Research Article

Effect of Low-Dose Ketamine Infusion on Quality and Duration of Post-Operative Pain in Patients undergoing Laparoscopic Cholecystectomy under General Anesthesia

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Abstract: Background: Because of its analgesic properties and cardiovascular stability, ketamine has been used extensively in anesthesia practice. In a range of surgical procedures, low-dose ketamine infusions (<0.3 mg/kg/hr) have demonstrated effectiveness in lowering pain scores.

Objective: To determine the effect of low-dose ketamine infusion on quality and duration of post-operative pain in patients undergoing laparoscopic in a tertiary care hospital.

Materials and Methods: This Double-blinded randomized control trial was performed in Department of Anesthesia at Fazaia Ruth Pfau Medical College, Pakistan Air Force Hospital, Base Faisal, Karachi from 1st October 2024 to 30th April 2025. Group A received ketamine at 0.2mg/kg bolus intravenously followed by ketamine infusion at rate of 0.2mg/kg/hr. Whereas control group was served as Group B which received normal saline at an equivalent infusion rate. Pain was assessed using Numeric Rating Scale.

Result: A total of 58 patients per group were studied. Mean score was significantly lower in ketamine group at 0 hour (1.6±0.9 versus 2.7±1.2, p<0.001) and at 2 hours than control group (2.3±0.9 versus 4.8±1.2, p<0.001). Mean pain score at 4 hours (p=0.168), 6 hours (p=0.362), 12 hours (p=0.151) and 24 hours (p=0.272) was not significantly different. Time to first rescue analgesia was significantly longer in group A than group B (4.8 ± 1.7 versus 1.5 ± 0.8, p<0.001) whereas analgesic consumption was higher in group B than group A (2.5 ± 1.1 versus 1.6 ± 0.8, p<0.001).

Conclusion: The administration of low-dose ketamine infusion intraoperatively was effective in reducing post-operative pain during the early post-operative period which is also evident by lower number of analgesics requirement and a longer time to first rescue analgesia in ketamine than control group.

Keywords: Analgesia, Cholelithiasis, Cholecystectomy, Ketamine, Laparoscopic surgery, Hypertension.

INTRODUCTION

Following surgery, acute pain is a typical issue with a variety of implications. Operating team including anesthesia specialists and surgeons and patients as well, all desire effective pain management with the fewest possible adverse effects. Most patients still stay overnight after a laparoscopic cholecystectomy (LC) due to post-operative pain, which continues to be the principal obstacle to early patient discharge. On the first postoperative day following laparoscopic procedures, patients may have mild to moderate postoperative pain, with increased pain intensity in the shoulder area (from the subdiaphragmatic region), particularly intra-abdominal and local discomfort at the incision site [1-3].

Due to postoperative pain, 17-41% of patients who had LC must stay in the hospital for at least one day, and their recuperation takes a lengthy time. Effective analgesic treatment should be multimodal because acute pain following LC is complex and differs from pain following other laparoscopic procedures. Numerous techniques, such as patient-controlled analgesia and nonsteroid anti-inflammatory drugs, have been used to lessen postoperative discomfort after LC [4-6].

Because of its analgesic properties, ketamine has been used extensively in anesthesia practice. It non-competitively blocks N-methyl-D-aspartate (NMDA) receptors. As an addition to multimodal perioperative pain management, ketamine has grown in favor in recent years. Ketamine, either by itself or in conjunction with other anesthetics, is said to preserve analgesia and decrease postoperative opioid usage [7-11].

At low dosages (<0.3 mg/kg/hr) and large doses (>1 mg/kg), ketamine is utilized as an analgesic and an anesthetic (6). Ketamine at high dosages causes dissociative anesthesia with little impact on breathing or airway reflexes. In a range of surgical procedures, low-dose ketamine infusions (<0.3 mg/kg/hr) have demonstrated effectiveness in lowering pain scores and minimizing the need for postoperative opioids. Regarding the reduc-

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tion of pain and analgesic demand, ketamine has demonstrated conflicting effects. Although this medication is a powerful analgesic, its usage is restricted due to it leads to agitation and hallucinations during awakening. Nevertheless, it has a potent analgesic effect when administered at a sub-anesthetic dose, and ketamine's psychotomimetic side effects are rare at these dosages [12-15].

We intended to examine the role of low-dose for post-operative pain control in patients undergoing LC, despite the fact that numerous studies have been conducted on the subject and that the results have been inconsistent. Additionally, there is a dearth of literature from Pakistan. The study objective was to determine the effect of low-dose ketamine infusion on quality and duration of post-operative pain in patients undergoing laparoscopic in a tertiary care hospital.

MATERIALS AND METHODS

This double-blinded randomized control trial was performed in Department of Anesthesia at Fazaia Ruth Pfau Hospital, Karachi with approval of institutional Review Board (IRB#FRP-MC-IRB-2024-38). The trial was registered with trial number NCT06964555. The study was performed during 1st October 2024 to 30th April 2025. Patients were enlisted with their written informed consent. Both male and female patients were included in this study. Inclusion criteria includes age of minimum 18 years, elective LC and ASA grade I-II. Obese patients (BMI≥30 kg/m²), patients with history of alcohol abuse, drug abusers, uncontrolled hypertension and diabetes, patients with chronic pain, those allergic to study drugs, patients with neurological disorders, longer surgical duration (>80 minutes) and those unable to understand pain scoring system and procedures converted to open Cholecystectomy were all excluded.

Previous similar study reported that following surgery in recovery room, 16% patients received low-dose ketamine required analgesics whereas 36.4% patients in control group received routine pain control [16]. Using two proportion calculation approach, at power of 80% and 95% confidence interval, a sample of 58 per group was calculated. WHO sample size calculator was used to perform sample size calculation. Consecutive sampling technique was used to enroll participants into the study whereas group allocation was done in a simple random method using sequentially numbered opaque sealed envelope [17]. Patients receiving ketamine were labelled as group A whereas control group was labelled as group B. To ensure blinding, both ketamine and lignocaine infusions were prepared in identical syringes by an independent anesthesiologist not involved in patient care or outcome assessment. Neither the patients nor the investigators collecting data were aware of the group allocation.

Patients planned to undergo LC were admitted a day before surgery for pre-anesthesia assessment as per hospital protocol. Patients' consent was obtained during pre-anesthesia assessment. After completion of pre-anestheia assessment checklist, patients were shifted to in-patient holding area first. Principal investigator in the patient holding area explain the numeric rating scale (NRS) pain score to the study participants. Patients were randomly assigned to study groups using sequentially numbered opaque sealed envelope (SNOSE) protocol [17]. Both patients and study investigators were blinded to study groups. Only anesthetist who prepared the medication and was not part of this study, had correct knowledge of group identification.

After shifting patient to operating room, monitors were attached and their vitals including blood pressure, heart rate and mean arterial blood pressure was continuously monitored. For induction of anesthesia, premedication was done with 0.1 mg/kg nalbuphine, 2 mg/kg propofol, 0.5 mg/kg Atracurium and 0.15 mg/kg ondansetron. Just before the skin incision, Group A received ketamine at 0.2mg/kg bolus intravenously followed by ketamine infusion at rate of 0.2mg/kg/hr throughout the surgery. Whereas control group received normal saline intravenously at an equivalent infusion rate till skin closure to maintain double blinding. Anesthesia was maintained on oxygen 3 liters, isoflurane 1%-1.5%, 0.1 mg/kg atracurium and 10mg/kg paracetamol intravenously.

After procedure completion, patients were shifted to post-operative recovery room where they stayed till next 12 hours and then were shifted to ward and were discharged after 24 hours if found stable as per hospital protocol. In post-operative recovery room patients were under close monitoring. Pain status was continuously monitored post-operatively at 0 hour, 2 hours, 4 hours, 6 hours, 12 hours and then finally at 24 hours. Analgesia was administered to patients on their demand or if their pain score was 5 or above. The assigned residents collected the data from time to time and recorded in study proforma.

Pain was assessed using NRS which is a ten point scoring scale ranging from 0-10 for ranking pain where 0 means no and 10 means worst pain [18]. Time to rescue analgesia was defined as time point at which patient was given rescue analgesia (IV toradol 30 mg) for pain of score 5 or above. The time between the incision and the wound's closure was used to define the length of the surgery.

STATISTICAL ANALYSIS

The collected data was put up in statistical package SPSS version 26 to perform data analysis. Frequencies and percentages were computed for categorical variables. Numerical variables were expressed as mean ± standard deviation or median with inter-quartile range (IQR) based on assumption of normality that was tested using Shapiro-Wilk test. Categorical variables were compared among study variables using Chi-square or Fisher-exact test. Numerical variables were compared using independent t-test or Mann-Whitney U test as appropriate. A p-value less than or equal to 0.05 was taken as statistically significant.

RESULT

Total 125 patients were assessed for eligibility of the study, out

of them 99 were excluded. Hence a total of 116 patients were enrolled with 58 patients in each group. Consort diagram depicts the flow of patient enrolment (Fig. **1**).

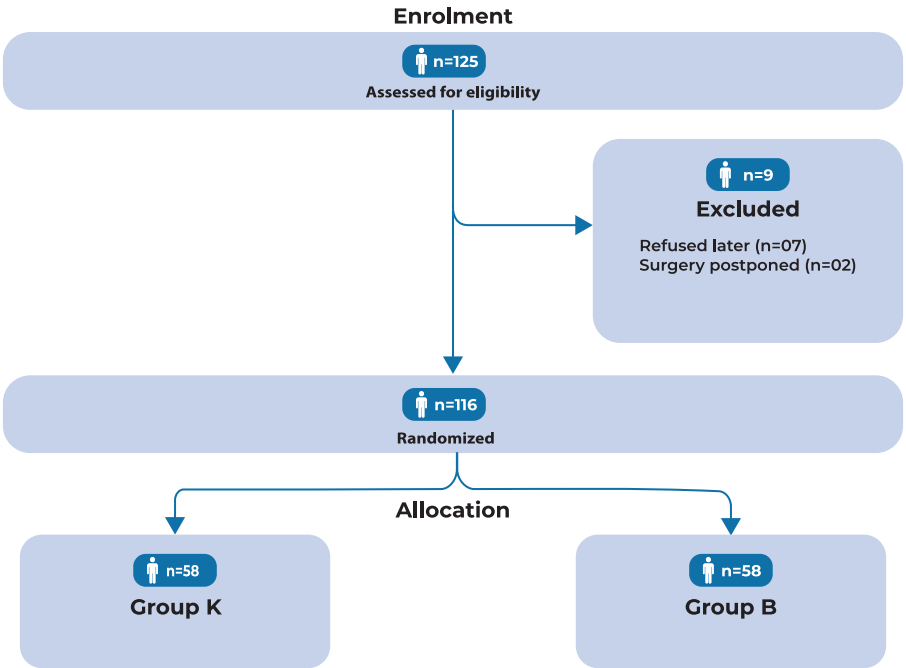

Fig. (1). Consort Diagram Depicting the Patient Enrolment Details.

Table **1** displays patients' sociodemographic and baseline features among the two groups. Two groups did not differ on the basis of age (p=0.317), gender (1.000), hypertension (p=0.166), diabetes (p=0.186), ASA grade (p=0.537), surgery duration (p=0.334). At baseline, patients' vitals including systolic blood pressure (p=0.608), diastolic blood pressure (p=0.091), heart rate (p=0.731), and mean arterial pressure (p=0.679) were not significantly different among the two groups. At the end of surgery, two groups did not differ on the basis of systolic (p=0.856) and diastolic blood pressure (p=0.914), heart rate (p=0.243) and mean arterial pressure (p=0.982).

Table 1. Patients' Sociodemographic and Baseline Features among the Two Groups.

Variables	Group A	Group B	p-value
Age (in years)[a]	38.0 ± 3.6	38.8 ± 5.3	0.317
Gender[b]			
Male	24(41.4)	24(41.4)	1.000
Female	34(58.6)	34(58.6)	
Comorbidity[b]			
Controlled Hypertension	5(8.6)	10(17.2)	0.166
Controlled Diabetes	3(5.2)	7(12.1)	0.186
ASA grade[b]			
ASA-I	43(74.1)	40(69)	0.537
ASA-II	15(25.9)	18(31)	
Surgery duration (in minutes)[a]	67.1 ± 18.9	70.4 ± 16.9	0.334
Baseline Features			
Systolic blood pressure(mmHg)[c]	133 (130-134)	131 (127-137.3)	0.608
Diastolic blood pressure(mmHg)[c]	85.5 (79.7-90)	81 (78.7-87.3)	0.091
Heart rate (BPM)[c]	78 (74-80)	79 (70-81)	0.731
Mean arterial pressure (mmHg)[c]	98 (95-100.3)	98 (95-100)	0.679

Continued

Continued

Feature at End of Surgery			
Systolic blood pressure (mmHg)[c]	133 (131-134)	133 (131-135)	0.856
Diastolic blood pressure (mmHg)[c]	84 (76.8-90)	81 (80-84.3)	0.914
Heart rate (BPM)[c]	90 (81-93)	88 (79-95.5)	0.243
Mean arterial pressure (mmHg)[c]	102 (96-106)	101 (98-106.5)	0.982

a: Normally distributed numerical data is expressed as mean± SD, b: Categorical data is expressed as n(%), c: Non-normal numerical data is presented as median (Q3 – Q1).

Fig. (**2**) compared patients' pain status from 0-24 hours post-operatively. Mean score was significantly lower in ketamine group at 0 hour (1.6±0.9 versus 2.7±1.2, p<0.001) and at 2nd hour than control group (2.3±0.9 versus 4.8±1.2, p<0.001). Mean pain score at 4 hours (p=0.168), 6 hours (p=0.362), 12 hours (p=0.151) and 24 hours (p=0.272) was not significantly different.

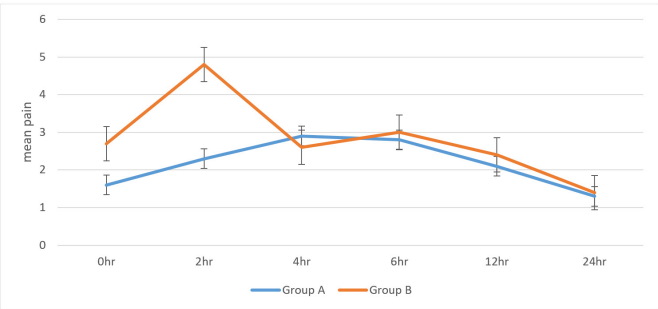

Fig. (2). Comparison of Mean Pain Score among Two Group at Different Time Interval Post-operatively.

Table **2** compares analgesic status among two study groups. Time to first recue analgesia was significantly higher in group A than group B (p<0.001) whereas analgesic consumption was higher in group B than group A (p<0.001). Hospital stay was not significantly different among two groups (p=0.248).

Table 2. Analgesic Status and Hospital Stay among Two Study Groups.

Variables	Group A	Group B	p-value
Time for first rescue analgesia (in hours)[a]	4.8 ± 1.7	1.5 ± 0.8	*<0.001
Total number of analgesics[a]	1.6 ± 0.8	2.5 ± 1.1	*<0.001
Hospital stay (in days)[a]	1.8 ± 0.5	1.9 ± 0.2	0.248

a: Normally distributed numerical data is expressed as mean± SD, *Significant at p<0.05.

DISCUSSION

Currently, no concordance exists regarding the timings, route and optimal dose of ketamine for perioperative management, which resulted in considerable variability in techniques for ketamine administration in available literature [8, 10, 19-21]. Though literature provide evidence of ketamine efficacy in pain control during early post-operative period, concern still prevail regarding dose-related side effects such as hallucinations and long-term psychological impacts [22, 23]. These adverse reactions are usually associated with higher ketamine doses or prolonged exposure [24].

For alleviation of these associated known risks, current study administered a low-dose intraoperative infusion, throughout the procedure. This approach of low-dose and intraoperative infusion was adopted to explore ketamine efficacy balancing the analgesics impacts and potential adverse effects simultaneously.

In present study, we administered ketamine at a dose of 0.2 mg/kg. Intraoperative infusion of ketamine is practically beneficial because its administration is comparatively simple and involves minimal postoperative nursing care in ward stay. The approach simultaneously assures continuous analgesia in between the procedure while diminishing the need of additional interventional postoperatively. Considering the obvious variations in dosing regimens in existing literature, the choice of low-dose ketamine at 0.2 mg/kg/hr was chosen based on the recommendations from Gorlin *et al.* [12] suggesting an infusion of 0.1-0.2 mg/kg/hr with an initial bolus of dose ranging from 0.1-0.3 mg/kg.

The present study found that ketamine group reported considerably lowered pain levels in immediate post-operative period (i.e. from 0 to 2 hours post-operatively). This finding suggests that at a low-dose, ketamine brought an effective analgesic effect in early post-operative recovery period. However, it is noticed that as post-operative period progressed beyond 2 hours, pain levels in both groups become same. This infers that low dose ketamine infusion may be efficient enough for pain relief in early post-operative period. The infusion throughout the surgical procedure may be beneficial for acute pain management without sustaining its impact for long-term pain control over placebo during post-operative recovery period. This needs an exploration and validation through a larger clinical trial for verification of low dose ketamine performance for long-term pain relief as well.

There are studies investigating preemptive low-dose ketamine impact in pain control and analgesia requirement [8, 10, 16]. Jain S. and co-workers [8] studied preemptive low-dose ketamine in LC patients for pain control also reported that pain was significantly lower in early post-operative period and it did not find to be significantly different among ketamine and control group. In contrast to our study, Atif *et al.* [19] found longer pain controlling impact of low-dose ketamine till 12 hour as compared to control group. A similar dose of ketamine was administered in his study that we used. However, a bolus of ketamine was given 10 minutes prior to the surgery and then ketamine infusion was also continuously given at a rate of 0.15mg/kg/hr till the skin closure but before extubation [19]. Our findings are conflicting with another studying preemptive low-dose of ketamine for post-operative pain control after LC [10]. The study demonstrated that low-dose ketamine is not only effective for

pain controlling in the immediate post-operative period but it also maintained analgesia up to 24 hours. This is noticeable that their protocol differed in terms of dosing. Although they labeled their study as "low-dose ketamine" but they utilized dose of 0.5 mg/kg which is higher than our study. Additionally, in that study patients received ketamine intravenously 10 minutes before the incision, whereas in our study, ketamine infusion was continuously administered throughout the procedure. These techniques differences might be accountable for the sustained pain relief, emphasizing the potential impacts of timing and dosing regimens of ketamine.

In the present study, low-dose ketamine group found to have significantly less number of analgesic requirement during 24 hours and a longer time to first rescue analgesia than a control group, suggesting that quality of pain relief in ketamine group was superior than control group in early post-operative phase. Since ketamine is an NDMA receptor antagonist [25], so it is more likely to contribute for reducing central sensitization and avoiding hyperalgesia, resulting in lower analgesic requirement and longer time to first analgesia. These findings of our study are consistent with earlier studies [8, 10, 19].

In the present study, overall hospital stay did not differ among the two groups, which may be attributed to multiple factors. Although the ketamine provided effective analgesia in early post-operative phase but with the time, the pain levels in both groups converged diminishing ketamine impact for longer-time. Moreover, the procedure is minimally invasive and all patients received standard care as per hospital protocol due to which we believe hospital stay was similar in both groups, which is again a consistent finding with available literature.

LIMITATIONS

In our view the present study has multiple limitations. First, it only studied the pain levels and analgesia requirement in first 24 hours. Second, the sample size could be insufficient for comparing secondary outcome such as analgesia requirement and hospital stay. Third, the study did not evaluate potential psychiatric impacts such as hallucinations or dysphoria which is concern for patients' safety. These shortcomings should be addressed in a future studies to investigate low-dose ketamine impact comprehensively.

CONCLUSION

The administration of low-dose ketamine infusion intraoperatively was effective in reducing post-operative pain during the early post-operative period which is also evident by lower number of analgesics requirement and a longer time to first rescue analgesia in ketamine than control group.

ABBREVIATIONS

ASA: The American Society of Anesthesiologists.

IQR: Inter-Quartile Range.

LC: Laparoscopic Cholecystectomy.

NMDA: N-methyl-D-Aspartate.

NRS: Numeric Rating Scale.

SNOSE: Sequentially Numbered Opaque Sealed Envelope.

WHO: World Health Organization.

AUTHORS' CONTRIBUTION

Syeda Hajrah Rehman: Conceptualization, Study Design, Writing draft, Final Approval, Final Proof to be published.

Zahid Akhtar Rao: Study Design, Critical Review and Revision the Manuscript.

Syed Sammiuddin and **Muhsan Sultan Abbasi**: Writing draft.

Muhammad Khalid: Methodology, Data analysis and Interpretation.

ACKNOWLEDGEMENTS

Declared none.

DECLARATIONS

Data Availability

Data will be available from the corresponding author upon a reasonable request

Ethical Approval

The study was commenced with the approval of Institutional Review Board of Fazaia Ruth Pfau Medical College (IRB#FRP-MC-IRB-2024-38).

Clinical Trial Registration

The trial was registered with trial number NCT06964555.

Consent to Participate

All the study participants were enlisted with their written informed consent.

Consent for Publication

All authors give consent for the publication of this work.

Conflict of Interest

Declared none.

Competing Interest/Funding

Declared none.

Use of AI-Assisted Technologies

The authors declare that no generative artificial intelligence (AI) or AI-assisted technologies were utilized in the writing of this manuscript, in the creation of images/graphics/tables/captions, or in any other aspect of its preparation.

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