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Effectiveness of Subcutaneous Ketamine Injection at the Port Site for Postoperative Pain Management Following Laparoscopic Surgery: A Randomized Controlled Trial

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ABSTRACT

Background and Objective: Effective control of postoperative pain is a vital component of patient recovery after laparoscopic interventions. Although laparoscopic surgery is associated with smaller incisions, the patient still experiences significant postoperative pain, often due to tissue trauma, port site irritation, and peritoneal stretching. This study investigates the analgesic efficacy of subcutaneous ketamine at the port site in reducing postoperative laparoscopic pain.

Methods: This prospective, randomized controlled trial was conducted at Shar Hospital, Sulaymaniyah, over four months, enrolling 100 patients aged 18–65 years undergoing elective laparoscopic surgery. Participants were randomly assigned to two equal groups: the intervention group received subcutaneous ketamine infiltration at the port site, whereas the control group received normal saline. Baseline demographics and preoperative pain scores were recorded. Postoperative pain intensity was assessed at 1, 6, and 12 hours using a 0–10 numerical rating scale. Statistical analysis employed repeated-measures ANOVA and ANCOVA.

Results: Baseline characteristics were comparable ($p > 0.05$). Pain scores were significantly lower in the ketamine group at 1 hour ($p < 0.001$), 6 hours ($p < 0.001$), and 12 hours ($p < 0.001$). Within-group pain reduction was also significant over time ($p < 0.001$). Adverse effects were mild but more frequent with ketamine, including nausea (20%), vomiting (14%), dizziness (28%), and tachycardia (10%).

Conclusion: Subcutaneous ketamine injection at the port site markedly reduces postoperative pain following laparoscopic surgeries. This treatment has few side effects and appears to be a complement to conventional pain relief techniques..

KEYWORDS: Laparoscopic Surgery, Postoperative Pain, Subcutaneous Ketamine..

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INTRODUCTION

Introduction

Laparoscopic surgery is widely adopted for abdominal procedures because it decreases incision size, intraoperative blood loss, postoperative pain, recovery time, and length of stay compared with open approaches; nonetheless, port site pain remains common and can prolong recovery and increase postoperative opioid requirements. 1, 2 Port site pain is primarily driven by trocar-related tissue injury to skin, fascia, and muscle, and may be exacerbated by pneumoperitoneum, trocar angulation, and manipulation during instrument exchanges. 3, 4 Even when transient, suboptimal control of this somatic pain leads to higher early analgesic requirements, delayed mobilization, and lower patient satisfaction, highlighting the need for effective, opioid sparing strategies tailored to minimally invasive surgery. 3, 4

Ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, attenuates central sensitization and wind-up phenomena implicated in postoperative hyperalgesia and opioid tolerance. At subanesthetic doses within multimodal regimens, perioperative ketamine has been associated with reductions in pain intensity and opioid consumption

across diverse surgical populations without compromising safety when appropriately dosed and monitored. [5, 6] Intravenous administration is the most widely studied route; however, local or subcutaneous delivery at the incision has gained interest because targeting the nociceptive source may provide meaningful analgesia while limiting systemic exposure and related adverse effects such as sedation, dysphoria, or tachycardia. [7, 8] Infiltration around incisions is already standard for local anesthetics in many laparoscopic pathways; therefore, substituting or supplementing with low-dose ketamine at the port site represents a practical, workflow-compatible approach that could enhance somatic pain control early after surgery. [7, 8]

Prior studies of perioperative ketamine in laparoscopy generally report modest reductions in early pain scores and opioid use, but most evaluate intravenous dosing, combine heterogeneous operations, or measure outcomes that are difficult to attribute specifically to port-site nociception. [5, 6] Evidence for localized administration, particularly a single subcutaneous infiltration at trocar sites, remains limited and methodologically variable with respect to dose, volume, timing (pre-incision vs closure), and pain assessment scales. [3, 7] Consequently, despite biological plausibility and encouraging signals from broader ketamine literature, it is uncertain whether a standardized, low-dose subcutaneous ketamine technique at the port site meaningfully improves early postoperative pain and decreases opioid requirements compared with standard local infiltration or placebo.

Knowledge gap and rationale: There is a specific need to determine the effectiveness, optimal dosing strategy, and tolerability of subcutaneous ketamine administered at laparoscopic port sites using consistent pain metrics and transparent reporting. [3, 7] This study tests the hypothesis that a single subcutaneous ketamine infiltration at the port site reduces early postoperative pain scores measured on a prespecified, consistently used scale (VAS or NRS) and lowers opioid consumption within the first 24 hours after surgery, while monitoring common adverse effects to inform implementation within multimodal postoperative analgesia pathways. [3, 9] By focusing on port-site–specific somatic pain and using standardized outcomes, the trial aims to provide clinically interpretable evidence for or against incorporating subcutaneous ketamine into routine laparoscopic recovery protocols.

Materials and Methods

This prospective, randomized, single blind controlled trial was designed to evaluate the impact of subcutaneous ketamine injections at the port site on POP levels in patients undergoing laparoscopic procedures. Conducted at Shar Hospital in Sulaymaniyah City over four months, the study compared pain scores between two groups: one receiving subcutaneous ketamine and the other receiving a placebo. Eligible participants were required to meet the following criteria: Aged 18 to 65 years, undertaking elective laparoscopic surgery (such as cholecystectomy or appendectomy), American Society of Anesthesiologists (ASA) score, physical status I, II, or III, baseline pain score of less than 3 on a 0-10 numeric pain scale, excluding those with chronic pain disorders, known allergies or contraindications to ketamine, history of severe psychiatric conditions (e.g., schizophrenia, major depression), recent substance abuse (within the past year), pregnant or breastfeeding women, use of medications that could interfere with ketamine's effects or alter pain perception, such as chronic opioid use, severe comorbidities (e.g., uncontrolled cardiovascular disease, diabetes). This study received ethical approval from the Kurdistan Higher Council of Medical Specialties, Research Protocol Ethics Committee under Reference Number (1275) dated 2/3/2024. Informed consent was obtained from all participants before enrolment.

Sample size was determined using an a priori power analysis in G-Power. Assuming a minimum clinically significant difference of 1.0 points in the numerical pain score between groups, a standard deviation of 1.6, $\alpha = 0.05$, and 80% power, the necessary sample size was 45 participants per group. To account for potential dropouts, we enrolled 100 patients (50 per group).

Participants were randomly allocated to the ketamine (intervention) or placebo (control) group using a computer-generated randomization schedule. To maintain blinding, patients were unaware of their group allocation. The study drugs were

made up by an anesthesia nurse who did not participate in patient evaluation. Immediately following the laparoscopic procedure under general anesthesia, Patients in the intervention group received a subcutaneous infiltration of ketamine at two port sites: the umbilical and epigastric ports. A dose of 1 mg/kg was diluted in 20ml of normal saline. The dose was selected because it provides effective peripheral analgesia at sub-anesthetic, low systemic absorption levels, minimizing psychomimetic side effects. Prior studies evaluating peri-incisional or local infiltration of ketamine in laparoscopic, orthopedic, and soft-tissue procedures have shown that doses between 0.5–2 mg/kg produce significant postoperative pain reduction without causing sedation or delayed recovery. 10ml was injected at the umbilical port, and another 10ml was injected at the epigastric port. Using aseptic technique after the surgical procedure and before skin closure, while the control group received a subcutaneous infiltration of 20 mL of normal saline at the same port sites. The subcutaneous infiltration of the drugs was administered directly at the incision site. Before surgery, demographic data, including age, sex, weight, medical history, and ASA classification, were recorded. Initial pain levels were measured using a numerical scale (0-10), where 0 denotes no pain and 10 the worst possible pain. The NRS (0–10) was used because it is simple, validated, reliable, and highly sensitive for postoperative pain assessment. It is easier for patients to use than the VAS and is recommended for repeated pain measurement in clinical trials.

Anesthesia was induced using fentanyl in combination with propofol (2 mg/kg) and rocuronium (0.5 mg/kg) to facilitate endotracheal intubation. Anesthesia was maintained by sevoflurane or isoflurane, supplemented with muscle relaxants. All patients received an acetaminophen infusion of 1 g after induction. Standard intraoperative monitoring comprised non-invasive blood pressure measurement, electrocardiography, pulse oximetry, and capnography. All procedures were performed by experienced surgeons following standardized laparoscopic techniques specific to each operation. POP was also assessed using the numerical scale. Pain assessments were conducted at 1, 6, and 12 hours postoperatively. Any adverse effects related to the ketamine injection, such as nausea, dizziness, allergic reactions, injection site issues, tachycardia (PR more than 100 bpm), and hypertension (BP 140/90 or more). They were closely monitored and documented. Additionally, the need for supplementary pain management (e.g., opioid use) was recorded at each assessment interval.

Analyses were executed using IBM SPSS Statistics, version 25. A Kolmogorov-Smirnov test was used to determine whether the sample data originated from a normally distributed population. Descriptive statistics and chi-square/Fisher's exact tests were utilized for categorical variables. Based on normality, either the Independent Student t-test or the Mann-Whitney U test was used for non-categorical data. Additionally, repeated-measures analysis of covariance (ANCOVA) was utilized to assess the impact of the intervention. P-values less than 0.05 were deemed significant. Since the ASA classification was significantly different between the two groups at baseline ($p = 0.01$), the ASA score was included as a covariate in the repeated-measures ANCOVA to adjust for its potential confounding effect.

Results

The study included 100 patients, who were randomly allocated equally between two groups. Fifty individuals received ketamine (intervention group) and fifty received a placebo (control group). Table (1) presents the baseline demographic and clinical characteristics of the study cohort. The mean age (44.5 ± 13.9 vs. 44.8 ± 12.3 years, $p = 0.91$) and BMI (29.3 ± 3.2 vs. 28.1 ± 2.9 kg/m², $p = 0.055$) were similar across the intervention and control groups. Gender distribution did not differ significantly (male: 42.0% vs. 52.0%, $p = 0.36$). A notable difference was observed in ASA classification: a higher proportion of ASA I patients in the intervention group (68.0% vs. 40.0%) and a higher proportion of ASA II patients in the control group (54.0% vs. 30.0%) ($p = 0.01$). Baseline pain scores were similar between groups (0.18 ± 0.39 vs. 0.11 ± 0.32, $p = 0.33$). The prevalence of allergies (4.0% vs. 0.0%, $p = 0.23$) and drug or alcohol abuse (10.0% vs. 12.0%, $p = 0.82$) did not differ significantly. Nearly all participants underwent laparoscopic cholecystectomy, with only one appendectomy

recorded in the intervention group (p = 0.48).

Table (1): Baseline Demographic and Clinical Characteristics of Study Participants

Variable	Intervention	Control	p-value
Age (years), Mean ± SD	44.48 ± 13.90	44.77 ± 12.27	0.91
BMI (kg/m²), Mean ± SD	29.3 ± 3.2	28.1 ± 2.9	0.055
Gender (Male/Female)	21 (42.0%) / 29 (58.0%)	26 (52.0%) / 24 (48.0%)	0.36
ASA Classification	I: 34 (68.0%) II: 15 (30.0%) III: 1 (2.0%)	I: 20 (40.0%) II: 27 (54.0%) III: 3 (6.0%)	0.01
Baseline Pain Score, Mean ± SD	0.18 ± 0.39	0.11 ± 0.32	0.33
Allergies (Yes/No)	2 (4.0%) / 48 (96.0%)	0 (0.0%) / 50 (100.0%)	0.23
Drug or Alcohol Abuse (Yes/No)	5 (10.0%) / 45 (90.0%)	6 (12.0%) / 44 (88.0%)	0.82
Type of Laparoscopic Procedure	Cholecystectomy: 49 (98.0%) Appendectomy: 1 (2.0%)	Cholecystectomy: 50 (100.0%)	0.48

Statistical tests: Independent t-test, Mann–Whitney U test, Chi-square/Fisher's exact test as appropriate.

Postoperative pain assessments were recorded at 1, 6, and 12 hours. The findings indicate that patients administered subcutaneous ketamine reported substantially lower pain levels across all measured intervals compared with the control group, and the observed differences reached statistical significance (p < 0.05) Table (2).

Table (2): Postoperative pain scores at 1, 6, and 12 hours postoperatively in intervention and control groups

Time Point	Intervention Group (Mean, 95% CI)	Control Group (Mean, 95% CI)	P-value
1 Hour Post-op	5.86 (5.3–6.4)	8.94 (8.2–9.7)	<0.001
6 Hours Post-op	3.52 (3.0–4.1)	5.81 (5.2–6.4)	<0.001
12 Hours Post-op	1.52 (1.1–2.1)	2.45 (2.0–2.9)	<0.001

Comparison of postoperative pain scores at 1, 6, and 12 hours between the subcutaneous ketamine (intervention group) and the control group. Bars represent mean pain scores with error bars indicating standard deviations. Throughout all measured time points, patients receiving ketamine consistently reported significantly lower pain scores than the control group (p < 0.001). Figure 1

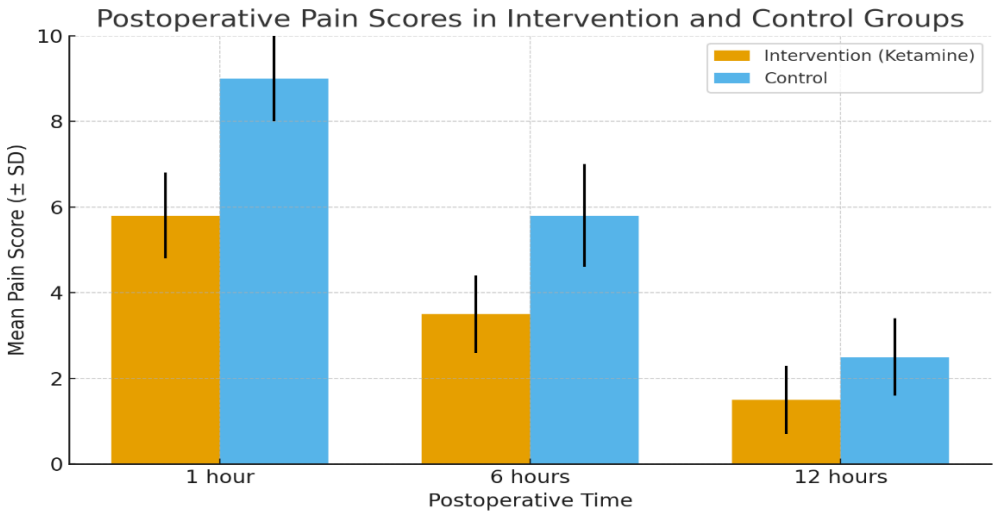

Figure (1) Postoperative Pain Scores in Intervention and Control Groups

A repeated-measures ANOVA within the intervention group demonstrated significant variation in pain scores over time. A repeated-measures ANCOVA further showed that both the treatment modality (ketamine versus control) and the timing

of assessment had a strong, statistically significant effect on postoperative pain scores ($p < 0.001$). Moreover, a significant treatment–time interaction was observed ($p < 0.001$), indicating that the analgesic benefit of ketamine varied across the different postoperative time intervals. These results are detailed in Table 3.

Table (3): Results of repeated measures ANCOVA: effect of treatment, time, and interaction on pain score

Source	F	Sig.	Partial Eta Squared
Treatment	210.465	<.001	.814
Time	2026.320	<.001	.977
Treatment * Time	79.507	<.001	.624

The intervention group experienced significantly higher incidences of nausea (20.0% vs. 0.0%, $p < 0.001$), vomiting (14.0% vs. 0.0%, $p = 0.005$), dizziness (28.0% vs. 0.0%, $p < 0.001$), and tachycardia (10.0% vs. 0.0%, $p = 0.02$) compared with the control group. Hallucinations were rare and did not differ significantly between groups (2.0% vs. 0.0%, $p = 0.48$). No cases of postoperative hypertension were reported in either group. Only 56% of patients in the intervention group required supplemental analgesia, whereas all patients in the control group did ($p < 0.001$). table (4)

Table (4): Postoperative Complications

Complication	**Intervention**	**Control**	**p-value**
Nausea	10 (20.0%) / 40 (80.0%)	0 (0.0%) / 50 (100.0%)	<0.001
Vomiting	7 (14.0%) / 43 (86.0%)	0 (0.0%) / 50 (100.0%)	0.005
Dizziness	14 (28.0%) / 36 (72.0%)	0 (0.0%) / 50 (100.0%)	<0.001
Hallucinations	1 (2.0%) / 49 (98.0%)	0 (0.0%) / 50 (100.0%)	0.48
Tachycardia	5 (10.0%) / 45 (90.0%)	0 (0.0%) / 50 (100.0%)	0.02
Was additional pain medication required	28 (56.0%) / 22 (44.0%)	50 (100.0%) / 0 (0.0%)	< 0.001

Statistical tests: Chi-square/Fisher's exact test.

Discussion

The current research sought to determine the effectiveness of subcutaneous ketamine injections at the port site in reducing POP after laparoscopic procedures, comparing the intervention group (ketamine injection) with a control group (placebo). The results indicated that subcutaneous ketamine administration significantly reduced pain at 1, 6, and 12 hours after the operation compared with the control group. It also provides evidence of the possibility of subcutaneous ketamine being effective for pain management during the immediate postoperative period following laparoscopic surgery. In this study, subcutaneous ketamine produced a statistically significant reduction in postoperative pain at all time points ($p < 0.001$), with the magnitude of this reduction exceeding the minimum clinically important difference, demonstrating both statistical and clinical significance. The timing of subcutaneous injection of ketamine at the port site is an important factor that influences the outcome after laparoscopic surgery. Evidence from multiple studies suggests that postoperative ketamine infusion can decrease pain scores and opioid consumption when compared to a placebo, mainly within the first 12 hours after operation. Thus, if not administered early enough, the analgesic outcome might be adversely affected. In a related study, Safavi et al. demonstrated that both intravenous and subcutaneous preincisional ketamine significantly reduced postoperative pain following open cholecystectomy, and that subcutaneous ketamine induced prolonged local analgesia at the incision site. [10] These findings could be interpreted as supporting the hypothesis that subcutaneous infiltration has advantages over systemic administration, as it allows the drug to reach the site of nociceptive input. Other research has supported this hypothesis of localized analgesic benefit. For example, it has been reported that subcutaneous ketamine infiltration at surgical sites reduces opioid requirements and improves postoperative recovery profiles in abdominal surgery. [10] Despite the statistical findings, this study's results showed a clinically meaningful effect. The reduction in pain scores at 1 hour exceeded 3 points, exceeding the 1-point MCID used in the sample size calculation. Moreover, only 56% of patients in the intervention group required supplemental analgesia compared with 100% in the control group, demonstrating a marked decrease in early analgesic use. Similarly, in gynecological and general surgeries, peri-incisional ketamine infiltration was observed to reduce early postoperative pain intensity, further highlighting the

potential of subcutaneous delivery as part of a multimodal approach to pain management. [11] By contrast, intravenous ketamine is the most studied route currently, with robust evidence regarding its effectiveness for various types of surgeries. One Cochrane systematic review found that low-dose intravenous ketamine reduced the intensity of acute postoperative pain and the need for opioids in the first 24 postoperative hours. [12] Radvansky et al. further confirmed these findings in a meta-analysis of laparoscopic cholecystectomy, showing that a single dose of 0.5 mg/kg IV ketamine reduced pain scores by 1.2 points on the numerical pain scale at 12 hours and lowered morphine usage during the first 24 hours. [8] More recently, Wang et al. conducted a systematic review and meta-analysis that reinforced the benefits of perioperative intravenous S-ketamine in reducing acute pain and improving recovery. [3] Collectively, the existing literature supports the role of ketamine—delivered either intravenously or through local subcutaneous infiltration-as an effective option for early postoperative pain control in laparoscopic procedures. Notably, current evidence suggests that subcutaneous infiltration may provide localized analgesia with potentially fewer systemic side effects than intravenous delivery. Building upon this body of evidence, our results demonstrate that administering 1 mg/kg of subcutaneous ketamine at the port sites following wound closure yields clinically meaningful reductions in pain within the first 12 postoperative hours, while maintaining an acceptable safety profile. In this study, the administration of subcutaneous ketamine at the site of the port was related to a higher incidence of some adverse effects compared to the control group. Importantly, patients in the ketamine group experienced increased rates of nausea (20%), vomiting (14%), dizziness (28%), and tachycardia (10%), although serious complications such as hallucinations were rare (2%). These findings are in agreement with previous studies that subcutaneous or parenteral ketamine can increase the incidence of mild to moderate side effects, mainly neurological and gastrointestinal side effects. A randomized controlled trials by Brinck et al. reported similar rates of nausea and dizziness among patients receiving low-dose ketamine for postoperative analgesia. [13] Another study showed that both intravenous and subcutaneous ketamine were associated with increased risk of nausea and mild psychotomimetic effects in surgical patients. [10] Furthermore, a review by Radvansky et al. (2015) demonstrated a higher incidence of transient nausea and dizziness. However, severe hallucinations or persistent psychosis remain rare with perioperative doses of ketamine. [8] These evidences show that while ketamine is clinically significant in pain relief and reductions in opioid requirements, the clinician must be watchful for milder neurological and gastrointestinal side effects and should appropriately counsel patients and monitor them in perioperative protocols.

The ASA classification between the groups differed significantly (P = 0.01). However, despite this baseline difference, no significant differences in baseline pain scores were observed between the groups, and ASA status did not appear to affect postoperative pain outcomes. [14] The repeated-measures ANCOVA, which adjusted for baseline differences, supports the reliability of our results and indicates that group imbalances, such as ASA classification, are unlikely to explain the observed analgesic effect. Early clinical studies suggest that subcutaneous ketamine injections can be effective in reducing port-site pain and opioid consumption after laparoscopic surgery. In one randomized controlled trial, patients who received subcutaneous ketamine at the port site reported markedly lower pain scores compared to those who received a placebo. [15] Other studies have confirmed that subcutaneous ketamine administration is linked to decreased opioid needs during the immediate postoperative phase. [10] Therefore, the present study aims to explore the concept of subcutaneous ketamine injection at the port site as a strategy for reducing POP following laparoscopic procedures.

The sample size of 100 patients was adequate for detecting significant differences; a larger sample size may reduce statistical power to detect less common adverse effects. Pain assessment only at three time points (1, 6, 12 hours post-surgery). This study was conducted at a single center, limiting the generalizability of the findings to broader or more diverse patient populations. Moreover, the follow-up duration was small, which prevents assessment of prolonged analgesic effects or late-onset complications.

A notable limitation of this study is the baseline imbalance in ASA classification between groups, which may introduce residual confounding despite statistical adjustment; therefore, the findings should be interpreted with this limitation in mind.

Conclusion

This study supports the use of subcutaneous ketamine infiltration at the port site as an effective strategy for reducing POP following laparoscopic procedures. Significant reductions in pain scores at 1-, 6-, and 12-hours post-surgery indicate that ketamine may offer an effective alternative to traditional analgesics, especially during the initial postoperative phase.

Conflicts of Interest

THE AUTHORS ASSERT THAT THEY POSSESS NO CONFLICTS OF INTEREST

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