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Research article

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The effect of preemptive ketamine on postoperative analgesia in lower extremity surgery

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Ethics Committee Approval
Ankara Training and Research Hospital Local Ethics Committee, 2005/01/033
The study was carried out at University of Health Sciences, Ankara Health Application and Research Center.
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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Preventing sensitization by an analgesic administered before a painful stimulus is the basis for preemptive analgesia. Preemptive use of pain medication prior to the application of painful stimuli results in better-controlled pain. This study aimed to compare the effects of preoperatively administered low-dose ketamine and lornoxicam on postoperative analgesia, their side effects and patient satisfaction in orthopedic operations on the lower extremities.

Methods: Seventy-eight patients aged 18-70 years who were admitted for lower extremity surgery under general anesthesia were enrolled in this prospective, randomized, and double-blind study. The patients were randomly allocated to one of the three following groups: Four milliliters of physiological saline were administered to the patients in Group P, 0.15 mg kg^{-1} ketamine was given to the patients in Group K and 8 mg lornoxicam was administered to those in Group L, all in 4 ml of volume, intravenously, 15 minutes before anesthesia induction. Postoperative pain was evaluated at rest and during movement at 0^{th}, 2^{nd}, 4^{th}, 6^{th}, 8^{th}, 12^{th}, 20^{th} and 24^{th} postoperative hours with the Visual Analogue Scale (VAS) and the Verbal Pain Scale (VPS). Total fentanyl consumption, additional meperidine usage, side effects and patient satisfaction were recorded at these times.

Results: The mean area under the VAS and VPS at rest and movement-time curves were lower in Group K compared to the other groups. Group P and Group L were comparable in terms of the area under the VAS at rest and movement-time curves, but the mean area under the VPS at rest and movement-time curves were higher in Group P compared to Group L. Total fentanyl consumption was lower in Group K than the other two groups (P=0.001).

Conclusion: Low-dose ketamine administered preoperatively to patients for lower extremity surgery decreased postoperative pain scores more than lornoxicam or placebo.

Keywords: Ketamine, Preemptive analgesia, Lornoxicam, Lower extremity orthopedic surgery

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Introduction

Postoperative pain, estimated as moderate by 20-40% and severe by 50-70% of the patients, starts with surgical trauma and gradually resolves with tissue healing. Opioid analgesics, used frequently for postoperative pain treatment, are potent and effective drugs; however, respiratory and cardiovascular side effects limit their use and make them inadequate for pain management [1]. Multimodal analgesia, defined as analgesic drugs and methods with different mechanisms of action used together, increases the quality and efficacy of pain treatment while possibly decreasing side effects [2], hospital stay and cost [3]. It is reported to be effective for pain control after lower extremity surgeries [4]. Opioids have been combined with various nonopioid analgesics for this purpose [2].

When an analgesic is administered before a painful stimulus, sensitization may be diminished in the first place. Preventing sensitization is the basis for preemptive analgesia. It has been documented that the preemptive use of pain medication prior to noxious stimuli results in better-controlled pain versus waiting to treat pain until the noxious stimuli has already occurred [5]. The use of preoperative nonsteroidal anti-inflammatory drugs (NSAIDs) for pain treatment in orthopedic surgical interventions decreases the requirement for postoperative opioids or other analgesics and their relevant side effects. Lornoxicam, a member of the oxicam group of NSAIDs, possesses potent anti-inflammatory and analgesic activities. Lornoxicam is widely recommended for the symptomatic treatment of pain and inflammation in patients with osteoarthritis and rheumatoid arthritis, as well as preoperative and postoperative pain associated with gynecologic, orthopedic, abdominal, and dental surgeries [6].

The NMDA receptor antagonist ketamine has a direct analgesic effect and plays a key role in preventing the hyper-excitability of the spinal cord neurons and central sensitization to peripheral nociceptor stimulation [7]. Preventing central sensitization is of great importance in preemptive analgesia. Pain activation areas in the brain show decreased activity when ketamine is used, correlating with a decrease in pain sensing and processing [8].

This study aimed to compare the effects of preoperatively administered low-dose ketamine and lornoxicam on postoperative analgesia quality, side effects and patient satisfaction in lower extremity orthopedic surgeries.

Materials and methods

After the approval of the local ethics committee (Ankara Training and Research Hospital Ethics Committee-2005/01/0033) was obtained, a total of 78 patients aged 18-70 years, with ASA I-II, admitted for lower extremity surgery under general anesthesia were enrolled in this prospective, randomized and double-blind study. Exclusion criteria included a history of chronic pain, chronic intake of analgesics or opioids, psychiatric disease, history of a drug or alcohol use, peptic ulcers, pregnancy, body mass index≥35 kg/m^2 and known allergy to NSAIDs and/or opioid analgesics.

The patients were informed about the patient-controlled analgesia device, the Visual Analog Scale (VAS) and the Verbal Pain Score (VPS) at the preoperative visit, the day before the surgery, by an investigator who was not informed of the study drugs used. For VAS, the patients were shown a ruler, 10 cm long, and asked to mark it. VPS scores were 0 for no pain, 1 for mild pain, 2 for moderate pain and 3 for severe pain.

The patients were taken into the operation room without premedication and 0.9% NaCl infusion was started after intravenous access was obtained with a 20 Gauge catheter. Electrocardiogram, peripheral oxygen hemoglobin saturation (SpO_2) and blood pressure (noninvasive) monitorization were performed (DRAGER PM 8060 Vitara). The patients were randomly allocated to one of the three groups using a computer-generated random number sequence. The study drugs were prepared by an anesthesiologist who did not participate in the study. All group of drugs were at the same volume, and not labeled. Another anesthetist administered 4 ml physiological saline to the patients in Group P, 0.15 mg kg^{-1} ketamine (KETALAR® Pfizer Pharmaceuticals Ltd., Istanbul-Turkey) to the patients in Group K and 8 mg lornoxicam (XEFO® Abdi İbrahim Pharmaceuticals, Istanbul-Turkey) to the patients in Group L in a total volume of 4 ml intravenously 15 minutes before anesthesia induction.

In all groups, anesthesia was induced with thiopental 5-7 $mg.kg^{-1}$, vecuronium 0.1 $mg.kg^{-1}$ and maintained with sevoflurane 2% in $N_2O50\%$-$O_250\%$. 0.01 mg/kg vecuronium was used as required for maintaining the muscle relaxation. Remifentanil 1 µg/kg was administered intravenously within 30 seconds when the heart rate or mean blood pressure during surgery reached 20% higher than the pre-induction value. The hemodynamic interventions used for the patients, consisting of remifentanil administration and the total amount administered, were noted.

Anesthesia maintenance was stopped once the surgical procedure was over (last skin suture) and the remaining neuromuscular junction block was antagonized with 2.5 mg neostigmine and 0.5 mg atropine. All patients were extubated when they fulfilled the recovery criteria. The anesthesia duration (the period between the start of anesthesia induction and the end of anesthesia maintenance), the surgery duration (the period between the first surgical incision and the last skin suture) and the recovery period (the period between the end of anesthesia maintenance and opening of the eyes on verbal stimuli) were noted. The PCA (patient control analgesia) (fentanyl) device was adjusted to 5 mcg/ml with a 25-mcg loading dose, 15-mcg bolus dose and a 15-minute lock duration.

Postoperative pain was evaluated at rest and during movement at the 0^{th}, 2^{nd}, 4^{th}, 6^{th}, 8^{th}, 12^{th}, 20^{th} and 24^{th} postoperative hours with VAS and VPS by an independent investigator who was unaware of the study drugs administered. Total fentanyl consumption, additional meperidine usage, side effects and patient satisfaction were recorded at these times.

Patients who were not within the evaluation range were not awakened. The results of these patients from this period were obtained by the retrospective evaluation of the patient at the next evaluation if the patient was awake. Meperidine 100 mg was administered intramuscularly if the patient reported a VAS value of 4 or more. The total meperidine amount administered was noted.

The patients were queried 24 hours after the surgery on nausea, vomiting, dry mouth, dyspepsia, lightheadedness and itching (yes/no) within the last 24 hours. They were evaluated regarding hypotension, respiratory depression, bronchospasm or allergic reaction (yes/no) following the surgery.

Statistical analysis

A power analysis was performed before the initiation of the study to determine the minimum number of patients for each group. Twenty-six patients per group were needed to ensure a type-1 error of 0.05 and a type-2 error of 0.20. All statistical analyses were performed with the statistical package program, SPSS version 21.0 (Statistical Program for Social Sciences, Chicago, IL, USA) with an IBM-compatible personal computer. Demographic data such as age, weight and operation time were analyzed with the one-way analysis of variance (ANOVA) with the Bonferroni test as a post-hoc analysis. Analysis of variance for repeated measures with the t-test was used to assess the pain. Global patient satisfaction scores, postoperative total meperidine and fentanyl consumption data were also analyzed with one-way analysis of variance (ANOVA) with the Bonferroni test as a posthoc analysis and the data were presented as mean and standard deviation. The incidence of side effects (such as nausea, vomiting, itching, sedation, hypotension, etc.) was evaluated with the Chi-square test and the Fisher's exact test. The area under the pain variables versus time curves were calculated and further analyzed with one-way ANOVA with Bonferroni correction. Data were presented as mean and standard deviation, percentages, and the number of patients. *P*-values of less than 0.05 were considered significant.

Results

The data of 75 patients were analyzed. One patient from Group K and two patients from Group L were excluded from the study because of not adjusting to the PCA device. There were no differences between the groups regarding demographic data such as age, sex, height and weight, and the anesthesia and surgery duration (Table 1), or the amount of preoperative remifentanil administered.

Table 1: Patient characteristics

	Group P (n=26)	Group K (n=25)	Group L (n=24)	*P*-value
Age (years)	52(14)	46(15)	52(14)	0.112
Gender (F/M) (n)	17/13	12/18	14/15	0.342
Height (cm)	164(7)	169(9)	165(8)	0.823
Weight (kg)	75(9)	74(9)	73(10)	0.843
Anesthesia time (min)	89(22)	81(12)	87(23)	0.169
Surgery time (min)	83(21)	78(13)	81(21)	0.217
Total remifentanil use (μg)	74 (0-92)	80 (0-94)	70 (0-86)	0.357
Recovery time (min)	4.3(1.1)	4.5(1)	3.9(1.2)	0.425

Data mean (SD), median (interquartile distribution) and number of patients. Group P: Control, Group K: Ketamine, Group L: Lornoxicam

The results of the area under the pain scores (VAS and VPS at rest and movement)-time curves were calculated and presented in Table 2. The mean area under the VAS and VPS at rest and movement-time curves were lower in Group K compared to other groups (P=0.001). On the other hand, Group P and Group L were comparable in terms of area under the VAS at rest and movement-time curves, but the mean area under the VPS at rest and movement-time curves were higher in Group P compared to Group L (P=0.012 and P=0.026).

The total amount of fentanyl consumed was 1127(73) μg in Group P, 705(26) μg in Group K and 1152(64) μg in Group L. The total fentanyl consumption was lower in Group K than the other two groups (P=0.001).

The number of patients who did not receive meperidine as an additional analgesic was higher in Group K (13) than in Group P (2) or Group L (3) (P=0.001).

The patients experienced nausea, vomiting and hypotension as side effects. The number of patients with nausea and vomiting was statistically significantly lower in Group K, who received ketamine, than in Groups P or L (Table 3).

Table 2: Area under the curve values for VAS and VPS at rest and movement-time and global satisfaction-time curves

	Group P (n=26)	Group K (n=25)	Group L (n=24)	*P*-value
VAS at rest x time (cm^2)	30.6(6.7)	15.0(3.7)*	28.1(5.3)	0.001*
VAS at movement x time (cm^2)	42(9.6)	17.9(3.6)*	37.9(6.7)	0.001*
VPS at rest x time (cm^2)	17(3.3)**	10.1(1.1)*	15.2(2.2)	0.001* 0.026**
VPS at movement x time (cm^2)	22(4)***	12.7(1.97)*	19.6(2.8)	0.001* 0.012***
Global satisfaction x time (cm^2)	79(14)	83(12)	80(15)	0.524

Data are mean (standard deviation), Group P: Control, Group K: Ketamine, Group L: Lornoxicam, * P=0.001 Group K vs Group L and Group P, ** P=0.026 Group P vs Group L, ***P=0.012 Group P vs Group L

Table 3: Side effects

	Group P (+/-) (n=26)	Group K (+/-) (n=25)	Group L (+/-) (n=24)	*P*-value
Nausea	13/13	2/23*	7/17	0.001
Vomiting	1/25	0/25**	6/18	0.005
Hypotension	2/24	0/25	2/22	0.610

Group P: Control, Group K: Ketamine, Group L: Lornoxicam, *P=0.001 Group K vs. Group P and Group L, **P=0.005 Group K vs Group P and Group L

The ketamine group performed better than the other groups regarding preemptive analgesia.

Discussion

We evaluated the effects of preoperative low-dose ketamine and lornoxicam on postoperative pain parameters and analgesic use in patients who had undergone surgery for lower extremity fracture in this randomized, double-blind, and placebo-controlled study. The most important result of the study was the decreased pain severity, increased patient satisfaction and decreased 24-hour fentanyl consumption in the postoperative period with low-dose ketamine administered preoperatively.

Postoperative pain causes various problems and complications for the patient and the physician and is caused by the changes created in the medulla spinalis, posterior horn neurons by the surgical incision. The painful stimuli that may develop during the surgical intervention or the perioperative period are known to increase postoperative pain by causing changes in the nervous system. Analgesia administration before a surgical trauma has been shown to decrease the posttraumatic sensitivity and secondary hyperalgesia in the spinal cord [9]. We therefore administered our study drugs 15 minutes before the surgical incision.

Peripheral sensitization is defined as a decrease in the threshold value of afferent terminal receptors while central sensitization is an increase in spinal neuron excitability due to activity [10, 11]. Stimulation of C fibers through surgical stimuli triggers central sensitization and this sensitization continues during the postoperative period. Considering that orthopedic surgery consists of quite painful interventions and that it may cause adequate central sensitization and peripheral hypersensitivity, orthopedic lower extremity fracture surgical cases are selected in our study to compare the effects of these two drugs.

Many previous studies have evaluated the role of various NSAIDs on moderate to severe postoperative pain treatment [2]. However, there are very few painful conditions where NSAIDs are adequate for postoperative pain treatment as a single agent. NSAIDs provide a more effective analgesia profile in a multimodal analgesia approach in addition to other agents or techniques, as an alternative to conventional postoperative pain treatment [2]. Lornoxicam is reported to be safe and effective when used as a part of multimodal postoperative pain management in adults [12]. A study comparing the postoperative analgesic efficacy of preoperative intramuscular 8 mg lornoxicam and 100 mg ketoprofen in abdominal hysterectomy found both drugs to be effective when compared to the control group; however, lornoxicam was more effective than ketoprofen in the early postoperative period [13]. Although we found a decrease in postoperative pain in patients who received lornoxicam in our study, there was no statistically significant difference between the placebo group and Group L that received lornoxicam. The efficacy of lornoxicam was less than that of ketamine in decreasing postoperative pain. The results of our study differ from the study of Karaman et al. [13]. Nevertheless, another study of the same author which compared patients to whom 8 mg lornoxicam was administered prior to a laparoscopic cholecystectomy with the patients who received 1 g paracetamol and a control group reported that lornoxicam and paracetamol had similar analgesic efficacy, but the use of analgesics was higher in the lornoxicam group [14].

Ketamine is a non-competitive antagonist of NMDA receptors and plays a key role in preventing central sensitization via the nicotinic and muscarinic receptors [15]. High-dose intravenous ketamine provides analgesia by affecting the spinal cord and brain. However, it also makes recovery after anesthesia difficult, and the patients are confused for a long time [16]. We therefore administered low doses of ketamine in our study. Various results were obtained in different studies with low-dose ketamine administration for postoperative pain treatment. Low-dose ketamine administered for anterior cruciate ligament repair surgery provides postoperative analgesia without any side effects while increasing the duration until the first analgesic requirement [17].

In this study, we evaluated the effect of low-dose ketamine and the NSAID lornoxicam administered preoperatively on pain parameters and total fentanyl use in the postoperative period. Preoperative ketamine (0.15 mg kg^{-1}) decreased postoperative pain scores more than lornoxicam (8 mg) or placebo and decreased fentanyl consumption in the postoperative period. The areas under pain vs. time curves that evaluate the postoperative period globally were lower in the group receiving ketamine. These data show that using preoperative low-dose ketamine decreased postoperative pain levels.

Roytblat et al. [18] have similarly found that the pre-incisional administration of 0.15 mg kg^{-1} IV ketamine led to a 40% decrease in the postoperative opioid requirement. Fu et al. [19] administered pre-incisional 0.5 mg kg^{-1} ketamine as an intravenous bolus, 10 mcg kg^{-1} ketamine infusion during surgery to one group and 0.5 mg kg^{-1} ketamine iv bolus to another group post-incisionally in patients undergoing abdominal surgery. Although there was no difference regarding postoperative pain scores between the two groups, the group receiving pre-incisional ketamine showed a significant decrease in the 1st and 2nd-day opioid requirement.

In a recent meta-analysis by Wang et al, [20] in which twenty-one randomized controlled trials about the analgesic effect of perioperative ketamine use for hip and knee arthroplasties are analyzed, perioperative ketamine was reported as a safe and an effective analgesic. Of these twenty-one studies, in one study [21], intravenous ketamine was used only pre-incisionally. In the remaining studies, ketamine was either used via the neuraxial route or infused throughout the operation after the initial bolus dose. A single low-dose ketamine seems an easier method of administration. In that study, Özbakış et al. [21] reported that the administration of small doses of intravenous ketamine and midazolam improved postoperative pain, patient satisfaction, and second day VAS scores, decreased total postoperative meperidine consumption, and delayed the time of first analgesic administration compared with the control group. However, the combination did not improve these results significantly over the intravenous ketamine-only group. Our results support the main findings of this study in lower extremity operations.

Patient satisfaction following the procedure is currently considered one of the most important postoperative monitoring parameters. Inadequate pain treatment also prolongs patient recovery, increases hospital expenses, and decreases patient satisfaction [22, 23]. A study evaluating patient satisfaction found the most important factor regarding satisfaction to be "worst pain score" [24].

We did have not any unsatisfied patients in our study. The highest satisfaction scores were in the ketamine group.

We evaluated the efficacy of preoperatively administered lornoxicam and ketamine in decreasing postoperative pain and found low-dose ketamine to be more efficient than lornoxicam in decreasing pain. The rest and motion VAS and VPS values, as well as fentanyl consumption, were much lower in the ketamine group than in the control and lornoxicam groups. Additional analgesic requirement was also significantly lower in the group which received ketamine. Although various factors play a role in the etiology of postoperative nausea and vomiting, opioids are the most important factor in its increase. We believe that the reason for the significantly higher incidence of nausea and vomiting in the group receiving placebo and lornoxicam compared to the group receiving ketamine was the higher fentanyl consumption in these two groups.

Conclusion

Low-dose ketamine administered preoperatively to patients for lower extremity surgery decreased postoperative pain scores more than lornoxicam (8 mg) or placebo in the postoperative period and enabled the patient to have a more comfortable postoperative period.

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