Effects of intraperitoneal levobupivacaine on pain after laparoscopic cholecystectomy: a prospective, randomized, double-blinded study

İntraperitoneal levobupivakain uygulamasının laparoskopik kolesistektomi sonrası ağrı üzerine etkisi: Prospektif, randomize, çift-kör çalışma

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Summary

Objectives: We aimed to determine the effects of intraperitoneal administration of levobupivacaine on pain after laparoscopic cholecystectomy in a prospective, randomized, double-blinded, placebo-controlled trial.

Methods: In all patients, infiltration of levobupivacaine 0.25% (15 mL) was used prior to skin incisions for trocar insertion. After pneumoperitoneum was achieved, patients were allocated randomly to receive intraperitoneally either 40 mL of 0.25% levobupivacaine (LB group, n=20) or normal saline (NS group, n=20) under direct vision into the hepatodiaphragmatic lodge and above the gallbladder. Data of intraoperative variables, postoperative pain relief, rescue analgesic consumption, side effects, and patient satisfaction were followed in both groups.

Results: The postoperative pain scores were significantly lower in the first half-hour period in the LB group than in the NS group ($p<0.05$). However, the incidence of right shoulder pain was not significantly different between the LB group (10%) and NS group (15%). The mean dose of meperidine consumption and the number of patients needing rescue meperidine were significantly lower in the LB group than in the NS group ($p<0.05$). Significantly lower vomiting incidence and increased patient satisfaction were determined in the LB group compared to the NS group ($p<0.05$).

Conclusion: Intraperitoneal administration of 40 mL levobupivacaine 0.25% given immediately after pneumoperitoneum into the hepatodiaphragmatic lodge and above the gallbladder demonstrated useful effects on postoperative pain relief after laparoscopic cholecystectomy, especially in the early postoperative period, and reduced postoperative rescue analgesic requirement, with excellent patient satisfaction. There were no LB-related complications or side effects.

Key words: Intraperitoneal instillation; laparoscopic cholecystectomy; levobupivacaine; postoperative pain.

Özet

Amaç: *İntraperitoneal levobupivakain uygulamasının laparoskopik kolesistektomi sonrası ağrı üzerine etkisinin randomize, çift kör, plasebo-kontrollü çalışma olarak araştırılması amaçlandı.*

Gereç ve Yöntem: *Tüm hastalara trokar giriş yerlerine levobupivakain %0.25'lik (toplam 15 mL) infiltrasyonu ile birlikte, pnömoperiton sonrası, randomizasyon şemasına göre, intraperitoneal olarak hepatodiyafragmatik alana ve safra kesesi üst lojuna toplam 40 mL %0.25'lik levobupivakain (Grup LB, n=20) veya 40 mL normal salin (Grup NS, n=20) uygulandı. İki grubun intraoperatif özellikleri, postoperatif ağrı durumu ve ek analjezik gereksinimi, yan etkiler ve hasta memnuniyeti ilk 24 saatlik dönemde karşılaştırıldı.*

Bulgular: *Postoperatif ağrı skoru, postoperatif ilk 30. dk'da, Grup LB'de Grup NS'ye göre anlamlı olarak daha düşüktü ($p<0.05$). Omuz ağrısı sıklığı iki grupta benzerdi (Grup LB'de %10 ve Grup NS'de %15). Ek analjezik (meperidin) gerektiren hasta sayısı ve ortalama dozu Grup LB'de Grup NS'ye göre daha azdı ($p<0.05$). Levobupivakain grubunda normal salin grubuna göre, postoperatif kusma daha az ve hasta memnuniyeti daha tatmin edici bulundu ($p<0.05$).*

Sonuç: *Çalışmamızda, laparoskopik kolesistektomilerde operasyonun başında uygulanan intraperitoneal 40 mL %0.25'lik levobupivakainin postoperatif ağrıyı ve ek analjezik ihtiyacını yan etkileri artırmadan azalttığı ve postoperatif hasta memnuniyeti üzerine etkilerinin daha iyi olduğu bulunmuştur.*

Anahtar sözcükler: İntraperitoneal uygulama; laparoskopik kolesistektomi; levobupivakain; postoperatif ağrı.

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Laparoscopic cholecystectomy (LC) is one of the most frequently performed elective surgical operations. The benefits of LC compared with open surgery are less postoperative pain and/or reduced analgesic consumption and more rapid return to normal daily activities.[1,2] However, postoperative pain remains the most prevalent complaint after this type of surgery, and several studies have shown that visceral pain is the major component.[3] Intraperitoneal administration of local anesthetic (LA) is a model of multimodal analgesic techniques to provide adequate postoperative pain relief after LC. In many trials, intraperitoneal bupivacaine has been shown to be the most widely used LA because of its long duration of analgesic action and high potency.[4] However, there is little evidence with regard to which type of LA is the most effective because limited data are available for drugs other than bupivacaine.[5] Levobupivacaine, an isomer of racemic bupivacaine, has been presented as a safer LA with a reduced risk of systemic toxicity and with long action.[6] There is limited data regarding the use of levobupivacaine administered intraperitoneally.

The purpose of the study was to investigate the effects of intraperitoneal levobupivacaine administered immediately after pneumoperitoneum on postoperative pain of LC in a prospective, randomized, double-blinded, placebo-controlled study design.

Materials and Methods

After acquiring ethics committee approval and written informed consent, 40 ASA I-II patients scheduled for LC were enrolled in this prospective, double-blind, randomized controlled trial. Exclusion criteria were acute cholecystitis, hypersensitivity to LAs and morbid obesity. Prior to the surgery, the patients were informed regarding postoperative pain and asked to evaluate their pain using a visual analog scale (VAS) ranging from 0 = no pain to 10 = worst pain imaginable.

On arrival in the preoperative area, all patients received midazolam 2 mg i.v. as premedication. After standard monitoring with electrocardiography, noninvasive arterial blood pressure and peripheral oxygen saturation in the operation room, anesthesia was induced using propofol 2-2.5 mg/kg, fentanyl 2 μg/kg, and rocuronium 0.6 mg/kg i.v., and was maintained using nitrous oxide 60% in oxygen with 2-2.5% sevoflurane and additional boluses of fentanyl and rocuronium as required. Ventilation was adjusted to maintain the end-tidal CO_2 concentration between 32-35 mmHg. In all patients, all skin port sites were infiltrated with levobupivacaine 0.25% (total of 15 mL) before trocar insertion. Standard laparoscopic procedure was done under four-trocar technique. During laparoscopy, intraabdominal pressure was maintained at 12 mmHg with continuous CO_2 insufflation. After pneumoperitoneum was achieved, patients were randomly assigned to one of the two groups using a computer-generated random number table to receive either 40 mL of 0.25% levobupivacaine (LB group, n=20) or 40 mL of normal saline (NS group, n=20). Under direct vision, study solutions were instilled with a catheter inserted in the right subcostal region into the hepatodiaphragmatic lodge and above the gallbladder. Solutions were prepared by another anesthesiologist so that neither the surgeon performing the intraperitoneal instillation nor the anesthesiologist following up the patient was aware of which drug was injected. After instillation of the solutions, patients were positioned in a 15 degree head-down for two minutes then reversed to the anti-Trendelenburg position for the surgery.

Hemodynamic and ventilatory parameters were recorded every 5 minutes together with any additional doses of fentanyl. Before the end of the surgery, paracetamol 1 g i.v. infusion was given to all patients. After the surgical procedure was completed, sevoflurane and nitrous oxide were stopped, and atropine 10 μg/kg and neostigmine 20-40 μg/kg were given for pharmacologic reversal of neuromuscular blockade.

The time of arrival at the postoperative unit was defined as zero hour postoperatively. The intensity of postoperative abdominal pain was assessed using a VAS, with evaluation at 0, 0.5, 1, 2, 4, 6, 8, 12 and 24 hours postoperatively. In patients with VAS scores >4, meperidine 1 mg/kg i.m. was administered as rescue analgesia treatment. Postoperative nausea and vomiting (PONV) were also recorded in the follow-up period and patients with PONV were treated with metoclopramide 10 mg i.v., when required.

Table 1. Patient characteristics

	LB (n=20)	NS (n=20)
Age (year)	43 (8)	44 (6)
Gender (M/F)	3 / 17	3 / 17
Weight (kg)	70 (8)	71 (6)
Height (cm)	165 (5)	166 (6)
Duration of surgery (min)	68 (15)	71 (19)
Intraoperative fentanyl consumption (µg)	22.5 (30.2)	42.5 (43.7)

Data are expressed as mean (SD) and number of patients.

Table 2. Postoperative rescue medications

	LB (n=20)	NS (n=20)
Meperidine consumption (mg)	75 (58)*	120 (57)
Patients requiring meperidine (n)	15*	20
Metoclopramide consumption (mg)	5 (6)	11.5 (10.8)
Patients requiring metoclopramide (n)	9	13

Data are expressed as mean (SD) and number of patients.
* p<0.05 between groups.

Table 3. Patient satisfaction*

	LB (n=20)	NS (n=20)
Excellent	18	11
Good	1	8
Satisfactory	1	1

* p<0.05 between groups.

Data of intraoperative fentanyl consumption, postoperative abdominal pain, the incidence of right shoulder pain, requirements of rescue analgesic (meperidine) and antiemetic (metoclopramide), incidence of nausea and vomiting, and patient satisfaction in the follow-up period of 24 h were compared between the two groups.

Data analysis was performed using SPSS version 15.0 for Windows. Demographic data, duration of surgery, and total mean doses of fentanyl, meperidine and metoclopramide consumptions were analyzed using t-test and chi-square tests. Pain intensity (VAS scores) was compared between groups by repeated measures of analysis of variance. Data were expressed as mean ± standard deviation. A p-value of less than 0.05 was considered statistically significant.

Results

Both groups had similar characteristics in terms of age, gender, body measures and the duration of surgery (Table 1). While the mean dose of intraoperative fentanyl consumption was higher in the NS group versus the LB group, the difference was insignificant (p=0.132). During the first half hour, VAS scores were significantly lower in the LB group compared to the NS group (Figure 1, p<0.05). However, the incidence of right shoulder pain was not significantly different between the LB group (10%) and NS group (15%). The mean dose of meperidine consumption and the number of patients needing rescue meperidine were significantly lower in the LB group than in the NS group (Table 2, p<0.05). The incidence of nausea was not significantly different between the LB group (45%) and the NS group (65%). A statistically significant increase in vomiting was found in the NS group versus the LB group (8 vs 0 patients, p<0.05). Patient satisfaction was also significantly increased in the LB group than in the NS group (Table 3). No patient developed side effects related to levobupivacaine administration.

Discussion

This study demonstrates that intraperitoneal administration of 40 mL 0.25% levobupivacaine immediately after pneumoperitoneum had useful effects on postoperative pain relief especially in the

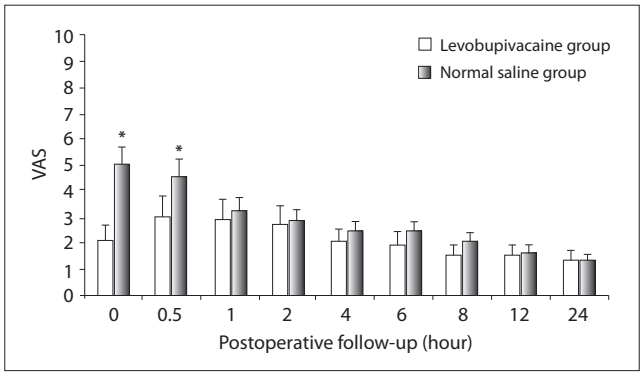

Fig. 1. Postoperative pain visual analog scale (VAS) scores at rest.
* p<0.05 between groups.

early postoperative period after LC. The advantages of intraperitoneal levobupivacaine in this study were reduced postoperative pain intensity during 0-30 min, lower consumption of meperidine postoperatively, lower incidence of vomiting, and improved patient satisfaction.

It appears that the analgesic efficacy of intraperitoneal LA with only a single dose after LC is variable. The reasons for these different results with respect to pain intensity are thought to be related with the time and the site of administration as well as the type, dose and concentration of LA used in the heterogeneous groups.[7-9] In a meta-analysis published in 2006 including intraperitoneal administration of bupivacaine, lidocaine, ropivacaine, or levobupivacaine in LC, 12 of 24 trials reported a significant improvement in pain during the early postoperative period without a significant effect on total amount of analgesia delivered.[5]

The administration of LA immediately after pneumoperitoneum has been previously shown to be especially more effective than the administration before the removal of the trocars in LC. It was suggested that administration of LA at the beginning of the operation served as preemptive analgesia via suppression of central neural sensitization before the nociceptive stimulus triggered the activation of pain pathways.[5] Szem and colleagues[10] reported that intraperitoneal 0.1% bupivacaine 100 mL, administered before surgery, offered advantages with respect to postoperative pain after LC for the first 6 h. Furthermore, Pasqualucci and colleagues[11] showed that the timing of administration of 0.5% bupivacaine 40 mL with epinephrine before surgery was important with respect to postoperative pain relief and analgesic consumption. Bupivacaine has been the most widely used LA agent for postoperative analgesia after LC. Unfortunately, it is seen that the type of LA and its most effective dose and concentration are not yet clear. The literature shows that 0.25% to 0.5% concentrations and 30 mL to 40 mL volumes of bupivacaine might be the proper doses to attenuate postoperative pain. It was reported that 0.125% bupivacaine 80 mL after pneumoperitoneum was not effective in treating postoperative pain after LC.

Levobupivacaine is also known as a safer agent than bupivacaine in terms of its cardiovascular and central nervous system effects. Only two studies have been presented evaluating the effect of intraperitoneally administered levobupivacaine. Louizos and colleagues[12] used 0.25% levobupivacaine 20 mL intraperitoneally following the removal of the gallbladder. They found that the combination of preincisional local infiltration and intraperitoneal instillation of levobupivacaine had an advantage for postoperative analgesia versus the group with only intraperitoneal NS, intraperitoneal LA without local infiltration and local infiltration without intraperitoneal LA. They also determined lower VAS scores than those in our study, even though their doses of levobupivacaine were twice as low as those used in our study. Intraperitoneal instillation of 30 mL of levobupivacaine 0.25% with epinephrine, prior to wound closure, did not significantly reduce total abdominal pain at rest while it was significantly reduced during inspiration. They concluded that the modest analgesic effect in their study was due to inadequate dose used and rapid dilution of LA in the peritoneal cavity.[13]

The originality of our study is the volume of levobupivacaine 0.25% used and the timing of its application. In this presented study, we used the same concentration as in the two studies reported by Louizos and colleagues and Ng and colleagues, but we used a greater volume of levobupivacaine. A total of 40 ml of levobupivacaine was used immediately after the creation of pneumoperitoneum. These doses of levobupivacaine were well tolerated by the patients and had no side effects. In general, lower VAS scores were achieved at each time period in the follow-up for both groups. The first half hour in the postoperative period, pain scores were significantly lower in the levobupivacaine group compared to the NS group. This significant difference in the first half hour period might be explained by the duration of levobupivacaine. Insignificant VAS differences in the remaining postoperative period were due to decreased effect of levobupivacaine in the LB group and increased rescue analgesic consumption in the NS group. In fact, the postoperative pain scores in both groups of the study were at a mild/moderate level. This might be related to the pre-incisional infiltration of the port sites with LA combined with i.v. paracetamol given just before the end of the surgery

in all patients. Shoulder pain is a frequent complication of laparoscopic surgery with an incidence of 35% to 60% in the postoperative period.[3] The proposed mechanism of shoulder pain includes phrenic nerve neurapraxia of short duration, stretching of the subdiaphragmatic fibers by an increased concavity of the diaphragm induced by pneumoperitoneum, and reference of pain from the traumatized area.[14] Louizos and colleagues[12] reported that the incidence of shoulder pain was significantly lower in patients who received intraperitoneal levobupivacaine. In our study, the incidence of right shoulder pain was generally low in both groups in the follow-up period of 24 h ($p>0.05$, between the groups). Thus, the lower incidences of shoulder pain might be due to balanced analgesia and an experienced surgical team not causing increased intraperitoneal pressure and properly desufflating the pneumoperitoneum during LC.

In conclusion, a single intraperitoneal administration of 40 mL levobupivacaine 0.25% given immediately after pneumoperitoneum into the hepatodiaphragmatic lodge and above the gallbladder demonstrated useful effects on postoperative pain relief, especially in the early postoperative period after LC, and reduced postoperative rescue analgesic requirement, with excellent patient satisfaction; there were no levobupivacaine-related complications or side effects.

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