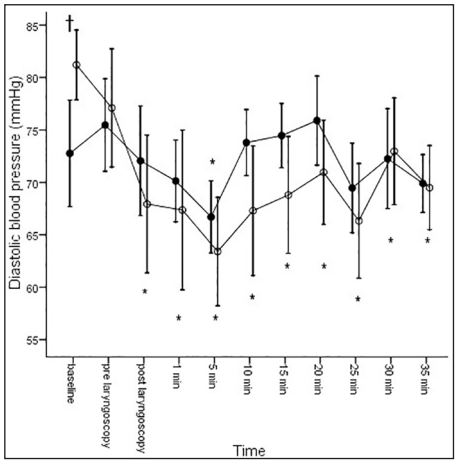


**Figure 4:** Comparison of mean diastolic blood pressure e between ketamine group (•) and saline group (o). The symbol *indicates a significant difference from baseline and †indicates intergroup significant difference

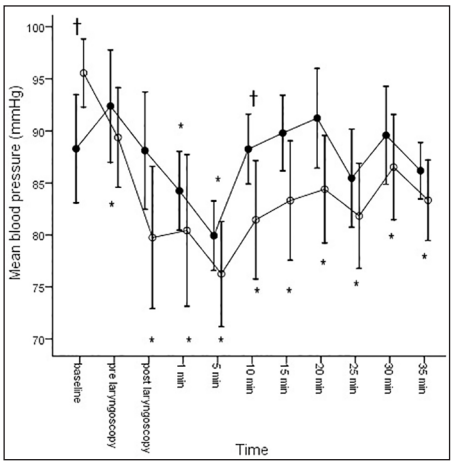


**Figure 5:** Comparison of mean blood pressure between ketamine group (•) and saline group (o). The symbol *indicates a significant difference from base line and †indicates intergroup significant difference

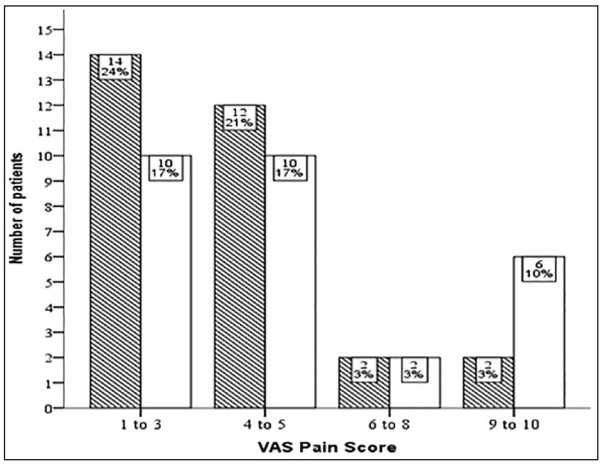


**Figure 6:** Comparison of severity of pain between ketamine group (▨) and saline group (□□)

the saline group. Sedation was observed postoperatively in two patients in both groups.

## DISCUSSION

Opioids are conventionally used as part of balanced anesthesia technique; however, availability of narcotics is an issue in less affluent countries due to various reasons, therefore there is a need to explore alternate methods or techniques that reduce consumption of narcotics. Ketamine is a potent analgesic which prevents "wind-up," when neurons in the spinal cord become sensitized to painful stimuli and can be used as an alternative analgesic of choice in those parts of the world that have limited availability of narcotics.[5] It has a good safety profile.

A major barrier in use of ketamine has been the fear of hemodynamic instability and side effects resulting from its induction dosing. Use of low-dose ketamine has not been associated with significant changes in hemodynamic status according to previous studies. One of these studies by Bilgin *et al*.[6] described the use of 0.5 mg/kg ketamine IV bolus, and ketamine infusion 600 μg/kg/h. This dosage was associated with good hemodynamic stability, less morphine consumption and significantly less pain scores on VAS postoperatively. Their findings were similar to our results.

In another study in patients undergoing laparoscopic gynecological procedures ketamine 0.15 mg/kg showed no significant difference among groups with respect to hemodynamic variables or side effects. This may be explained by the minimally invasive procedure with a subsequent minimal inflammatory process in the postoperative period, and, therefore, limited subsequent central sensitization.[7] In our study, ketamine 0.3 mg/kg did not affect hemodynamic or respiratory variables, and there was no difference in the incidence of postoperative nausea and vomiting among groups. Hemodynamic stability of low-dose ketamine has also been observed in pediatric patients undergoing magnetic resonance imaging without affecting the duration and quality of recovery.[8]

Low-dose ketamine 50-100 μg/kg IV has been shown to enhance morphine induced analgesia without any significant effect on phase I recovery.[9] Combining these low-doses with other agents in a balanced anesthetic technique like fentanyl 1 μg/kg also decreased the associated side effects. This was observed in our study when we combined 300 μg/kg bolus with fentanyl 1 μg/kg. This technique is of particular value in day care surgery in developing countries because of its narcotic sparing effects. Drug availability specially narcotics analgesics is an issue in the developing world. The narcotic sparing effect of low-dose ketamine has been studied by other authors however these results may have limitations in their applicability in different racial groups. Pharmacogenomics is an emerging field, and narcotic requirements have been shown to vary in different races.[10] Hence, there is a need to study these combinations in different populations. This was one of our rationale for doing this study.

Most studies with low-dose ketamine have been conducted in postoperative settings. Weinbroum[11] evaluated the effects of postoperative co administration of 0.25 mg/kg of ketamine and morphine on pain intensity in surgical patients who complained of pain. This dose provided satisfactory analgesia in 68% of patients compared with only 3.5% of patients who received 0.03 mg/kg of morphine alone. In our study, 13.3% of patients received morphine in ketamine fentanyl group, and 53.3% required it in saline fentanyl group.

One of the issues with the use of ketamine anesthesia has been its side effects. At anesthetic doses of ketamine

(i.e., 1-3 mg/kg), more than one-third of patients have unpleasant dreams or acute psychosis-like symptoms that may or may not be associated with hallucinations on emergency. Use of benzodiazepine premedication has been reported to reduce these psychotomimetic manifestations effectively during and after emergence from ketamine anesthesia. <15% of our patients had hallucinations; this was significantly less than seen with higher doses.[12] Schmid *et al*.[13] reported that the incidence of psychomimetic effects and cognitive impairment was negligible at dose <2.5 μg/kg/min IV but increased with higher doses, and reported significantly higher sedation scores. Larger doses of ketamine (500 μg/kg) are associated with dysphoria.[14] Low-doses 100-500 μg/kg may also produce drowsiness, and impair some domains of cognitive function, such as attention, free recall, recognition memory, and thought processes.[15,16] This dose may also alter mood states and produce dose-related impairment of sensory perception or the process of sensory integration.[17] Javery *et al*.[18] reported in elective micro discectomy were administered either 1 mg/ml of morphine or 1 mg/m1 of both morphine and ketamine via IV patient controlled analgesia for postsurgical pain control and found one patient in ketamine group experienced dysphoria, compared with three in the control group. In our study, only two patients had nystagmus and hallucination (6.6%) in ketamine group, which were relieved spontaneously after few minutes without any treatment.

Sedation is also seen with ketamine and some studies have reported increased sedation in the ketamine-treated group in a dose of 0.3 mg/kg and after 24 h of surgery.[19,20] Guignard *et al*.[19] reported that patients administered ketamine in dose of 0.15 mg/kg followed by 2 μg/kg/min, had higher sedation scores for the first 15 min after extubation. Mathisen *et al*.[20] found that the placebo treated group opened their eyes significantly faster and were extubated earlier than the R (-) ketamine 1 mg/kg treated groups. Subramaniam *et al*.[21] reported high sedation scores in six patients in the ketamine group (ketamine 1 mg/kg), compared with none in the control group, for the first 2 h after surgery, but no difference afterward. In our study, two patients in each group had increased sedation.

Elia and Tramèr[22] in a systematic review found that ketamine in a dose of 0.4 mg/kg (range: 0.1-1.6) did not reduce morphine-related adverse effects. They also found the highest risk of hallucinations in awake or sedated patients receiving ketamine without benzodiazepine.

Our study has some limitations, foremost is that we did not get the direct feedback from the patients postoperatively. We also did not note discharge time from the hospital.

## CONCLUSION

Low-dose ketamine (0.3 mg/kg) was found to be effective in reducing morphine requirement in immediate postoperative period with minimal of adverse effects. We recommend the use of this combination for day care anesthesia in developing countries where availability of narcotics is limited.

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