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Comparison of the Analgesic Effects of Preemptive Lornoxicam and Paracetamol after Laparoscopic Cholecystectomy

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Abstract

Objectives: Despite increasing knowledge about pain, postoperative pain management is still a challenge. Opioids are widely used drugs in the treatment, but the side effects of the opioids lead to investigations about the novel pain management strategies. We aimed to compare the effects of preemptive intravenous lornoxicam and paracetamol on postoperative pain scores, opioid consumption, and patient satisfaction during laparoscopic cholecystectomy recovery.

Materials and methods: Sixty patients scheduled for laparoscopic cholecystectomy surgery were randomized into three treatment groups that received lornoxicam (8 mg), paracetamol (1000 mg), or normal saline (control) 30 minutes before surgery. Time to the first analgesic requirement, visual analog scale scores, tramadol consumption, side effects, and patient satisfaction were recorded.

Results: Time to the first analgesic requirement and tramadol consumption were higher in the control group than in the paracetamol and lornoxicam groups ($p < 0.001$). Tramadol consumption of the lornoxicam group was higher than that of the paracetamol group at the 1-, 2-, and 8-hour measurements ($p = 0.048$, $p = 0.047$, $p = 0.040$, respectively). However, total tramadol consumption in lornoxicam and paracetamol groups was not statistically different at 24 hours.

Conclusion: Preemptive intravenous lornoxicam and paracetamol equally reduce opioid consumption, compared to placebo, after laparoscopic cholecystectomy. Both drugs may be viable alternatives for postoperative pain treatment to avoid opioid-related side effects.

Keywords

Acute pain, Cholecystectomy, Acetaminophen, Lornoxicam

Introduction

Pain is a personal unpleasant sensation that is affected by multiple factors, including sensorial status and previous pain experience [1]. Due to tissue damage during surgery, nociceptive inputs result in the development of central sensitization and hyperexcitability; hence pain is a predictable part of postoperative periods. It is also the most common cause of delayed recovery and poor postoperative outcomes [2]. Despite increasing knowledge about pain mechanisms and the development of technological devices to alleviate pain, it is still a challenge to provide adequate pain relief.

Though opioids are widely used for postoperative analgesia they have adverse side effects, including nausea, vomiting, itching, and respiratory depression, that may limit their use [3,4]. Novel pain management strategies therefore focus on reducing opioid-related side effects and providing more effective pain relief, both of which can affect patient satisfaction. One strategy, preemptive analgesia, involves administering analgesics before a painful stimulus occurs, thus preventing central sensitization.

Several research trials have tested the preemptive analgesic efficacy of various medications and techniques, such as nonsteroidal anti-inflammatory drugs (NSAID), also known as non opioid analgesics [5-7]. NSAIDs restrict cyclooxygenase enzymes, leading to inhibition in prostaglandin synthesis. The nonselective NSAID lornoxicam, prescribed for moderate to severe pain, has analgesic, anti-inflammatory, and antipyretic effects. Lornoxicam's effects last longer than do those of other NSAIDs, and it has both enteral and parenteral forms. These characteristics make lornoxicam a viable option for management of postoperative pain [8,9].

Paracetamol, another non opioid drug, is similar to an NSAID, but its action mechanism is not precisely known. It is widely accepted that paracetamol acts centrally to inhibit the synthesis of prostaglandin by cyclooxygenases 1 and 2. Recent studies have stated that paracetamol has an inhibitory effect on peripheral prostaglandin synthesis and acts in descending serotonergic pathways and spinal 5-HT receptors to prevent central nociception [10]. The analgesic effect of paracetamol is not higher than that of NSAIDs, but it has fewer side effects and can rapidly reach high concentration levels in the cerebrospinal fluid, which is important for analgesic effects [11].

Both lornoxicam and paracetamol are frequently used for

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postoperative pain therapy. However, the clinical trials comparing the effects of preemptive lornoxicam and paracetamol in postoperative opioid consumption is restricted and the results have been contradictory [7,12,13]. Thus, the aim of this placebo-controlled study was to compare the efficacy of preemptive lornoxicam and paracetamol treatment in reducing postoperative pain scores and opioid (tramadol) consumption, and in increasing patient satisfaction, in patients who undergo laparoscopic cholecystectomy.

Materials and Methods

After obtaining the approval of the Kartal Dr. Lutfi Kirdar Training and Research Hospital Clinical Researches Ethics Committee and written informed consent, 60 patients (15 male, 45 female) were included in the study. Patients were aged 20-65 years, met American Society of Anesthesiologists (ASA) physical status 1 or 2, and were scheduled for laparoscopic cholecystectomy. Patients who had a history of allergic reactions to NSAIDs; malignancy; bronchial asthma; chronic alcohol abuse; gastric or duodenal ulcers; or severe cardiac, pulmonary, renal, hepatic, neurological or hematological disease were excluded. One day before their operation, patients were instructed in the anesthesia method, the visual analog scale (VAS), and the patient-controlled analgesia (PCA) pump.

Patients were randomized into three groups of 20 by using a computer-generated random table. The lornoxicam group received 8 mg intravenous lornoxicam; the paracetamol group received 1000 mg intravenous paracetamol; and the control group received intravenous 0.9% normal saline (5 ml/kg) as a placebo. All treatments were infused by 30 min duration and finished at 30 min before surgery. All drugs were diluted with 0.9% normal saline and prepared as 100 ml final volume and injected by a researcher who was not involved in patient care.

Intraoperative monitoring included lead II electrocardiogram, noninvasive blood pressure, pulse oximetry and capnography. Anesthesia was induced with propofol (1.5 mg/kg), vecuronium (0.1 mg/kg), and fentanyl (1.5 mcg/kg), maintained with 1-2% sevoflurane titration, in a 50:50 nitrous oxide and oxygen mixture according to the intraoperative hemodynamic changes. At the end of the surgery, atropine (0.01 mg/kg) and neostigmine (0.04 mg/kg) were administered to reverse residual muscle relaxation. All patients received intravenous metoclopramide (10 mg) as an antiemetic prophylaxis. After extubation, patients were transferred from the operating theater to the recovery room; tramadol infusion by PCA pump was started when the patient's VAS score was greater than or equal to 3. The PCA pump was programmed to infuse 1 mg/kg loading dosage, 5 mg/hr background dosage, 1 mg/kg bolus dosage with a 10-min lockout interval and a maximum 200 mg per 4 hours. The time to the first tramadol requirement was recorded. In addition, VAS score, heart rate, noninvasive blood pressure, side effects (such as emesis, vomiting, and respiratory failure), and tramadol consumption were recorded at postoperative times 20 min, 1 hr, 2 hr, 8 hr, 12 hr, and 24 hr. Postoperative patient satisfaction was measured on a 5-point Likert scale (1 = bad; 2 = fair; 3 = good; 4 = very good; 5 = excellent). Patients' pain was assessed using a VAS from 0 (no pain) to 10 cm (worst imaginable pain). Sedation level was assessed using the Ramsey Sedation Scale (RSS).

All statistical analyses were performed using Number Cruncher Statistical System 2007 software (NCSS, LLC, Kaysville, UT, USA). Pearson correlation tests were used for correlations between parameters. In addition to descriptive statistical methods (mean, standard deviation), independent t tests were used for between-group comparisons involving two groups, chi-square tests were used for data comparisons, and paired sample t tests were used for within-group comparisons. For variables that did not have a normal distribution, the Kruskal-Wallis test was used for intergroup comparisons, and the Wilcoxon test was used for within-group comparisons. Between-group parameter differences were analyzed using the Mann-Whitney U test. A value of $p < 0.05$ was considered significant.

A sample size was calculated using a formal sample size calculation. In the literature, a reduction to 38% in PCA opioid consumption is regarded as a clinically significant result that is primary outcome of this study [14]. Based on preliminary results from our department, the anticipated consumption of tramadol was 162 mg (standart deviation = 88). At two-sided level of $\alpha = 0.01$ with a 80% power sample size was required as 18 patients per group and total 60 patients were enrolled study for possible dropouts.

Results

There were no significant differences between groups in patients' mean age, gender, height, weight, or operation and anesthesia duration (Table 1).

However, the time to first tramadol requirement in the control group (M ± SD: 4.75 ± 4.72 min) was significantly higher than in the paracetamol (22.75 ± 17.43 min) and lornoxicam groups (21.25 ± 10.75 min, $p < 0.001$). The VAS scores progressively decreased over time, with no statistically differences between groups in any measurement period (Table 2). There were significant differences between groups in tramadol consumption in all times ($p < 0.001$); however, consumption was always highest in the placebo group ($p < 0.01$). The lornoxicam group consumed more than the paracetamol group in all times (except 20 min), but the differences were only statistically significant at 1 hr ($p = 0.048$), 2 hr ($p = 0.047$), and 8 hr ($p = 0.040$) (Table 3).

There were no significant differences in side effects between groups. The most common side effects in all groups were nausea and vomiting. None of the patients had gastrointestinal bleeding, or sedation or respiratory failure that required treatment (Table 4).

Finally, postoperative patient satisfaction was similar for all groups. Satisfaction was rated as "excellent" by 55% of the lornoxicam group and 50% of the paracetamol group, while only 35% of patients in the control group gave this rating (Table 5).

Table 1: Characteristics of patients undergoing laparoscopic cholecystectomy.

	Lornoxicam	Paracetamol	Control	*p*
Patient (n)	20	20	20	-
Sex (male/female)	5/15	5/15	5/15	-
Age (years)	50.85 ± 06.94	45.05 ± 13.38	52.05 ± 06.85	0.68
Height (cm)	165.9 ± 07.90	168.15 ± 07.81	163.2 ± 08.64	0.96
Weight (kg)	75.15 ± 13.63	73.80 ± 13.73	75.15 ± 13.63	0.94
Surgery duration (min)	57.25 ± 14.00	61.50 ± 15.65	56.00 ± 10.46	0.41
Anesthesia duration (min)	62.25 ± 14.00	66.50 ± 25.65	61.00 ± 10.46	0.41

Data were expressed as numbers or mean ± standard deviation

Table 2: Postoperative visual analog scale (VAS) scores.

Time	Lornoxicam	Paracetamol	Control	*p*
20 min	3.1 ± 0.59	3.8 ± 1.18	4.2 ± 1.07	0.90
1 hr	2.2 ± 0.83	3.2 ± 0.79	2.6 ± 0.81	0.90
2 hr	1.5 ± 0.69	2.5 ± 0.76	2.1 ± 0.72	0.90
8 hr	1.3 ± 0.49	1.9 ± 0.55	1.5 ± 0.69	0.90
12 hr	1.2 ± 0.44	1.7 ± 0.57	1.3 ±0.49	0.90
24 hr	1.2 ± 0.41	1.2 ± 0.44	1.1 ± 0.31	0.90

Data were expressed as mean ± standard deviation

Table 3: Postoperative tramadol consumption.

Time	Lornoxicam	Paracetamol	Control
20 min	40.2 ± 46.27	49.2 ± 43.42	**100.5 ± 17.46***
1 hr	**120.3 ± 35.87 †**	94.0 ± 46.61	**162.2 ± 22.68***
2 hr	**162.5 ± 34.91 †**	128.5 ± 45.77	**216.0 ± 24.09***
8 hr	**211.3 ± 41.37 †**	180.8 ± 47.00	**271.8 ± 29.76***
12 hr	235.7 ± 46.60	224.9 ± 50.72	**322.7 ± 39.59***
24 hr	259.5 ± 52.46	255.5 ± 53.16	**363.5 ± 41.8***

Data were expressed as mean ± standard deviation

*: $p < 0.001$ versus other groups †: $p < 0.05$ versus paracetamol group

Table 4: Postoperative side effects.

	Lornoxicam	Paracetamol	Control
Nausea	3 (15)	3 (15)	5 (25)
Vomiting	1 (5)	1 (5)	3 (15)
Hypotension	1 (5)	0	1 (5)
Hypertension	1 (5)	1 (5)	1 (5)
Tachycardia	1 (5)	0	1 (5)
Bradycardia	0	0	1 (5)
GIS bleeding	0	0	0

Data were expressed as patient number, (%). GIS = Gastro intestinal system

Table 5: Postoperative patient satisfaction level.

Level	Lornoxicam	Paracetamol	Control	*p*
Excellent	11 (55)	10 (50)	7 (35)	0.63
Very good	11 (55)	10 (50)	7 (35)	0.63
Good	-	-	1 (5)	
Average	-	-	-	
Poor	-	-	-	

Data were expressed as patient number (%)

Discussion

Our results show that, in patients who had undergone laparoscopic cholecystectomy, both preemptive intravenous paracetamol and lornoxicam significantly reduced postoperative opioid consumption in the first 24 hours, compared to placebo. They also prolonged time to the first analgesic requirement.

Ever since Crile [15] first described the concept of "preemptive analgesia," many researchers have investigated this idea. That preemptive analgesia reduces postoperative pain has been supported by experimental and clinical studies, but there has been no conclusive evidence for the ideal drug [16]. However, NSAIDs and paracetamol are still the most popular analgesics worldwide for the treatment of pain, and the preemptive use of these drugs has been effective in relieving postoperative pain and reducing opioid consumption and patient VAS scores [14,17-19].

A study similar to ours found that, compared to placebo, preemptive lornoxicam reduced VAS scores following laparoscopic cholecystectomy [20], while another study involving laparoscopic surgery showed that preemptive paracetamol reduced early postoperative pain compared to placebo [14]. In our study, however, neither paracetamol nor lornoxicam or placebo had a significantly differ VAS scores. This contradiction could be due to differences in the postoperative pain management method. Whereas we provided opioid self-administration via an intravenous PCA pump, in the other studies [14,20], researchers administered opioid without the PCA pump. However, a primary goal of our study was to reduce opioid consumption without compromising pain management, which we achieved. Preemptive paracetamol and preemptive lornoxicam both reduced time to the first analgesic requirement and opioid usage in the first 24 hours. And although VAS scores were not reduced in these groups, they were not increased either. Our results suggest that both drugs effectively treated postoperative pain-with less reliance on opioids.

Although it is generally thought that paracetamol acts centrally, recent studies have shown that it affects both central and peripheral cyclooxygenase enzymes. This characteristic, alongside NSAIDs' common side effects (e.g., bleeding, kidney failure, and gastrointestinal ulcers and hemorrhaging) make paracetamol a more attractive option for postoperative pain treatment [21]. However, there is little data comparing the effectiveness of paracetamol and lornoxicam in postoperative pain management, and results vary.

Korkmaz et al. [7] reported that paracetamol but not lornoxicam provided effective analgesia as a supplement to morphine PCA during the 24 hours following lumbar disc surgery. The non opioid drugs were administered at the time of wound closure rather than preemptively, which may account for the difference between their findings and ours. Indeed, studies that focused on preemptive analgesia support our results, including finding no differences in postoperative pain between paracetamol and lornoxicam [22,23].

In contrast, Mowafi et al. [12] concluded that lornoxicam was superior to paracetamol for postoperative analgesia after lower abdominal surgery. This result may be due to the higher dosage of lornoxicam used in their study. Analgesic dosage is an important factor in efficacy assessment studies. The recommended dose of lornoxicam for postoperative pain is at least 8 mg [24]. In Mowafi et al. [12] study, the lornoxicam group received 16 mg, while we administered only 8 mg in our study.

Similarly, Guzel et al. [25] found that 8 mg oral lornoxicam was more effective than 500 mg oral paracetamol in managing postoperative endometrial sampling pain. Lornoxicam is completely absorbed after oral administration and reaches peak plasma concentration within 2.5 hours, and there appear to be no differences in postoperative analgesic efficacy between oral, intramuscular, and intravenous administration [8,26]. However, absorption of oral paracetamol is slow and unpredictable because it has to first undergo metabolism in the liver. The estimated bioavailability of oral paracetamol is between 63% and 89% in adults, whereas intravenous administration provides more predictable early plasma paracetamol concentrations [27,28]. Thus, the differences in paracetamol administration and dosage in Guzel et al. [25] study may account for the contrasting results found in our study, in which a higher dosage, 1000 mg, of paracetamol was administered intravenously.

Another goal of our study was to determine if preemptive paracetamol and lornoxicam could improve patient satisfaction. However, all groups reported high levels of satisfaction regardless of the treatment condition. And this result may be based on the relationship of patient satisfaction with postoperative pain [29]. The equal VAS scores provided the similar patient satisfaction in all groups.

This study was limited by scheduled measurement times, gender disparity, and sample size. We measured pain scores only during the initial postoperative rest period (at 20 min) and then at five specific times during the initial 24 hours; as a result, some episodes of high pain intensity might have been missed. Additionally, our sample size was relatively small and females made up a large portion of each treatment group, prohibiting consideration of possible gender differences in postoperative pain features. Future studies to replicate our results should include larger samples sizes and a balanced mix of genders so that findings can be generalized to a broader population.

Conclusion

As a conclusion, our finding that preemptive intravenous lornoxicam and paracetamol reduced postoperative opioid consumption equally and produced the similar patient satisfaction suggests that both drugs may be viable alternatives for postoperative pain treatment in patients undergoing laparoscopic cholecystectomy.

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