ORIGINAL ARTICLE

Analgesic effects of lornoxicam after total abdominal hysterectomy

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ABSTRACT

The authors investigated, in a randomized, placebo-controlled, double-blinded study, the efficacy and safety of lornoxicam on pain after abdominal hysterectomy and on tramadol consumption in patients. Fifty patients were randomized to receive either oral placebo or lornoxicam 8 mg one hour before surgery. Anesthesia was induced with propofol and maintained with sevoflurane in 50 percent N_2O/O_2 with a fresh gas flow of 2 L/min (50 percent N_2O in O_2) and fentanyl (2 μg/kg). All patients received patient-controlled analgesia with tramadol with loading dose of 50 mg; incremental dose of 20 mg; lock out interval of 10 minute; and four-hour limit 300 mg. The incremental dose was increased to 30 mg if analgesia was inadequate after one hour. Patients were studied at one, two, four, eight, 12, and 24 hours for visual analogue (VAS) pain scores, heart rate, mean arterial pressure, periferic oxygen saturation, sedation, tramadol consumption, and length of hospitalization. VAS scores at one hour were significantly lower in the lornoxicam group ($p < 0.001$). The tramadol consumption at one, two, four, eight, and 12 hours was significantly lower in the lornoxicam group when compared with the placebo group ($p < 0.001$, $p = 0.008$, $p = 0.029$, $p = 0.034$, $p = 0.042$, respectively). Sedation scores were similar at all the measured times in the groups. Length of hospitalization was significantly shorter in lornoxicam group (4.8 ± 0.4 day) than placebo group (5.2 ± 0.5 day) ($p = 0.005$). There was difference in the incidence of nausea between the groups ($p = 0.047$). The number of patients and the doses of antiemetics given during the first 24 hours after surgery in lornoxicam group were less than those in placebo group ($p = 0.003$, $p = 0.034$, respectively).

In conclusion, a single oral dose of lornoxicam given preoperatively enhanced the analgesic effect of tramadol, decreasing tramadol consumption and side effects, and shortened the length of hospitalization.

Key words: analgesics opioid, tramadol, lornoxicam, postoperative pain, hysterectomy

INTRODUCTION

Postoperative pain is a factor that affects recovery from surgery and anaesthesia. The use of opioids by patient controlled analgesia (PCA) is popular, but is limited by side effects and by the fact that certain types of pain respond poorly to opioids.[1] Because of the multiplicity of mechanisms involved in postoperative pain, a multimodal analgesic regimen, using a combination of opioid and nonopioid analgesic drugs, is often used to enhance analgesic efficacy and to reduce opioid requirements and side effects.[2]

Lornoxicam is a member of the oxicam group of nonsteroidal anti-inflammatory drugs (NSAIDs). It is rapidly eliminated, having a short plasma elimination half-life of three to five hours, which suggests its suitability for acute use during the postoperative period.[3,4] The clinical trials published so far, mostly comparative, clearly document lornoxicam's efficacy as a potent analgesic with excellent anti-inflammatory properties in a range of painful and/or inflammatory conditions, including postoperative pain. Lornoxicam has been shown to be at least as effective as comparable NSAIDs, and more effective than 10 mg morphine, when used at doses of 3 8 mg to control pain after oral surgery.[5,6]

The present study's aim was to determine the lornoxicam's effect on postoperative pain and on patient controlled tramadol consumption in patients after abdominal hysterectomy.

METHODS

After obtaining the approval of the Institutional Ethics Committee (Trakya University, Edirne, Turkey) and written informed consent from the patients, 50 patients, ASA physical status I-II, undergoing elective total abdominal hysterectomy with salpingo-oophorectomy were studied. Patients were eligible for participation if they were at least 18 years old, weighed more than 40 kg, and could operate a patient controlled analgesia (PCA) device. Exclusion criteria were known allergy to opioids,

Table 1. Demographic characteristics and perioperative data*		
Variable	**Placebo (n = 25)**	**Lornoxicam (n = 25)**
Age (years)	48.24 ± 7.95	47.72 ± 8.01
Weight (kg)	67.36 ± 13.3	68.04 ± 13.40
Height (cm)	158.0 ± 5	156 ± 7
Body mass index (kg/m^2)	28 ± 1.2	28.4 ± 2
ASA physical status (I/II)	15/10	16/9
Duration of anesthesia (min)	130.88 ± 31.51	129.12 ± 30.07
*Values are shown as number (n) of patients or mean ± SD. No significant differences were found between the groups.		

asthma, contraindications to tramadol or any drug used, renal insufficiency, a history of a peptic ulcer, or a history of a bleeding diathesis.

The patients were randomly divided into two groups of 25 patients each. The study design was randomized and double-blinded: Patients were randomly allocated according to computer-generated randomization. For premedication, midazolam 0.07 mg/kg and atropine 0.01 mg/kg were administered IM 45 minutes before the surgical procedure. Patients in the control group received an oral placebo capsule, and those in the lornoxicam group received 8 mg lornoxicam (Xefo, 8 mg, Abdi Ibrahim, Istanbul, Turkey) (n = 20, Group I) one hour prior to surgery. The study drugs were prepared by the pharmacy, and an appropriate code number was assigned.

In the operating room, a crystalloid infusion was started through an IV cannula inserted in an antecubital vein, and the mean arterial pressure (MAP), heart rate (HR), and peripheral oxygen saturation (SpO_2) were monitored (Cato PM 8040; Dräger, Lübeck, Germany). Anesthesia was induced with propofol (2 mg/kg) and atracurium (0.5 mg/kg), and maintained with sevoflurane with a fresh gas flow of 2 L/min (50 percent N_2O in O_2) and fentanyl (2 µg/kg). Surgery was performed via a Pfannenstiel incision. The lungs of the patients were mechanically ventilated (Cato; Dräger, Lübeck, Germany), and ventilation was adjusted to maintain end-expiratory CO_2 between 34 and 36 mmHg. At the end of surgery, neuromuscular block was antagonized with neostigmine 1.5 mg and atropine 0.5 mg.

Table 2. Postoperative HR and MAP*			
Hours after operation		**Placebo (n=25)**	**Lornoxicam (n = 25)**
1	HR	78.80 ± 6.45	79.24 ± 9.79
	MAP	88.35 ± 11.22	88.52 ± 9.69
2	HR	79.20 ± 6.19	78.96 ± 8.93
	MAP	88.20 ± 10	88.96 ± 9.76
4	HR	79.44 ± 7.88	78.88 ± 7.10
	MAP	88.84 ± 10.50	89.52 ± 8.80
8	HR	81.04 ± 5.89	80.56 ± 4.86
	MAP	89.76 ± 9.81	88.04 ± 9.89
12	HR	80.16 ± 4.96	81.12 ± 5.66
	MAP	86.52 ± 8.25	89.52 ± 8.91
24	HR	80.0 ± 6.53	80.48 ± 7.60
	MAP	88.64 ± 8.50	87.04 ± 7.49
*HR, heart rate (beats/min); MAP, mean arterial pressure (mmHg). HR and MAP are presented as mean ± SD. No statistical difference was found between groups.			

Table 3. Postoperative pain and sedation scores in lornoxicam and placebo groups*				
Variable (h)	Placebo (n = 25)		Lornoxicam (n = 25)	
	Sedation	VAS	Sedation	VAS
1	2 (1-3)	4 (1-8)	2 (1-3)	2 (0-5)†
2	2 (1-3)	3 (2-6)	2 (1-3)	2 (0-5)
4	2 (2-2)	3 (0-4)	2 (2-3)	2 (0-6)
8	2 (2-2)	2 (0-3)	2 (2-3)	1 (0-3)
12	2 (2-3)	0 (0-3)	2 (2-3)	0 (0-2)
24	2 (2-2)	0 (0-2)	2 (2-2)	0 (0-1)

*Pain and sedation scores are median (min-max). †The VAS scores were significantly lower one hour postoperative in the lornoxicam group than in the placebo group ($p < 0.001$).

After tracheal extubation, patients were transferred to the postanaesthesia care unit (PACU). Postoperative pain was assessed based on the visual analogue score (VAS, where 0 cm, "no pain" and 10 cm, "worst pain imaginable"). Postoperative analgesia was provided with IV-PCA tramadol. The PCA technique and the VAS were explained to the patients during their preoperative visit. Patients were connected to the PCA device (Abbott Pain Management Provider, North Chicago, IL) upon their arrival in the PACU. All patients received tramadol PCA (3 mg/mL) with a loading dose of 50 mg, an incremental dose of 20 mg, a lockout interval of 10 minute, and a four-hour limit of 300 mg. The incremental dose was increased to 30 mg if the analgesia was inadequate after one hour. Sedation was assessed by the Ramsay sedation scale.[7] During the first hour in the PACU, and then at two, four, eight, 12, and 24 hours, the patients' pain scores were evaluated. HR, SpO_2, MAP, sedation, tramadol use, and total dose of tramadol were assessed by an anaesthesiology resident not otherwise involved in the study. The occurrence of any side effects, such as nausea and vomiting, constipation, respiratory depression, dizziness, somnolence, peripheral edema, diarrhea, headache, and pruritis, was recorded. Tramadol was stopped if a patient had an oxygen saturation, measured by pulse oximetry, less than 95 percent, or a serious adverse event related to opioid administration. On the patient's request, or if nausea and vomiting occurred, ondansetron 4 mg IV was given. All measurements were recorded by the same anaesthesia resident, who was blinded to the study drugs administered.

Statistical analysis

A sample size of 25 patients by group was calculated to detect a significant difference of 15 percent or more in tramadol consumption with a power of 85 percent and a significance level of 5 percent. Descriptive statistics are expressed as mean ± SD unless otherwise stated. All variables were tested for normal distribution by Kolmogorov-Smirnov test. Student t test was used for comparison of the means of continuous variables and normally distributed data. Mann-Whitney U test was used otherwise. Two-way analysis of variance or Friedman test was used for variable differences in groups, and Bonferroni or Tukey HSD test was used for multiple comparisons. Categorical data were analyzed using χ^2 test analysis or the Fisher exact, as appropriate. Significance was determined at $p < 0.05$.

RESULTS

Fifty consecutive patients who fulfilled the inclusion criteria were included in the study. All the patients allocated completed the study; data from all 50 patients were therefore analyzed.

The groups were comparable with respect to age, body weight, height, ASA status, and duration of surgery (Table 1). MBP and HR did not differ between the groups at any of the measured times (Table 2).

The VAS scores were significantly lower one hour postoperative in the lornoxicam group than in the placebo group ($p < 0.001$) (Table 3). Sedation scores were similar at all the measured times in the lornoxicam and placebo groups (Table 3). No patient exhibited excessive sedation requiring alteration of the PCA settings or discontinuation.

Tramadol consumption at one, two, four, eight, and 12 hours was significantly lower in the lornoxicam group than in the placebo group ($p < 0.001$, $p = 0.008$, $p = 0.029$, $p = 0.034$, $p = 0.042$, respectively) (Table 4).

Length of hospitalization was significantly shorter in the lornoxicam group (4.8 ± 0.4 days) than in the placebo group (5.2 ± 0.5 days) ($p = 0.005$).

Table 4. Total tramadol consumption (mg) in the lornoxicam and placebo groups*			
Hours	**Placebo (n = 25)**	**Lornoxicam (n = 25)**	**p**
1	110.57 ± 27.54	80.54 ± 27.54	< 0.001
2	168.01 ± 38.55	132.85 ± 50.51	0.008
4	222.62 ± 45.54	177.27 ± 68.15	0.029
8	310.54 ± 70.11	262.02 ± 86.35	0.034
12	350.14 ± 86.01	295.45 ± 98.40	0.042
24	392.89 ± 111.03	331.89 ± 111.03	0.082

*Tramadol doses are expressed as mean ± SD. Tramadol consumption at one, two, four, eight, and 12 hours was significantly lower in the lornoxicam group than in the placebo group.

The most common side effects seen during the study were nausea and vomiting (Table 5), and there was a difference in the incidence of nausea between the groups (p = 0.047). The number of patients and the doses in patients receiving antiemetics during the first 24 hours after surgery was less in the lornoxicam group than in the placebo group (p = 0.003, p = 0.034, respectively) (Table 6). No patient had oxygen saturation less than 95 percent or a serious adverse event related to opioid administration.

DISCUSSION

The results of our preoperative oral single-dose study investigating lornoxicam's acute postoperative analgesic effects in patients after total abdominal hysterectomy show that: 1) Lornoxicam decreased postoperative tramadol consumption, 2) Lornoxicam was not associated with more side effects than the placebo, and 3) Lornoxicam shortened the length of hospitalization.

The main aim of combining different analgesic drugs is to obtain synergistic or additive analgesia, allowing a lower dose of each agent and improving the safety profile. This can be achieved by combining analgesics acting at different locations, e.g., centrally and peripherally acting analgesics. Tramadol can be used in PCA for moderate-to-severe postoperative pain. Its efficacy arises from two complementary mechanisms of action: stimulation of opioid receptors and inhibition of norepinephrine and 5-hydroxytryptamine reuptake in pain pathways.[8]

The NSAIDs act at peripheral nociceptors, preventing pain by inhibiting cyclo-oxygenase and thus reducing biosynthesis of pain-promoting prostoglandin derivatives in the periphery, produced in response to tissue injury. In addition, increasing evidence suggests that NSAIDs directly inhibit spinal nociceptor processing, an effect that correlates with various NSAIDs' ability to inhibit cyclo-oxygenase.[9,10]

The NSAIDs are commonly used analgesics for minor surgery and are useful adjunctive analgesics in patients undergoing major surgery, decreasing their pain and opioid requirements. They are well established, effective, and inexpensive. Trampitsch et al.[11] demonstrated that lornoxicam (8-mg bolus every eight hours for a total dose of 24 mg in the first 24 hours) administered preemptively improved the quality of postoperative analgesia and led to reduced consumption of opioid

Table 5. Incidence of side effects*			
Side effect	**Placebo (n = 25)**	**Lornoxicam (n = 25)**	**p**
Nausea	17 (68 percent)	10 (40 percent)	0.047
Vomiting	5 (20 percent)	5 (20 percent)	1.000
Ortastatic hypotension	0 (0 percent)	1 (4 percent)	0.820
Flushing	1 (4 percent)	0 (0 percent)	0.820

*Values are shown as number (n) of patients. The incidence of nausea was less in the lornoxicam group than in the placebo group.

Table 6. Number of patients receiving antiemetics, and doses in patients receiving antiemetics during the first 24 hours after surgery*			
	Placebo (n = 25)	**Lornoxicam (n = 25)**	**p**
Number of patients receiving antiemetics	16/25	7/25	0.034
Number of doses in patients receiving antiemetics	7.36 ± 6.08	3.84 ± 5.22	0.003
*Values are shown as number (n) of patients. The number of patients and doses in patients receiving antiemetics during the first 24 hour after surgery was less in the lornoxicam group than in the placebo group.			

analgesics postoperatively in patients undergoing gynecological operations. Ilias and Jansen[12] found that intravenous lornoxicam at a dose of 8 mg is superior to a placebo and is at least as effective as intravenous tramadol 50 mg in relieving moderate to intolerable posthysterectomy pain. Karaman et al.[13] found that lornoxicam 8 mg administered preemptively reduced postoperative pain and morphine consumption in patients undergoing gynecological operations in the early postoperative period. In our study, a single oral dose of lornoxicam given preoperatively enhanced tramadol's analgesic effect, decreasing tramadol consumption.

Assessment of acute pain utilizing the VAS in a scientific clinical investigation is inadequate. Sometimes this practice relies on subjective evaluation by a person who has little power to modify an inadequate prescription.[14] Fosnocht et al.[15] found that VAS is not a valid indicator of pain relief for individual patients. The concept of PCA may be regarded as a simple closed-loop system. The patient determines the dose required to maintain adequate analgesia. The optimum plasma concentration, as determined by the patient, is that which satisfies his subjective requirement for analgesia.[14]

Lornoxicam was well tolerated and was associated with a lower incidence of adverse events than tramadol alone. It may be an effective adjuvant to PCA tramadol for postoperative pain control. This combination reduces the total consumption of PCA tramadol and reduces side effects. Length of hospitalization was significantly shorter in the lornoxicam group than in the placebo group. Lornoxicam is well tolerated, elicited few side effects, and decreased patients' tramadol requirement; these effects may speed recovery and discharge.

In conclusion, a single oral dose of lornoxicam given preoperatively enhanced the tramadol's analgesic effect, decreasing both tramadol consumption and side effects. In addition, this strategy also may contribute to early discharge from the hospital after total abdominal hysterectomy. Further studies, however, are required in different pain models to investigate this drug's efficacy alone or in combination with other analgesics.

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