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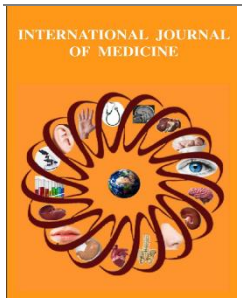

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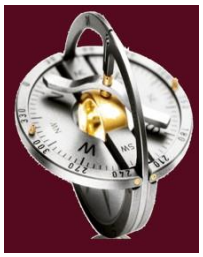

Research Article

Comparative Evaluation of Pre- versus Post-Incisional Levobupivacaine Infiltration for Postoperative Pain Management in Laparoscopic Cholecystectomy

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Abstract

Background: Postoperative pain remains a major concern even after minimally invasive procedures such as laparoscopic cholecystectomy. Local anaesthetic infiltration at trocar sites is an established technique for postoperative analgesia. This study compared the efficacy of pre-incisional versus post-incisional infiltration of levobupivacaine in controlling postoperative pain and the need for rescue analgesia. Aim: To compare postoperative pain relief following pre- and post-incisional trocar site infiltration with 0.5% levobupivacaine in laparoscopic cholecystectomy under general anaesthesia. ***Materials and Methods***: A prospective, randomized, single-blind comparative study was conducted on 66 patients (33 per group) undergoing elective laparoscopic cholecystectomy. Group A received pre-incisional infiltration and Group B received post-incisional infiltration of 0.5% levobupivacaine at trocar sites (total 10 mL). Postoperative pain was assessed using the Visual Analogue Scale (VAS) at 3, 6, 12, and 24 hours. Rescue analgesia (Tramadol 100 mg IV) was administered for VAS ≥3. The incidence of adverse effects was recorded. Data were analyzed using SPSS v25, with $p<0.05$ considered significant. ***Results***: At 12 hours postoperatively, the pre-incisional group showed a lower rescue analgesia requirement (12.1%) compared to the post-incisional group (27.3%), though the difference was not statistically significant ($p=0.215$). VAS scores increased up to 12 hours and declined by 24 hours in both groups, indicating effective analgesic coverage. Adverse effects were minimal and comparable (nausea 9.1% in each group). ***Conclusion***: Pre-incisional infiltration of levobupivacaine provided better postoperative pain control and reduced rescue analgesic requirement compared to post-incisional infiltration, though differences were not statistically significant. The technique was safe, well tolerated, and may be recommended as part of multimodal analgesia in laparoscopic cholecystectomy.

Keywords: Levobupivacaine infiltration, Pre-emptive analgesia, Laparoscopic cholecystectomy.

Introduction:

Pain, as defined by the International Association for the Study of Pain (IASP), is an “unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” Postoperative pain remains a major concern in surgical practice because it adversely affects patient comfort, prolongs recovery, delays mobilization, and can increase hospital stay and healthcare costs. Although laparoscopic cholecystectomy has replaced open cholecystectomy as the gold standard treatment for benign gallbladder disease, it is not a completely pain-free procedure. Pain following laparoscopic cholecystectomy is multifactorial in origin and is composed of three distinct components - incisional (somatic), visceral, and referred shoulder pain, each requiring a tailored management approach.[1]

While laparoscopic surgery is minimally invasive, postoperative pain is primarily visceral due to peritoneal stretching and diaphragmatic irritation caused by carbon dioxide insufflation. This pain often gets referred to the right shoulder and subdiaphragmatic regions. The parietal component, on the other hand, arises from trocar insertion sites. Despite being less severe than the pain after open surgery, it is significant enough to interfere with early ambulation and recovery. Pain intensity usually peaks within the first 24 hours postoperatively and then gradually diminishes over 3-4 days. However, approximately 10-15% of patients continue to experience moderate to severe discomfort during this period, highlighting the need for effective multimodal analgesic strategies.

A variety of pharmacologic and non-pharmacologic interventions have been proposed to minimize postoperative pain after laparoscopic cholecystectomy. These include the use of low-pressure pneumoperitoneum, warmed CO_2 gas, peritoneal saline wash, and careful surgical technique to minimize tissue trauma. Pharmacologic interventions include systemic analgesics, intraperitoneal instillation of local anaesthetics, trocar site infiltration, and regional nerve blocks. Among these, local anaesthetic infiltration at trocar sites has been shown to be more effective than intraperitoneal infiltration in reducing early postoperative pain.[2]

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Bupivacaine has long been a preferred local anaesthetic owing to its prolonged duration of action. However, the racemic mixture of bupivacaine contains two enantiomers - the levo-rotatory (S-) and dextro-rotatory (R+) isomers. The R+ isomer has been associated with significant cardiotoxicity and neurotoxicity, prompting the development of the pure S-enantiomer, Levobupivacaine, which exhibits similar efficacy but with a superior safety profile. Levobupivacaine offers a comparable onset of action, prolonged analgesia, and fewer adverse effects on the central nervous and cardiovascular systems due to its faster protein binding and slower dissociation rate from cardiac sodium channels.[3]

Levobupivacaine has a pKa of 8.1 and exhibits high lipid solubility and strong plasma protein binding (>97%), which contribute to its long duration of action - often exceeding six hours. Its metabolism occurs mainly via the hepatic cytochrome P450 enzymes CYP3A4 and CYP1A2 into inactive metabolites, with minimal unchanged drug excreted in urine. Clinical trials and comparative studies have established that levobupivacaine provides effective sensory and motor block, with better hemodynamic stability and reduced toxicity compared to bupivacaine.[4]

The concept of pre-emptive analgesia, introduced by Crile and redefined in modern anesthesiology, involves administering analgesics before surgical injury to prevent central sensitization. Pre-incisional infiltration of local anaesthetic blocks nociceptive afferent input at the site of injury, thereby attenuating the subsequent “wind-up” phenomenon in the spinal cord and reducing postoperative pain intensity. Conversely, post-incisional infiltration aims to reduce pain by blocking nociceptor activation after surgical trauma has occurred. Both strategies have demonstrated efficacy, but the optimal timing of local anaesthetic infiltration remains controversial.[5]

Aim

To compare postoperative pain relief in pre- versus post-incisional local infiltration of levobupivacaine in laparoscopic cholecystectomy under general anaesthesia.

Objectives

1. To evaluate the postoperative pain relief after trocar site infiltration with levobupivacaine.
2. To compare the efficacy of pre- versus post-incision levobupivacaine infiltration on pain intensity and analgesic requirement.
3. To assess the need for rescue analgesia and record any adverse effects related to local infiltration

Materials and Methods

Source of Data

The study was conducted at a tertiary care hospital in Mumbai after obtaining approval from the Institutional Ethics Committee (ECARP) and written informed consent from all participants.

Study Design

A prospective, randomized, single-blinded, comparative clinical trial.

Study Location

Department of Anaesthesiology, Tertiary Care Teaching Hospital, Mumbai.

Study Duration

Twelve months following Ethics Committee approval (2023-2024).

Sample Size

A total of 66 patients were enrolled and randomized into two groups of 33 each.

Calculation was based on detecting a significant difference in mean postoperative VAS score (α=0.05, power=80%) derived from prior studies.

Inclusion Criteria

- Patients aged 18-65 years.
- ASA physical status I or II.
- Elective laparoscopic cholecystectomy for gallbladder calculi or polyp without acute cholecystitis.

Exclusion Criteria

- Known hypersensitivity to levobupivacaine.
- ASA grade > II.
- Conversion to open cholecystectomy.
- Acute cholecystitis or choledocholithiasis.
- Preoperative opioid, steroid, or NSAID use.
- Neurological or psychiatric disorders that affect pain perception.
- Inability to comprehend the Visual Analogue Scale (VAS).

Procedure and Methodology

Patients were randomly assigned into two equal groups (n=33 per group):

Group A (Pre-incisional): Levobupivacaine 0.5% infiltration before skin incision.

Group B (Post-incisional): Levobupivacaine 0.5% infiltration after trocar removal at closure.

Each patient received a total of 10 mL (50 mg) levobupivacaine divided proportionally across trocar sites (3 mL for 10 mm ports, 2 mL for 5 mm ports). Anaesthesia was standardized: premedication with glycopyrrolate 0.004 mg/kg and fentanyl 1 µg/kg; induction with propofol 2 mg/kg and succinylcholine 2 mg/kg for intubation; maintenance with oxygen, inhalational agent, and atracurium boluses as needed. Ventilation was adjusted to maintain normocapnia ($EtCO_2$ 34-38 mmHg). At the end, neuromuscular blockade was reversed with neostigmine (0.05 mg/kg) and glycopyrrolate (0.008 mg/kg).

Postoperatively, patients were observed in the PACU for two hours and then in the ward for 24 hours. Pain intensity was recorded using the VAS scale (0-10) at 3, 6, 12, and 24 hours after surgery. Patients reporting VAS ≥3 received Tramadol 100 mg IV as rescue analgesia. Time to first analgesic request, total analgesic consumption, and adverse effects (nausea, vomiting, hypotension, bradycardia, or allergic reactions) were documented.

Sample Processing and Data Collection

All data, including demographic variables, intraoperative vitals, and postoperative pain scores, were recorded in a standardized proforma by a single observer blinded to the group allocation.

Statistical Methods

Data were entered into Microsoft Excel and analyzed using SPSS version 25.0. Quantitative variables were expressed as mean ± SD and compared using unpaired t-test or Mann-Whitney U test as appropriate. Qualitative variables were analyzed with Chi-square or Fisher’s exact test. Normality was verified using Shapiro-Wilk test. A p-value <0.05 was considered statistically significant

Results

Table 1: To compare postoperative pain relief in pre- versus post-incisional local infiltration of levobupivacaine in laparoscopic cholecystectomy under general anaesthesia

Time after surgery	POST-incisional: Rescue given n/N (%)	PRE-incisional: Rescue given n/N (%)	Difference in % (POST-PRE)	95% CI for difference	P value
3 h	1/33 (3.0%)	1/33 (3.0%)	0.0%	-8.27% to +8.27%	1.00
6 h	1/33 (3.0%)	0/33 (0.0%)	+3.03%	-2.82% to +8.88%	1.00
12 h	9/33 (27.3%)	4/33 (12.1%)	+15.15%	-3.69% to +33.99%	0.215
24 h	12/33 (36.4%)	11/33 (33.3%)	+3.03%	-19.95% to +26.01%	1.00

Table 1 compares the proportion of patients requiring rescue analgesia at different postoperative intervals between the pre-incisional and post-incisional groups. At 3 hours post-surgery, both groups showed an identical rescue analgesia requirement of 3.0%, indicating equivalent early pain control. At 6 hours, a single patient (3.0%) in the post-incision group required additional analgesia, whereas none did in the pre-incisional group, but this difference was statistically insignificant (p=1.00). By 12 hours, the demand for rescue analgesia rose to 27.3% in the post-incisional group compared to 12.1% in the pre-incisional group, with a difference of +15.15%. Although this trend favored pre-incisional infiltration, the result did not reach statistical significance (p=0.215; 95% CI: -3.69% to +33.99%), likely due to the small sample size. At 24 hours, the requirement plateaued, with 36.4% and 33.3% of patients in the post- and pre-incisional groups respectively requiring analgesia. The minimal difference (3.03%) again failed to achieve statistical significance (p=1.00

Table 2: To evaluate postoperative pain relief after trocar site infiltration with levobupivacaine

Time point	VAS Mean (pooled)
Immediate post-op	1.03
30 min	1.45
3 h	2.67
6 h	2.79
12 h	4.09
24 h	3.05

Table 2 depicts the pooled postoperative pain trajectory, expressed as mean Visual Analogue Scale (VAS) scores for all 66 patients combined, irrespective of group allocation. The findings demonstrate a characteristic postoperative pain pattern. The mean immediate postoperative VAS score was low (1.03), rising gradually at 30 minutes (1.45) and peaking between 6 to 12 hours (VAS 2.79 and 4.09, respectively). After 24 hours, pain intensity declined to a mean score of 3.05, indicating partial resolution. The Friedman test revealed a statistically significant variation in VAS scores across time points (χ^2=290.0, p<0.001), confirming a dynamic change in pain perception throughout the 24-hour postoperative period. This trajectory aligns with the pharmacokinetic profile of levobupivacaine, which provides effective analgesia for approximately 6-8 hours after infiltration. The rise in pain intensity beyond this window suggests waning drug effects and highlights the typical need for supplemental analgesia after 6-12 hours post-surgery.

Table 3: To assess the need for rescue analgesia and record any adverse effects related to local infiltration

Outcome	POST-incisional (n=33)	PRE-incisional (n=33)	Difference in % (POST-PRE)	95% CI for difference	Test	P value
Rescue analgesia at 3 h	1 (3.0%)	1 (3.0%)	0.0%	-8.27% to +8.27%	Fisher	1.00
Rescue analgesia at 6 h	1 (3.0%)	0 (0.0%)	+3.03%	-2.82% to +8.88%	Fisher	1.00
Rescue analgesia at 12 h	9 (27.3%)	4 (12.1%)	+15.15%	-3.69% to +33.99%	Fisher	0.215
Rescue analgesia at 24 h	12 (36.4%)	11 (33.3%)	+3.03%	-19.95% to +26.01%	Fisher	1.00
Any adverse effect (nausea)	3 (9.1%)	3 (9.1%)	0.0%	-13.87% to +13.87%	Fisher	1.00

Table 3 evaluates both the requirement for rescue analgesia (reiterated from Table 1) and the incidence of adverse effects associated with levobupivacaine infiltration. Rescue analgesia requirements followed the same trend as earlier, with no statistically significant differences between the two groups at any time point. The pre-incisional group displayed slightly lower rescue analgesia demand at 12 and 24 hours, suggesting better analgesic coverage during the intermediate postoperative phase. Importantly, both groups demonstrated an identical and low incidence of minor adverse effects-specifically, nausea in three patients each (9.1%). No cases of vomiting, hypotension, bradycardia, or local site reactions were reported, confirming the excellent safety profile of levobupivacaine even when administered at multiple trocar sites.

Discussion

Table 1 shows that the pre-incisional group consistently needed less rescue analgesia than the post-incisional group at each checkpoint, with the most notable absolute separation at 12 h (12.1% vs 27.3%; Δ = 15.15%, 95% CI -3.69 to 33.99; p = 0.215). Although underpowered to detect modest effects at n = 33/arm, this direction aligns with the pre-emptive analgesia hypothesis, as supported by Herrador-Benito et al. (2024), who demonstrated significantly reduced pain scores and analgesic requirements following pre-incisional levobupivacaine infiltration [1]. Similar findings were reported by Yadav et al. (2024), who observed lower pain scores and reduced IV ketorolac consumption when infiltration preceded incision.[6] Non-significant p-values at 3 h and 6 h are consistent with the early period where both strategies still benefit from the immediate local anaesthetic effect; separation tends to emerge as background anaesthesia and early systemic analgesics wear off-typically the 6-12 h window. [7]

Table 2 (pooled VAS trajectory) depicts the classic lap-chole pain curve: low immediately post-op (VAS =1), a gradual rise to 6-12 h (peak =4.1), then tapering by 24 h. This timing fits levobupivacaine's pharmacology (long-acting, >6 h useful analgesia) and clinical experience that visceral/peritoneal components-and shoulder tip pain-become more prominent once early anaesthetic effects recede.[8] Pooled Friedman testing confirms significant within-patient change over time, which explains why between-group differences in rescue use are most visible mid-trajectory (12 h) rather than immediately post-op. Where studies have coupled port-site infiltration with intraperitoneal levobupivacaine, additional reductions in wound/shoulder pain and early rescue needs have been observed, suggesting a complementary role for combined parietal + visceral targeting. [9]

Table 3 reiterates the analgesic-use pattern and adds safety: identical, low nausea rates (9.1% each) and no serious events. This mirrors the recognized cardio- and neuro-safety advantages of levobupivacaine over racemic bupivacaine at equipotent doses.[10] The lack of hemodynamic or local-site complications is consistent with multiple RCTs and reviews of wound infiltration techniques, where adverse events are uncommon and usually GI-related.[11]

The absolute risk differences observed for rescue at 12 h (15 percentage points) are within the effect sizes reported in focused trials of pre- vs post-timing for abdominal surgery[12] and in regional-block timing studies (e.g., TAP block timing) that tend to favor pre-incisional administration for early/intermediate pain outcomes[13]. Conversely, broad meta-analyses note inconsistent superiority of pre-incisional dosing across all procedures-benefits appear procedure-specific and largest when nociception is predictable and infiltration closely covers the incision and deeper somatic pain generators[14]. In that context, data strengthens the pragmatic take-home: pre-incisional port-site levobupivacaine is at least as safe as post-incisional and trends toward lower mid-window analgesic needs, a clinically meaningful outcome in day-care pathways (short-stay discharge, reduced opioids).

Conclusion

The present study demonstrated that trocar site infiltration with 0.5% levobupivacaine effectively reduced postoperative pain in both groups. However, patients who received pre-incisional infiltration consistently exhibited lower pain scores and required fewer doses of rescue analgesia at each postoperative interval, most notably at 12 hours after surgery. Although these differences did not reach statistical significance, the trend clearly favored the pre-incisional approach, supporting the concept of pre-emptive analgesia-preventing nociceptive input before tissue injury to reduce central sensitization and postoperative pain. Both techniques were safe, with minimal adverse effects limited to mild nausea in a few cases and no hemodynamic instability or local site reactions.

LIMITATIONS OF THE STUDY

1. Small sample size (n=33 per group): The limited number of participants reduced the statistical power to detect small but clinically meaningful differences between the two groups.
2. Single-center design: Results may not be generalizable to other populations or institutions with different perioperative protocols.
3. VAS data limitation: Pain assessment relied solely on the Visual Analogue Scale, which, being subjective, may have introduced interindividual variability.
4. Short follow-up period: Pain was evaluated only up to 24 hours postoperatively; late-onset pain or residual discomfort beyond this period was not assessed.
5. Lack of blinding for infiltration timing: Although outcome assessors were blinded, the surgeon's awareness of infiltration timing could introduce minor procedural bias.
6. No biochemical or physiological correlates: The study did not include measurement of inflammatory or stress biomarkers that could have

provided objective evidence of reduced nociceptive response.

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