ORIGINAL ARTICLE

Pre-incisional local infiltration with levobupivacaine in laparoscopic cholecystectomy: a randomized and clinical trial

Infiltración local preincisional con levobupivacaína en colecistectomía laparoscópica: ensayo clínico aleatorizado

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Abstract

Objective: *Laparoscopic cholecystectomy (LC), despite its minimally invasive nature, requires effective control of postoperative pain. The use of local anesthetics (LA) has been studied, but the level of evidence is low, and there is little information on important parameters such as health-related quality of life (HRQoL) or return to work. The objective of the study was to evaluate the efficacy of 0.50% levobupivacaine infiltration of incisional sites in reducing POP after LC.* **Methods:** *This was a prospective, randomized, double-blind study. Patients undergoing elective LC were randomized into two groups: no infiltration (control group) and port infiltration (intervention group). POP intensity (numerical rating scale, NRS), need for rescue with opioid drugs, PONV incidence, HRQoL, and return to work data, among others, were studied.* **Results:** *Two hundred and twelve patients were randomized and analyzed: 105 (control group) and 107 (intervention group). A significant difference was observed in the NRS values (control group mean NRS score: 3.41 ± 1.82 vs. 2.56 ± 1.96) ($p < 0.05$) and in the incidence of PONV (31.4% vs. 19.6%) ($p = 0.049$).* **Conclusions:** *Levobupivacaine infiltration is safe and effective in reducing POP, although this does not lead to a shorter hospital stay and does not influence HRQoL, return to work, or overall patient satisfaction.*

Keywords: *Local anesthesia. Levobupivacaine. Laparoscopic cholecystectomy. Pain. Randomized clinical trial.*

Resumen

Objetivo: *la colecistectomía laparoscópica (CL), a pesar de su carácter mínimamente invasivo, requiere un control efectivo del dolor postoperatorio (POP). El uso de anestésicos locales (AL) ha sido estudiado pero el nivel de evidencia es bajo y existe poca información acerca de parámetros relevantes como la calidad de vida relacionada con la salud (CVRS) o la reincorporación laboral. El objetivo de este estudio es analizar la eficacia de la infiltración de los sitios incisionales con levobupivacaína 0,50% en la reducción del dolor postoperatorio tras la CL.* **Material y métodos:** *estudio prospectivo, aleatorizado y doble ciego. Pacientes sometidos a CL programada fueron aleatorizados en dos grupos: sin infiltración (grupo control) y con infiltración preincisional (grupo intervención). La intensidad del dolor (escala de puntuación numérica, NRS), la necesidad de rescates con opioides, la incidencia de náuseas o vómitos postoperatorios (NVPO) y datos de CVRS o reincorporación laboral, entre otros, fueron recogidos.* **Resultados:** *212 pacientes fueron aleatorizados y analizados: 105 en el grupo control y 107 en el grupo de intervención. Se observó una diferencia estadísticamente significativa en la intensidad del dolor (puntuación media NRS: 3.41 ± 1.82 vs. 2.56 ± 1.96) ($p < 0.05$) y en la incidencia de NVPO (31.4% vs. 19.6%) ($p = 0.049$).*

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Conclusiones: *La infiltración con levobupivacaína es segura y efectiva en la reducción del dolor postoperatorio, aunque esto no conlleva una menor estancia hospitalaria y no influye en los resultados de CVRS, reincorporación laboral o satisfacción del paciente.*

Palabras clave: *Anestesia local. Levobupivacaína. Colecistectomía laparoscópica. Dolor. Ensayo clínico aleatorizado.*

Introduction

Laparoscopic cholecystectomy (LC) is one of the most performed surgical procedures in the world, with over 300,000 patients in the USA every year[1] and about 80,000 in Spain[2]. Most patients are adults (mainly women) with symptomatic cholelithiasis, and it can be performed as an inpatient surgery or a day-case surgery. Despite the minimally invasive nature of the laparoscopic approach, it is not a POP-free procedure. Pain may have different origins: visceral pain, parietal pain, and irritation secondary to residual pneumoperitoneum[3]. POP is especially important in the first 24 h and is related to a greater use of opioid analgesics, which can present certain unwanted side effects, mainly PONV. In this way, POP can interfere with the first steps of recovery (oral tolerance, ambulation, etc.)[4]. Trying to prevent and minimize POP is not only mandatory to avoid patient discomfort and suffering but may also allow earlier hospital discharge and perhaps a better recovery after hospital discharge as well.

There are previous studies focusing on the use of LA both at surgical incision sites and intraperitoneally. However, although results point to a reduction in POP, the level of evidence is very low, and there is little information on important parameters such as HRQoL or return to work[5].

The aim of this study is to improve the existing scientific evidence about the use of levobupivacaine in the incisional sites of LC, focusing on POP, use of opioid drugs, incidence of PONV, and patient recovery, including the mentioned parameters as HRQOL and return to work.

Materials and methods

Before approval by the Ethics and Research Committee, a prospective, randomized, and double-blind study was conducted. It conformed to CONSORT guidelines for reporting parallel group randomized trials and was registered at ClinicalTrials.gov under code NCT04697329.

The inclusion criteria were patients over 18 years old scheduled for elective LC. American Society of Anesthesiologists (ASA) 1, 2, and 3 patients were included. The exclusion criteria were: cognitive impairment, previous adverse reactions to LA, coronary heart disease, and accompanying chronic pain disorders. Patients underwent inpatient surgery with at least an overnight stay at the hospital. All the operations were performed by surgeons experienced in laparoscopy.

A simple randomization was performed for each patient, which determined their assignment to a control group and an intervention group. In the latter, the LA was administered in the operating room immediately before skin incisions, already under general anesthesia. 20 ml of a 5 mg/ml levobupivacaine solution was administered to the incision sites, infiltrating skin, fascia, and preperitoneal space.

Surgery was performed laparoscopically, first placing a Hasson-type trocar at the umbilical level using the open technique, followed by an 11-mm epigastric trocar and two 5-mm trocars in the right midclavicular and midaxillary lines. Intra-abdominal pressure was maintained at 12 mmHg.

The fascia of the umbilical orifice was sutured with an absorbable braided thread (polyglycolic acid), and the skin of the four incisions was closed with staples.

Post-operative routine analgesia was metamizole 1 g IV every 6 h and paracetamol 1 g IV every 6 h. Morphine chloride, 3 mg IV every 3 h, was also administered at the patient's request, always according to the criteria, and under the supervision of the nursing staff. After hospital discharge, patients received a protocol for the administration of different non-opioid analgesics, usually 575 mg metamizole every 8 h, alternating with 1 g paracetamol every 8 h.

Follow-up with each patient was carried out from the surgical intervention until the moment of hospital discharge. In addition, 1 month after the intervention, data were collected in a face-to-face hospital review and by telephone review.

The first primary outcome was pain intensity using a numerical rating scale (NRS), ranging from zero to ten, where 0 represents "no pain" and 10 represents "the most intense pain imaginable". Pain was rated at 4, 8, 12, and 24 h after surgery. Two other primary outcomes were analyzed: the need for rescue with opioid drugs and the presence of PONV. Secondary

Table 1. Demographic data

n	Global	Control	Intervention	p - value
	212	105	107	
Mean age (year)	54.7 ± 15.2	53.9 ± 14.9	55.4 ± 15.5	0.482
Gender (n [%])	M: 72 (34.0%)/ F: 140 (66.0%)	M: 39 (37.1%)/ F: 66 (62.9%)	M: 33 (30.8%)/ F: 74 (69.2%)	0.333
ASA 1 (n [%])	31 (14.6%)	19 (18.1%)	12 (11.2%)	
ASA 2 (n [%])	162 (76.4%)	81 (77.1%)	81 (75.7%)	0.054
ASA 3 (n [%])	19 (9.0%)	5 (4.8%)	14 (13.1%)	
Mean BMI (kg/m^2)	27.9 ± 4.7	27.4 ± 4.5	28.3 ± 4.8	0.157
Active employment status (n [%])	106 (50.0%)	52 (49.5%)	54 (50.5%)	0.891
Previous open abdominal surgery (n [%])	79 (37.3%)	37 (35.2%)	42 (39.3%)	0.546
Symptomatic cholelithiasis (n [%])	199 (93.9%)	99 (94.3%)	100 (93.5%)	0.802
Gallbladder polyps (n [%])	13 (6.1%)	6 (5.7%)	7 (6.5%)	
Previous acute pancreatitis (n [%])	26 (12.3%)	8 (7.6%)	18 (16.8%)	0.041*
Previous acute cholecystitis (n [%])	25 (11.8%)	11 (10.5%)	14 (13.1%)	0.556
Previous acute colangitis (n [%])	8 (3.8%)	6 (5.7%)	2 (1.9%)	0.142
Previous ERCP (n (%)]	15 (7.1%)	7 (6.7%)	8 (7.5%)	0.818

*p < 0.05 was considered statistically significant.
ASA: American Society of Anesthesiologists; BMI: body mass index; ERCP: endoscopic retrograde cholangiopancreatography.

outcomes were oral intake initiation time, time to ambulation, and length of hospital stay. In addition, different intraoperative and post-operative parameters were recorded. HRQoL data related to the first days after hospital discharge were collected using the EuroQol-5D-3L questionnaire. This quiz includes five parameters (dimensions) scored from 1 to 3: mobility, self-care, usual activities (e.g., work, study, housework, family or leisure activities), pain or discomfort, and anxiety or depression. The following parameters were also analyzed 1 month after LC: development of hematoma or surgical site infection (SSI), number of days of analgesic intake, return to work, oral tolerance, and patient satisfaction.

Table 2. Intraoperative parameters

IO parameter	Global	Control	Intervention	p-value*
Mean operative time (min)	48.5 ± 16.7	46.4 ± 15.7	50.5 ± 17.4	0.102
Cholecystitis (n (%))	43 (20.3%)	21 (20.0%)	22 (20.6%)	0.919
Bile spillage (n (%))	60 (28.3%)	28 (26.7%)	32 (29.9%)	0.601
Dose of fentanyl (mcg/kg)	3.33 ± 1.46	3.40 ± 1.47	3.26 ± 1.46	0.519

*p < 0.05 was considered statistically significant.

Statistical analysis

The sample size was calculated with a 95% confidence level, a statistical power of 95%, and a loss to follow-up of 1%. A sample of 210 patients was considered necessary. Patients, nurse staff, and data collectors were blinded.

Data are expressed as the percentage of patients or mean ± standard deviation. Statistically significant differences were those with $p < 0.05$. Numerical data were compared by the *t* test or Mann–Whitney U test. Nominal variables were analyzed using Chi-square tests. The effect of the intervention was evaluated with the odds ratio (OR) and its confidence interval (CI) adjusted for the different covariates with a backstep logistic regression model, thus controlling possible confounding factors. Statistical analysis was performed with the IBM SPSS Statistics v.22 program (IBM Corp., Armonk, NY, USA).

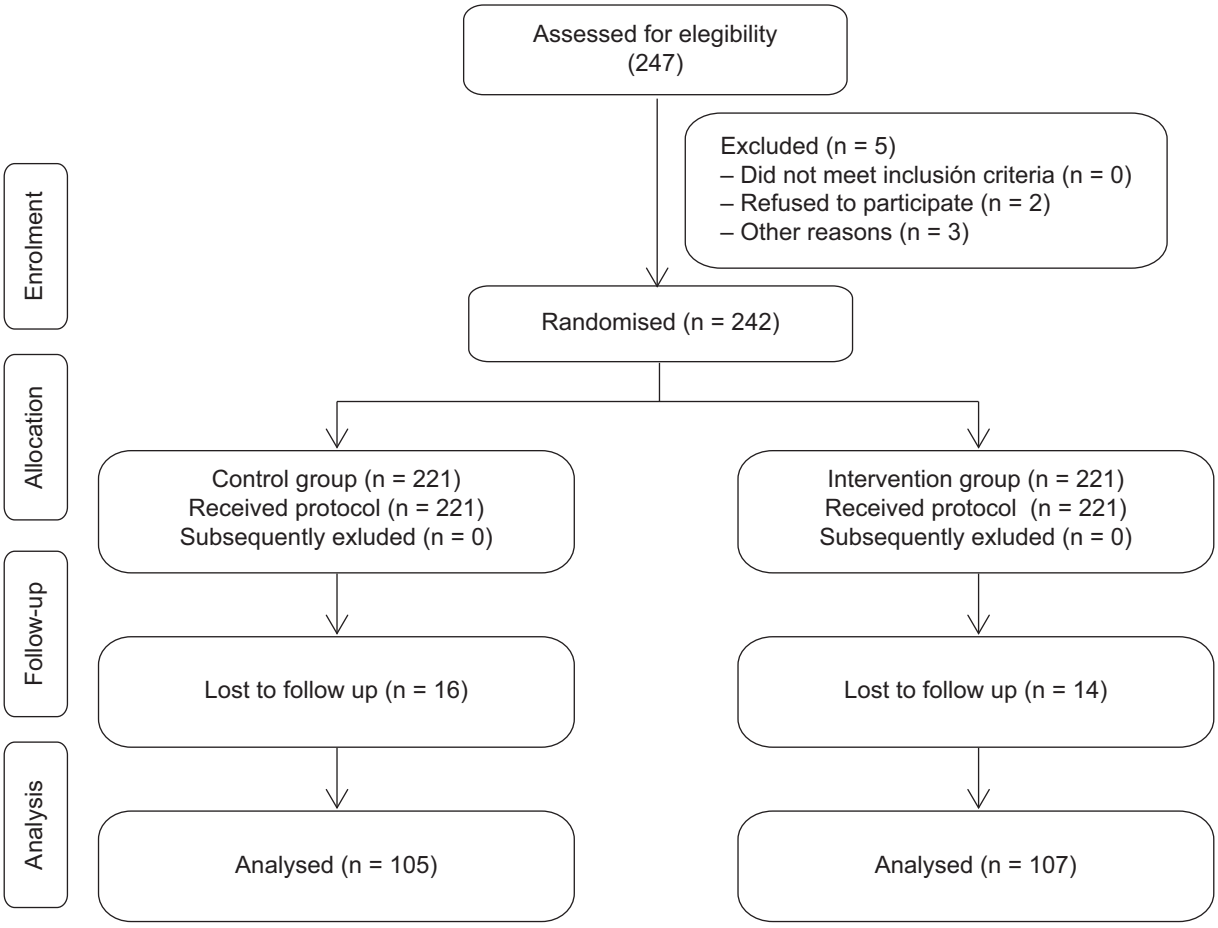

Figure 1. *Consort flow chart.*

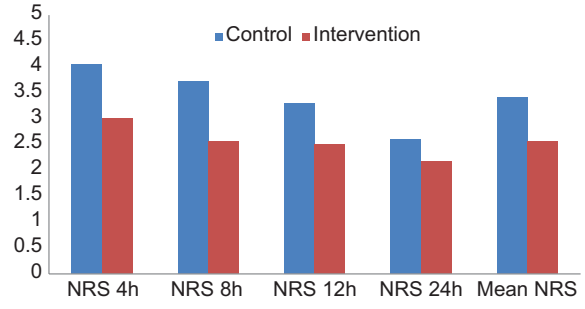

Figure 2. *NRS score.*
NRS: numeric rate scale.
Note: 4, 8, 12, and 24 h after surgery.

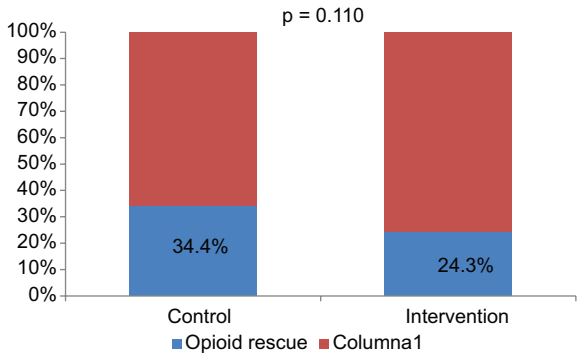

Figure 3. *Need for opioid rescue.*

Results

A total of 242 patients were enrolled and randomized from December 2020 to May 2022. The patient flow chart is shown in figure 1 (Consort Diagram). 30 patients were lost to follow-up, and 212 patients were finally analyzed. The main causes of loss of follow-up were drain placement (12 patients), open surgery conversion (nine patients), reintervention (three patients), and lack of collaboration (two patients).

Of the 212 patients analyzed, 105 underwent surgery without local infiltration (control group), while LA was administered to 107 patients (intervention group). There were no significant differences between both

Table 3. Inhospital postoperative parameters

Postoperative parameter	Global	Control	Intervention	p-value
NRS 4 h	3.52 ± 2.58	4.05 ± 2.45	3.01 ± 2.61	0.001*
NRS 8 h	3.14 ± 2.35	3.72 ± 2.34	2.56 ± 2.24	< 0.001*
NRS 12 h	2.89 ± 2.00	3.29 ± 1.86	2.50 ± 2.05	0.001*
NRS 24 h	2.39 ± 1.16	2.60 ± 1.53	2.18 ± 1.71	0.014*
Mean NRS	2.98 ± 1.93	3.41 ± 1.82	2.56 ± 1.96	< 0.001*
Opioid rescue (n [%])	62 (29.2%)	36 (34.3%)	26 (24.3%)	0.110
Nausea/vomiting (n [%])	54 (25.5%)	33 (31.4%)	21 (19.6%)	0.049*
Antiemetics rescue (n [%])	45 (21.2%)	23 (21.9%)	22 (20.6%)	0.811
Mean systolic blood pressure (mm Hg)	131.3 ± 18.1	130.9 ± 18.3	131.7 ± 18.0	0.667
Mean diastolic blood pressure (mm Hg)	74.2 ± 9.7	74.9 ± 9.2	73.5 ± 10.01	0.460
Mean heart rate (bpm)	72.5 ± 10.9	73.3 ± 11.4	71.7 ± 10.4	0.161
Mean PACU length of stay (min)	210.6 ± 127.0	205.6 ± 123.5	215.4 ± 132.64	0.665
Shoulder pain (n [%])	44 (20.8%)	25 (23.8%)	19 (17.8%)	0.277
Mean oral intake initiation time (h)	9.6 ± 4.8	9.7 ± 4.6	9.4 ± 5.0	0.425
Mean ambulation initiation time (h)	13.9 ± 5.0	13.9 ± 5.1	13.8 ± 5.0	0.828
Mean discharge time (h)	26.0 ± 8.7	26.6 ± 9.7	25.3 ± 7.8	0.603
Mean second night stay	12 (5.7%)	6 (5.7%)	6 (5.6%)	0.973

*p < 0.05 was considered statistically significant.
NRS: numeric rate scale; PACU: post-anesthesia care unit.

Table 4. Multivariate analysis of risk factors for pain intensity ≥ 3

Risk factor	OR	95% CI	p value
LA infiltration	0.34	0.10-0.65	0.001*
Bile spillage	1.79	0.87-3.67	0.111
Cholecystitis	1.17	0.51-2.66	0.708
Dose of fentanyl < 3 mcg/kg	0.56	0.27-1.13	0.106

*p < 0.05 was considered statistically significant.
OR: odds ratio; CI: confidence interval; LA: local anesthetic

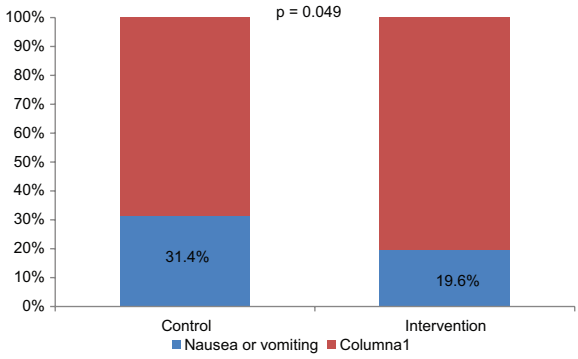

Figure 4. *Nausea/vomiting.*

groups except for previous episodes of acute pancreatitis (p = 0.041). The characteristics of the patients are shown in table 1. There were no allergic reactions or toxicity in the group of patients with port infiltration (PI).

Intraoperative parameters recorded are shown in table 2. There were no statistically significant differences in the operative time, presence of cholecystitis, bile spillage, or dose of opioid (fentanyl).

Parameters recorded in the post-operative period, both in the post-anesthesia care unit (PACU) and in the hospitalization ward, are shown in table 3. Intervention group patients showed lower NRS values than those in the control group, both at 4 h (3.01 ± 2.61 vs. 4.05 ± 2.45) and in the successive measurements at 8 h (2.56 ± 2.24 vs. 3.72 ± 2.34), 12 h (2.50 ± 2.05 vs. 3.29 ± 1.86) and 24 h (2.18 ± 1.71 vs. 2.60 ± 1.53). The mean NRS score was 2.56 ± 1.96 in the intervention group and 3.41 ± 1.82 in the control group (Fig. 2).

Table 5. Data collected 1 month after the intervention

Parameter	Global	Control	Intervention	p-value*
Mean of analgesic intake (days)	4.0 ± 5.46	3.8 ± 5.4	4.1 ± 5.5	0.544
Hematoma (n [%])	54 (25.5%)	26 (24.8%)	28 (26.2%)	0.814
Surgical Site Infection (n [%])	14 (6.6%)	7 (6.7%)	7 (6.5%)	0.971
Return to work (n [%])	27/106 (25.5%)	15/52 (28.8%)	12/54 (22.2%)	0.434
Full oral tolerance (n [%])	96 (45.3%)	46 (43.8%)	50 (46.7%)	0.669
Quite/very satisfied (n [%])	201 (94.8%)	99 (94.3%)	102 (95.3%)	0.733

*p < 0.05 was considered statistically significant.

Table 6. EuroQol-5D questionnaire

EuroQol dimension	Global	Control	Intervention	p-value
Mobility				
No problems in walking about	133 (62.7%)	65 (61.9%)	68 (63.6%)	
Some problems	74 (34.9%)	39 (37.1%)	35 (32.7%)	0.403
Confined to bed	5 (2.4%)	1 (1.0%)	4 (3.7%)	
Self-care				
No problems	153 (72.2%)	76 (72.4%)	77 (72.0%)	
Some problems	53 (25.0%)	26 (24.8%)	27 (25.2%)	0.997
Unable to wash/dress	6 (2.8%)	3 (2.9%)	3 (2.8%)	
Usual activities				
No problems	150 (70.8%)	76 (72.4%)	74 (69.2%)	
Some problems	59 (27.8%)	27 (25.7%)	32 (29.9%)	0.654
Unable	3 (1.4%)	2 (1.9%)	1 (0.9%)	
Pain/discomfort				
No pain/disconfort	157 (74.1%)	78 (74.3%)	79 (73.8%)	
Moderate	51 (24.1%)	25 (23.8%)	26 (24.3%)	1.000
Extreme	4 (1.9%)	2 (1.9%)	2 (1.9%)	
Anxiety/depression				
Not anxious/depressed	201 (94.8%)	99 (94.3%)	102 (95.3%)	
Moderately	10 (4.7%)	5 (4.8%)	5 (4.7%)	0.873
Extremely	1 (0.5%)	1 (1.0%)	0 (0.0%)	

These differences were statistically significant, with values $p < 0.05$.

The need for rescue with opioid drugs among patients with levobupivacaine infiltration was lower than that of patients in the control group (24.3% vs. 34.3%), without reaching a statistically significant difference ($p = 0.110$) (Fig. 3). The incidence of PONV did show a significant difference between both groups (control group: 31.4%/ intervention group: 19.6%; $p = 0.049$) (Fig. 4). This statistically significant difference was not observed among rescues with antiemetic drugs (control group: 21.9%; intervention group: 20.6%; $p = 0.881$). The values of systolic blood pressure, diastolic blood pressure, heart rate (HR), and length of stay in PACU did not show significant differences. There were also no significant differences in oral intake initiation time, time to ambulation, or time to hospital discharge. Patients in the control group did not require a second night in the hospital more often than patients in the intervention group (5.7% vs. 5.6%, $p = 0.973$).

In the multivariate analysis (Table 4), we studied the risk factors for a NRS score ≥ 3 that were statistically significant after the univariate analysis (PI with LA) and those that were considered of interest even though they did not reach statistical significance (bile spillage, cholecystitis, and a dose of fentanyl < 3 mcg/kg). Only LA infiltration showed statistical significance, with an odds ratio (OR) = 0.34 ($p = 0.001$).

Regarding the data collected 1 month after the intervention, shown in table 5, we did not observe differences in the incidence of hematoma or SSI, as well as in the number of days of analgesic intake or full oral tolerance. Rates of return to work were not statistically different either. Global patient satisfaction did not show differences between the two groups. HRQoL data (EuroQol-5D-3L questionnaire) are shown in table 6.

Discussion

Since the laparoscopic approach has definitely spread in performing cholecystectomy, different studies have tried to bring scientific evidence about the use of LA in order to reduce postoperative pain. These works are based on the use of LA either intraperitoneally[6-10], either at the incision sites[11-13] or using both routes of administration[14-17], some at the beginning of the intervention and others at the end of it. The most frequently used drug has been bupivacaine; fewer studies have used other anesthetics such as levobupivacaine or ropivacaine[14,18].

Various systematic reviews and meta-analyses pool and analyze the existing literature[5,19,20]. Loizides et al. concluded that there is a very low level of scientific evidence in favor of infiltration of incisional sites, with a reduction in POP in patients with low anesthetic risk and little clinical relevance derived from it. In addition, they recommend that future studies should have a lower risk of bias and include results about return to work and HRQoL.

These conclusions and recommendations have been taken into account when designing this study.

Our results show, with statistically significant differences, lower NRS values and lower PONV incidence in patients with PI. Although the need for rescue with opioid drugs among patients with PI was also lower, differences did not reach statistical significance. From our perspective, this is attributable to the fact that not all patients with high NRS values received opioid rescue, and some patients with low NRS values did. This is so because opioid rescue administration depends on the criteria of the responsible nursing staff, and the NRS value is not a single or rigid parameter that determines the administration.

The times of oral intake initiation, ambulation, and hospital discharge were similar, so when LC is performed in an inpatient surgery program with a protocol that significantly delays the onset of oral tolerance and ambulation (remember that our patients began to tolerate liquids more than 9 h after surgery and to ambulate almost 14 h after it), PI does not imply significant differences in these parameters. Instead, in a day-case surgery program, when recovery times need to be notably shorter, patients with more pain or PONV would probably show statistically significant longer recovery times compared to the rest of the patients.

We have also focused on clinical outcomes after hospital discharge. To compare recovery immediately after hospital discharge, we used the HRQoL data provided by the EuroQol-5D-3L questionnaire. We decided to use this questionnaire not only because of its simplicity and speed of completion but also because the dimensions it includes fit well with the nature of this part of the study, that is, to compare postoperative recovery (especially at a physical level) between the two groups of patients.

Our results confirm that 24 h after the LC, the evolution is independent of the use of LA. In addition to the absence of differences between the two groups, we would point out the good results collected, with up to 48.6% of patients scoring 1 on the 5 dimensions of the questionnaire and only 13 patients scoring 3 on any of them.

One month after LC, we studied the rate of return to work without finding differences between the two groups. We must highlight that of the 212 patients analyzed, only 106 (50.0%) had an active employment status at the time of the operation, 52 in the control group and 54 in the intervention group, which may limit the validity of the findings.

We would also include, as a limitation of the study, the absence of recording of intraoperative anesthetic parameters that could point to a contribution of the PI to better hemodynamic behavior.

Conclusions

Our results are in line with other studies showing that preoperative infiltration of LC incision sites with 0.50% levobupivacaine is safe and reduces POP, the need for rescue with opioid drugs, and the incidence of PONV. The rest of the parameters studied do not show significant differences, highlighting oral intake initiation time, time to ambulation, and hospital discharge time. Outside of an outpatient cholecystectomy program, these results do not translate into earlier hospital discharge.

On the other hand, the recovery of the patient once at home is independent of the use or not of the LA, showing the same need for analgesics intake and similar data on HRQoL, return to work, or global satisfaction.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

References

1. Hassler KR, Collins JT, Philip K, Jones MW. Laparoscopic cholecystectomy. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2022. Available from: http://www.ncbi.nlm.nih.gov/books/NBK448145
2. Ministerio de Sanidad. Base CMBD. Available from: https://www.sanidad.gob.es/estadEstudios/estadisticas/cmbdhome.htm
3. Verma GR, Lyngdoh TS, Kaman L, Bala I. Placement of 0.5% bupivacaine-soaked surgicel in the gallbladder bed is effective for pain after laparoscopic cholecystectomy. Surg Endosc. 2006;20:1560-4.
4. Bisgaard T, Klarskov B, Kristiansen VB, Callesen T, Schulze S, Kehlet H, et al. Multi-regional local anesthetic infiltration during laparoscopic cholecystectomy in patients receiving prophylactic multi-modal analgesia: a randomized, double-blinded, placebo-controlled study. Anesth Analg. 1999;89:1017.
5. Loizides S, Gurusamy KS, Nagendran M, Rossi M, Guerrini GP, Davidson BR. Wound infiltration with local anaesthetic agents for laparoscopic cholecystectomy. Cochrane Database Syst Rev. 2014;3:CD007049.
6. Rademaker BM, Kalkman CJ, Odoom JA, de Wit L, Ringers J. Intraperitoneal local anaesthetics after laparoscopic cholecystectomy: effects on postoperative pain, metabolic responses and lung function. Br J Anaesth. 1994;72:263-6.
7. Pasqualucci A, Contardo R, Da Broi U, Colo F, Terrosu G, Donini A, et al. The effects of intraperitoneal local anesthetic on analgesic requirements and endocrine response after laparoscopic cholecystectomy: a randomized double-blind controlled study. J Laparoendosc Surg. 1994;4:405-12.
8. Pasqualucci A, de Angelis V, Contardo R, Colò F, Terrosu G, Donini A, et al. Preemptive analgesia: intraperitoneal local anesthetic in laparoscopic cholecystectomy. A randomized, double-blind, placebo-controlled study. Anesthesiology. 1996;85:11-20.
9. Mraović B, Jurisić T, Kogler-Majeric V, Sustic A. Intraperitoneal bupivacaine for analgesia after laparoscopic cholecystectomy. Acta Anaesthesiol Scand. 1997;41:193-6.
10. Maestroni U, Sortini D, Devito C, Kohan Brunaldi FP, Anania G, Pavanelli L, et al. A new method of preemptive analgesia in laparoscopic cholecystectomy. Surg Endosc. 2002;16:1336-40.
11. Suragul W, Tantawanit A, Rungsakulkij N, Muangkaew P, Tangtawee P, Mingphrudhi S, et al. Effect of local anaesthetic infiltration on postoperative pain after laparoscopic cholecystectomy: randomized clinical trial. BJS Open. 2022;6:zrac066.
12. Liu YY, Yeh CN, Lee HL, Wang SY, Tsai CY, Lin CC, et al. Local anesthesia with ropivacaine for patients undergoing laparoscopic cholecystectomy. World J Gastroenterol. 2009;15:2376-80.
13. Inan A, Sen M, Dener C. Local anesthesia use for laparoscopic cholecystectomy. World J Surg. 2004;28:741-4.
14. Karaman Y, Kebapci E, Gorgun M, Guvenli Y, Tekgul Z. Post-laparoscopic cholecystectomy pain: effects of preincisional infiltration and intraperitoneal levobupivacaine 0.25% on pain control-a randomized prospective double-blinded placebo-controlled trial. Turk J Anesth Reanim. 2014;42:80-5.
15. Yeh CN, Tsai CY, Cheng CT, Wang SY, Liu YY, Chiang KC, et al. Pain relief from combined wound and intraperitoneal local anesthesia for patients who undergo laparoscopic cholecystectomy. BMC Surg. 2014;14:28.
16. Souto MM, Radaelli E, Giordani AE, Savaris A, Bassols GF. Effectiveness of local anesthetics in laparoscopic cholecystectomy: a randomized clinical trial. Surg Laparosc Endosc Percutan Tech. 2015;25:317-20.
17. Protic M, Veljkovic R, Bilchik AJ, Popovic A, Kresoja M, Nissan A, et al. Prospective randomized controlled trial comparing standard analgesia with combined intra-operative cystic plate and port-site local anesthesia for post-operative pain management in elective laparoscopic cholecystectomy. Surg Endosc. 2017;31:704-13.
18. Liang HS, Feng Y, Liu YZ, An HY, Yang BX. Effect of flurbiprofen combined different concentrations of ropivacaine local infiltration on postoperative analgesia after laparoscopic cholecystectomy. Beijing Da Xue Xue Bao. 2011;43:753-6.
19. Rutherford D, Massie EM, Worsley C, Wilson MS. Intraperitoneal local anaesthetic instillation versus no intraperitoneal local anaesthetic instillation for laparoscopic cholecystectomy. Cochrane Database Syst Rev. 2021;10:CD007337.
20. Gupta A. Local anaesthesia for pain relief after laparoscopic cholecystectomy a systematic review. Best Pract Res Clin Anaesthesiol. 2005;19:275-92.