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Research Article

Prophylactic Analgesic Effect of Adding Ketamine to Bupivacaine in Lumbar Fusion Surgery: A Randomized Controlled Trial

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ABSTRACT

Background: This randomized controlled trial evaluated the analgesic effect of adding subcutaneous ketamine to bupivacaine in lumbar fusion surgery.
Methods: 46 adult patients were randomized to receive subcutaneous bupivacaine with or without ketamine before incision. Pain scores (VAS), time to first rescue analgesia, opioid use, extubation time, and patient satisfaction were assessed.
Results: The ketamine group had higher early postoperative pain (30 and 60 min; $P < 0.05$) but showed prolonged time to rescue analgesia ($P = 0.037$) and reduced opioid use (not statistically significant). Extubation time was significantly longer. Satisfaction scores were similar.
Conclusion: Subcutaneous ketamine delayed opioid use but increased early pain and extubation time. It may be considered in selected patients, pending further research.

Introduction

Postoperative pain is a significant concern after spinal surgeries, especially lumbar fusion, which has seen a global rise due to broader indications and improved techniques [1]. In the United States, elective lumbar fusion procedures increased by 62.3% from 2004 to 2015, reaching nearly 200,000 cases in 2015, with the largest increase among patients aged 65 years and older [2]. Despite technical advancements, most patients experience moderate to severe pain immediately after surgery [3]. Inadequate pain control can delay recovery, prolong hospitalization, increase opioid use, and reduce patient satisfaction [4, 5]. Optimizing perioperative pain management is essential for improving short-term outcomes after lumbar fusion.
Inadequate management of acute postoperative pain may lead to chronic postsurgical pain (CPSP), which affects about 10% to 40% of patients after spine surgery and can impair long-term function and quality of life [6, 7]. Heavy reliance on opioids carries risks such as tolerance, dependence, respiratory depression, and gastrointestinal complications. These factors highlight the need to incorporate opioid-sparing approaches into modern multimodal pain management strategies [8]. Various multimodal pain management techniques have been studied, including regional anesthesia, non-opioid drugs, and adjunctive medications [9]. Bupivacaine, a widely used local anesthetic, is favored for its long duration and good safety profile [10]. However, in painful procedures like lumbar fusion, a local anesthetic alone may not provide enough pain relief [11]. Therefore, ketamine, a unique N-methyl-D-aspartate (NMDA) receptor antagonist with both central and peripheral effects, was chosen as an adjuvant due to its ability to enhance analgesia, prevent central sensitization, and reduce opioid requirements. At sub-anesthetic doses, it effectively prolongs local anesthetic effects and improves postoperative pain outcomes [12].

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The combination of bupivacaine and ketamine has been studied in various surgeries, including lower abdominal, cesarean, and arthroscopic procedures, with inconsistent results. Some studies found enhanced analgesia and longer sensory blockade, while others saw little benefit or mixed effects on early pain and patient satisfaction [13–15]. Differences in administration routes (spinal, epidural, infiltration, or subcutaneous) and dosing may contribute to these varied outcomes [16–18]. For example, Gökahmetoğ et al. showed that subcutaneous ketamine, alone or with bupivacaine, improved postoperative analgesia [18].

Despite limited evidence from other surgical specialties, there is little data on using ketamine and bupivacaine together for lumbar spine fusion, a procedure with significant pain and high opioid needs. No large randomized trial has evaluated the analgesic effect of subcutaneous ketamine with bupivacaine for lumbar fusion. Therefore, a randomized double-blind trial was conducted to see if preincisional subcutaneous ketamine with bupivacaine improves postoperative pain. The primary endpoints were pain scores, time to first rescue analgesia, and total analgesic use. It was hypothesized that the combination would improve pain control, delay opioid use, and increase patient satisfaction compared to bupivacaine alone.

Methods

Study Design and Setting

This study is a randomized, interventional clinical trial conducted after approval by the Ethics Committee of Isfahan University of Medical Sciences. Written informed consent was obtained from all participants prior to enrollment. The study was carried out on 46 patients aged 18 to 75 years, classified as American Society of Anesthesiologists (ASA) physical status I–II, who were candidates for lumbar fusion surgery at Kashani Hospital, affiliated with Isfahan University of Medical Sciences, Iran. The study was carried out from October 2024 to March 2025 in the Department of Anesthesiology and Operating Rooms. Exclusion criteria were known allergy to local anesthetics or nonsteroidal anti-inflammatory drugs (NSAIDs), long-term opioid use, renal or hepatic failure, neoplastic diseases, body mass index (BMI) > 30, local sepsis, unstable cardiomyopathy or pulmonary disease, coagulation disorders, severe diabetes, and preexisting psychiatric or cognitive impairment.

Randomization and Blinding

A total of patients meeting the eligibility criteria were enrolled through consecutive sampling. Patients were randomly assigned to one of the two intervention groups (n = 23 each) using a computer-generated randomization list. The trial was conducted in a double-blind manner: patients, anesthesiologists administering study medications, and investigators collecting postoperative data were all blinded to group allocation. Study drugs were prepared by an independent anesthesiology staff member not involved in patient management or data analysis, thereby maintaining allocation concealment and blinding throughout the study.

Intervention

Before surgery, all participants were instructed on pain assessment using a visual analogue scale (VAS). Group A (Bupivacaine group) received 20 mL of 0.5% bupivacaine administered subcutaneously. Group B (Bupivacaine + Ketamine group) received 20 mL of 0.5% bupivacaine combined with ketamine 1 mg/kg, also administered subcutaneously. Injections were performed five minutes before the surgical skin incision.

In the operating room, standard monitoring was applied, including noninvasive blood pressure, heart rate, respiratory rate, and oxygen saturation. General anesthesia was induced with intravenous midazolam (1 mg/kg), fentanyl (2–2.5 µg/kg), and propofol (2–2.5 mg/kg). Neuromuscular blockade was achieved using cisatracurium (0.15 mg/kg) to facilitate endotracheal intubation and optimize surgical conditions. Postoperative pain scores were assessed and recorded in the recovery room and at prespecified follow-up time points.

Outcomes

Primary outcomes were postoperative pain intensity at specified time intervals and time to first rescue analgesia within the first 180 minutes after surgery. Secondary outcomes included intraoperative parameters (mean arterial pressure (MAP), heart rate (HR), duration of anesthesia, and extubation time). Postoperative outcomes included duration of recovery, the need for additional analgesia, the total dose of rescue analgesics administered, and patient satisfaction—assessed at 24 hours after surgery.

Data Collection and Follow-up

Data were collected by trained research personnel blinded to group allocation. Pain was measured using a 10-point VAS (0 = no pain, 10 = worst imaginable pain) at predefined intervals: 30 minutes, 60 minutes, 120 minutes, 6 hours, 12 hours, and 24 hours postoperatively. Hemodynamic variables (HR and MAP) were monitored continuously and recorded at baseline (before induction of anesthesia) and every 30 minutes up to 180 minutes after surgery.

Intraoperative data included duration of anesthesia (from induction to discontinuation of anesthetic agents), extubation time (from the end of surgery to removal of the endotracheal tube), surgical duration, and total operating room time. Recovery time was defined as the interval from extubation to discharge from the post-

anesthesia care unit (PACU) and was recorded for all patients.

Rescue analgesia was standardized as intravenous pethidine 0.5 mg/kg administered when VAS pain scores exceeded 4. Time to first request for rescue analgesia and total rescue dose within the first 180 minutes postoperatively were documented. In addition, any episodes of nausea, vomiting, or other adverse effects were recorded. Patient satisfaction with postoperative pain control was assessed using a 10-point VAS (0 = not satisfied at all, 10 = completely satisfied) at 24 hours after surgery during the follow-up evaluation.

Sample Size Calculation

The sample size was calculated based on prior research evaluating postoperative pain after lumbar spine surgery. Assuming a clinically meaningful between-group difference of 1.5 points in VAS pain scores, a standard deviation of 2.0, a two-tailed alpha of 0.05, and 80% power, the estimated required sample size was 28 patients per group. However, due to logistical constraints, the final enrolled sample consisted of 23 patients per group, totaling 46 participants [19-20].

Statistical Analysis

All statistical analyses were performed using SPSS software version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were tested for normality using the Shapiro–Wilk test. For normally distributed continuous data, comparisons between the two groups were made using the Welch's t-test due to unequal variances. Non-normally distributed data were analyzed using the Mann–Whitney U test.

Categorical variables were compared using the Fisher's exact test. Time-to-event data (i.e., time to first rescue analgesia) were analyzed using Kaplan–Meier survival curves and compared between groups using the Log-rank test. Data were expressed as mean ± standard deviation (SD) for continuous variables and frequency (percentage) for categorical variables. A two-sided P-value < 0.05 was considered statistically significant.

Results

Baseline demographic characteristics are summarized in (Table 1). There were no statistically significant differences between groups in terms of age (mean ± SD: 56.3 ± 12.2 vs 55.6 ± 12.7 years; $P = 0.86$) or gender distribution (Male/Female: 12/11 vs 8/15; $P = 0.37$).

As shown in (Table 2), intraoperative MAP was significantly higher in the Bupivacaine + Ketamine group (87.6 ± 5.3 mmHg) compared to the Bupivacaine group (80.6 ± 6.9 mmHg; $P = 0.001$).

The heart rate was slightly lower in the ketamine group (71.9 ± 9.2 bpm vs 75.8 ± 8.0 bpm), but this difference was not statistically significant ($P = 0.13$). No significant differences were observed between groups in anesthesia duration (226.3 ± 49.5 vs 219.8 ± 48.5 minutes), recovery time (83.7 ± 11.5 vs 90.2 ± 31.8 minutes), or procedure duration (both groups: approximately 190.2 minutes).

Postoperative pain was evaluated using VAS at multiple time points (Table 3). VAS scores were significantly higher in the Bupivacaine + Ketamine group during the early postoperative period, at both 30 minutes (7.04 ± 1.97 vs 5.39 ± 2.17; $P = 0.010$) and 60 minutes (6.83 ± 2.06 vs 5.17 ± 2.21; $P = 0.012$). No statistically significant differences were noted at 120 minutes, 6 hours, 12 hours, or 24 hours postoperatively.

Analgesic outcomes are detailed in (Table 4). The Bupivacaine + Ketamine group experienced significantly longer extubation times (35.2 ± 7.1 vs 24.3 ± 13.3 minutes; $P = 0.001$).

Fewer patients in the ketamine group required rescue analgesia (6/23 vs 13/23), although the difference was not statistically significant ($P = 0.079$). Also, a significantly longer time to first rescue analgesia has been shown in the ketamine group ($P = 0.037$), with the median not reached within 180 minutes, compared to 60 minutes in the Bupivacaine group.

The average rescue dose across all patients was lower in the ketamine group (6.8 ± 13.5 mg vs 17.4 ± 23.0 mg; $P = 0.054$). Among only those who received rescue medication, the difference in dosage was not significant (28.3 ± 11.7 mg vs 33.5 ± 21.8 mg; $P = 0.52$). Patient satisfaction, measured by VAS, showed no significant difference between groups (5.74 ± 1.39 vs 5.48 ± 2.33; P = 0.65).

Table 1- Baseline demographic characteristics of study participants

Variable	Bupivacaine (n = 23)	Bupivacaine + Ketamine (n = 23)	P value
Age (years), mean ± SD	56.3 ± 12.2	55.6 ± 12.7	0.86[1]
Gender, n (%) – Male / Female	12 (52%) / 11 (48%)	8 (35%) / 15 (65%)	0.37[2]

[1]Welch's *t*-test; [2]Fisher's exact test. Abbreviations: SD = standard deviation.

Table 2- Intraoperative variables and recovery times

Variable	Bupivacaine (n = 23)	Bupivacaine + Ketamine (n = 23)	P value
Mean arterial pressure (mmHg)	80.6 ± 6.9	87.6 ± 5.3	0.001[1]
Heart rate (bpm)	75.8 ± 8.0	71.9 ± 9.2	0.13[1]

Duration of anesthesia (min)	219.8 ± 48.5	226.3 ± 49.5	0.65[1]
Duration of recovery (min)	90.2 ± 31.8	83.7 ± 11.5	0.36[1]
Duration of procedure (min)	190.2 ± 46.9	190.2 ± 50.0	1.00[1]

[1]Welch's *t*-test; values expressed as mean ± SD. Abbreviations: bpm = beats per minute; mmHg = millimeters of mercury; SD = standard deviation.

Table 3- Postoperative pain scores (VAS, 0–10) at specified intervals

Time point	Bupivacaine (n = 23)	Bupivacaine + Ketamine (n = 23)	P value
30 minutes	5.39 ± 2.17	7.04 ± 1.97	0.010[1]
60 minutes	5.17 ± 2.21	6.83 ± 2.06	0.012[1]
120 minutes	5.45 ± 2.06	6.55 ± 1.82	0.070[1]
6 hours	5.62 ± 1.36	5.30 ± 1.38	0.461[1]
12 hours	5.24 ± 1.41	4.60 ± 1.39	0.153[1]
24 hours	4.86 ± 1.62	4.35 ± 1.42	0.293[1]

[1]Welch's *t*-test; values shown as mean ± SD. Abbreviations: VAS = Visual Analogue Scale; SD = standard deviation.

Table 4- Extubation and rescue-analgesia outcomes (0–180 min window)

Variable	Bupivacaine (n = 23)	Bupivacaine + Ketamine (n = 23)	P value
Extubation time (min)	24.3 ± 13.3	35.2 ± 7.1	0.001[1]
Patients requiring rescue analgesia, n (%)	13 (52%)	6 (24%)	0.079[2]
Time to first rescue dose (median, KM)	60 (IQR: 45–60)	NR (> 180)	0.037[3]
Rescue dose (mg), all patients	17.4 ± 23.0	6.8 ± 13.5	0.054[1]
Rescue dose (mg), only recipients	33.5 ± 21.8 (n = 13)	28.3 ± 11.7 (n = 6)	0.52[4]
Patient satisfaction (VAS 0–10)	5.48 ± 2.33	5.74 ± 1.39	0.65[1]

[1]Welch's *t*-test; [2]Fisher's exact test; [3]Log-rank test; [4]Mann–Whitney *U* test. Abbreviations: IQR = interquartile range; KM = Kaplan–Meier; NR = not reached; SD = standard deviation; VAS = Visual Analogue Scale.

Discussion

This RCT assessed the prophylactic analgesic effect of adding subcutaneous ketamine to bupivacaine in lumbar fusion surgery. Results showed higher early postoperative pain scores in the ketamine group, but a significantly longer time to first rescue analgesia and lower overall opioid use. Extubation time was also prolonged in ketamine group. No significant differences were found in patient satisfaction, heart rate, anesthesia duration, or recovery time.

The findings of this RCT present a nuanced view of the prophylactic analgesic role of subcutaneous ketamine when combined with bupivacaine in patients undergoing lumbar fusion surgery—a high-pain, high-opioid procedure. Contrary to our initial hypothesis, early postoperative pain scores at 30 and 60 minutes were significantly higher in the Bupivacaine + Ketamine group compared to the Bupivacaine-only group. This result contrasts with the common assumption that ketamine, even at sub-anesthetic doses, uniformly enhances early analgesia when used as an adjuvant [18,21-22].

A possible explanation for higher early pain is that subcutaneous ketamine may be less effective for analgesia than spinal or intravenous administration. Although ketamine's NMDA receptor antagonism reduces central sensitization and may prevent chronic pain, it is uncertain whether subcutaneous delivery achieves adequate concentrations at target sites soon after surgery [23, 24]. Spinal and intravenous routes are more likely to provide reliable central analgesia, while subcutaneous administration may not ensure sufficient early central exposure [25]. Local tissue factors and pharmacokinetics may influence ketamine absorption and distribution when administered subcutaneously[26]. Although ketamine is known to have some vasodilatory properties, its clinical relevance at subcutaneous doses in humans remains uncertain. It is therefore unlikely that ketamine meaningfully altered the pharmacokinetics of bupivacaine in this context [27]. Other contributors to higher early pain may include patient variability, surgical technique, or insufficient local anesthetic coverage. As there is no strong evidence that low-dose ketamine causes local nerve excitation, the observed increase in early pain scores should be interpreted cautiously and warrants further investigation.

Despite higher early pain scores, patients in the ketamine group experienced a longer interval before requiring additional analgesia, with the median time not reached within 180 minutes postoperatively. This suggests that ketamine may offer prolonged analgesic effects after the initial period. By blocking NMDA receptors, ketamine can reduce spinal sensitization and support longer-term pain control, potentially decreasing opioid use over time [23, 24). Although the reduction in opioid consumption was not statistically significant, it may still be clinically relevant.

Patients in the ketamine group also had longer extubation times. Ketamine's sedative and dissociative properties, even with local administration, may delay recovery if systemic absorption occurs [28]. These effects, even at low doses, could prolong emergence,

particularly in older adults or those with slower drug metabolism.

Our findings partially align with Gökahmetoğ et al., who showed that subcutaneous ketamine reduced opioid use and improved pain after cesarean sections. However, unlike our results, they reported better early pain scores, possibly due to anatomical and procedural differences between abdominal and spinal surgeries, as well as varying hormonal and psychological pain responses [28]. Other studies show mixed results. our findings are consistent with Rizk et al., who described reduced pain and opioid use with ketamine in cesarean delivery, whereas Wernberg et al. found no early pain relief after renal surgery—similar to our results beyond the first hour [13,29]. Similarly, meta-analyses by Heesen et al. and Akram et al showed that ketamine decreases opioid consumption and delays the need for rescue analgesia, though its effect on severe early postoperative pain (within 3–6 hours) is limited—especially in surgeries like lumbar fusion [30-31]. Shah et al. further emphasized that ketamine's analgesic benefit is context-dependent and may be more pronounced in selected clinical scenarios [32].

Patient satisfaction at 24 hours postoperatively was similar between groups. Satisfaction is influenced by multiple factors, including pain control, expectations, comfort, side effects, and communication. Higher early pain scores in the ketamine group may have reduced overall satisfaction, despite lower subsequent opioid requirements.

The higher mean arterial pressure (MAP) during surgery in the ketamine group aligns with ketamine's known effects of increasing sympathetic activity, which can help stabilize blood pressure. This is useful in spinal surgery, where low blood pressure can be risky for the spinal cord (33]. This result agrees with earlier studies showing that low-dose ketamine helps maintain stable heart and blood vessel function during anesthesia. While heart rate did not differ much, higher MAP might indicate a lower need for blood pressure-raising drugs [33, 34].

This double-blind randomized trial provides valuable data on subcutaneous ketamine with bupivacaine in lumbar fusion surgery. Strengths include the randomized, double-blind design, the use of validated pain scales, and standardized anesthesia and recovery protocols, which enhance the reliability of the results. Limitations include a smaller sample size than planned, potentially reducing power for secondary outcomes. The ketamine dose and administration route may differ from other studies, limiting generalizability. Additionally, the absence of long-term follow-up precludes assessment of chronic pain or late adverse effects.

Clinically, subcutaneous ketamine delayed opioid use and extended the time before additional analgesia was needed, but also resulted in higher early pain and prolonged extubation. These trade-offs suggest it is not yet suitable for routine use. Subcutaneous ketamine may be considered for patients with high opioid requirements, but should be used cautiously. Further research is needed to determine optimal dosing, administration route, and timing. Larger studies with long-term follow-up, patient-reported outcomes, and cost analysis are necessary to clarify ketamine's role in spine surgery pain management.

Conclusion

In this randomized trial, subcutaneous ketamine added to bupivacaine for lumbar fusion surgery delayed opioid requirements and reduced overall opioid use, but increased early pain scores and prolonged extubation. These findings indicate that ketamine's benefits may be delayed, while early effects are less favorable. Ketamine may serve as an opioid-sparing option for select patients, but should be reserved for specific cases until larger studies confirm its safety, efficacy, and optimal use.

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Ethical approval

The study obtained the approval of the institutional review board at, School of Medicine, Isfahan (IR.MUI.MED. REC.1403.084). Registration code in the Clinical Trials Registry Center: IRCT20160307026950N63

Informed consent

All patients provided informed consent before participation in this study.

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