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Research Article

Investigating the Effect of Two Intraoperative Low-Dose Ketamine Infusions on Postoperative Pain Intensity in Upper Limb Orthopedic Surgery

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ABSTRACT

Background: Effective analgesia following upper limb orthopedic surgery reduces opioid consumption and enhances recovery. Ketamine demonstrates opioid-sparing and antihyperalgesic properties; however, the optimal low-dose regimen is not well established. This study compared two ketamine infusion regimens for their effects on postoperative pain outcomes.

Methods: In this triple-blind, placebo-controlled randomized trial conducted at Kashani Educational and Medical Center in 2024, 93 adults aged 18–65 years with American Society of Anesthesiologists (ASA) physical status I–II undergoing upper limb orthopedic surgery under anesthesia were randomized into three groups. The low-dose group received ketamine 0.5 mg/kg followed by 0.25 mg/kg/h; the high-dose group received 0.75 mg/kg followed by 0.5 mg/kg/h; the control group received normal saline. Pain was assessed using a visual analog scale at 2, 4, 6, 12, and 24 hours postoperatively. Timing of rescue analgesic administration, total analgesic consumption, hemodynamic parameters, recovery variables, and patient satisfaction were recorded.

Results: All 93 patients completed the study, with 31 participants in each group. Baseline characteristics were similar across groups. Both low- and high-dose ketamine groups demonstrated reduced total analgesic consumption compared to controls (0.64 ± 1.21 and 0.58 ± 1.14 vs 1.76 ± 2.08; P = 0.043). The time to first rescue analgesic request was significantly longer in the ketamine groups (317.25 ± 25.62 and 326.84 ± 36.28 vs 73.48 ± 20.71 minutes; P < 0.001). Patient satisfaction scores were higher in both ketamine groups (8.24 ± 2.09 and 8.35 ± 2.15 vs 5.82 ± 1.64; P < 0.001). Mean arterial pressure and heart rate varied over time and between groups.

Conclusion: Intraoperative low-dose ketamine infusion reduced postoperative analgesic requirements and prolonged the time to rescue analgesia. The higher-dose regimen did not provide additional benefit.

Introduction

Postoperative pain affects approximately 80% of surgical patients in the United States, with 88% reporting moderate to severe intensity. Inadequate management is associated with increased mortality, higher hospitalization costs, reduced quality of life, prolonged opioid use, and persistent postsurgical pain (PPP) [1]. As outpatient upper-limb surgeries become standard and postoperative monitoring decreases, these challenges have intensified [2]. Orthopedic surgeons are the third-highest prescribers of opioids in the United

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States, responsible for 7.7% (6.1 million) of the 79.5 million opioid prescriptions written in 2009. Kaplan et al. found that over 60% of opioid prescriptions by orthopedic surgeons in 2009 were for patients who had received opioids in the preceding month [3]. Additionally, prescribing patterns among hand surgeons may contribute to the opioid crisis, with 13% of opioid-naive patients continuing to fill opioid prescriptions 90 days after hand surgery [4].

Intraoperative analgesic administration is critical for postoperative pain control and for minimizing opioid use during surgery. Lidocaine is frequently used for this purpose. Intravenous lidocaine has demonstrated efficacy in reducing pain scores and opioid requirements after procedures such as thyroidectomy and laparoscopic cholecystectomy. Its analgesic, anti-hyperalgesic, and anti-inflammatory properties contribute to improved postoperative pain control and recovery outcomes [4-5]. However, some studies have reported limited effectiveness, highlighting the need to explore alternative agents [6]. Ketamine represents one such alternative.

Ketamine is commonly employed in resource-limited settings due to its safety, ease of use, and low cost. The use of sub-anesthetic doses as an adjunct to opioids for acute pain management has increased in recent years. Current evidence indicates that low-dose ketamine, when administered preemptively, reduces postoperative pain and morphine consumption and delays the need for additional analgesics [7-8].

Despite these findings, limited research has evaluated the efficacy of intraoperative ketamine infusion for reducing postoperative pain and determining optimal dosing strategies. This clinical trial assessed the effectiveness of two intraoperative ketamine doses in reducing postoperative pain in patients undergoing upper-limb surgery.

Methods

A triple-blind, placebo-controlled, randomized clinical trial was conducted at Kashani Educational and Medical Center in 2024 to evaluate the efficacy of two intraoperative low-dose ketamine infusions on postoperative pain intensity following orthopedic upper-limb surgery. The study population included patients treated at this center. Ethical approval was obtained in accordance with the Declaration of Helsinki and was reviewed and registered by the Ethics Committee of Isfahan University of Medical Sciences (code IR.MUI.MED.REC.1403.192). The study was also registered in the Iranian Registry of Clinical Trials (IRCT) (code IRCT20240912063019N1). Results were reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement.

Inclusion and Exclusion Criteria

The inclusion criteria for the study were patients aged 18-65 years, with an American Society of Anesthesiologists (ASA) physical status I or II, who provided informed consent and were candidates for upper-limb orthopedic surgery. The exclusion criteria included drug addiction (including addiction to opium, methadone, or other psychoactive substances), a history of allergy or anaphylactic reactions to ketamine, inability to express pain intensity due to factors like not being fluent in Persian, pregnancy, any change in the anesthesia method, and the occurrence of hypersensitivity or anaphylactic reactions following drug administration.

Intervention Procedure

Patients were informed of the study objectives and provided written informed consent. They were also advised of their right to withdraw from the study at any time.

Patients underwent standard pre-anesthetic evaluation and preparation in the operating room. General anesthesia was induced with propofol, atracurium, fentanyl, and isoflurane, followed by endotracheal intubation. Vital signs, including heart rate, respiratory rate, blood pressure, and electrocardiography (ECG), were continuously monitored and recorded throughout the procedure. Patients were randomly assigned to one of three groups. In the first group, patients received an intravenous bolus dose of ketamine at 0.5 mg/kg, followed by a continuous intravenous infusion at a rate of 0.25 mg/kg per hour. In the second group, patients received an intravenous bolus dose of ketamine at 0.75 mg/kg, followed by a continuous intravenous infusion at a rate of 0.5 mg/kg per hour. In the third group, patients received only normal saline. Drug administration in all three groups was performed using an infusion pump. Notably, all patients received an intravenous dose of morphine at 0.1 mg/kg.

Blinding and Equalization

Medications were prepared in advance by the study implementer. Three drug packages (A, B, and C) were used, each containing two syringes (5 cc and 20 cc). In package A, the 5-cc syringe (A1) contained ketamine at 5 mg/cc; a bolus dose of 0.1 cc/kg was administered according to patient weight, followed by a continuous infusion from syringe A2 (2.5 mg/cc) at 0.1 cc/kg/h. In package B, the 5-cc syringe (B1) contained ketamine at 7.5 mg/cc; a bolus dose of 0.1 cc/kg was administered, followed by a continuous infusion from syringe B2 (7.5 mg/cc) at 0.1 cc/kg/h. In package C, both syringes (C1 and C2) contained normal saline, with a dose of 0.1 cc/kg administered. The patient, analyst, and prescriber were all blinded to the syringe contents.

Following the completion of surgery and extubation, patients were transferred to the recovery room, where they were monitored for the return of consciousness. The

total anesthesia time and length of stay in the recovery room were recorded. Pain intensity was assessed at 2, 4, 6, 12, and 24 hours postoperatively using the visual analog scale (VAS). The timing of the first supplementary analgesic dose was documented. Intravenous pethidine (0.5 mg/kg) was administered if the VAS score exceeded four. The total analgesic dose and patient satisfaction, measured by VAS at 24 hours postoperatively, were also recorded.

Patient allocation to the three groups was performed using randomization software. Patients, clinical assessors, and the statistician were blinded to group assignments.

The sample size was calculated based on previous studies, with a statistical power of 0.90 and a 95% confidence interval, resulting in 30 participants per group.

For data analysis, SPSS software version 26 was used. Quantitative variables were described using means and standard deviations, while qualitative variables were presented as frequencies and percentages. The normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Quantitative variables across the three groups were compared using analysis of variance (ANOVA). The comparison of qualitative variables among the three groups was conducted using the chi-square test. Furthermore, the effects of temporal changes on variables such as pain intensity and vital signs were examined using a repeated-measures ANOVA. A significance level of 0.05 or less was used for all tests.

Results

A total of 93 patients were examined across three groups (Figure 1).

The majority of patients were male (80.6%), with a mean age of 30.8 years. No significant differences were observed among the three groups regarding baseline variables, including age, gender, anesthesia score, and body mass index (BMI) (Table 1).

As shown in Table 2, a repeated-measures ANOVA revealed significant effects of time ($P < 0.001$) and group ($P < 0.001$) on mean arterial pressure (MAP). In other words, the mean MAP showed a significant change over time, and this change was significantly different among the three groups. Additionally, a repeated-measures ANOVA revealed significant effects of time ($P = 0.000$) and group ($P = 0.000$) on heart rate (Table 2).

The time to initial analgesic use and the total dose received in the three groups were also recorded. The results demonstrated no significant difference between the two ketamine groups, but a significant difference between these two groups and the control group in both analgesic use and initial analgesic use time. In addition, anesthesia duration was compared across the three groups, and the results revealed a significant difference between the ketamine and control groups. There was also a significant difference between the two ketamine groups. The mean satisfaction scores across the three groups were also compared, and those in the placebo group were significantly lower (Table 3).

Table 1- Distribution of Demographic and Clinical Variables in the Three Study Groups

Variable	Ketamine 0.25	Ketamine 0.75	Control group	P value
Age (years)	45.30 ± 5.23	31.14 ± 4.37	30.78 ± 5.09	0.89*
Sex (Male)	25 (80.6%)	23 (74.2%)	27 (87.1%)	0.437**
Sex (Female)	6 (19.4%)	8 (25.8%)	4 (12.9%)	
Weight (kg)	70.5 ± 10.32	72.24 ± 8.51	71.18 ± 9.42	0.87*
Height (cm)	170.35 ± 10.17	169.82 ± 9.46	171.26 ± 9.88	0.85*
BMI (kg/m²)	24.75 ± 2.48	25.03 ± 2.2	24.67 ± 2.36	0.88*
ASA I	27 (87.1%)	28 (90.3%)	29 (93.5%)	0.69**
ASA II	4 (12.9%)	3 (9.7%)	2 (6.5%)	
Mean surgery duration (min)	99.9 ± 8.51	103.7 ± 2.46	94.2 ± 2.37	0.70
Mean anesthesia duration (min)	116.7 ± 56.3	125.9 ± 52.6	109.3 ± 42	0.40

* Comparison performed using one-way ANOVA. ** Comparison performed using Chi-square test.

Table 2- Comparison of Mean Arterial Pressure (MAP) and Heart Rate in the Three Study Groups

Variable	Ketamine 0.25	Ketamine 0.75	Control group	P value
MAP before drug (mmHg)	86.45 ± 6.46	89.14 ± 7.16	84.78 ± 6.19	<0.001
MAP at 30 min (mmHg)	96.38 ± 5.23	98.27 ± 7.49	86.32 ± 7.11	<0.001
MAP at 60 min (mmHg)	99.26 ± 5.23	99.23 ± 6.94	87.73 ± 4.64	<0.001
MAP at 90 min (mmHg)	97.14 ± 5.23	99.53 ± 8.43	88.93 ± 6.17	<0.001
MAP at 120 min (mmHg)	100.23 ± 5.23	100.23 ± 8.83	91.32 ± 7.24	<0.001
HR before drug (bpm)	75.96 ± 5.11	73.97 ± 5.14	75.87 ± 5.08	<0.001
HR at 30 min (bpm)	78.33 ± 4.97	77.33 ± 5.06	76.25 ± 5.00	<0.001
HR at 60 min (bpm)	79.16 ± 5.13	81.03 ± 4.85	72.84 ± 5.07	<0.001
HR at 90 min (bpm)	80.47 ± 5.00	85.23 ± 5.12	76.12 ± 4.94	<0.001
HR at 120 min (bpm)	84.06 ± 5.01	86.84 ± 5.09	73.60 ± 4.97	<0.001

Different P values indicate significant differences between the groups.

Table 3- Comparison of Total Analgesic Dose and Time to First Analgesic Request in the Three Groups

Variable	Low-dose ketamine	High-dose ketamine	Placebo	P value
Total analgesic dose (g)	0.64 ± 1.21	0.58 ± 1.14	1.76 ± 2.08	0.043
Time to first analgesic request (min)	317.25 ± 25.62	326.84 ± 36.28	73.48 ± 20.71	<0.001
Duration of anesthesia (min)	99.26 ± 25.47	99.331 ± 24.66	84.84 ± 19.42	0.028
Patient satisfaction score	8.241 ± 2.09	8.351 ± 2.15	5.82 ± 1.64	<0.001

Different numbers indicate significant differences between groups.

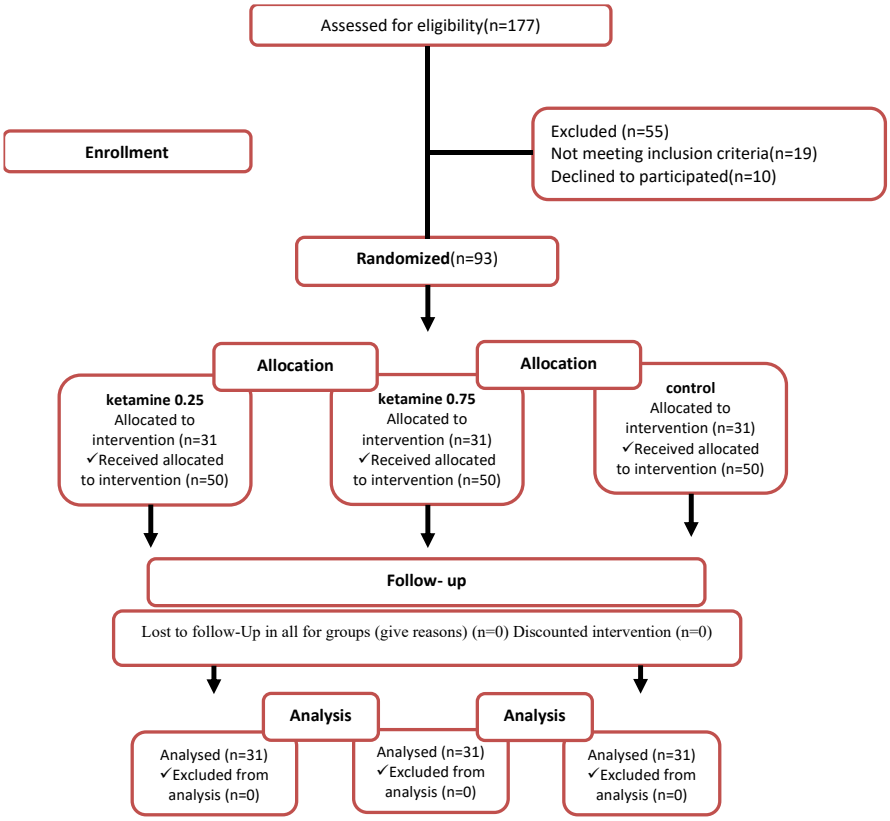

Figure 1- Flow chart of study

Discussion

Postoperative pain remains a significant concern for surgical patients, necessitating proactive prevention and early management. Uncontrolled pain can delay discharge, reduce patient satisfaction, and contribute to persistent postsurgical pain (PPP), which imposes substantial burdens on patients and the healthcare system. Recent studies report that PPP incidence may reach 40%, with 18.3% of patients experiencing moderate to severe pain [9]. Anesthesiologists must recognize the severity of this issue and the range of available pharmacological options. Opioids such as morphine and fentanyl are primary treatments but may not always provide adequate relief and can result in tolerance and adverse effects. Misconceptions about inevitable addiction following opioid use persist among patients and some clinicians [10]. Ketamine, an intravenous anesthetic, has demonstrated multiple therapeutic effects. Systematic reviews indicate that intraoperative ketamine administration reduces postoperative inflammatory markers [11], pain, and opioid consumption [12-14]. However, comparative evidence regarding different ketamine dosing regimens remains limited.

The results of this study revealed no significant difference between the ketamine groups, although pain intensity in both groups was significantly lower compared to the control group. It is worth noting that the present findings are consistent with previous studies. Intraoperative administration of low-dose ketamine has been shown to decrease morphine use and reduce the need for opioid analgesics for postoperative pain control. A systematic review of 30 randomized controlled trials on patients undergoing spine surgery showed that patients who received low-dose ketamine reported significantly lower pain intensity at 12, 24, and 48 hours

postoperatively and had a reduced opioid use [15]. Additionally, the results of previous studies demonstrated that in total knee replacement and lumbar spine surgeries, patients who received ketamine had lower pain scores compared to the control group [16]. A comparison of pain scores at various time points showed reduced pain intensity up to six hours postoperatively. However, pain intensity decreased from 12 to 24 hours postoperatively. The increase in pain intensity after six hours can be justified by the half-life of ketamine. Studies have shown that the half-life of this drug can be extended up to five hours depending on the administration method [17]. After six hours, opioid use increased, culminating in decreased pain intensity in the ketamine groups. The pain scores in the control group also consistently decreased, which is justified by the immediate administration of opioids upon regaining consciousness.

Ketamine produces central anesthetic effects by interacting with N-methyl-D-aspartate (NMDA) receptors in the brain. In ischemic pain models, brain ketamine concentrations have been directly correlated with analgesic effects. This interaction reduces pain activation in the secondary somatosensory cortex, insula, thalamus, and anterior cingulate cortex. Functional magnetic resonance imaging (fMRI) studies have shown that both pain and ketamine alter the connectivity of brain regions involved in endogenous pain regulation. Specifically, ketamine reduces connectivity in regions responsible for pain sensation and emotional processing [18]. The present study also found lower analgesic use in the ketamine groups, consistent with previous research indicating that intraoperative low-dose ketamine prolongs the time to first request for additional analgesics.

Heart rate and mean arterial pressure (MAP) increased following ketamine administration, consistent with previous studies. Ketamine stimulates the sympathetic nervous system and increases catecholamine release, such as norepinephrine, resulting in elevated heart rate and blood pressure, even at sub-anesthetic doses [19]. These findings align with those of Rahat DahMardeh et al., who reported that low-dose intravenous ketamine administered after spinal anesthesia effectively reduced postoperative pain and analgesic use in orthopedic surgery patients [20].

This study has several limitations, including a small sample size, recruitment from a single hospital, evaluation limited to upper-limb surgeries, and the absence of long-term follow-up for pain assessment.

In conclusion, low-dose ketamine was effective in reducing postoperative pain. However, multicenter trials with larger sample sizes are required to further validate these findings.

Conclusion

Ultimately, the results of this study demonstrate the efficacy of low-dose ketamine in reducing postoperative pain, although multicenter studies with larger sample sizes are needed to more accurately assess its efficacy.

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