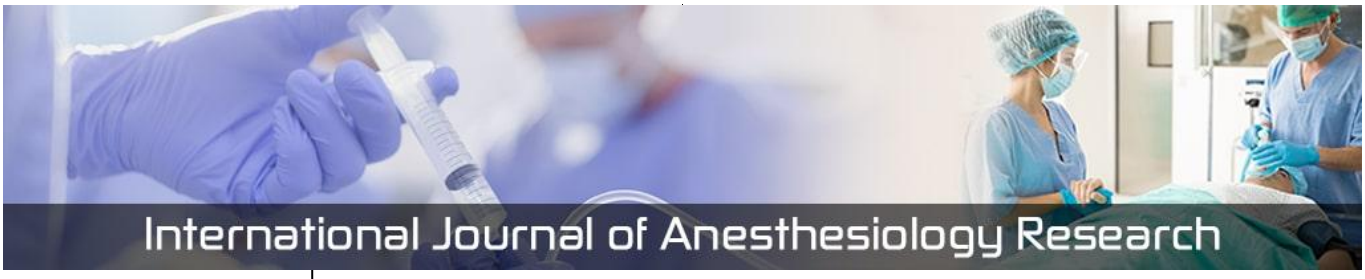

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A randomized controlled study comparing the intraperitoneal instillation of diluted bupivacaine and non-diluted bupivacaine after laparoscopic cholecystectomy

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Abstract
Background: After a laparoscopic cholecystectomy (LC), postoperative pain is still a major issue even though the procedure is less invasive. Intraperitoneal instillation of local anesthetics such as bupivacaine is commonly used for pain control. However, the impact of dilution on analgesic efficacy remains unclear.
Methods: Seventy adult patients receiving elective LC were included in this prospective single-blind randomized controlled research. Patients were randomly allocated to one of two groups: Group A received 20 ml of 0.5% undiluted bupivacaine, and the same dosage was given to Group B, diluted in 480 milliliters of saline.
Results: The amount of fentanyl consumed during surgery didn't change considerably in between the two groups. Compared to group A, group B's time to first request rescue analgesia was noticeably delayed (p<0.001). Group B consumed far less tramadol overall within the first twenty-four hours than group A (p<0.001). Group B's VAS score was considerably lower than group A's at 2, 4, 6, and 12 hours, while There wasn't any noteworthy difference between the two groups' scores at PACU and 24 hours (p<0.05).
Conclusions: Intraperitoneal instillation of diluted bupivacaine provides more prolonged and effective postoperative analgesia, reduces early pain intensity and opioid requirements, without increasing adverse events, compared to the same dose of non-diluted bupivacaine.

Keywords: Laparoscopic cholecystectomy, bupivacaine, intraperitoneal instillation, pain, dilution

Introduction

A common elective minimally invasive procedure is Laparoscopic Cholecystectomy (LC), yet is frequently followed by significant postoperative pain particularly visceral, parietal, and referred shoulder pain leading to increased analgesic use and delayed recovery. Multimodal analgesia strategies are essential to improve patient outcomes and accelerate discharge [1].

Intraperitoneal administration of local anesthetics such as bupivacaine has been investigated as an adjunct to multimodal regimens to manage visceral pain after LC. Prior randomized controlled trials show that instilled bupivacaine can significantly reduce early postoperative pain scores and decrease Needs for opioids in contrast to placebo [2, 3].

Contemporary studies comparing intraperitoneal bupivacaine to ropivacaine, as well as combinations with adjuvants such as dexmedetomidine, have yielded nuanced findings: ropivacaine may offer longer duration or lower pain scores, and bupivacaine-dexmedetomidine combinations can prolong analgesia beyond bupivacaine alone [4, 5].

Recent evidence indicates that High-Volume, Low-Concentration (HVLC) intraperitoneal bupivacaine (e.g., 500 ml of 0.02%) achieves broader peritoneal coverage, longer analgesic duration, and reduced opioid consumption compared to low-volume, high-concentration solutions. These findings underline the importance of solution formulation on clinical outcomes [2].

Despite the emerging HVLC paradigm, conflicting approaches remain particularly regarding the dilution of standard-dose bupivacaine (e.g. 100 mg in 20 ml versus diluted into larger saline volumes).

There is yet limited rigorous evidence directly comparing diluted versus non-diluted bupivacaine instillation at fixed dose for post-operative pain management in LC [6].
This study's objective is to compare the effectiveness of postoperative analgesia of bupivacaine diluted in saline vs undiluted bupivacaine after LC.

Patients and Methods

70 adult patients, both sexes, with American Standards Association (ASA) physical status I-II, 18 to 60 years old, who had elective LC were the subjects of this prospective randomized single-blinded trial. The study was approved by the institutional ethics committee, and all participants supplied their written informed consent.
Among the exclusion criteria were allergy to local anesthetics, pregnancy or lactation, chronic opioid use, significant hepatic or renal dysfunction, psychiatric disorders, and intraoperative conversion to open cholecystectomy.

Randomization and blindness

An online program for randomization (http://www.randomizer.org) was utilized to create a random list, and an opaque sealed envelope with each patient's code was maintained. In parallel fashion, patients were divided into two equal groups at random using a 1:1 allocation ratio: Group A received intraperitoneal instillation of 20 ml of undiluted 0.5% bupivacaine (100 mg), while Group B received 100 mg bupivacaine diluted in 480 ml of normal saline (final volume 500 ml). The trial was single blind, meaning that neither the study allocation nor the results were visible to the outcome assessors.
The patients' medical and surgical histories were obtained, they underwent clinical examinations, and common laboratory tests such coagulation studies, and complete blood counts, kidney function and liver function were carried out.
Each patient was instructed about postoperative pain assessment with the VAS. VAS (Zero represents “no pain” while ten represents “the worst pain imaginable”) [7].

Anaesthesia protocol

Standardized general anesthesia was administered to all patients. After establishing intravenous access, 2 mg of IV midazolam was given as a premedication. Fentanyl (1 µg/kg) and intravenous propofol (1.5-2.5 mg/kg) were used to establish general anesthesia. Cisatracurium (0.15 mg/kg IV) was subsequently given to facilitate tracheal intubation. 2% sevoflurane in a 50% oxygen and air combination was used to maintain anesthesia, and additional doses of cisatracurium (0.03 mg/kg) were given as needed. In order to maintain the end-tidal CO_2 at 30 to 35 mmHg, mechanical ventilation was adjusted. After pain was ruled out as a potential cause, bolus doses of fentanyl (1 µg/kg) were given if there was an initial rise of over 20 percent in either the Mean Arterial Blood Pressure (MAP) or the Heart Rate (HR).

Surgical technique

All laparoscopic cholecystectomies were carried out using a standard 4-port. Pneumoperitoneum was maintained at 12-14 mmHg. After removal of the gallbladder and just before trocar withdrawal, the allocated solution either 20 ml of 0.5% bupivacaine or the same dose diluted in 480 ml of saline was instilled slowly under direct laparoscopic visualization. To optimize analgesic coverage, the fluid was injected into the pelvic cavity, the gallbladder bed, and the hepato-diaphragmatic region. The peritoneal cavity was then completely desufflated to reduce residual CO_2-related shoulder pain.

Postoperative

During the following surgery, a regular pain medication schedule was given. VAS score was measured at PACU, 2h, 4h, 6h, 12h and 24h. For patients with VAS $\geq$ 4, rescue analgesia was given with intravenous tramadol 1 mg/kg following recovery (defined as 0 hours) and 24 hours after surgery. The total amount of tramadol used in the first 24 hours after surgery, and the time of the initial analgesic request were all noted.
In order to evaluate the adverse effects, the following were administered: IV ephedrine 5-10 mg for hypotension (a 20% decrease in basal MAP), IV atropine 0.02 mg/kg for bradycardia (a 20% decrease in basal HR), oxygen supplementation was needed for respiratory depression (a SpO2 < 95%), and 0.1 mg/kg IV ondansetron for postoperative nausea and vomiting (PONV).
The primary outcome was the total amount of postoperative analgesic consumption (tramadol). The secondary outcomes were pain intensity, intraoperative use of fentanyl, and adverse events.

Sample size calculation

G*Power 3.1.9.2 was used to determine the sample size (Universitat Kiel, Germany). A prior investigation found [6], the mean ± SD of total amount of postoperative analgesic consumption (tramadol) was 63 ± 31.16 mg with Group A and 7.2 ± 19.9 mg with Group B. The sample size was determined by considering the following parameters: group ratio 1:1, 95% confidence level, 95% study power, and 0.977 effect size and to overcome dropout, each group was given six cases. Thus, for each group, we gathered 35 patients.

Statistical analysis

SPSS v27 was used for statistical analysis (IBM©, Armonk, NY, USA). The normality of the data distribution was assessed using histograms and the Shapiro-Wilks test. The unpaired student t-test was used to analyse the mean and standard deviation of quantitative parametric data (SD). The Mann-Whitney test was used to assess quantitative non-parametric data, which were then shown as the median and Interquartile Range (IQR). The Chi-square test or Fisher's exact test, as applicable, were used to analyse the qualitative variables, which were shown as frequency and percentage. A two-tailed P value was deemed statistically significant if it was less than 0.05.

Results

In this research, 87 patients had their eligibility assessed; 10 patients did not fit the requirements, and seven patients declined to take part. The patients who are left were divided into two equal groups of 35 at random. Every patient assigned was monitored and subjected to statistical analysis.

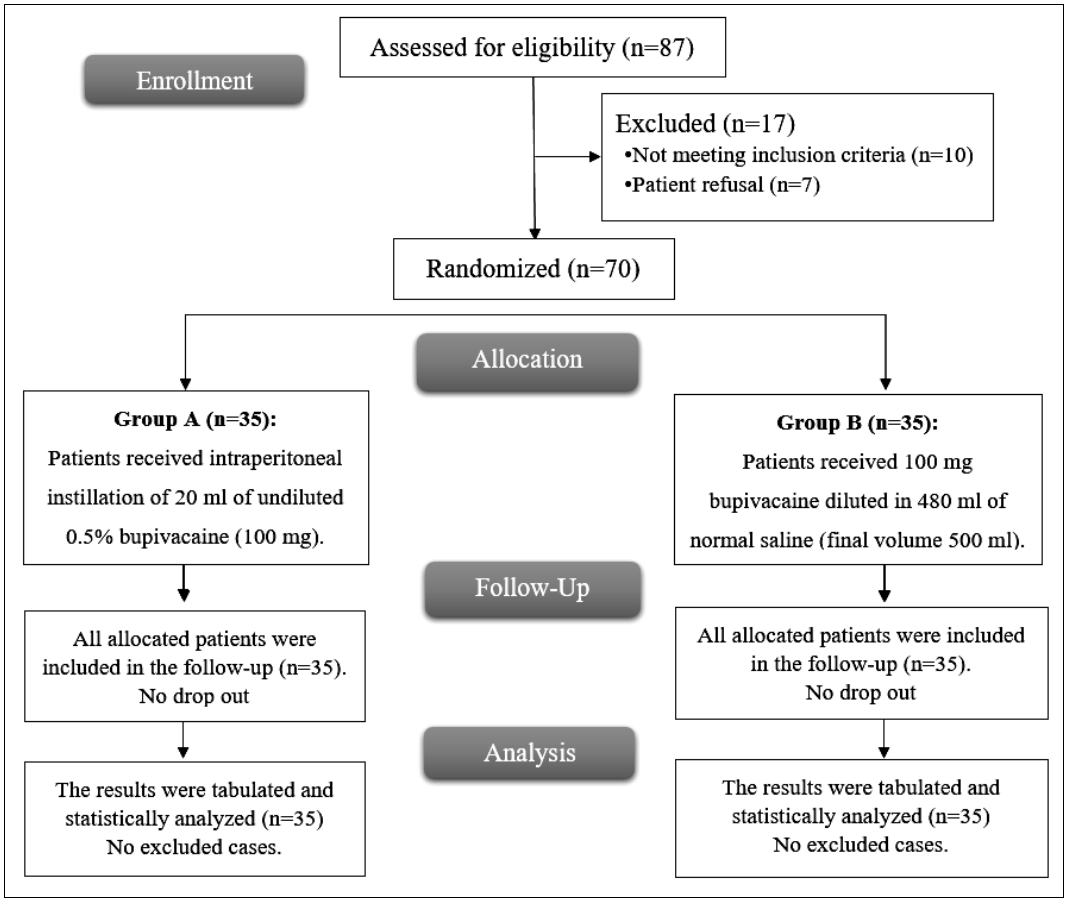

Fig 1: CONSORT flow chart of the enrolled patients

The two groups' demographic information and surgical time did not differ significantly.

Table 1: Demographic data and duration of surgery of the studied groups

		Group A (n=35)	Group B (n=35)	P value
Age (years)		42.29 ± 10.79	41.03 ± 11.29	0.635
Sex	Male	13 (37.14%)	20 (57.14%)	0.094
	Female	22 (62.86%)	15 (42.86%)	
Weight (kg)		76.97 ± 12.8	74.34 ± 11.18	0.363
Height (cm)		167.66 ± 7.36	169.83 ± 6.04	0.182
BMI (kg/m^2)		27.8 ± 5.6	26.06 ± 4.16	0.144
ASA physical status	I	27 (77.14%)	23 (65.71%)	0.668
	II	8 (22.86%)	12 (34.29%)	
Duration of surgery (min)		64.71 ± 12.24	68.29 ± 13.5	0.250

Data are presented as mean ± SD or frequency (%).

The two groups' intraoperative fentanyl intake differed negligibly. Group B experienced a considerably longer time to initially request rescue analgesia than group A (p<0.001). Group B consumed considerably less tramadol overall than group A over the first 24 hours (p<0.001).

Table 2: Fentanyl consumption, time to first request of rescue analgesia and total tramadol consumption in the first 24 hours of the studied groups

	Group A (n=35)	Group B (n=35)	P value
Intraoperative fentanyl consumption	6 (17.14%)	2 (5.71%)	0.259
Time to first request of rescue analgesia (h)	6.6 ± 1.42	15.69 ± 1.69	<0.001
Total tramadol consumption in the first 24 hours (mg)	165.26 ± 51	110.54 ± 41.56	<0.001

Data are presented as mean ± SD or frequency (%).

There was no discernible difference in the VAS score at PACU and 24h between the two groups and was greatly reduced at 2, 4, 6 and 12h in group B as opposed to group A (p<0.05).

Table 3: VAS score of the studied groups

	Group A (n=35)	Group B (n=35)	P value
PACU	1 (0 - 1)	0 (0 - 1)	0.341
2 h	2 (1 - 2.5)	1 (0.5 - 2)	<0.001
4 h	2 (1 - 3)	1 (1 - 2)	0.003
6 h	3 (1 - 3)	2 (1 - 2)	0.003
12 h	4 (2 - 5)	2 (2 - 3)	0.018
24 h	4 (3 - 5)	3 (2 - 5)	0.108

Data are presented as median (IQR).

There was no discernible difference in bradycardia, hypotension, nausea, or vomiting between the two groups. Patients in both groups did not experience respiratory depression.

Table 4: Adverse events of the studied groups

	Group A (n=35)	Group B (n=35)	P value
Nausea	3 (8.57%)	1 (2.86%)	0.613
Vomiting	2 (5.71%)	1 (2.86%)	1
Bradycardia	1 (2.86%)	4 (11.43%)	0.356
Hypotension	2 (5.71%)	6 (17.14%)	0.259
Respiratory depression	0 (0%)	0 (0%)	---

Data are presented as frequency (%).

Discussion

After LC, postoperative discomfort remains a problem that requires attention. In order to effectively treat pain and lessen the negative effects of systemic analgesics, many surgeons use intraperitoneal local anesthetic administration [2].

Our study revealed that compared to group A, group B's time to first request rescue analgesia was noticeably extended. Group B consumed far less tramadol overall within the first 24 hours than group A. At 2, 4, 6, and 12 hours, group B's VAS score was noticeably lower than group A's.

Enhanced peritoneal distribution: Dilution allows the same dose of local anesthetic to spread over a larger surface area, enabling broader nerve blockade across peritoneal and visceral surfaces. Decreased local anesthetic concentration may reduce chemical irritation or neurotoxicity at nerve endings [2].

Concurring with our finding, Abdelraheem et al. [8] who compared intraperitoneal diluted versus non-diluted bupivacaine in LC. They supported the greater analgesic duration by reporting a noticeably longer time to seek an analgesic initially in the diluted group, also showed significantly lower total tramadol consumption in the diluted bupivacaine group. In the same line, Jain *et al*. [2] found that amount of rescue analgesic was substantially reduced in diluted bupivacaine than intraperitoneal irrigation with normal saline in post-LC analgesia. Moreover, Manan *et al*. [9] shown that when diluted in large quantities and administered intraperitoneally in LC, bupivacaine produces sustained analgesia for 16.53 ± 2.65 hours, and the amount of tramadol used as a rescue analgesic was 31.00 ± 14.98 mg, in comparison to irrigation with 500 ml of normal saline.

Unlike what we found, Joris *et al*. [10] found that administering 80 ml of 0.125% bupivacaine intraperitoneally did not work well for controlling pain following LC; this is likely due to the low dose and concentration of bupivacaine used. Furthermore, Jiranantarat *et al*. [11] showed that the VAS, the overall amount of analgesics consumed, and the time at which analgesia was initially needed showed no statistically significant differences between the two groups. This discrepancy can result from using varying amounts of regular saline. Also, Zmora *et al*. [12] study where 60 patients who had elective LC were prospectively split into two groups: one group received normal saline, while the other group got 100 mg of bupivacaine in 50 cc of saline, which was injected into the right subphrenic region and the gallbladder bed. For postoperative analgesia after LC, they found no advantages to IP bupivacaine instillation. This could be explained by the fact that their study included fewer individuals—nine patients were eliminated because they had an open cholecystectomy and a drain left in the peritoneal cavity. Furthermore, an evaluation of their pain was conducted at various points in time (at 1-, 2-, 4-, and 14-hours following surgery).

In our result, there was no discernible difference in the prevalence of bradycardia, hypotension, nausea, or vomiting between the two groups.

Aligned with our findings, Jain *et al*. [2] showed that no discernible change in adverse effects between diluted bupivacaine and intraperitoneal irrigation with normal saline. In addition, Vijayaraghavalu *et al*. [13] demonstrated that both individuals who received 30 ml of normal saline and those who received 30 ml of plain bupivacaine 0.5% intraperitoneally experienced identical adverse effects, including nausea and vomiting.

Our study limitations included small sample size and was carried out in one location. Further studies are required using various concentrations and volumes.

Conclusion

Intraperitoneal instillation of diluted bupivacaine provides more prolonged and effective postoperative analgesia, reduces early pain intensity and opioid requirements, without increasing adverse events, compared to the same dose of non-diluted bupivacaine.

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Author's Contribution

Not available

Conflict of Interest

Not available

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