Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1724244

J Health Sci Med. 2025;8(6):1060-1064

The effectiveness of low-dose intravenous ketamine on postoperative pain management in arthroscopic knee surgery under spinal anesthesia

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Cite this article as: Özkavak D, Yılmaz A, Kılıç Y, Özkavak S, Göğüş N. The effectiveness of low-dose intravenous ketamine on postoperative pain management in arthroscopic knee surgery under spinal anesthesia. *J Health Sci Med.* 2025;8(6):1060-1064.

Received: 20.06.2025 ◆ **Accepted**: 09.10.2025 ◆ **Published**: 25.10.2025

ABSTRACT

Aims: This study aimed to determine the efficacy of intraoperative low-dose intravenous ketamine on postoperative analgesia in patients who were underwent arthroscopic knee surgery under spinal anesthesia.

Methods: Forty patients were equally classified as control and ketamine groups. In the ketamine group, 0.15 mg/kg intravenous ketamine was administered between 35-45. minutes of the surgery, whereas the patients in the control group received no medication. Postoperative pain was assessed using a visual analogue score. An analgesic, intravenous tramadol, was administered if the patients showed a value of at least 5 on the VAS. The need of first analgesic drug, the time to first analgesic drug administration, and additional (second and third) analgesic requirement during the postoperative period were compared between the groups.

Results: All patients in the control group and 8 (40%) patients in the ketamine group required first analgesic drug ($p<0.001$) postoperatively. The mean time to first analgesic drug administration was longer in the ketamine group (8.5 hours) than in the control group (4.2 hours) ($p=0.008$). Ten patients in the control group needed second analgesic drug whereas only one patient needed the second analgesic in the ketamine group. Third analgesic drug was required in three patients of the control group while none of the patients in the ketamine group needed third analgesic. For patient satisfaction, 11 (55%) patients marked "good" and 9 (45%) marked "very good" in the control group whereas all patients in the ketamine group marked "very good" ($p<0.001$).

Conclusion: Intraoperative subanesthetic dose IV ketamine prolongs the duration of postoperative analgesia and reduces the need for analgesics in elective arthroscopic knee surgery, with an acceptable side effect rates.

Keywords: Arthroscopic knee surgery, ketamine, postoperative analgesia, spinal anesthesia

INTRODUCTION

Spinal block is a frequently used anesthesia method, especially in lower abdominal and extremity surgeries. It is easy to apply, has a rapid onset of action, and provides adequate analgesia and muscle relaxation. Inability to extend the duration of anesthesia in prolonged surgeries due to inadequate block and the need of other methods for pain relief in the postoperative period are its main disadvantages.[1,2] Postoperative pain is an acute clinical phenomenon that begins with surgical trauma and gradually decreases with tissue healing. It can be influenced with various factors such as the patient's physiological structure and psychological status, the type and duration of surgery, anesthetic drugs and techniques, and the quality of postoperative care. Effective pain management should provide decreased analgesic use in the postoperative period, shorter hospital stay, reduced health costs, and increased patient satisfaction.[3]

Although many treatment modalities have been recommended for postoperative pain management to date, opioids remain to be among the most commonly used agents in routine practice. However, opioids have numerous adverse effects such as respiratory depression, addiction, drug adaptation, nausea, and vomiting.[4] On the other hand, ketamine, a noncompetitive N-Methyl-D-Aspartate (NMDA) receptor antagonist, is still used in subanesthetic doses for intra- and postoperative pain control, without major side effects.[4-7]

In this study, it was aimed to determine the effects of subanesthetic or low-dose intravenous (IV) ketamine administered close to the end of the surgical procedure on hemodynamic parameters, sensory and motor block levels, and postoperative analgesia in patients who were underwent arthroscopic knee surgery under spinal anesthesia.

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METHODS

After obtaining approval from Ankara Numune Training and Research Hospital Ethics Committee (Date: 04.04.2007, Decision No: 1), adult patients who were scheduled for elective arthroscopic surgery in Ankara Numune Training and Research Hospital between May 2007 and January 2008 were included in this prospective study. All patients were informed about the operation and anesthesia technique preoperatively. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Forty patients were randomly and equally divided into two groups: control group and ketamine group, in consecutive order (control group, ketamine group, control group, …). The patient was blinded about his/her group. The anesthesiologist was also blinded to randomization and performed postoperative tests and assessments without knowledge of the patient group. Between 35-45. minutes of the operation (near the end of the surgery), low (subanesthetic) dose ketamine (0.15 mg/kg bolus IV) was administered in the ketamine group by another anesthesiologist who was fully blinded to study. The patients in the control group received no medication.

The patients less than 18 years old, who had ≥3 ASA physical status, central/peripheric neurological disease, drug use that may affect the neurological response, allergy to the ketamine and other anesthetic drugs, and those who had any contraindication to spinal anesthesia were excluded from the study.

Anesthesia Management

Standard monitoring included electrocardiogram (ECG), heart rate (HR), mean arterial pressure (MAP), and peripheral oxygen saturation (SpO_2) values. A 0.9% NaCl infusion (at the rate of 7 ml/kg/hour) was started through the IV access (via 20-gauge venous catheter) at the back of the hand. All patients were premedicated with IV midazolam (0.02 mg/kg).

Spinal anesthesia was performed in the sitting position under appropriate asepsis-antisepsis conditions. A 22-gauge spinal needle was inserted from the midline through the L4-L5 interspinal space, and hyperbaric bupivacaine (0.5%, 2.5 ml) was administered intrathecally after free cerebrospinal fluid flow was observed. Subsequently, the patients were placed in a supine position, and the sensory block levels were checked with pin-prick method. Motor block level was evaluated by Bromage scale (Table 1). When the sensory block level achieved T10, the patients were placed in a semi-sitting position and surgical procedure was initiated. The patients were given 2 L/min oxygen via mask. Standard hemodynamical parameters and sensory block levels were recorded at regular intervals. A 25% decrease in the systolic blood pressure compared with the baseline value was accepted as hypotension, and 10 mg ephedrine was administered intravenously. If the HR was below 50 beats/min, 0.5 mg IV atropine was given. In both groups, hemodynamic parameters, sensory and motor block levels were recorded postoperatively.

Primary and Secondary Endpoints

The effectiveness of subanesthetic IV ketamine administration on postoperative pain status was the primary endpoint of the present study. Postoperative pain was assessed using a visual analogue score (VAS), scored from 0 (no pain) to 10 (worst pain possible). An opioid analgesic, IV Tramadol (1 mg/kg), was administered if the patients marked a value of 5 or above on the VAS. In this context, the need of "first analgesic drug", the time to "first analgesic drug" administration, additional (second and third) analgesic drug requirements were compared between the groups. The regression time of sensory block to L1, motor block to reach 0, and side effect profiles were the secondary endpoints. Finally, patient satisfaction (poor, good, very good) was evaluated.

Table 1. Motor block levels (Bromage Scale)

0	No motor block
1	Able to flex knee and ankle but unable to lift leg
2	Able to flex ankle but unable to flex hip and knee
3	Complete paralysis

Statistical Analysis

Data analysis was performed using the SPSS (Statistical Package for Social Science) package program. Based on the study by Wu et al.,[8] the sample size was found at least 36 patients (18 per group) to have a confidence level of 95% that the real value is within ±5% of the measured value. The data were examined for normal distribution using the Shapiro Wilk test. Continuous and categorical variables were shown as mean±standard deviation (SD) and number (%), respectively. Whether there was a statistically significant difference between the groups was examined using students T test, Mann-Whitney U test or Chi-square tests. Whether there was a statistically significant difference between repeated hemodynamic measurements within the groups was investigated using Repeated Measurement Analysis of Variance. In cases where the variance analysis result was found to be statistically significant, Bonferroni Corrected multiple comparison test was performed to determine the measurement times that caused the difference. All results were considered statistically significant for $p<0.05$.

RESULTS

A total of 40 patients were divided as control group (n=20) and ketamine group (n=20). The groups were statistically similar in terms of age, gender, and operation time. Mean sensory block time to reach T10 and motor block time to reach grade 3 were also similar between the two groups (Table 2).

Table 2. Comparison of basic characteristics and block times between the groups

	Control group	Ketamine group	p
Age (mean, y)	48.9±9.4	42.1±14.3	0.398
Gender (F/M)	11/9	8/12	0.342
Operation time (mean, min)	46.1±10.7	50.4±8.9	0.102
Sensory block time to reach T10 (mean, min)	6.5±1.7	7.3±2.3	0.327
Motor block time to reach grade 3 (mean, min)	5.2±1.6	6.1±2.1	0.183

y: year, F: female, M: male, min: minute

In both groups, hemodynamical parameters (HR, MAP, and SpO_2) were recorded several times at regular intervals during the perioperative period. There were no statistically differences in all hemodynamical parameters between the groups (p>0.05) (**Figure**).

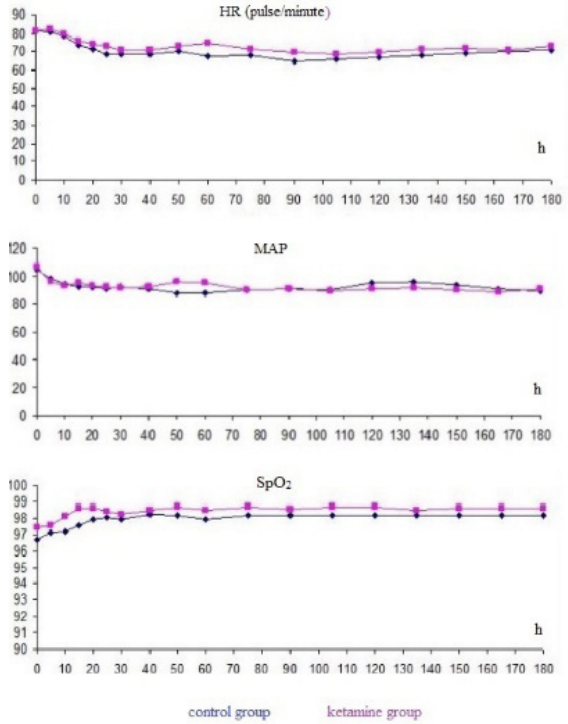


Figure. The courses of HR, MAP, and SpO_2 during the anesthesia period

Postoperatively, the pain levels were assessed with VAS, of which scores of 5 and above was accepted as 'the patient needs analgesic'. In this contex, all (100%) patients in the control group and 8 (40%) patients in the ketamine group required "first analgesic drug" (p<0.001). The mean time to "first analgesic drug" administration was longer in the ketamine group (8.5 hours) than in the control group (4.2 hours) (p=0.008). Ten patients in the control group needed an additional (second) analgesic drug whereas only one patient needed the second analgesic. Thereafter, an additional (third) analgesic drug was required in three patients of the control group while none of the patients in the ketamine group needed third analgesic.

Postoperatively, the regression time of sensory block to L1 was significantly higher in the ketamine group (85.5±24.3 minutes) compared to the control group (40.2±23.7 minutes) (p<0.001). There was no statistically significant difference between the groups in terms of the time for postoperative motor block to reach 0 according to the Bromage Scale (111.7±42 minutes in ketamine group vs 109.5±35.7 minutes in control group, p=0.718).

In terms of postoperative satisfaction, 11 (55%) patients marked "good" and 9 (45%) marked "very good" in the control group. On the other hand, all patients in the ketamine group marked "very good" (p<0.001). No side effects were observed in both groups during the intraoperative period. In the ketamine group, no hallucinations were encountered whereas short-term mild amnesia was observed in all patients. Nausea and vomiting were observed only in one patient in the ketamine group.

DISCUSSION

This study demonstrated the analgesic efficacy of intraoperative low-dose IV ketamine in arthroscopic surgery under spinal anesthesia. In the postoperative period, all patients in the control group and 8 out of 20 patients in the ketamine group required first analgesic drug. In addition, the time to first analgesic request was 4.2 hours in the control group whereas the time to first analgesic was found 8.5 in the 8 patients of ketamine group, indicating a statistically significance. Moreover, 10 patients in the control group required second analgesic drug while only one patient in the ketamine group was given second analgesic.

As known, ketamine acts multiple sites such as opioid, monoaminergic and muscarinic receptors, induces central summation in second-order pain neurons, thereby provides analgesia by preserving airway patency, ventilation, and cardiovascular stability at subanesthetic doses.[9,10] Additionally, ketamine reduces the incidence of hypotension induced by spinal anesthesia by increasing heart rate and arterial blood pressure through sympathetic nervous system activation.[9] In our study, there were no statistical differences in hemodynamic data between the groups. In the literature, there are several studies with conflicting results on the role of ketamine in postoperative pain management when used in low or subanesthetic doses (0.1-0.5 mg/kg) with local anesthetics, opioids or other analgesics.[12-14] There is a similar study in the literature investigated the effect of low-dose IV ketamine on postoperative pain in knee arthroscopy. In this study, the authors divided patients into three groups; group I (saline control); group II (ketamine 0.15 mg/kg i.v.); and group III (ketamine 0.15 mg/kg + midazolam 0.01 mg/kg i.v.). In conclusion, the authors found that ketamine improved the postoperative pain patient satisfaction.[15]

In fact, the studies investigated the role of ketamine on postoperative pain management have focused on two important issues; the administration time (pre/intra/postoperative) and the dose.[16] For example, Wu et al.,[8] showed that preincisional analgesia with morphine, bupivacaine, and ketamine was better than postincisional application. In parallel, Samuel et al.[4] reported that low-dose IV ketamine before skin incision was extended postoperative first analgesia request time and decrease total analgesia consumption in 24 hours. In another study conducted on the patients who underwent total hip arthroplasty, the authors demonstrated the analgesic efficacy of both low-dose preincisional and a 24-hour infusion IV ketamine.[17] On the other hand, Najam and Jafri[7] compared the postoperative analgesic effects of intradermal lidocaine with IV ketamine in patients who underwent elective inguinal hernia repair under spinal anesthesia. The authors gave the patients 50 mg bolus ketamine after the completion of the surgery. Based on their results, administering bolus ketamine significantly decreased overall pain scores and reduce the incidence of chronic postsurgical pain, compared to lidocaine infiltration. In another study, intraoperative low-dose ketamine (0.15 mg/kg)

was determined to reduce the need of postoperative morphine and accelerate mobilization after 24 hours; however, the time of ketamine administration (before incision or at the end of surgery) did not affect the outcomes.[18] As a result, ketamine was given until the end of surgery in most studies, although the timing of administration varied. In parallel, ketamine was administered near the end of surgery in our study.

Another important issue in the use of ketamine is the dosage. At high doses, ketamine provides both anesthesia and analgesia, and is often used in diagnostic and surgical procedures that do not require skeletal muscle relaxation. Ketamine is used as an adjunct to other anesthetic drugs because of its ability to maintain heart rate and cardiac output, to increase blood pressure via sympathetic stimulation, to provide bronchodilation, and to preserve protective pharyngeal and laryngeal reflexes without depressing respiration.[19] Its safety profile also makes it suitable for anesthesia and sedation in areas with limited medical equipment. However, the fact that ketamine may cause a range of psychosomatic symptoms, such as delusions, hallucinations, delirium, and confusion, greatly limits its widely use.[20] On the other hand, ketamine acts as an effective analgesic and causes fewer psychotomimetic side effects at low or subanesthetic doses.[21] In a randomized double-blinded study investigated the effect of low-dose intraoperative ketamine on postoperative pain after total knee replacement surgery, the authors reported decreased pain scores, prolonged time to first analgesic request, and reduction in morphine consumption, without affecting the incidence of side effects.[22] Similarly, low-dose ketamine was used in our study cohort, and no hallucinations or other serious psychotomimetic symptoms were observed during the postoperative period. However, all patients in the ketamine group experienced amnesia which was mild, transient, and clinically insignificant. Indeed, the development of psychotomimetic symptoms is dose-dependent in ketamine use, and mild amnesia is a common and well-known side effect in its subanesthetic doses.[23] The factors limiting the use of high doses of ketamine also include postoperative nausea, vomiting, and visual disturbances such as blurred vision and nystagmus.[24,25] In the current study, no patient developed any visual problem, and only one patient in the ketamine group experienced mild vomiting in the recovery room.

As the secondary outcomes of the present study, the regression time of sensory block was prolonged in ketamine group whereas the duration of motor block and the onset times of motor and sensory blocks were found to be similar between the groups. These results were consistent with a recent meta analysis regarding the use of ketamine as an adjuvant to regional anesthesia.[26] This large-scale study clearly showed that ketamine provides advantages in postoperative pain control through different pain pathways and by prolonging the sensory block time.

Limitations

There were several limitations to our study. First, all blocks were performed by a single anesthesiologist in a single center, which facilitated standardization but limited the generalizability of the results. Second, the relatively small sample of subgroups may be considered another limitation of this work. The fact that no medication (placebo) was given to the control group and that side effects such as hallucinations, amnesia, nausea, and vomiting were assessed only clinically can also be considered as another limitations of this study. Finally, body-mass index, which is an important factor affecting drug metabolism and may influence the results of the study, was not compared between the groups because of the irregular records. This can be considered as another limitation.

CONCLUSION

The results obtained from the study showed that the administration of subanesthetic dose IV ketamine, as an adjuvant to intrathecal bupivacaine provided longer postoperative analgesia and less need of postoperative analgesic use in elective arthroscopic surgery, with an acceptable side effect profile.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ankara Numune Training and Research Hospital Ethics Committee (Date: 04.04.2007, Decision No: 1).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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