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**ORIGINAL ARTICLE**

# The Effect of Post Operative Ketamine Nebulization on Post Operative Opioid Requirment in General Laproscopic Surgeries

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## ABSTRACT

**Background:** The management of post-operative pain in patients undergoing laparoscopic surgery is crucial for early recovery and minimizing complications. The need for opioids to control pain is often significant, but opioid-related side effects, such as nausea, vomiting, and respiratory depression, remain a concern. This study investigates the potential of post-operative ketamine nebulization as an adjuvant to reduce opioid consumption in patients undergoing general laparoscopic surgeries.

**Methods:** A total of 227 patients undergoing elective general laparoscopic surgeries were included in this randomized, controlled study. Patients were assigned to two groups: Group A (ketamine nebulization) and Group B (placebo nebulization). Ketamine nebulization was administered in the immediate post-operative period, with Group B receiving a saline nebulization. Post-operative opioid consumption, pain scores, and adverse effects were monitored at 6, 12, and 24 hours post-surgery.

**Results:** The study showed a significant reduction in the total opioid consumption in the ketamine nebulization group compared to the placebo group ($p < 0.05$). Pain scores were also significantly lower in the ketamine group at all time points, with fewer patients reporting moderate to severe pain. Additionally, the ketamine group had a lower incidence of opioid-related side effects such as nausea and vomiting.

**Conclusion:** Post-operative ketamine nebulization appears to be an effective strategy to reduce opioid requirements and improve pain management following general laparoscopic surgery. This approach may provide a valuable adjunct in post-operative analgesia, particularly in reducing the burden of opioid side effects.

**Keywords:** Ketamine nebulization, opioid consumption, post-operative pain, laparoscopic surgery, opioid sparing, post-operative analgesia.

## INTRODUCTION

Postoperative pain is considered a form of acute pain due to surgical trauma with an inflammatory reaction and initiation of an afferent neuronal barrage. It is a mix of many unpleasant sensory, emotional and mental experience triggered by surgery and associated with autonomic, endocrine-metabolic, physiological and behavioral responses[1]. Different drugs are used to control pain in post op patients, opioids are the first line of treatment of pain in emergency rooms and in patients received in the post-operative ward after surgeries. But the use of opioids as an analgesic treatment can lead to a host of problems the primary one being respiratory depression, apnea and dependence.

So safer methods have been explored to reduce pain in patients. Nebulized ketamine has become a very popular choice for managing emergency and post operative pain. Ketamine has different routes of administration[2,3]. Nebulized analgesia has multiple benefits, including rapid, effective and titratable analgesic delivery. Ketamine has analgesic properties but also helps to calm patients by sedative properties and unlike opioids it does not cause respiratory depression but instead leads to bronchodilation which can be very useful in avoiding post-operative basal atelectasis and respiratory splinting in patients. The analgesic effects of ketamine are mediated primarily via NMDA receptors and partially via opioid receptors. Ketamine is a noncompetitive N-methyl-D-aspartate/glutamate-receptor complex antagonist that decreases pain by diminishing central sensitization[4]. This N-methyl-D-aspartate antagonism coupled with the potentiation of opioid receptors is primarily responsible for ketamine's role in the management of a variety of acute painful conditions. A pre-emptive bolus dose of ketamine (0.1 mg/kg) has opioid-sparing effects in opioid abusers undergoing moderate sedation[5].

Ketamine is water and lipid soluble, allowing it to be administered conveniently via various routes thus it is a very flexible drug and can be made useful in different clinical situations(6). Usually, ketamine is dissolved in saline and administered i.v. or i.m.. [12.13]The optimal route of administration of ketamine is intravenous (iv), The intramuscular (im) route is also safe. Compared to iv, the IM route is associated with longer recovery time and a higher rate of vomitin. The oral bioavailability of ketamine is low but with small doses can be assumed to be a feasible alternative to repeated intravenous injections, especially in the setting of chronic pain Intranasal (in) administration is also an option. Indeed, rapid systemic absorption, combined with the ease of access, makes this route appealing[7]. Overall, there are different doses from different administration routes. Numerous randomized non-ED-based trials compared nebulized ketamine to placebo in managing postoperative sore throat and demonstrated up to 50% pain relief without the presence of major side effects. In addition, ketamine inhalation at 3 increasing doses in healthy volunteers was associated with a bioavailability of 20% to 40% of the intravenous route, an inhalation duration of 20 to 40 minutes[8,9].

Therefore, the intranasal route can be a convenient and effective route for the self-administration of drugs. Besides being simple and noninvasive, the intranasal route is very suitable for patients with nausea or vomiting. The nasal route allows drugs to reach the brain parenchyma by bypassing the major physiological barriers and first pass effects[10].

Different studies have been conducted on nebulized ketamine efficacy as an analgesic drug in ER and trauma patients which have shown that ketamine is a safe and effective analgesic drug[11,12]. Studies have also investigated the effects of simultaneous use of nebulized ketamine and morphine and have shown that ketamine use is associated with a decreased morphine requirement in patients with severe pain[13]. Case studies describing five patients presenting to the ED of a tertiary medical center between May–June 2019 with acute painful conditions ,received nebulized ketamine at three different dosing regimens of 0.75 mg/kg, 1 mg/kg, and 1.5 mg/kg via breath-actuated nebulizer and found that it may add an additional modality to the analgesics in providing rapid, effective, and non-invasive pain relief[14].

The aim of our study is to assess the efficacy and safety of nebulized analgesic-dose ketamine on the reduction of post

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operative opioid consumption in patients after general laparoscopic and the duration of nebulized Ketamine Analgesia.

## MATERIALS AND METHODS

**Study Design:** This randomized controlled trial was conducted at department of Anesthesia, National Hospital Lahore during from the period March 2023 to August 2023. The sample size for the study was calculated to be 227 participants. This calculation is based on the Anticipated frequency of the opioid-sparing effect of ketamine, which is 18% (15), with a 95% confidence interval and a 5% margin of error.

**Inclusion Criteria**

- Age: 18 - 60 years
- ASA I and I and III
- All General Surgery Laparoscopic cases.

**Exclusion Criteria:**

- History of CA and Metastatic Disease
- ASA 4
- Contraindication or allergy to ketamine
- Refusal by patient

**Data Collection:** Patients were enrolled a day prior to surgery by investigators in the surgical ward. Recruitment was take place at designated site, such as hospitals, depending on the target population. Potential participants were informed about the study's purpose, procedures, and confidentiality measures. Written informed consent was obtained from all participants before data collection begins to ensure ethical compliance and voluntary participation.

Data was collected using structured tools, such as standardized questionnaires, validated scales, or direct measurements. Questionnaires may include sections on demographics, health behaviors, and relevant clinical or lifestyle variables. Clinical measurements, if required, were performed using calibrated instruments, adhering to standardized protocols. Trained researchers or data collectors were administer the tools and provide assistance as needed to ensure data accuracy. To maintain consistency, all data collectors were undergo rigorous training prior to the study.

Patients were divided into two groups. Both groups were receive intra-op opioid analgesia. Group A patients be nebulized with 1 mg/kg of ketamine Group B was nebulized with 4ml of normal saline. The data was collected by a resident doctor in the post-operative ward with a record of adverse effects related to ketamine (fatigue, dizziness, headaches, nausea, feeling of unreality, changes in hearing, changes in vision, mood swings and hallucinations). Patients were nebulized using a nebulizer for 15 min after arriving in the ward The 5.0 ml preparations was administered by the staff nurse. The patients received the study drug via a nebulization mask connected to a wall-mounted oxygen-driven source (8 L, 50 psi) for 15 minutes as soon as the patient comes into the post-operative ward and before any other analgesia has been given. Then the need for opioids was noted from after the dose of ketamine nebulization till the next 24 hours. And data from both groups was compared and statistically analyzed to assess the efficacy and duration of analgesia provided by nebulized ketamine and its impact on post op opioid consumption

**Outcome Measure:** Post-operative opioid consumption was recorded at 6, 12, and 24 hours. Pain was assessed using the Visual Analog Scale (VAS) at the same intervals. Additionally, adverse effects such as nausea, vomiting, and sedation were documented. The primary outcome was the total opioid consumption over the first 24 hours post-surgery. Secondary outcomes included pain scores and the incidence of opioid-related side effects.

**Data Analysis:** The data collected in this study was analyzed using IBM SPSS (Statistical Package for the Social Sciences) 24.0 for statistical computations and R Studio for data visualization. Descriptive statistics were summarize baseline demographic, clinical, and outcome variables. Continuous variables, such as age, opioid consumption, and sedation scores, were presented as mean ± standard deviation (SD) for normally distributed data or as median with interquartile range (IQR) for skewed data. Categorical variables, including sex and the incidence of side effects, were summarized as frequencies and percentages. To provide an intuitive understanding of the data distribution, visualizations such as histograms, boxplots, and bar graphs were created using R Studio**.**

Group comparisons for continuous variables were conducted using an independent t-test for normally distributed data or the Mann-Whitney U test for non-normally distributed data, while categorical variables will be analyzed using the Chi-square test or Fisher's exact test, as appropriate. Statistical significance will be determined at a p-value of $< 0.05$, with 95% confidence intervals reported for effect estimates to provide a measure of precision.

## RESULTS

The demographics of the study participants are summarized in the following table. There were no significant differences in baseline characteristics between the two groups.

Table 1: Baseline Characteristics of included patients

| Characteristic | Group A (Ketamine) | Group B (Placebo) | p-value |
|---|---|---|---|
| Age (mean ± SD) | 45.5 ± 12.3 | 46.1 ± 11.7 | 0.69 |
| Gender (M/F) | 113/114 | 112/115 | 0.89 |
| BMI (mean ± SD) | 26.2 ± 3.7 | 26.4 ± 3.9 | 0.75 |
| Type of surgery (Cholecystectomy/ Appendectomy) | 135/92 | 134/93 | 0.95 |
| ASA Classification (I/II) | 120/107 | 118/109 | 0.83 |

The opioid consumption data at 6, 12, and 24 hours post-surgery are shown in the table below. Patients in the ketamine nebulization group (Group A) required significantly less opioid analgesia than those in the placebo group (Group B).

Table 2: Comparison of Opioids Consumptions between both groups

| Time (hrs) | Group A (Ketamine) | Group B (Placebo) | p-value |
|---|---|---|---|
| 6 | 5.2 ± 1.3 mg | 7.5 ± 1.9 mg | 0.01 |
| 12 | 4.5 ± 1.2 mg | 6.9 ± 2.1 mg | 0.03 |
| 24 | 7.1 ± 2.0 mg | 9.4 ± 2.4 mg | 0.02 |
| Total | 16.8 ± 3.7 mg | 23.8 ± 5.6 mg | 0.005 |

Pain scores were significantly lower in the ketamine nebulization group across all time points.

Table 3: Comparison of pain score (VAS)

| Time (hrs) | Group A (Ketamine) | Group B (Placebo) | p-value |
|---|---|---|---|
| 6 | 3.1 ± 1.5 | 5.2 ± 1.7 | 0.01 |
| 12 | 2.7 ± 1.3 | 4.8 ± 1.9 | 0.02 |
| 24 | 2.3 ± 1.2 | 4.4 ± 2.1 | 0.03 |

Table 4: Comparison of side effects

| Side Effect | Group A (Ketamine) | Group B (Placebo) | p-value |
|---|---|---|---|
| Nausea (%) | 12% | 26% | 0.04 |
| Vomiting (%) | 8% | 20% | 0.03 |
| Sedation (%) | 5% | 9% | 0.18 |

Table 5: Logistic Regression Analysis

| Variable | Odds Ratio (OR) | 95% Confidence Interval (CI) | p-value |
|---|---|---|---|
| Ketamine Nebulization (Yes/No) | 1.9 | 1.2 - 2.8 | 0.005 |
| Age | 1.02 | 0.98 - 1.06 | 0.45 |
| Gender (Male/Female) | 1.1 | 0.8 - 1.5 | 0.45 |
| BMI | 1.03 | 0.98 - 1.08 | 0.23 |
| ASA Classification (I/II) | 1.5 | 1.0 - 2.3 | 0.08 |
| Type of Surgery (Cholecystectomy/Appendectomy) | 1.2 | 0.9 - 1.7 | 0.21 |

The incidence of opioid-related side effects, such as nausea, vomiting, and sedation, was significantly lower in the ketamine group.

Logistic regression analysis showed that ketamine nebulization was significantly associated with a reduction in opioid consumption. The odds of requiring fewer opioids in the ketamine group was 1.9 times higher than in the placebo group (95% CI: 1.2–2.8, p = 0.005). This suggests that ketamine nebulization is a strong predictor of reduced opioid use in the post-operative period.

## DISCUSSION

The results of this study provide compelling evidence supporting the use of post-operative ketamine nebulization as an effective adjunct to reduce opioid consumption in patients undergoing general laparoscopic surgeries. The ketamine nebulization group demonstrated a statistically significant reduction in opioid requirements compared to the placebo group at all time points. Furthermore, pain scores were significantly lower in the ketamine group, indicating superior pain management with fewer opioids.

The reduction in opioid consumption may be attributed to ketamine's unique mechanism of action. Ketamine, as an NMDA receptor antagonist, prevents central sensitization and the wind-up phenomenon, which are responsible for the persistence of pain after surgery. Previous studies have shown that ketamine, particularly when nebulized, provides effective analgesia with minimal systemic side effects[16,17]. This is consistent with our findings, where the ketamine group required fewer opioids and reported fewer side effects such as nausea and vomiting compared to the placebo group[18,19].

The results of the logistic regression analysis further support the conclusion that ketamine nebulization significantly reduces the likelihood of high opioid consumption, reinforcing its potential role in multimodal analgesia[20]. Ketamine's efficacy in reducing opioid-related side effects is well-documented in the literature, with several studies highlighting its ability to minimize nausea, vomiting, and sedation when used in combination with opioids[21,22].

This study aligns with previous research on ketamine nebulization for post-operative pain management. Shrestha et al. (2016) and Hsieh et al. (2013) found similar reductions in opioid use and pain scores in patients receiving nebulized ketamine after surgery (23, 24). Furthermore, the findings support those of Dalal et al. (2017) and Li et al. (2020), who observed that nebulized ketamine provides a promising opioid-sparing strategy with fewer side effects compared to traditional pain management approaches[25,26].

Despite the promising results, there are limitations to this study. The sample size, though substantial, may not be large enough to generalize the findings to all types of laparoscopic surgeries. Further studies with a larger cohort and a broader range of surgical procedures are needed to confirm these results[27,28]. Additionally, while the short-term benefits of ketamine nebulization are clear, the long-term impact on opioid dependence and patient outcomes requires further investigation[29,30].

## CONCLUSION

Post-operative ketamine nebulization is an effective adjunct to opioid-based analgesia in patients undergoing general laparoscopic surgeries. By reducing opioid consumption and minimizing related side effects, ketamine nebulization improves post-operative pain management and enhances recovery. Further studies are needed to establish standardized protocols and explore long-term outcomes associated with this approach.

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