# Efficacy of Preventive Analgesia with Tramadol or Lornoxicam for Percutaneous Nephrolithotomy: A Prospective, Randomized, Double-Blind, Placebo-Controlled Study

Kenan Kaygusuz, MD[1]; Gokhan Gokce, MD[2]; Iclal Ozdemir Kol, MD[1]; Semih Ayan, MD[2]; and Sinan Gursoy, MD[1]

[1]Department of Anesthesiology, Cumhuriyet University School of Medicine, Sivas, Turkey; and [2]Department of Urology, Cumhuriyet University School of Medicine, Sivas, Turkey

## ABSTRACT

**Background:** Prevention of postoperative pain provides better and more rapid convalescence for patients.

**Objective:** The aim of this study was to compare the preventive analgesic effect of tramadol and lornoxicam in the early postoperative period in patients undergoing percutaneous nephrolithotomy (PCNL).

**Methods:** Patients who were scheduled for elective PCNL at the Cumhuriyet University Hospital, Sivas, Turkey, were enrolled in this prospective, double-blind, placebo-controlled study. The patients were randomly assigned to 1 of 3 groups: tramadol, lornoxicam, and normal saline (NS). Ten minutes before induction of anesthesia, the tramadol group received tramadol 100 mg IV, the lornoxicam group received lornoxicam 8 mg IV, and the NS group received NS 2 mL IV. Anesthesia was induced using fentanyl 1 µg/kg and thiopental sodium 4 to 7 mg/kg. Vecuronium 0.1 mg/kg was used for muscle relaxation. Desflurane 4% to 6% and 50%:50% oxygen/nitrous oxide were used for maintenance. Oxygen saturation, heart rate, and mean blood pressure were recorded before induction and during the postoperative period. During the postoperative period, visual analogue scale (VAS) scores, time to first analgesic (TFA), total analgesic consumption (TAC), and patient satisfaction scores were determined. Data about postoperative nausea and vomiting and other adverse events and complications were also collected.

**Results:** Seventy-three patients were assessed for enrollment and 60 (33 women, 27 men; mean [SD] age, 44.69 [11.27] years; age range, 20–62 years) were included in the study. The baseline demographic characteristics and duration of surgery were similar in all 3 groups. The mean (SD) VAS scores in the tramadol group were significantly lower than in the NS group at 15 and 30 minutes and 1, 2, 4, and 12 hours after surgery (all, $P < 0.05$). The VAS scores in the lornoxicam

group were significantly lower than in the NS group at 15 and 30 minutes and 1 hour (all, $P < 0.05$). The VAS score at 1 hour after surgery was significantly lower in the tramadol group than in the lornoxicam group (18 [8] vs 32 [16]; $P < 0.05$); however, there were no other significant differences in VAS scores between the active groups. A significantly shorter TFA was associated with the NS group when compared with the tramadol and lornoxicam groups (46 [27] vs 354 [187] and 180 [118], respectively; both, $P < 0.05$). TFA was significantly shorter in the lornoxicam group when compared with the tramadol group (180 [118] vs 354 [187]; $P < 0.05$). TAC was significantly higher in the NS group than in the tramadol and lornoxicam groups (270 [47] vs 115 [74] and 145 [72], respectively; both, $P < 0.05$). Patient satisfaction score (range) was significantly lower in the NS group when compared with the tramadol and lornoxicam groups (0 [0–1] vs 3 [0–3] and 2 [0–3], respectively; both, $P < 0.05$). There were no other significant between-group differences observed.

**Conclusions:** Tramadol and lornoxicam were more effective than NS in preventing early postoperative pain. The preventive analgesic effect of tramadol was comparable with that of lornoxicam, except at 1 hour when tramadol was more effective among these patients undergoing PCNL. Both drugs were well tolerated. (*Curr Ther Res Clin Exp.* 2007;68:205–216) Copyright © 2007 Excerpta Medica, Inc.

**Key words:** preventive analgesia, lornoxicam, percutaneous nephrolithotomy, tramadol.

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## INTRODUCTION

The concept of preventive analgesia is generally known and often used for postoperative pain control.[1–4] Therefore, appropriate postoperative pain treatment may start before surgery, last long enough after surgery to avoid pain-induced sensitization processes, and include effective analgesic interventions (preventive analgesia). The concept of preventive analgesia includes multimodal antinociceptive techniques with analgesics that exceed the expected duration of action and that attenuate peripheral or central hypersensitivity.[5]

Tramadol is an opioid analgesic widely used in anesthesia and particularly suitable for postoperative analgesia.[6,7] It has a lower affinity for opioid receptors than morphine, resulting in analgesic potency that is 10 times weaker than that of morphine, but similar to that of pethidine. The mean elimination $t_{1/2}$ of tramadol is 5 to 6 hours. Furthermore, only 40% of the analgesic effect of tramadol is antagonized by naloxone, suggesting an additional nonopioid mechanism that contributes to the overall analgesic effect of tramadol.[8] This second mechanism is associated with the activation of the descending antinociceptive system and consists of both inhibition of the reuptake mechanisms for noradrenaline and serotonin (5-HT) and increased release of 5-HT.[8–10]

Lornoxicam is an NSAID that belongs to the enolic acid chemical class, which also includes tenoxicam and piroxicam. Its analgesic potency in experimental

pain models exceeds that of tenoxicam and piroxicam by ~12- and 3-fold, respectively, and that of diclofenac and indomethacin by 6- and 4-fold, respectively.[11] Lornoxicam is rapidly eliminated, having a short plasma elimination $t_{1/2}$ of 3 to 5 hours,[12,13] which suggests it is suitable for acute use in the postoperative period. In the treatment of postoperative pain, lornoxicam has been found to be as effective as morphine,[14] pethidine,[15] and tramadol.[16]

The aim of this study was to compare the preventive analgesic effect of tramadol and lornoxicam in the early postoperative period in patients undergoing percutaneous nephrolithotomy (PCNL).

## PATIENTS AND METHODS

Written informed consent was obtained from each patient, and the study protocol was approved by the local human ethics committee. Patients with American Society of Anesthesiologists'[17] physical status I and II, who were scheduled for elective PCNL at the Cumhuriyet University Hospital, Sivas, Turkey, were eligible for this prospective, double-blind, placebo-controlled study. Exclusion criteria were age <18 years, a history of drug or alcohol abuse, chronic use of drugs known to alter anesthetic or analgesic requirements, or allergy to any of the study medications. Patients were also excluded if they were receiving an experimental drug, including tramadol or lornoxicam; had a history of gastric, renal, cardiac, or respiratory disorder; or >50% above their ideal weight.

Before surgery, patients were instructed in the use of the 100-mm visual analogue scale (VAS) for pain assessment (0 = no pain to 100 = maximum pain). VAS scores were assessed under static conditions in our clinical setting.

None of the patients was premedicated. On arrival in the operating room, patients were administered lactated Ringer's solution 10 mL/kg · h IV after baseline measurements of heart rate (HR), noninvasive mean arterial pressure (MAP), and oxygen saturation ($SpO_2$) with a Criticare System 1100 monitor (Criticare System Inc., Waukesha, Wisconsin). Before induction of anesthesia, patients were allocated randomly to receive 1 of the 3 study drugs. Randomization was based on a computer-generated code that was prepared at a remote site and sealed in opaque, sequentially numbered envelopes. Randomization was based on blocks of 6 patients. The drugs were prepared by an anesthetist (who was not one of the study investigators) in three 2-mL syringes, which contained either tramadol hydrochloride 100 mg (Contramal, Grünenthal GmbH, Aachen, Germany), lornoxicam 8 mg (Xefo, Mefar Ilac Sanayii A.S., Istanbul, Turkey), or normal saline (NS) 2 mL. They were marked only with a coded label to maintain the double-blind nature of the study. Ten minutes before induction of anesthesia the appropriate study drug was administered.

Anesthesia was induced using fentanyl 1 µg/kg (Fentanyl citrate injection, Abbott Laboratories, North Chicago, Illinois) and thiopental sodium 4 to 7 mg/kg (Pental Sodyum, I.E. Ulagay Ilac Sanayii Turk A.S., Istanbul, Turkey). Vecuronium 0.1 mg/kg (Norcuron, Organon-Teknika, Boxtel, The Netherlands)

was used for muscle relaxation and maintained (0.03 mg/kg) by bolus administration at 30-minute intervals. Desflurane 4% to 6% (Suprane, Eczacıbaşi-Baxter Hastane Urunleri San. ve Tic. A.S., Istanbul, Turkey) and 50%:50% oxygen/nitrous oxide were used for maintenance. No opioids were administered intraoperatively.

Recovery was assessed using the objective criteria of the modified Aldrete scoring recommendations.[18] Each variable was scored on a 3-point scale—consciousness (2 = fully awake; 1 = able to be roused on calling; 0 = not responding), activity (able to move voluntarily or on command; 2 = 4 extremities, 1 = 2 extremities; 0 = 0 extremities), respiration (2 = able to breathe deeply and cough freely; 1 = dyspnea, shallow or limited breathing; 0 = apneic), circulation (2 = blood pressure [BP] ±<20 mm of preanesthetic level; 1 = BP ±20–50 mm of preanesthetic level; 0 = BP ±>50 mm of preanesthetic level), and $SpO_2$ (2 = >92% on room air; 1 = needs $O_2$ inhalation to maintain $SpO_2$ >90%; 0 = $SpO_2$ <90% even with $O_2$ supplementation)—with a maximum achievable score of 10. After total recovery from anesthesia (Aldrete score ≥9), patients were transferred to the recovery room for ≥1 hour and were then discharged to the ward. HR, MAP, and $SpO_2$ were recorded before induction of anesthesia. VAS, HR, MAP, and $SpO_2$ were recorded at 15 and 30 minutes, and at 1, 2, 4, 6, 12, and 24 hours, postoperatively.

Aldrete scores were recorded at 1, 15, and 30 minutes after extubation. Tramadol 50 mg IV was administered either at the patient's request or when the VAS score was >30 mm, and was repeated if the VAS score remained >30 mm. Time to first analgesic (TFA) and total analgesic consumption (TAC) were recorded at 24 hours. All patients were asked to rate their degree of satisfaction with the management of their pain (0 = poor; 1 = adequate; 2 = good; 3 = excellent) on a questionnaire administered after the study period. Primary efficacy assessment included the proportion of patients with *successful analgesia*, defined as no or mild pain with a respiratory rate of ≥11/min and an $SpO_2$ of ≥94% for the entire period after administration of the study drugs and with an excellent degree of satisfaction. Frequency of nausea, vomiting, and other adverse events (AEs) were recorded postoperatively.

The primary outcomes in this study were VAS, TFA, TAC, and patient satisfaction score. Secondary outcomes in this study were hemodynamic and respiratory variables and AEs.

## Statistical Analysis

Data are presented as mean (SD), median (range), or percentage, as appropriate. Statistical analyses were performed using Statistica 7.0 software (Statsoft, Inc., Tulsa, Arizona). Demographic variables, TFA, and TAC among the groups were compared using 1-way analysis of variance (ANOVA). The ratio of male/female patients and the prevalence of nausea and vomiting in the study groups were compared using the $\chi^2$ test. VAS scores were analyzed using Friedman's nonparametric repeated-measures ANOVA. HR, MAP, and $SpO_2$ among the groups were compared using repeated-measures ANOVA. Patient sat-

isfaction scores in the study groups were compared using Kruskal-Wallis 1-way ANOVA. All post hoc comparisons were performed using the Tukey test. $P < 0.05$ was considered statistically significant.

Using ANOVA to determine sample size, a mean difference of 15 mm on the 100-mm VAS used for pain assessment at 15 minutes postoperatively was defined as clinically relevant in all groups. It was expected that 95% of the reported VAS scores would range between 0 and 80 mm, resulting in an SD of 17 mm. A total sample size of 54 patients (18 in each arm of the study) was calculated to be necessary to detect a 15-mm reduction in VAS score with a power of 80% and an $\alpha$ error of 5%. It was assumed that the study dropout rate would be ~20%, and therefore a total sample of 66 patients was needed.

## RESULTS

During the study period between June 2005 and March 2006, 73 consecutive patients with the required PCNL indication were identified. Two had to be excluded because of obesity, 3 refused to participate, and 2 were missed because of high workload. Therefore, 66 patients were identified as suitable for the study and were randomly assigned to 1 of the 3 groups. Of these 66 patients, 2 in each of the groups had to be excluded from data analysis because of protocol violations. Therefore, 60 patients (33 women, 27 men; mean [SD] age, 44.69 [11.27] years; age range, 20–62 years) completed the study and were included in the data analyses.

There were no significant differences between the tramadol, lornoxicam, and NS groups with regard to age, sex, weight, or the duration of surgery (**Table**). There also were no statistically significant differences in hemodynamic data (MAP and HR) or in $SpO_2$ values at the induction of anesthesia or during the postoperative period. These values remained within the normal range through-

**Table. Baseline demographic characteristics and duration of surgery of the study patients undergoing percutaneous nephrolithotomy (n = 60). Data are mean (SD) unless otherwise specified.***

| Characteristic | Tramadol Group (n = 20) | Lornoxicam Group (n = 20) | Normal Saline Group (n = 20) |
|---|---|---|---|
| Age, y | 43.66 (11.43) | 43.86 (13.42) | 46.53 (9.11) |
| Sex, no. (%) | | | |
| Female | 10 (50) | 12 (60) | 11 (55) |
| Male | 10 (50) | 8 (40) | 9 (45) |
| Weight, kg | 72.4 (6.3) | 70.6 (10.1) | 76.0 (8.7) |
| Duration of surgery, min | 121.66 (45.34) | 108.66 (30.67) | 119.50 (29.91) |

*There were no significant between-group differences.

out the study period. Median (range) Aldrete scores for the tramadol, lornoxi-
cam, and NS groups within 1 minute after extubation were 9 (7–9), 9 (7–9), and
8 (6–9), respectively. All patients in the 3 groups had Aldrete scores of 9 at 15
and 30 minutes after extubation.

The mean (SD) VAS scores in the tramadol group were significantly lower
than in the NS group at 15 and 30 minutes and 1, 2, 4, and 12 hours after surgery
(all, $P < 0.05$). The VAS scores in the lornoxicam group were significantly lower
than in the NS group at 15 and 30 minutes and 1 hour (all, $P < 0.05$). The VAS
score was significantly lower in the tramadol group than in the lornoxicam group
at 1 hour (18 [8] vs 32 [16]; $P < 0.05$) (**Figure 1**). There were no other signifi-
cant differences in VAS scores between the active drug groups.

Mean (SD) TFA was significantly shorter in the NS group than in the tra-
madol and lornoxicam groups (46 [27] vs 354 [187] and 180 [118] minutes,
respectively; both, $P < 0.05$). TFA was significantly shorter in the lornoxicam
group than in the tramadol group (180 [118] vs 354 [187] minutes; $P < 0.05$)
(**Figure 2**).
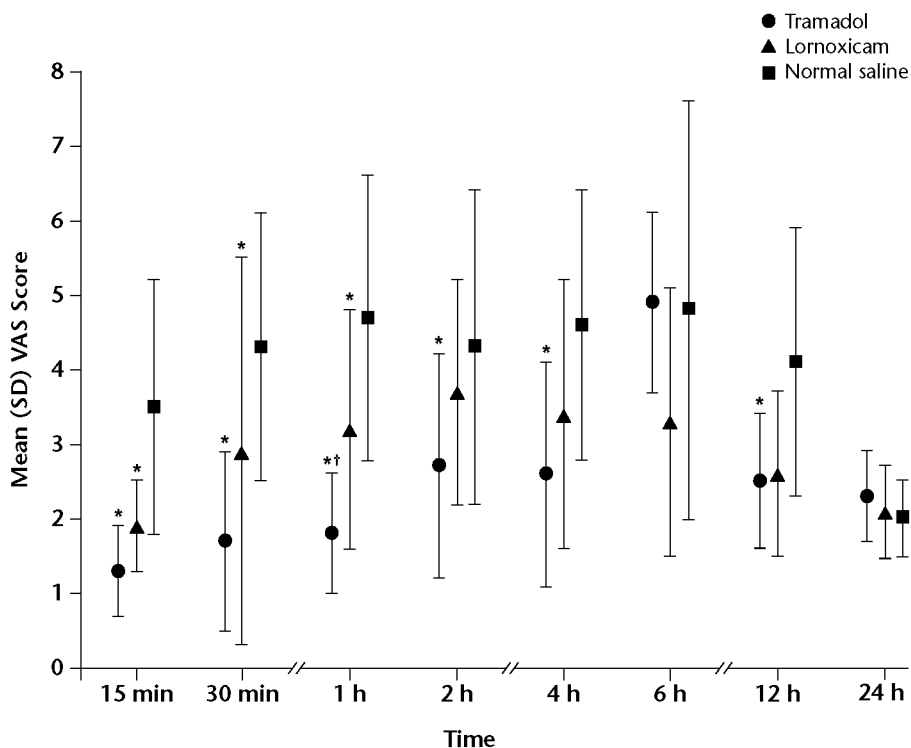


Figure 1. Reported mean (SD) visual analogue scale (VAS) scores by study group in
patients after percutaneous nephrolithotomy. *$P < 0.05$ versus normal saline;
†$P < 0.05$ versus lornoxicam. Scale: 0 = no pain to 100 = maximum pain.
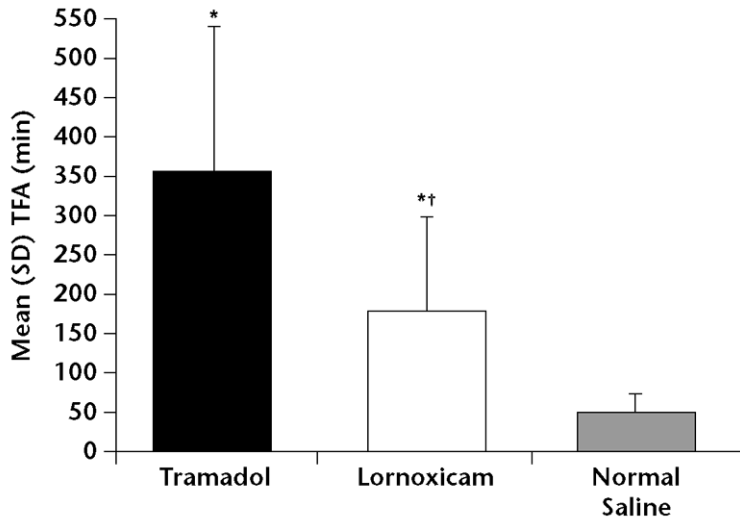
Figure 2. Mean (SD) time to first analgesic (TFA) by study group in patients undergoing percutaneous nephrolithotomy. *$P < 0.05$ versus normal saline; [†]$P < 0.05$ versus tramadol.

Mean (SD) TAC was significantly higher in the NS group than in the tramadol and lornoxicam groups (270 [47] vs 115 [74] and 145 [72] mg, respectively; both, $P < 0.05$) (**Figure 3**). There were no significant differences in TAC between the active drug groups.

The mean (range) patient satisfaction score in the NS group was significantly lower than in the tramadol and lornoxicam groups (0 [0–1] vs 3 [0–3] and 2 [0–3], respectively; both, $P < 0.05$) (**Figure 4**). There were no significant differences in patient satisfaction scores between the active drug groups.

There were no significant differences in the prevalence or proportion of patients with nausea and vomiting in the tramadol, lornoxicam, and NS groups (33%, 30%, and 40%, respectively). There were no other observed AEs or complications.

## DISCUSSION

We found that the effects of tramadol and lornoxicam were comparable with regard to HR, $SpO_2$, MAP, and AEs at the induction of anesthesia and during the postoperative period. During the postoperative period, the analgesic effect of tramadol and lornoxicam was significantly higher than that of NS. The analgesic effect of tramadol was significantly greater than that of lornoxicam only at 1 hour postoperatively; there were no other significant differences between the active groups at other time points. TFA was significantly longer in patients administered tramadol and lornoxicam than NS, and TFA was also significantly longer
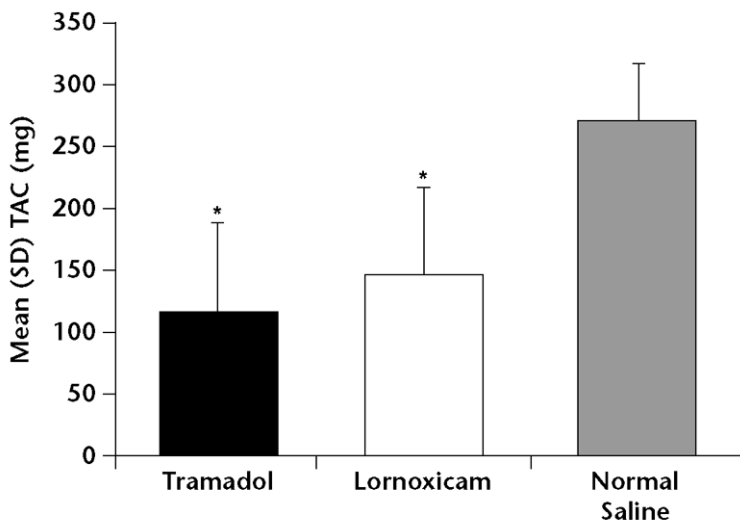
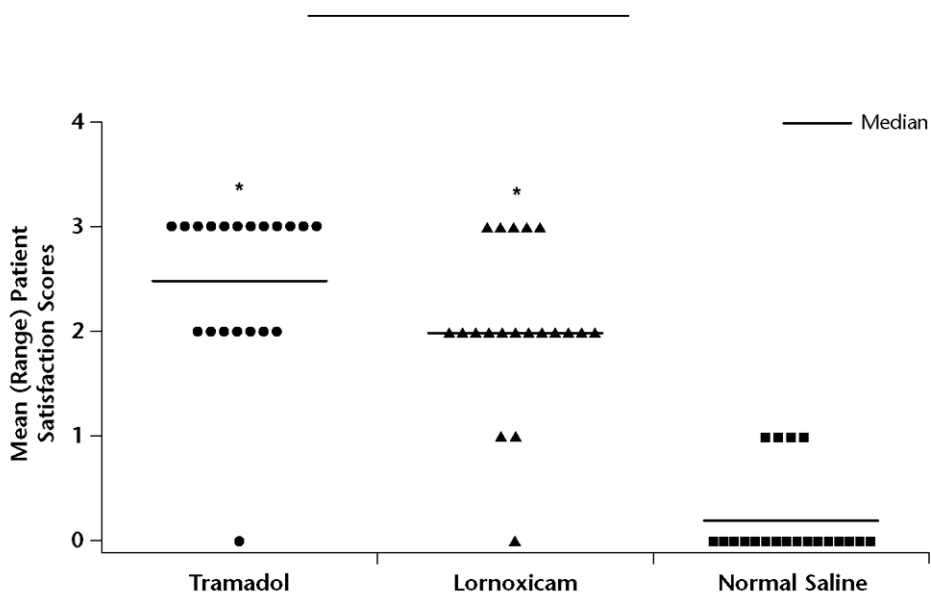Figure 3.  Mean (SD) total analgesic consumption (TAC) by study group. *P < 0.05 versus normal saline.



Figure 4.  Median (range) patient satisfaction scores by study group. Horizontal lines represent median values. *P < 0.05 versus normal saline. Scale: 0 = poor; 1 = adequate; 2 = good; 3 = excellent.

with tramadol than with lornoxicam. TAC and patient satisfaction score were comparable in the tramadol and lornoxicam groups. Our results suggest that tramadol and lornoxicam were more effective and as well tolerated as NS when used as a preventive analgesic administered before general anesthesia for PCNL.

Schug et al[19] suggested that 20% to 40% of patients experience postoperative pain of moderate intensity and another 50% to 70% experience severe postoperative pain. Postoperative pain not only causes considerable distress to the patient, but it also contributes to prolonging recovery time and may adversely affect patient outcome.[20]

Tramadol is a μ-opioid receptor agonist that inhibits serotonin and norepinephrine reuptake, enhancing inhibitory effects on pain transmission in the spinal cord.[8] Lornoxicam inhibits cyclooxygenase enzymes and decreases peripheral and central prostaglandin production.[11,12] In addition to reducing the inflammation that accompanies tissue injury, decreasing prostaglandin production attenuates the response of the peripheral and central components of the nervous system to noxious stimuli.[11,12] The flow of nociceptive information in the perioperative period is biphasic. The first phase is directly connected with nociceptive stimulation that accompanies injuries brought about by surgical procedures. The second phase, manifesting itself in the postoperative period, is the result of inflammatory responses associated with this injury and is caused by the first-phase changes in nociceptive structures of the spinal cord.[11,12] The aim of preventive analgesia is to prevent or inhibit the first phase and thus to protect the central nervous system from increased noxious stimulation during surgery.[21,22] Several studies[1–4] of preventive analgesia found that preoperative administration of systemic opioids was more effective in reducing postoperative pain than in control conditions (placebo use or preoperative use of study drugs). Therefore, in this study we administered the study drugs before the induction of anesthesia.

Although opioid analgesics are the traditional first-line treatment in this setting,[19] they have the potential to cause AEs such as respiratory depression, confusion, drowsiness, nausea, and vomiting, which often lead to a reluctance to increase doses to achieve adequate analgesia.[23] NSAIDs provide effective analgesia in patients with acute pain after minor and major surgery, either as a substitute for, or as an adjunct to, opioid analgesia.[23,24] The major advantage of NSAIDs is that, compared with opioid analgesics, they are relatively well tolerated when used in selected patients for short-term postoperative analgesia.[25]

Tramadol, which possesses bidirectional action via opioid receptors and activation of the descending antinociceptive system, used as preemptive analgesia may successfully inhibit the development of the nociceptive process and its consequences in the perioperative period. This has been suggested in experimental and clinical observations[26] of the effect of preemptive analgesia induced by drugs activating the noradrenergic and serotoninergic systems, indicating that not only opioids but drugs that activate the descending antinociceptive system may inhibit central sensitization.

In a prospective, randomized, double-blind study, Naguib et al[27] compared the efficacy of tramadol and morphine for intra- and postoperative analgesia in 100 patients undergoing laparoscopic cholecystectomy. Ten minutes before induction of anesthesia, patients received tramadol 100 mg or morphine 10 mg IV. They reported no significant difference between the use of tramadol and morphine to treat pain. The prospective, randomized, double-blind, controlled study by Unlugenc et al[6] suggested that in patients who underwent major abdominal surgery, tramadol 1 mg/kg administered after induction of anesthesia was associated with postoperative pain relief, recovery, and patient-controlled analgesia morphine consumption similar to patients administered morphine 0.1 mg/kg.

Wordliczek et al[7] investigated the influence of preemptive IV tramadol administered before general anesthesia in 90 patients, immediately after peritoneal closure, or immediately after surgery on the tramadol requirement in the first 24 hours after surgery. They concluded that the pre- or intraoperative use of tramadol significantly reduced the opioid requirement in the early postoperative period, confirming the possibility that tramadol used in this way may inhibit the activation of sensitization processes connected with Phase I of nociceptive information flow. In our study, after the administration of tramadol as a preventive analgesic agent, the early postoperative analgesic requirement was significantly lower than those of lornoxicam and NS.

Preoperative cyclooxygenase inhibitors had clear benefits in terms of reduced postoperative pain and analgesic consumption and increased patient satisfaction compared with placebo.[3] Effects on postoperative nausea and vomiting remain uncertain, as do those on recovery from surgery or economic benefit.[3] Beneficial effects have been reported with NSAIDs in orthopedic surgery[28] and during laparoscopic tubal ligation.[29] In contrast, other authors have reported no benefit of preoperative administration of NSAIDs on postoperative analgesia after orthopedic or laparoscopic gynecologic surgery.[4,30,31] In the present study, preoperative administration of lornoxicam relieved pain after PCNL significantly more effectively than NS and similar to tramadol, except at 1 hour when tramadol was significantly more effective.

We believe that the major limitation of this study was the possible analgesic contribution of the general anesthesia agents used.

## CONCLUSIONS

Tramadol and lornoxicam were more effective than NS in preventing early postoperative pain. The preventive analgesic effect of tramadol was comparable to that of lornoxicam, except at 1 hour, when tramadol was more effective among these patients undergoing PCNL. Both drugs were well tolerated.

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**Address correspondence to:** Kenan Kaygusuz, MD, Department of Anesthesiology, Cumhuriyet University School of Medicine, 58140 Sivas, Turkey. E-mail: kaygusuzkenan@gmail.com