Evaluation of intraperitoneal levobupivacaine with and without sufentanil for postoperative analgesia after laparoscopic cholecystectomy

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Background and objectives
Postoperative pain after laparoscopic cholecystectomy (LC) is unpredictable, which explains the need for systematic prevention of pain before the patient wakes up from anesthesia. The study was conducted to evaluate the effect of intraperitoneal levobupivacaine with or without sufentanil for postoperative analgesia after LC.
Patients and methods
Ninety patients who underwent elective LC completed the study. Group C (n=29) received 50 ml of intraperitoneal normal saline, group L (n=31) received 50 ml of intraperitoneal levobupivacaine 0.25%, and group LS (n=30) received 50 ml of intraperitoneal levobupivacaine 0.25% plus 20 μg sufentanil. Visual analog score was recorded immediately postoperatively, and at 4, 8, and 12 h postoperatively. In addition, time to first rescue analgesia (diclofenac), total diclofenac consumption in 12 h, and complications (pruritus, emesis, shoulder pain, bradycardia, and hypotension) were recorded.
Results
Visual analog score until 8 h postoperatively was significantly higher in group C compared with groups L and LS. However, the difference was nonsignificant between groups L and LS, except at 8 and 12 h postoperatively. Time to first rescue analgesia was significantly longer in group LS (134.16±36.5) compared with group C (11.96±5.92) and group L (114.83±35.49) (P<0.001). Total diclofenac consumption in the first 12 h postoperatively was significantly lower in group L (92.5 ±32.26) and group LS (82.5±22.88) compared with group C (152.5±13.69).
Conclusion
Intraperitoneal instillation of levobupivacaine with sufentanil reduces not only the intensity of postoperative pain but also the total rescue analgesic dose consumption after LC.

Keywords:
intraperitoneal;, laparoscopic cholecystectomy, levobupivacaine, postoperative analgesia, sufentanil

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Introduction

The most common operation of the biliary tract performed these days is cholecystectomy, which is the second most common operation [1]. Laparoscopic cholecystectomy (LC) has the advantage of reduced pain and shorter hospital stay and recovery period [2]. Pain following LC is multifactorial and is differentiated into three components: visceral, abdominal wall, and referred pain to the shoulder [3]. Visceral pain after laparoscopy results from the stretching of abdominal cavity, peritoneal inflammation, and phrenic nerve irritation caused by residual CO_2 in the peritoneal cavity [4–6].

Several studies are available on the efficacy of intraperitoneal administration of a local anesthetic (LA) with or without opioids for analgesia after laparoscopic surgery [7–9].

To date, there has been no study that evaluated the use of intraperitoneal levobupivacaine and sufentanil for reducing postoperative analgesia. Therefore, this study was conducted to evaluate the efficacy of levobupivacaine with or without sufentanil intraperitoneally on postoperative pain after LC.

Patients and methods

This study was conducted in Benha University Hospitals between September 2014 and October 2015. After obtaining approval from the local ethical committee and informed written consent from patients, this prospective, controlled, double-blind,

randomized clinical trial was conducted on 90 patients between 18 and 60 years of age and of American Society of Anesthesiologists physical status class I and II who underwent elective LC. Patients with known hypersensitivity to LA, those on NSAIDs, those having a history of alcohol or drug abuse, pregnant women or those in the lactation period, obese patients (BMI>30), and patients having any renal or hepatic dysfunction were excluded from the study.

Patients were randomly allocated into three groups. An online randomization program was used to generate random number list. Patient randomization numbers were concealed in opaque envelops and were opened by the study investigator.

Group C (the control group) received 50 ml of normal saline intraperitoneally.

Group L (the levobupivacaine group) received 50 ml of levobupivacaine 0.25% intraperitoneally.

Group LS (the levobupivacaine plus sufentanil group) received 50 ml of levobupivacaine 0.25% plus 20 µg sufentanil intraperitoneally.

Members of the study group involved in obtaining functional data were blinded to randomization during the period of data acquisition and analysis.

One day before surgery, all patients were interviewed for preoperative evaluation and to explain visual analog scale (VAS) using a 100 mm scale (0, no pain, and 100 mm, worst possible pain).

Thirty minutes before induction of general anesthesia, an intravenous line was inserted and patients were premedicated with 0.01 mg of midazolam and 8 mg of dexamethasone.

Anesthesia was induced with fentanyl 3 µg/kg and propofol 2 mg/kg followed by atracurium 0.5 mg/kg to facilitate endotracheal intubation. Anesthesia was maintained with isoflurane 1.2% and 0.1 mg atracurium every 20 min. Ventilation parameters were as follows: maintenance of end-tidal CO_2 between 35 and 45 mmHg and peak inspiratory pressure below 30–35 cmH_2O.

LC was performed according to the standard surgical technique: a classic four-port surgical technique that consists of the placement of 2 mm port through the umbilical incision, a 10 mm port in the epigastric area, and two 5 mm port on the right side of the abdomen. A 20-G multiple side holes epidural catheter (B. Braun) was inserted through the lateral port under direct vision of a laparoscope. The LA or placebo solution was sprayed on the upper surface of the liver and on the right subdiaphragmatic space, to allow it to diffuse into the hepatodiaphragmatic space, near and above the hepatoduodenal ligament, and above gallbladder bed. The study solution was injected with the patient in the Trendelenburg position; 25 ml was injected before dissection and the other 25 ml at the end of surgery before CO_2 deflation.

At the end of surgery all patients received intravenous ondansetron 4 mg for postoperative nausea and vomiting; neuromuscular blockade was reversed with intravenous neostigmine (0.04–0.08 mg/kg) and intravenous atropine (0.01–0.02 mg/kg).

The following parameters were recorded in the first 12 h postoperatively: VAS immediately postoperatively and then every 4 h, time to the first rescue analgesia (diclofenac sodium 75 mg), and total diclofenac consumption. Complications such as pruritus, nausea, vomiting, shoulder pain, bradycardia (heart rate<60), and significant hypotension (mean arterial pressure<60 mmHg or dropped >20% of basal value) were also measured.

Statistical analysis

Analysis of data was performed using SPSS, version 16 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were presented as mean±SD. Qualitative data were presented as numbers and percentages. Quantitative data were analyzed using repeated-measure one-way analysis of variance test followed by post-hoc test. Qualitative data were analyzed using the χ^2-test. A *P*-value less than 0.05 was considered statistically significant. Sample size was calculated according to a pilot study of the first eight patients with power 80% and α -error 0.05. The primary outcome was the VAS. The effect size was 0.6769. Twenty-eight patients were considered in each group.

Results

A total of 112 patients were assessed for eligibility: 11 patients did not meet the inclusion criteria and five patients refused to participate in the study. Final tabulation was carried out for 96 patients. As a result of biliary spillage, one patient in group C was excluded from the study. Two more patients were excluded from group C and one patient from group LS due to the surgeon's decision to change to open surgery. One patient in group L was excluded because

of reopening. One patient in group LS was excluded because of hemorrhage. Ninety patients completed the study (Fig. 1).

Demographic characteristics and duration of surgery were comparable among groups (Table 1).

As regards VAS, there were significantly higher values at all times of measurement in group C compared with group LS ($P<0.001$), and higher values at all times of measurement in group C compared with group L, but the difference was not significant at 12 h postoperatively ($P>0.05$). There were significantly lower VAS values in group LS at 8 and 12 h compared with group L (Table 2 and Fig. 2).

As regards rescue analgesia consumption, the time to first rescue analgesia was significantly longer in group LS compared with groups C and L ($P<0.001$), and total diclofenac consumption at 12 h postoperatively was significantly lower in groups L and LS compared with group C (Table 3).

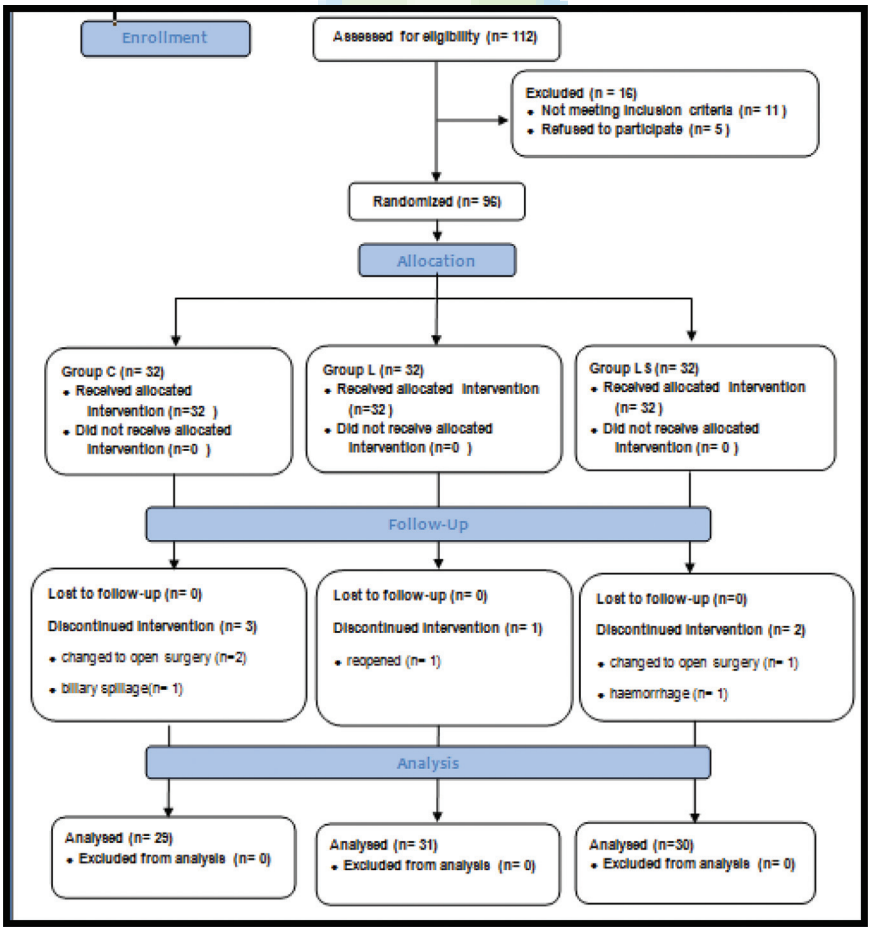
As regards complications, group LS showed a nonsignificantly higher incidence of pruritus and hypotension compared with groups C and L, and a

Table 1 Demographic characteristics and duration of surgery

	Group C (*n*=29)	Group L (*n*=31)	Group LS (*n*=30)	*P*-value
Age (years)	42.7±11.46	43.6±10.81	42.91±12.33	0.85
Sex (male : female) [*n* (%)]	9 (31) : 20 (69)	12 (38.7) : 19 (61.3)	8 (26.6) : 22 (73.4)	0.69
Height (cm)	168.46±7.5	169.83 ±7.62	167.83±7.12	0.56
Weight (kg)	76.96±8.43	74.56±8.6	75.3±8.29	0.52
Duration of surgery (min)	39.73 ±11.13	40.56 ±12.49	41.43±13.01	0.86

Data are presented as mean±SD; sex presented as numbers and percentage.
Group C, intraperitoneal saline; group L, intraperitoneal levobupivacaine; group LS, intraperitoneal levobupivacaine plus sufentanil.

Figure 1



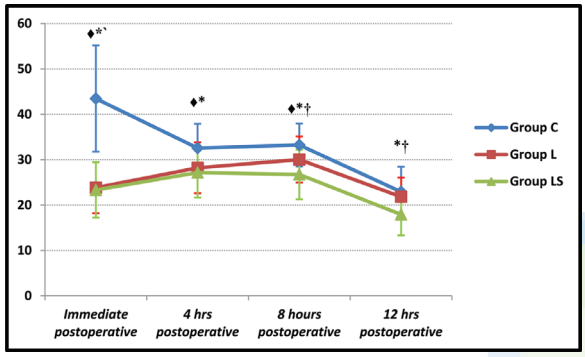
Consort flow diagramConsort flow diagram [group C (intraperitoneal saline), group L (intraperitoneal levobupivacaine), and group LS (intraperitoneal levobupivacaine plus sufentanil)].

Table 2 Visual analog score of the studied groups

	Group C (*n*=29)	Group L (*n*=31)	Group LS (*n*=30)	*P*-value
Immediately postoperatively	43.46±11.7	23.83±5.61*	23.33±6.11*	<0.001
4 h postoperatively	32.56±5.32	28.2±5.61*	27.16±5.49*	<0.001
8 h postoperatively	33.23±4.71	30.03±5.08*	26.73±5.45*,†	<0.001
12 h postoperatively	22.93±5.5	21.83±4.21	17.93±4.61*,†	<0.001

Data are presented as mean±SD.
Group C, intraperitoneal saline; group L, intraperitoneal levobupivacaine; group LS, intraperitoneal levobupivacaine plus sufentanil.
*Significant difference compared with group C.
†Significant difference compared with group L.

Figure 2



Visual analog score of the studied groups [group C (intraperitoneal saline), group L (intraperitoneal levobupivacaine), and group LS (intraperitoneal levobupivacaine plus sufentanil)]. ♢Significant difference in group L compared with group C, *Significant difference in group LS compared with group C, †Significant difference in group LS compared with group L.

Table 3 Rescue analgesia of the studied groups

	Group C (*n*=29)	Group L (*n*=31)	Group LS (*n*=30)	*P*-value
Time to first rescue analgesic dose (min)	11.96 ±5.92	114.83 ±35.49*	134.16 ±36.5*,†	<0.001
Total diclofenac consumption (mg)	152.5 ±13.69	92.5 ±32.26*	82.5 ±22.88*	<0.001

Data are presented as mean±SD.
Group C, intraperitoneal saline; group L, intraperitoneal levobupivacaine; group LS, intraperitoneal levobupivacaine plus sufentanil.
*Significant difference compared with group C.
†Significant difference compared with group L.

significantly higher incidence of bradycardia compared with groups L and LS. As regards shoulder pain, group C showed a significantly higher incidence compared with groups L and LS. As regards nausea and vomiting, group C showed a significantly higher incidence compared with groups L and LS (Table 4).

Table 4 Complications in the studied groups

	Group C (*n*=29)	Group L (*n*=31)	Group LS (*n*=30)	*P*-value
Pruritus	1	2	5	0.16
Nausea : vomiting	6 : 1	2 : 0	1 : 1	0.17
Shoulder pain	5	1	0*	**0.02**
Bradycardia	1	1	7*,†	**0.01**
Hypotension	0	1	3	0.16

Data are presented as numbers.
Group C, intraperitoneal saline; group L, intraperitoneal levobupivacaine; group LS, intraperitoneal levobupivacaine plus sufentanil.
*Significant difference compared with group C.
†Significant difference compared with group L.

Discussion

LC is a day-case or short-stay procedure, and therefore provision of adequate postoperative pain relief is considerably important.

During operation, interruption of nociceptive input and blockade of *N*-methyl d-aspartate activation by some drugs such as opioids or LA may be necessary to provide effective postoperative analgesia [10,11].

Instillation of intraperitoneal LA to reduce postoperative pain has been studied through randomized trials for more than 10 years [6].

Levobupivacaine has increasingly been used in clinical anesthesia practice since last few years because of its safer pharmacological profile. The concentration necessary to produce cardiac and neurotoxicity is higher for levobupivacaine than for racemic bupivacaine [12].

Our study showed that VAS scores were higher in group C than in group L and in group LS. There was a significant difference between VAS scores of groups C and L immediately postoperatively, and at 4 and 8 h postoperatively. However, the difference was not statistically significant at 12 h postoperatively. VAS scores were similar in groups L and LS up to 4 h postoperatively. However, at 8 and 12 h postoperatively, VAS score was found to be significantly lower in group LS compared with group L.

As regards VAS, our study is in agreement with a study by Gupta and colleagues, which showed that

intraperitoneal instillation of fentanyl (100 µg) along with bupivacaine (0.5% 20 ml) significantly reduces immediate postoperative pain. It also reduces the intensity of pain even after 24 h [6].

Our results are in agreement with those of Labaille *et al.* [13], who also found a significant reduction in visceral pain in patients receiving ropivacaine in the gallbladder bed immediately after trocar placement and at the end of surgery. Ingelmo *et al.* [14] found that preoperative nebulization of peritoneal cavity with ropivacaine significantly reduces postoperative pain.

Our study is in concordance with those of Trikoupi *et al.* [15], Kucuk *et al.* [8], Memedov *et al.* [16], Pavlidis *et al.* [17], and Park *et al.* [18], who have found that intraperitoneal instillation of local anesthesia decreases visceral pain after laparoscopic surgery.

However, a study conducted by Bisgaard *et al.* [19] failed to show any decrease in visceral pain after intraperitoneal instillation of ropivacaine. This could be due to a reduced dosage used for intraperitoneal instillation.

There are other studies by Newcomb *et al.* [20], Rademaker *et al.* [21], and Scheinin *et al.* [22], which did not find any benefit of intraperitoneal instillation of local anesthesia in decreasing pain after LC.

As regards rescue analgesia, time to requirement of first-dose rescue analgesia in our study was longer in group LS than in group L and was minimum in patients of group C, indicating better and longer pain relief in patients receiving levobupivacaine with sufentanil compared with patients receiving levobupivacaine alone and those receiving normal saline. Total analgesic consumption was also significantly lower in group LS and total analgesic consumption (diclofenac) was maximum in group C. Therefore, levobupivacaine along with sufentanil reduces not only the intensity of pain but also the total dose of analgesic consumption.

Our study is in agreement with a study conducted by Gupta *et al.* [6], which showed that total analgesic (diclofenac) consumption was lower in the fentanyl plus bupivacaine group compared with the bupivacaine only group. Moreover, time to requirement of first-dose rescue analgesia was shorter in the fentanyl plus bupivacaine group.

Moreover, it is in agreement with the study by Trikoupi *et al.* [15], who recorded the time to first-dose analgesic demand and the total amount of morphine received through patient-controlled analgesia in the first 24 h; their results are similar to our study results.

As regards complications, our study recorded the incidence of pruritus, emesis, hypotension, bradycardia, and shoulder pain in the three groups.

The incidence of pruritus was highest in group LS patients than in groups L and C, which was probably due to the absorption of sufentanil. Incidence of emesis was highest in patients receiving normal saline, and there was no difference in patients receiving levobupivacaine alone and with sufentanil. This shows that ropivacaine instillation reduces the incidence of nausea and vomiting. The cause could be the higher incidence of pain, and thus greater autonomic response in the placebo group, as well as repeated doses of analgesic given as rescue analgesia for these patients.

Incidence of hypotension and bradycardia was highest in patients receiving levobupivacaine with sufentanil than in those who received levobupivacaine alone or normal saline. Increased incidence of bradycardia may be due to sufentanil absorption, which is known to cause bradycardia as a side effect.

No shoulder pain was observed in patients receiving levobupivacaine with or without sufentanil even after 8 h postoperatively. The reason could be the blocking of nociceptive inputs generated by inflamed diaphragm peritoneum caused by the instillation of ropivacaine.

As regards complications, our study is in accordance with those of Gupta *et al.* [6], Trikoupi *et al.* [15], and Kucuk *et al.* [8]. Their results are similar to our study results.

Study limitation

The 12 h duration of observation might have led to the overestimation of rescue analgesic dose and underestimation of shoulder pain incidences, as after 12 h pain was found to decrease, requiring fewer analgesic doses. Duration of analgesia provided could have been ascertained more precisely if the study was conducted for longer periods.

Conclusion

Intraperitoneal levobupivacaine alone or with sufentanil for LC reduces pain in the initial

postoperative period; it is easy to administer with no adverse effects and may become a routine practice for this procedure

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Conflicts of interest
There is no conflict of interest.

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