

Comparison of Analgesic Effects of Intraperitoneal Lornoxicam and Ropivacaine Administration in Laparoscopic Cholecystectomy

Laparoskopik Kolesistektomi Sonrası Ağrı Tedavisinde İntraperitoneal Uygulanan Lornoksikam ve Ropivakainin Etkisinin Karşılaştırılması

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Objectives: In this randomized prospective study, we investigated the effects of lornoxicam vs. ropivacaine for the management of postoperative pain in patients undergoing elective laparoscopic cholecystectomy.

Patients and Methods: Patients were randomized into three groups and received 150 mg (80 mL) ropivacaine or 16 mg lornoxicam (80 mL) or placebo (80 mL saline) via multi-regional intraperitoneal instillation and port sites infiltration. Patient-controlled analgesia (PCA) device was used. Tramadol 50 mg tolerable dose, 5 mg/hour basal infusion, bolus dose 20 mg, locked 30 min, 4 hour limit were applied as 200 mg. Postoperative pain was assessed with 100-mm visual analog scale (VAS) at rest, while coughing, and during mobilization. Pain scores were recorded in the post-anesthesia care unit, and at 2, 4, 8, 12, 18 and 24 h after the surgery.

Results: At 24 h, VAS scores at rest and while coughing were found significantly lower in ropivacaine and lornoxicam group when compared with control group ($p=0.047$). The percentage of patients needing tramadol was significantly lower with ropivacaine and lornoxicam compared with control ($p<0.001$, $p=0.018$). There was no statistically significant difference between ropivacaine and lornoxicam group.

Conclusion: Multi-regional, intraperitoneal instillation and port site infiltration of ropivacaine and lornoxicam during laparoscopic cholecystectomy reduces the postoperative pain.

Key words: Laparoscopic cholecystectomy; ropivacaine; lornoxicam; postoperative pain.

Amaç: Prospektif randomize olarak yapılan bu çalışmada laparoskopik kolesistektomi sonrası ağrı tedavisinde lornoksikam ve ropivakainin etkisi araştırılmıştır.

Hastalar ve Yöntemler: Çalışmaya dahil edilen 45 hasta üç gruba randomize edildi. Hastalara 150 mg (80 mL) ropivakain, 16 mg lornoksikam (80 mL) ve plasebo (80 mL saline) intraperitoneal olarak püskürtüldü ve port bölgelerine infiltre edildi. Ameliyat bitiminde hasta kontrollü analjezi cihazı ile tramadol 50 mg yükleme dozu, 5 mg bazal infüzyon, bolus doz 20 mg, kilitle kalma süresi 30 dk, 4 saatlik limit 200 mg olarak planlandı. Hastaların ağrısı görsel analog skala (VAS) ile 0-100 olacak şekilde değerlendirildi. Ağrı skorları ilk saatte anestezi derlenme odasında ve 2., 4., 8., 12., 18., 24. saatlerde serviste değerlendirildi.

Bulgular: Ropivakain ve lornoksikam grubunda istirahat ve öksürük sonrası VAS değerleri kontrol grubuna göre daha düşük bulundu ($p=0.047$). Tramadol tüketimi açısından, ropivakain ve lornoksikam grupları arasında fark bulunmazken ($p>0.05$), kontrol grubuna göre bu iki grupta anlamlı düşük olarak bulundu ($p<0.001$, $p=0.018$). Ropivakain ve lornoksikam grubu arasında ise istatistiksel olarak anlamlı fark bulunmadı.

Sonuç: Ropivakain ve lornoksikamın port bölgelerine, intraperitoneal çoklu bölgeye laparoskopik kolesistektomi sonrası infiltrasyonu ameliyat sonrası ağrı tedavisinde etkin olarak bulunmuştur.

Anahtar sözcükler: Laparoskopik kolesistektomi; ropivakain; lornoksikam; ameliyat sonrası ağrı.

Laparoscopic cholecystectomy (LC) has become a gold standard and preferred surgical technique for gall bladder pathologies because of an improved postoperative course compared with open surgery.^[1,2] Although LC results in less postoperative pain and/or reduced analgesic consumption, better cosmetic results, and a shorter hospital stay compared with open cholecystectomy, however, it is not a pain-free procedure.^[2,3] Early postoperative pain is the most prevalent and dominant complaint that requires strong analgesia including opiates after elective laparoscopic cholecystectomy.^[4] For that reason, many efforts have been made to improve postoperative analgesia after LC, but postoperative pain, however, does not completely disappear and several studies have shown that visceral pain is the major component.^[5,6] Nonetheless, post-cholecystectomy pain may be moderate or even severe for some patients during the first 24 postoperative hours, and has frequently been treated with nonsteroid anti-inflammatory drugs (NSAIDs) or opioid treatment.^[7,8]

Local anesthetic infiltration is often used to improve pain relief after laparoscopic cholecystectomy.^[5,9-13] The postoperative analgesic effect of intraperitoneal administration of local anesthesia after laparoscopic gynecologic surgery has proved to be effective and safe but there is lack of consensus regarding the dose, concentration, site, and manner of administration.^[14-18] But the effect of the same procedure during laparoscopic cholecystectomy is controversial, and the reported results range from considerable pain reduction to no significant pain reduction. Therefore, we designed this prospective, randomized study to assess whether the intraperitoneal application of ropivacaine or lornoxicam yields any benefit in regard to postoperative pain and pulmonary function after laparoscopic cholecystectomy and compare these effects.

PATIENTS AND METHODS

The study protocol was approved by our hospital ethical committee, and informed consent was obtained from each patient. Forty-five patients with ASA physical status I-II scheduled to undergo laparoscopic cholecystectomy were included in this prospective and randomized study from January 2006 to June 2006 in General Surgery Clinic. The patients underwent elective laparoscopic cholecystectomy under general anesthesia and a multi-regional blockade with ropivacaine, lornoxicam or saline (placebo).

The criteria for exclusion were ASA physical status III or greater, and patients having papillotomy by endoscopic retrograde cholangiopancreatography within one month before operation, patients allergic to local anesthetics and those with a history of cardiac disease. Patients were also excluded if they had operation for acute cholecystitis or if the operation was converted to an open procedure. Also, to study the real analgesic effects of local anesthetics, patients were excluded

when they had postoperative complications, which could increase postoperative pain. Thus, only those who were likely to have a simple laparoscopic cholecystectomy were included. Before the end of the surgery, metoclopramide (10 mg) was given intravenously to all patients to reduce the incidence of nausea and vomiting. No patient underwent the placement of intraperitoneal drain. Patients were divided into three randomized groups with 15 patients in each group.

In the control group, at the end of the surgical process, 80 mL of saline was instilled under direct vision by the surgeon into the gallbladder bed after partial retrograde release of the gallbladder, right and left subdiaphragmatic area and instillation to the visceral peritoneum at the end of the procedure. The remaining 20 ml saline was injected into the four port access in which one port was injected 5 ml's. For the patients in the 2nd (ropivacaine) group, at the end of the surgical process, 80 ml ropivacaine (Naropin® 7.5 mg/ml 20 ml was diluted with 80 ml saline totally 100 ml solution) was instilled into the gallbladder bed, right and left subdiaphragmatic area and the visceral peritoneal surface respectively, then the remaining 20 ml was infiltrated around the port trocar sites in 5 ml's.

In the 3rd group, at the end of the surgical process, 80 ml lornoxicam (Xefo® flk 16 mg was diluted with 100 ml saline totally 100 ml solution) was instilled into the gallbladder bed, right and left subdiaphragmatic area and the visceral periton surface respectively, then the remaining 20 ml was infiltrated around the port trocar sites in 5 ml's.

All patients received the same anesthetic technique. The beginning of surgery for prophylaxis 0.5 mg atropin IM was injected to the patients and following the general anesthesia and intubation, after injecting giving fentanyl+lidocain as an induction for the anesthesia, in the following period %66 NO₂ + %33 O₂ + %1-1.5 isoflurane (Forane®) + Vecuronium bromide (Norcuron®) 2 mg/kg/hour IV; and in waking up period %100 O₂ + decurarisation were applied. Mean arterial pressure, HR and SpO₂ were recorded before and after induction, after intubation and every 5 min intervals until the end of the operation. The same three surgeons performed all operations. Before surgery, for measuring pain and nausea, the patients were educated to use a 100-mm visual analog scale (VAS).

Laparoscopic cholecystectomy was performed by the standard "American" technique.^[19] Intraoperative cholangiography was not performed. All patients were given cefamezin 1 g at the beginning of surgery. With infraumbilical incision, pneumoperitoneum formation was supplied with the carbon dioxide (CO₂) insufflation inside the abdomen from the Veres injector. During laparoscopy, intraabdominal pressure was maintained at 10-12 mm Hg. After the gallbladder was removed,

Table 1. Demographic variables and the duration of surgery

	Group I (n=15)	Group II (n=15)	Group III (n=15)	<i>p</i>
Gender (male/female)	4/11	5/10	2/13	0.93
Age (years)	55 (26-84)	46.5 (24-69)	47.5 (27-68)	0.86
Body weight (kg)	72 (55-100)	75 (60-98)	78 (58-95)	0.72
Height (cm)	165.4±10.2 (155-177)	163.8±9.7 (154-175)	168.0±9.4 (151-177)	0.77
ASA (I/II)	13/2	10/5	12/3	0.30
Duration of surgery (min)	84 (60-200)	74.9 (30-120)	70 (50-105)	0.44

the apparatus of the Air Pomp (Northgate Technologies Incorporated Chicago, IL, USA) device was placed into the abdomen from the subcostal trocar and the medicine was sprayed intraperitoneal aerosolization technique developed previously by Alkhamesi.^[20] The CO₂ was carefully evacuated at the end of surgery by manual compression of the abdomen with open trocars.

In the postoperative period, Abbott "Pain Management Provider" patient-controlled analgesia (PCA) device was used for all the patients and Tramadol 50 mg tolerable dose, 5 mg/hour basal infusion, bolus dose 20 mg, locked 30 min, 4 hour limit were applied as

200 mg form. The patients were asked about the location of pain, whether at the shoulder, incision sites, and/or inside the abdomen. The intensity of the different postoperative pain components were recorded on a 100-mm visual analog scale at rest (supine, 10°-15° head up), on coughing, and during mobilization (patients were asked to move from the supine to the sitting position). Patients were told to indicate the degree of their pain by VAS, when they were asked to evaluate the intensity of their pain. Standard patient monitoring was used. Pain scores, morphine consumption, nausea, and vomiting, sedation status, breathing rate/min, SpO₂, systolic and

Table 2. Hourly and general VAS averages according to the groups

Hours	Group I	Group II	Group III	General
0	80 (50-100)	60 (10-90)	50 (30-100)	67.5 (10-100)
2	65 (30-90)	40 (0-80)	50 (10-80)	48.7 (0-90)
4	50 (30-80)	20 (0-60)	20 (0-50)	30 (0-80)
8	40 (20-60)	10 (0-50)	10 (0-40)	20 (0-60)
12	30 (10-100)	10 (0-35)	10 (0-30)	20 (0-100)
18	20 (10-50)	5 (0-20)	0 (0-30)	10 (0-70)
24	10 (10-25)	0 (0-30)	0 (0-30)	5 (0-50)
Mean (24 hours)	42.8 (24.2-58.2)	22.8 (8.5-38.5)	22.8 (10.0-37.1)	30.1 (7.1-59.2)
Groups	<i>p</i>			
1 - 2	0,0001*			
1 - 3	0,0001*			
2 - 3	0.603			

*p<0.05 is statistically significant.

Table 3. The averages of VAS scores after hourly coughs according to the groups

Hours	Group I	Group II	Group III	General
0	90 (60-100)	70 (30-90)	60 (30-100)	77.5 (30-100)
2	77 (30-90)	50 (0-80)	60 (10-80)	59.4 (0-90)
4	60 (40-100)	20 (0-80)	30 (0-80)	40 (0-100)
8	60 (25-100)	10 (0-40)	20 (0-70)	27.5 (0-100)
12	42.5 (15-80)	10 (0-40)	10 (0-50)	25.6 (0-80)
18	30 (15-60)	10 (0-40)	10 (0-60)	20 (0-80)
24	20 (10-60)	10 (0-40)	10 (0-50)	15 (0-60)
Mean (24 hours)	56.7 (38.5-78.5)	25.7 (14.2-50.0)	32.8 (11.4-69.2)	39.8 (11.4-78.5)
Groups	<i>p</i>			
1 - 2	0,0001*			
1 - 3	0,0001*			
2 - 3	0.718			

*p<0.05 is statistically significant.

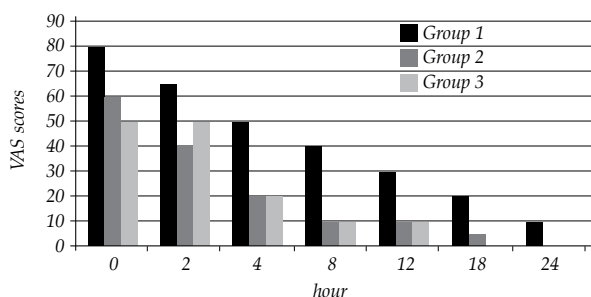


Fig. 1. General and hourly VAS scores according to groups.

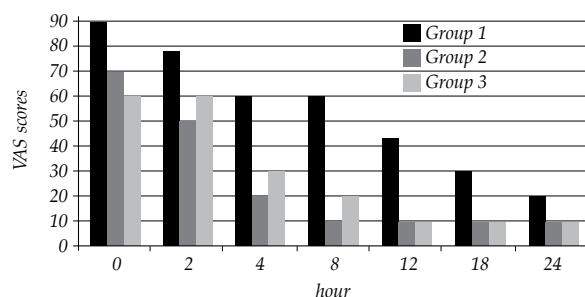


Fig. 2. Averages of VAS after hourly coughs according to groups.

diastolic blood pressures, pulse (rate/min) were recorded immediately at the arrival in the post-anesthesia care unit (PACU), and at 2, 4, 8, 12, 18 and 24 h after the surgery. If patients experienced nausea or vomiting, metoclopramide (0.5 mg/kg IV) was given.

At the 12th and 24th hours, the satisfaction of the patients were examined. At the 12th and 24th hours, the peristalsis and flatulence of the patients were recorded. After 12 hours from the surgery, the patients were mobilized. Daily analgesic consumption was also recorded. Patients in whom laparotomy was required during surgery and those with inadequate analgesia necessitating rescue analgesics were excluded from the study.

Statistical Analysis

An a priori power analysis was performed as a component of design to estimate required total sample size as a function of power $1-\beta=0.80$, with the medium effect size 0.55, and $\alpha=0.05$. The power calculation was computed using G power version 2 (Franz Faul & Edgar Erdfelder). Consequently, the adequate inclusion number was determined to be 15 patients in each study group (a total of 45 patients). We included 45 patients in the study. The results were given in terms of percentages and the mediums (lowest-highest). For the continuous variables in the evaluation of the differences between the groups Mann-Whitney U-test, for the discontinuous variables, Fisher's definitive test were used. For statistical significance, it was accepted as $p<0.05$. The statistical analysis was performed by the SPSS 10.0 statistical software package (SPSS Inc., Chicago, Illinois, USA).

RESULTS

A total of 45 patients had participated in the study with 15 patients in each group. Because three patients did not want to participate, the operations of four patients were started laparoscopically and after that, converted to open cholecystectomy, so they were left out of the study. Instead of these patients, other seven patients were included in the study. There were no significant differences between the groups with regard to demographic variables (age, gender, weight and height) and ASA physical status or the mean duration of surgery in minutes (Table 1). Hourly and general VAS averages according to the groups are shown in Table 2 and Fig. 1. According to the VAS averages, statistical significance between 1st and 2nd groups ($p=0.0001$), statistical significance between 1st and 3rd groups ($p=0.0001$), statistical non-significance between 2nd and 3rd groups ($p=0.603$) were found. The averages of VAS after hourly coughs according to the groups are shown in Table 3 and Fig. 2. According to the VAS averages after coughing, statistical significance between 1st and 2nd groups ($p=0.0001$), statistical significance between 1st and 3rd groups ($p=0.0001$), and statistical non-significance between 2nd and 3rd groups were found ($p=0.718$). The general patient satisfaction averages at 12th and 24th hours are shown in Figs. 3 and 4. According to the patient satisfaction averages, statistical significance between 1st and 2nd groups ($p=0.0001$), statistical significance between 1st and 3rd groups ($p=0.0001$), and statistical non-significance between 2nd and 3rd groups were found ($p=0.12$). The hourly and general sedation averages according to the groups are shown in Fig. 5. With regard to the seda-

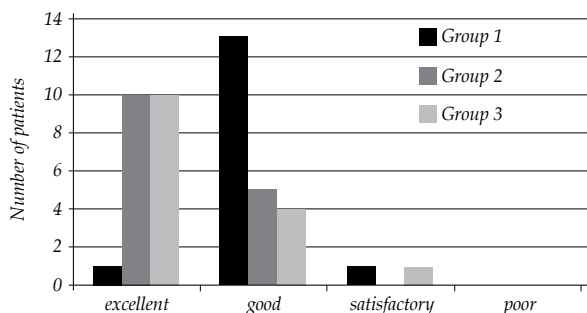


Fig. 3. General patient satisfaction average at the 12th hour.

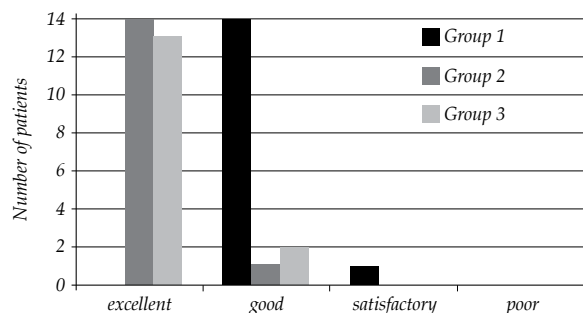


Fig. 4. General patient satisfaction average at the 24th hour.

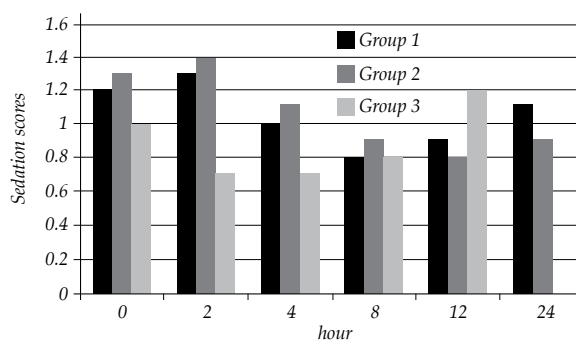


Fig. 5. Patient sedation scores.

tion averages, statistical insignificance between 1st and 2nd groups ($p=0.57$), statistical insignificance between 1st and 3rd groups ($p=0.12$), and statistical insignificance between 2nd and 3rd groups were found ($p=0.15$). Total tramadol consumption of the patients at the end of 24th hour and the PCA button pressing numbers are shown in Fig. 6. At the end of the 24th hour after the surgery, with regard to the total tramadol consumption and PCA button pressing numbers, statistical significance between 1st and 2nd groups ($p=0.0001$, $p=0.0001$), statistical significance between 1st and 3rd groups ($p=0.0001$, $p=0.0001$), and statistical insignificance between 2nd and 3rd groups were found ($p=0.52$, $p=0.21$).

With regard to the SpO₂ averages, statistical insignificance between 1st and 2nd groups ($p=0.86$), statistical insignificance between 1st and 3rd groups ($p=0.44$), and statistical insignificance between 2nd and 3rd groups were found ($p=0.87$).

With regard to the hourly peristaltisms of the patients according to the treatment protocols, no significant difference was found between the treatment groups ($p=0.39$).

With regard to the hourly flatulence of the patients according to the treatment protocols, no significant difference was found between the groups ($p=0.22$). With regard to the side effects according to the treatment protocols, statistical significance between 1st and 2nd groups ($p=0.0001$), statistical significance between 1st and 3rd groups ($p=0.03$), and statistical insignificance between 2nd and 3rd groups were found ($p=0.81$).

Shoulder pain was reported by eight patients (control group = 5, ropivacaine group = 1, lornoxicam group = 2) but this result was not statistically significant ($p>0.005$).

DISCUSSION

Minimal invasive surgery holds an important position in today's practice for many diseases in general and gynecologic surgery. Laparoscopic cholecystectomy (LC) results in less postoperative pain and/or reduced analgesic consumption as well as morphine as compared with open cholecystectomy. So it is thus logical to sug-

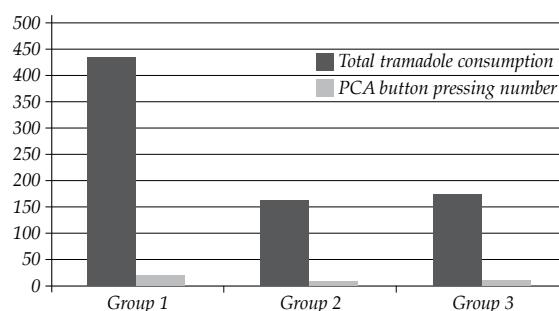


Fig. 6. Total tramadol consumption and PCA button pressing numbers according to groups.

gest that returning to normal daily activities is also more rapid with laparoscopy.^[21-24] Postoperative pain, however, does not completely disappear after laparoscopic cholecystectomy and, in the early postoperative period, serious pain and nausea may occur and a strong analgesia may be necessary.^[25-28]

The exact etiology of pain after laparoscopic cholecystectomy is still unclear, however, it appears to be multifactorial and the causes include, abdominal wall trauma by trocar entrances, diaphragmatic irritation secondary to CO₂ insufflation and pneumoperitoneum, type and temperature of insufflated gas and intraabdominal pH, residual intraperitoneal gas, intraabdominal trauma secondary to gallbladder removal, microruptures of the parietal peritoneum due to abdominal distension, chemical irritation of the peritoneum, etc.^[23,29-31] Therefore, multimodal analgesic techniques are necessary. For the decrement of postoperative pain after the laparoscopy, some methods such as rectus cover block,^[32] intraabdominal drain placement in order to throw out CO₂ pneumoperitoneum,^[33] intraabdominal instillation of local anesthetics,^[33] intraperitoneal infiltration of the local anesthetics or opioids,^[24,34,35] the use of intramuscular morphine injections, patient-controlled analgesia, and injection of local anesthetics into the port sites are suggested.^[36]

Because intraperitoneal injection of the local anesthetics during gynecologic surgery has proved to be effective and safe, it was thus logical to suggest that this technique may also provide an effective block of postoperative visceral pain after laparoscopic cholecystectomy.^[18,37] The clinical significance of this pain reduction is questionable. In the studies, after the laparoscopic surgeries, the intraperitoneal local anesthetics are found to be very effective for the decrement of the postoperative pain.^[38,39] This non-invasive method has a minimum risk and it can be easily applied. Besides, there are studies showing that the application of intraperitoneal anesthetic administration is not useful for the prevention of postoperative pain.^[40] Because laparoscopic surgery, a minimally invasive technique, is associated with reduced surgical trauma, the use of local anesthetic infiltration for effica-

cious postoperative analgesia should allow widespread use of laparoscopic day-case surgery. Non-steroidal anti-inflammatory drugs (NSAIDs) provide effective analgesia in patients with acute postoperative pain after laparoscopic cholecystectomy, either as a substitute for or as an adjunct to opioid analgesia.

COX-2 inhibitors are newer drugs having less adverse effects. Lornoxicam (Xefo[®]) which is a potent short acting new NSAID of the oxycam class, has been used worldwide.^[41,42] The short plasma half-life (three to five hours) of it may provide advantages over other NSAIDs.^[42,43] When inhibiting the cyclooxygenase enzyme as a non-selective form,^[43] in the gynecologic and orthopedics cases, for the pain relief after the surgery period, it is reported that it is as efficacious as morphine,^[44] meperidin,^[45] and tramadol.^[46] Lornoxicam has been successfully used in prevention and treatment of postoperative pain in patients undergoing gynecological operations. Studies showed that lornoxicam administered preemptively improved the quality of postoperative analgesia and opioid consumption.^[47]

Ropivacaine (1-propyl-2', 6'-pipercoloxylidide hydrochloride) a new long-acting amide local anesthetic that is formulated as the pure S-enantiomer, is chemically related to bupivacaine, but it has been shown to be less toxic to cardiac and central nervous system.^[48-50] This drug possesses anti-inflammatory activity that may further reduce pain when administered locally.^[51,52] The reason of preferring ropivacain in our study is that it is a long-acting agent (6-12 hours), has less motor blockages and a less cardiotoxicity than bupivacain.^[25] We have provided nearly total blocks by giving the local anesthetics agents to all regions that many surgical manipulation were applied, such as hepatoduodenal ligaman, gallbladder bed, subdiaphragmatic and subhepatic area. Through this application, we have decreased the pain of the patients in a satisfactory form. The fact that the general and after coughing VAS scores were statistically significant between the 1st and 2nd groups shows us that ropivacain is more effective than placebo significantly. As a result, somato-visceral local anesthetic block combined with 150 mg ropivacain decreases the opioid consumption and nausea in the first 24 hours of the postoperative pain treatment.

We have applied lornoxicam at the end of the surgical process to the same anatomical areas with the same volume. When the placebo and the lornoxicam groups are compared, it is stated that lornoxicam is more effective on the postoperative pain. Although lornoxicam is not a local anesthetic agent, since a COX inhibitor decreases the secretion of the pain mediators in the areas where surgical manipulation is applied and besides its analgesic effect, it also shows a local antinociceptive effect.

In this study, multiregional intraperitoneal instillation and injection of lornoxicam and ropivacaine by the

purpose of preventing the pain after laparoscopic cholecystectomy was performed and an effective postoperative analgesia was determined.

Shoulder pain is a common outcome and frequent complication after LC and can delay return to normal activities. It has been reported in 35%-63% of cases.^[53] It occurs after diaphragmatic stretching with phrenic nerve neuropraxia and reported after laparoscopic cholecystectomy is markedly lower than that reported after gynecologic laparoscopy.^[53-55] We found a low incidence of shoulder pain in all treatment groups, because the residual intraperitoneal CO₂ was carefully removed by the surgeon.

Although we did not encounter nausea and vomiting between the patients in the 2nd and 3rd treatment groups in the first postoperative 24 hours, nausea occurred in seven patients in SF group in the postoperative period. This finding is statistically significant and we think that this is related with the further consumption of opioid in SF group.

In conclusion, this study showed that the multi-regional intraperitoneal instillation and port sites infiltration of ropivacaine and lornoxicam during laparoscopic cholecystectomy is a noninvasive, rapid, safe and simple analgesic technique that reduces the pain and the total morphine consumption without adverse effects.

In summary, both lornoxicam and ropivacaine were effective at preventing pain over the first 24 h after laparoscopic cholecystectomy when intraperitoneally instilled and injected at the port sites at the end of cholecystectomy.

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