Post-Laparoscopic Cholecystectomy Pain: Effects of Preincisional Infiltration and Intraperitoneal Levobupivacaine 0.25% on Pain Control-a Randomized Prospective Double-Blinded Placebo-Controlled Trial

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Objective: The aim of this study was to compare the postoperative analgesic efficacy of preincisional and intraperitoneal levobupivacaine or normal saline in patients undergoing laparoscopic cholecystectomy.

Methods: Sixty patients who participated in the study were randomly divided into 3 groups. Group 1 received intraperitoneal levobupivacaine (0.25% 40 mL) immediately after the pneumoperitoneum. Group 2 received periportal levobupivacaine (0.25% 5 mL in each trocar incision area) before incision and intraperitoneal levobupivacaine (0.25% 40 mL) immediately after the pneumoperitoneum. Group 3 received for periportal and intraperitoneal instillation of normal saline. The visual analog scale (VAS) at 0, 1, 2, 4, 8, 12 and 24 hours for both shoulder and abdominal pain were recorded. Analgesia requirements and incidence of nausea and vomiting were also recorded.

Results: There were no difference between the groups for demographic data. The pain scores were lower in Groups 1 and 2 than Group 3 (control) during rest, cough and movement ($p < 0.05$). Rescue analgesic treatment was significantly lower in patients of Group 2 (15%) as compared with that of Groups 1 (35%) and 3 (90%) ($p < 0.05$). The incidence of shoulder pain was significantly lower in Group 2 (25%) and Group 1 (20%) than in any of the control group patients ($p < 0.05$).

Conclusion: The results indicated that 0.25% levobupivacaine was effective in preventing pain and the need for postoperative analgesic when intraperitoneal instillation or preincisional local infiltration in combination with intraperitoneal instillation. However, levobupivacaine for preincisional local infiltration in combination with intraperitoneal instillation is the better choice because of its higher efficacy.

Key Words: Laparoscopic cholecystectomy, levobupivacaine, intraperitoneal injection, postoperative pain injection, postoperative pain

Introduction

Currently, laparoscopic cholecystectomy is a common surgery that is associated with less surgical trauma and rapid recovery than open cholecystectomy. However, the majority of the patients suffer from severe abdominal and shoulder pain in the early postoperative period and require strong analgesia after laparoscopic surgery (1-5).

Causes of pain include incisional pain, visceral pain due to peritoneal irritation caused by entrapment of dissolved CO₂ in the abdomen, and shoulder pain due to irritation of diaphragmatic peritoneum (6). Less frequently, parietal abdominal pain may develop at the trocar insertion sites to the abdomen wall. Although opioids provide a powerful analgesia in the treatment of postoperative pain, they may lead to adverse effects such as sedation, nausea, vomiting and gastrointestinal ileus. Other methods used to decrease opioid use, such as non-selective non-steroidal anti-inflammatory drugs, selective cyclooxygenase 2 inhibitors and local anaesthetic infiltration are frequently used for additional analgesia. It has been demonstrated that among multimodal analgesia techniques, intraperitoneal application of different local anaesthetics is a beneficial method in the management of pain after laparoscopic surgery. Levobupivacaine, which has been introduced in the recent years, is advantageous for intraperitoneal use as it is a long-acting local anaesthetic with less cardiovascular toxicity. Although there are studies on intraperitoneal levobupivacaine application, the number of studies comparing it with combined use of preincisional periportal (at trocar incision sites) and intraperitoneal application is limited (7-9).

In the present study, it was aimed to evaluate the effects of intraperitoneal and local levobupivacaine application at trocar incision sites on postoperative pain, analgesic requirement and patient satisfaction in patients undergoing laparoscopic cholecystectomy.

Methods

The present study was performed on 60 patients who accepted to participate and provided written informed consents, after ethics committee approval of Tepecik Research and Education Hospital Ethics Committee (07.02.2008 date and number 72/11). Patients aged between 18 and 60 years with an American Society of Anaesthesiologists (ASA) anaesthesia risk classification, ASA I-II, who were scheduled to undergo laparoscopic cholecystectomy surgery were included in the study. Those with allergies to local anaesthetics, cooperation difficulty and morbid obesity and those with neurological or psychiatric disease were excluded.

The patients were informed about anaesthesia method and horizontal Visual Analogue Scale (VAS; 0: no pain, 100: unbearable pain) that would be used in pain evaluation one day before the intervention.

The patients were randomly assigned to three groups by closed envelope method as follows; Group 1 (n=20) receiving intraperitoneal levobupivacaine, Group 2 (n=20) receiving intraperitoneal and periportal (at trocar incision sites) levobupivacaine and Group 3 (control group; n=20) receiving intraperitoneal and periportal (at trocar incision sites) normal saline. The study was a double blind study, and the patients and the observer physician were blinded to the medication used.

Before the patients were taken into the operating room, vascular access was established and patients were premedicated with 2 mg of midazolam (Dormicum, Roche), and electrocardiography [heart rate (HR) and rhythm], non-invasive arterial blood pressure (NIABP), peripheral oxygen saturation (SpO_2) and end-tidal CO_2 (EtCO_2) monitoring was commenced. Propofol (Propofol, Fresenius Kabi) 2-2.5 mg kg^{-1} , fentanyl (Fentanyl Citrate, Meditera) 2 $\mu\text{g kg}^{-1}$ and rocuronium (Esmeron, Organon) 0.6 mg kg^{-1} were used for anaesthesia induction. After intubation, the patients underwent mechanical ventilation, the ventilator was adjusted to maintain EtCO_2 at 30-35 mmHg and respiratory parameters as follows; 50% FiO_2 /air mixture, tidal volume 6-7 mL kg^{-1} and respiratory frequency at 12-14 breaths min^{-1} . 1-2% sevoflurane (Sevorane, Abbott) and intermittent rocuronium at a dose of 0.1 mg kg^{-1} were used in anaesthesia maintenance.

After the intervention was started and an incision was made below the umbilicus (belly button), a trocar was inserted through the incision before application of infiltration anaesthesia in Group 1. The trocar was placed after periportal anaesthesia with 5 mL of 0.25% levobupivacaine (Chirocaine® 5 mg mL^{-1} Abbott) in Group 2 and 5 mL of normal saline in Group 3. Carbon-dioxide (CO_2) pneumoperitoneum was established and the intraperitoneal pressure was maintained at 12 mmHg. Thereafter, decision was made for continuing

cholecystectomy with laparoscopic method. While Group 1 and Group 2 patients were instilled 40 mL of 0.25% levobupivacaine, Group 3 patients were instilled 40 mL of normal saline solution, to the upper part of the liver, right supradaphragmatic space and over the gallbladder. Patients were positioned in a 15 degree trendelenburg position for two minutes, and then they were placed in 15-20 degrees head-up tilt and left lateral position. During the surgery HR, NIABP, SpO_2 , end-tidal CO_2 values and the total requirement of anaesthetic medication were recorded at 5 minute intervals. Before the intervention was terminated, the patients received 15-minutes IV infusion of 1 g paracetamol for postoperative analgesia. Before extubation, all patients underwent decurarization with atropine and neostigmine.

The time that the patients were taken into the postoperative recovery unit was defined as hour 0 and their first evaluations were made. In accordance with the standard postoperative applications, the patients were followed-up in terms of hemodynamic variables (HR, NIABP), pain at rest, coughing and movement (rising from lying position to sitting position), right shoulder pain, nausea-vomiting, headache and allergic reactions. The time to first analgesic requirement and additional analgesic requirements were recorded. Pethidine HCl (Aldolan, LIBA) 1 mg kg^{-1} and additional intramuscular analgesic was applied to the patients with a VAS score > 4. Pain scores (VAS) at postoperative 0, 1, 2, 4, 8, 12 and 24 hours were recorded. Patients with postoperative nausea and vomiting were given 10 mg of IV metoclopramide.

At the end of the study, the patients were questioned about their remarks and impressions on postoperative pain or other problems. They were requested to evaluate their satisfaction from the point of patient comfort as poor=0, fair=1, good=2, excellent=3 and the results were recorded, and the study was terminated (10).

Statistical analysis

NCSS and PASS 2000 programs were used to determine the number of patients that would be included in the study. The results of the preliminary studies estimated that 10 patients should be included in each group for 90% power and 5% significance level. We included 20 patients in each of the study groups in the present study.

Statistical analysis was performed using SPSS (Statistical Package for Sciences) program version 11.5. Kolmogorov-Smirnov test was used to test normal distribution for continuous variables. Descriptive statistics are presented as mean±standard deviation for continuous variables and patient number and percentages (%) for categorical variables. The significance of difference between the groups for continuous variables with normal distribution was tested with Variance Analysis (ANOVA), and the significance of difference for continuous variables with non-normal distribution and ordinal variables was analysed using the Kruskal-Wallis test.

Categorical data analysis was done with the Chi-square test. A p value <0.05 was considered to be statistically significant for all tests.

Results

There was no statistically significant difference between the groups in terms of gender, age, weight, ASA class and surgery duration (Table 1).

VAS pain scores at rest, coughing and movement were significantly lower in Group 1 and 2 than that in Group 3 at all measurement time points ($p<0.05$) (Table 2).

There was a statistically significant inter-group difference in terms of postoperative shoulder pain ($p<0.05$). There was shoulder pain in 12 patients (60%) in the control group, in 5 patients (25%) in Group 1 and in 4 patients (20%) in Group 2 (Table 3).

The additional analgesic requirement in Group 2 was significantly lower (15%) in comparison to that in Group 1 (35%) and Group 3 (90%) ($p<0.05$). Additional analgesic was given for one time in 6 patients (30%) and for two times in 12 patients (60%) in the control group, the patients in the other groups received an additional analgesic for one time (Table 3).

There was no significant difference between the groups in terms of postoperative nausea. Metoclopramide treatment was given to 9 patients (45%) in Group 1, 8 patients (40%) in Group 2 and 12 patients (60%) in Group 3, which was the control group. Vomiting was only experienced by one patient in Group 3.

Patient satisfaction was significantly higher in Group 1 and Group 2 when compared to that in Group 3 ($p<0.05$) (Table 4).

There was no intraoperative and postoperative complications related to levobupivacaine use.

Discussion

In this present study that compared the efficacy of intraperitoneal levobupivacaine infiltration (40 mL, 0.25%) and combined application of preincisional periportal and intraperitoneal levobupivacaine infiltration with normal saline on postoperative analgesia in patients undergoing laparoscopic cholecystectomy, we determined that levobupivacaine was safe and effective in pain management.

Numerous studies have been performed on the effects of intraperitoneal local anaesthetics on postoperative analgesia. In these studies, different local anaesthetics in different volumes and concentrations have been used before and after the intervention. Although there are studies indicating that intraperitoneal local anaesthetics decrease postoperative abdominal pain and analgesic consumption, there are some studies suggesting that they are ineffective (9-15). However, several

Table 1. Demographic characteristics, ASA physical status, and surgery duration of the patients according to study groups

	Group 1 (n=20)	Group 2 (n=20)	Group 3 (n=20)	p values
Male/Female (n)	9/11	11/9	11/9	0.766
Age (years)	49.4±11.3	48.4±10.5	51.7±14.4	0.235
Weight (kg)	73.1±9.8	71.3±7.9	76.5±8.5	0.198
ASA I/II (n)	12/8	14/6	14/6	0.741
Surgery duration (min)	45.3±8.2	48.2±10.5	46.2±7.8	0.211
Data are presented as patient number (n) or mean±SD				

Table 2. VAS (0-100 mm) pain scores during rest, coughing and movement at different time points

		Group 1 (n= 20)	Group 2 (n= 20)	Group 3 (n= 20)	*p values
0. hours	rest	20.1±8.9	17.6±2.9	42.3±8.4*	<0.001
	coughing	23.2±12.5	19.3±3.4	52.2±18.6*	<0.001
	movement	22.1±11.4	18.6±4.2	61.8±20.5*	<0.001
1 st hour	rest	22.6±8.5	20.1±8.9	52.3±9.9*	<0.001
	coughing	24.9±12.4	21.7±12.2	58.9±12.1*	<0.001
	movement	23.5±10.5	21.0±9.1	54.1±7.4*	<0.001
2 nd hour	rest	23.3±7.5	19.9±7.8	40.9±10.3*	<0.001
	coughing	31.6±10.3	23.2±5.3	49.8±11.1*	<0.001
	movement	29.8±9.7	21.2±6.9	48.9±9.7*	<0.001
4 th hour	rest	24.5±9.1	21.1±5.9	28.0±6.8*	0.024
	coughing	29.8±17.3	21.3±4.8	45.0±15.3*	0.008
	movement	26.8±11.9	20.7±5.1	38.6±8.9*	0.003
8 th hour	rest	23.4±6.9	19.1±6.3	30.2±7.3*	0.012
	coughing	26.8±7.2	22.3±5.8	41.2±16.2*	0.001
	movement	25.8±4.3	21.5±7.2	38.4±9.8*	0.022
12 th hour	rest	19.4±7.3	17.6±4.5	21.4±9.3*	0.036
	coughing	29.3±9.9	23.8±7.5	31.5±11.6*	0.023
	movement	31.2±9.6	24.3±6.7	29.9±10.8*	0.013
24 th hour	rest	14.9±7.6	9.7±2.2	24.3±5.4*	<0.001
	coughing	18.7±12.1	11.2±10.1	30.1±11.2*	0.006
	movement	19.7±9.7	12.5±9.6	28.5±9.5*	0.001
Data are presented as mean±SD.					
* $p<0.05$ Comparison of Group 1 and 2					

investigators reported that combination of somato-visceral local anaesthetic treatment decrease incisional and intraabdominal pain and shoulder pain after laparoscopic cholecystectomy (4, 16).

Although there are numerous studies on the use of different local anaesthetics in laparoscopic cholecystectomy, the number of studies on levobupivacaine use is few. Although there is no consensus on the concentration, volume, application site and timing of levobupivacaine application, there is no

Table 3. The incidence of shoulder pain, rescue analgesic and metoclopramide use in the first postoperative 24 hours [patient number (n) and (%)]

	Group 1 (n=20)	Group 2 (n=20)	Group 3 (n=20)	*p values
Shoulder pain	5 (25)	4 (20)	12 (60)*	0.015
Rescue analgesic	7 (35)	3 (15)	18 (90)*	0.0001
Metoclopramide	9 (45)	8 (40)	12 (60)	0.420
Data are presented as patient number (n). %				
*Comparison of Group 1 and 2; p<0.05				

study comparing intraperitoneal levobupivacaine application with combined preincisional periportal and intraperitoneal infiltration.

While some of the studies examining the timing of local anaesthetic application support that the timing of intraperitoneal local anaesthetic application does not have an effect on the intensity of postoperative pain, some of them indicate that timing is very important (7, 17). Dath et al. (5) compared bupivacaine with normal saline applied at the trocar incision site before closing the incision in patients undergoing laparoscopic cholecystectomy; they found that postoperative VAS values were significantly lower in patients receiving bupivacaine and recommended that local anaesthetic application at the trocar incision site should be standard after laparoscopic cholecystectomy. Another study comparing incisional bupivacaine and normal saline applied before trocar placement in laparoscopic cholecystectomy interventions and found that postoperative pain, analgesia and antiemetic medication use were significantly lower in patients receiving local anaesthetics (18). Lee and colleagues (19), in their study where they compared preoperative and postoperative application of incisional and intraperitoneal bupivacaine (60 mL, 0.25%), found that pain was significantly lower in the preincisional infiltration group compared to that in postoperative incisional infiltration group, and preoperative and postoperative intraperitoneal infiltration groups, they recommended the preoperative application of local anaesthetics in the incisional region.

It has been reported that preincisional local infiltration of local anaesthetics, suppress hyperexcitability state responsible from severe postoperative pain by preventing the transmission of nociceptive stimuli to the central nervous system (5, 7, 17). We, therefore, applied preincisional levobupivacaine at the trocar incision sites together with intraperitoneal infiltration to the patients in one of our study groups (Group 2). We determined that although postoperative pain scores and opioid consumption was lower in this group in comparison to the group that only received intraperitoneal levobupivacaine, there was no significant difference between the groups.

Postoperative shoulder pain is the most frequent complication with an incidence of 35-60% in laparoscopic surgery

Table 4. Patient satisfaction according to study groups

	Group 1 (n=20)	Group 2 (n=20)	Group 3 (n=20)	*p values
Excellent	16 (80)	18 (90)	10 (50)*	0.033
Good	2 (10)	2 (10)	4 (20)	0.356
Fair	2 (10)	-	5 (25)	0.143
Poor	-	-	1 (5)	0.221
Data are presented as patient number (n). %				
*Comparison of Group 1 and 2; p<0.05				

and it may prolong the time to return to normal daily activity (20). It has been proposed that the mechanisms of shoulder pain include short-term phrenic nerve neuropraxia, distension of diaphragmatic fibres due to the increased concavity of the diaphragm stimulated by pneumoperitoneum and stimuli arising from the traumatized area (21). Levobupivacaine given to the subdiaphragmatic region may block the nociceptive stimuli of diaphragmatic peritoneum. In the previous studies, intraperitoneal local anaesthetic application was found to be effective in reducing shoulder pain (12, 22, 23). In the study of Gharaibeh et al. (23), in which they compared intraperitoneal 0.25% bupivacaine with placebo in laparoscopic cholecystectomy surgeries, shoulder pain was found to be significantly lower in the group that received local anaesthetics and they reported that application of bupivacaine to gallbladder bed was effective in reducing shoulder pain. Louizos and colleagues (12) reported that 20 mL of levobupivacaine application is effective in decreasing right shoulder pain. In our study, as well, the incidence of right shoulder pain was significantly lower in the groups that received intraperitoneal local anaesthesia in comparison to the control group.

The current tendency in postoperative analgesia is to develop different pain treatment methods in the postoperative period to bring opioid analgesic requirement to minimum. In the present study, combined preincisional and intraperitoneal local anaesthetic application decreased postoperative additional analgesic requirement and lower pain scores were achieved in the postoperative period.

Nausea and vomiting are common complaints after laparoscopic cholecystectomy. Alper et al (24) reported that there was no significant difference between the group that received intraperitoneal levobupivacaine and control group in terms of nausea (45% versus 65%), however there was a significant difference regarding vomiting incidence (0 patient and 8 patients, respectively). However, similar to the results of Acar and colleagues (9) we determined that local anaesthesia methods we used had no effect on the incidence of nausea and vomiting.

Study limitations

We used 40 mL of 0.25% levobupivacaine in the present study. In the present study that determined that intraperi-

toneal levobupivacaine infiltration was effective on postoperative pain, we expected that statistically more significant results would be achieved by preincisional periportal levobupivacaine application. Therefore, we suggest that further studies using higher concentration and doses of levobupivacaine in combined treatment are needed.

Conclusion

Intraperitoneal 0.25% levobupivacaine at 40 mL dose is found to be effective and safe in postoperative analgesia in laparoscopic cholecystectomy surgeries. Combined use of levobupivacaine in doses and concentrations used in the present study as intraperitoneal and preincisional periportal (at trocar incision sites) infiltration, provided better patient satisfaction and clinical outcomes. However, as the results do not show a statistically significant difference, it has been concluded that combined use has no superiority over peritoneal use.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Tepecik Training and Research Hospital.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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