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Comparing The Efficacy Of Intraperitoneal Instillation Of Local Anesthetic Agent On Postoperative Analgesic Effect Vs No Local Anesthetic Agent Instillation In Patients Undergoing Laparoscopic Cholecystectomy

Article History:

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Abstract: ***Objective:*** To evaluate if intraperitoneal instillation of 0.5% bupivacaine is effective in reducing postoperative pain and analgesic requirements of patients undergoing elective LC compared to instillation of no local anaesthetic .***Study Design:*** This study was designed as a randomized controlled trial. ***Place and Duration of Study:*** Department of Surgery, Combined Military Hospital Lahore, from January 2025 to June 2025.***Methodology:*** A hundred and fifty patients, who underwent elective LC were randomly divided into two groups. Group A (N=75) intraperitoneally instilled with 20mL 0.5% bupivacaine hydrochloride, and Group B (N=75) had no instillation of the local anesthetic in the peritoneum. The Visual Analogue Scale (VAS) was used to measure postoperative pain 2, 6, 12 and 24 hours after surgery. Primary outcomes were VAS scores and time to T1RRA. Analysis of data was done using SPSS (26th).***Results:*** Group A demonstrated significantly lower VAS scores at 2 hours (3.1 ± 0.8 vs. 5.4 ± 1.2, $p < 0.001$), 6 hours (2.8 ± 0.7 vs. 4.6 ± 0.9, $p < 0.001$), and 12 hours (2.4 ± 0.6 vs. 3.8 ± 0.8, $p = 0.003$). The time was significantly longer for the first rescue analgesia in Group A than in Group B (7.4 ± 1.8 hours vs. 3.2 ± 0.9 hours; $p < 0.001$). The use of opioids decreased by 38.5% in group A ($p < 0.001$). A total of 12.0% of bupivacaine group patients and 28.0% of control group patients suffered from postoperative nausea and vomiting ($p = 0.014$).***Conclusion:*** ntraperitoneal instillation of bupivacaine, as a postoperative pain management solution, following laparoscopic cholecystectomy may be considered painless, simple, and safe management technique. Significantly decreases postoperative pain, reduces requirement for rescue analgesia, decreases opioid consumption and reduces incidence of postoperative nausea and vomiting.

Keywords:Laparoscopic cholecystectomy, Postoperative pain, Bupivacaine, Intraperitoneal anesthesia, Analgesia, Randomized controlled trial.

INTRODUCTION

Laparoscopic cholecystectomy (LC) is now considered standard surgical treatment for symptomatic gall stone problems throughout the world and has significant benefits compared to open cholecystectomy of less tissue injury, shorter hospital stay, quicker recovery and better cosmetics (1). However, postoperative pain is still a major clinical issue potentially delaying discharge, compromising early mobility, incurring extended hospital stays and compromising patient satisfaction. Managing post-surgical pain associated with minimally invasive surgery is a challenge, and novel analgesic approaches to enhance post-surgical outcomes are now being studied. Post-laparoscopic cholecystectomy pain is a multifactorial one and consists of three components: somatic pain from the port site incisions, visceral pain from the irritation of the raw hepatic bed and the peritoneum (2), hand shoulder tip pain from stretching the diaphragm during carbon dioxide pneumoperitoneum (3). Visceral pain is especially troublesome as the pain is deep, dull and hard to localize and is the major component of pain in the immediate postoperative period. There are several different pain mechanisms that make multimodal pain approaches necessary—where several pain pathways are stimulated at the same time (4).

The focus of contemporary perioperative pain management has been towards multimodal approaches in order to afford good management with a reduction in total systemic opioid use (4,5). Opioid analgesics are powerful and successful, but at the same time they are linked to a variety of side effects such as postoperative nausea and vomiting, respiratory depression, urinary retention, gastrointestinal ileus and delayed recovery (5,6). The resulting complications can undo the advantages of going through a small incision and lengthen the hospital stay. This fear has led to an increase in interest in regional anesthesia, and alternative modes of pain control providing selective analgesia without systemic opioid-related side effects (4,5). The intra-peritoneal injection of local anesthetics has been one of the promising ones. Intraperitoneal injection of local anesthetic agents is easy to do, risk-free, cheap and involves blocking nociceptive signals from damaged visceral peritoneal surfaces and raw liver tissue, which will stop the central sensitization and lessen neuroendocrine response to surgical trauma (9,12). Intraperitoneal instillation of long-acting amide local anaesthetics like bupivacaine, levobupivacaine and ropivacaine was shown to be effective in multiple international studies during laparoscopy (8,15,16) .Yet, when it comes to optimal time, level and definitive effectiveness, there are limited clinical findings in various population and health systems (11,14). Optimization of postoperative pain management with less consumption of opioid has a further significance in the era of limited resource countries like Pakistan where it helps to short the hospital stay, reduces the out-of-pocket cost of patient and maximizes utilization of tertiary care facilities (11,13). Although these intraperitoneal local anesthetic techniques have some potential advantages, very little research has been carried out to assess this method of anesthetic application in the Pakistani population (17).

Most of the studies available are from other advanced health care systems in countries with varying resource levels and patient populations. So, it was decided to conduct this randomized controlled trial to evaluate and compare the postoperative analgesic efficacy of instillation of bupivacaine in the cul de sac as compared to no bupivacaine in patients undergoing laparoscopic cholecystectomy at a tertiary care military hospital in Lahore. The aim was to establish if this simple and inexpensive technique was useful to decrease the postoperative pain, opioid consumption, and consequent opioid-related side effects in this local population. Study outcomes will be used to suggest evidence-based recommendations to incorporate this technique into the institutional pain management protocol to enhance patient satisfaction and outcomes.

MATERIALS AND METHODS

This randomized controlled trial was designed using a parallel-group design and began in January 2025 and ended in June 2025 at Department of General Surgery Combined Military Hospital (CMH), Lahore, Pakistan. This protocol was reviewed and approved by Institutional Review Board and Ethics Committee of Combined Military Hospital Lahore (IRB Reference: CMH/GS/2024-045). The trial was registered under Pakistan National Trial Registry (PNTR202401000456). All procedures were duly carried out according to the ethical requirements of the Declaration of Helsinki. Sample size was determined using World Health Organization (WHO) sample size calculator. It has been shown in previous studies that examined local anaesthetic blocks in laparoscopic surgery that there would be at least a 1.5 point difference on the Visual Analogue Scale (VAS) between groups (clinically meaningful difference). A required sample number of 75 patients per group (n=150 in the total) was calculated by using 95% confidence interval, 80% statistical power and an estimated 10% dropout rate. The patients visited the surgical outpatient clinic with symptomatic cholelithiasis and undergoing transabdominal

ultrasonography with a clear diagnosis of cholelithiasis were selected with non-probability consecutive sampling technique to undergo elective laparoscopic cholecystectomy.

Inclusion Criteria

- Male and female, between 18 and 65 years old.
- ASA Physical Status Classification I or II
- Symptomatic Cholelithiasis – Confirmed on Transabdominal Ultrasonography
- To undergo elective Laparoscopic Cholecystectomy (LC)

Exclusion Criteria

- Acute cholecystitis, choledocholithiasis or gallstone pancreatitis
- Major upper abdominal surgery that has a high risk of adhesions •
- History of amide local anesthetic allergy or documented amide local anesthetic hypersensitivity •
- Severe systemic comorbidities, such as chronic kidney disease (serum creatinine ≥1.5mg/dl) and major cardiac disease
- Persistent chronic opioid use, substance abuse or psychiatric disorders with impact on pain perception Intraop L to O (laparoscopic to open), and vice versa, cholecystectomy

After informed written consent, potentially eligible participants were randomized into two groups in a 1:1 ratio using a computer-generated, random number sequence (randomization.com). Assignments were assigned in numbered opaque, sealed envelopes that were opened by a circulating nurse who was not involved in data collection, and this occurred just before the surgical procedure. The double-blind design was used – those in each group were blinded to the interventions, postoperative ward nursing staff were blinded to the group of patients they cared for, and the researcher recording pain assessments was blinded to the group allocation. Since this intervention is not a 'blinding' procedure and due to the setting, however, the operating surgeon could not be blinded but was not involved in postoperative assessments.

Group A (Intervention): Received intraperitoneal instillation of 20 mL of 0.5% bupivacaine hydrochloride during surgery.
Group B (Control): Without intraperitoneal instillation of the local anesthetic, underwent standard surgical technique.

Standardized 4 port laparoscopic cholecystectomy was carried out under general anesthesia for all the patients. Propofol (2 mg/kg), nalbuphine (0.1mg/kg) and atracurium (0.5mg/kg) were administered intravenously to induce anaesthesia and allow endotracheal intubation. Isofluorane and oxygen/nitrous oxide mixture were used for maintenance anesthesia. Carbon dioxide was used to create pneumoperitoneum; the intra-abdominal pressure was kept between 11-13 mmHg during the procedure.

In group A, the surgeon performing the laparoscopy performed the instillation of 0.5% bupivacaine hydrochloride under direct vision, following pneumoperitoneum, in 20 mL. A total of 10 mL was then meticulously sprayed onto the liver surface and gallbladder bed with the use of a laparoscopic spray cannula and 10 mL was sprayed on subdiaphragmatic peritoneal surfaces. All patients were positioned at Trendelenburg position for two minutes to pool the local anesthesia in the subphrenic space after which the patients were placed in reverse Trendelenburg position for dissection of the gall bladder.

In Group B, no intraperitoneal instillation was performed;All surgery was done using standard technique immediately following pneumoperitoneum. Ideal surgical dissection techniques were maintained in both groups, such as careful dissection and clipping of cystic artery/duct, careful dissection of gallbladder from hepatic bed with monopolar electrocautery, and complete manual decompression of any residual carbon dioxide by opening valve ports prior to the removal of the specimen. In both groups all port sites were closed using non-absorbable sutures, but no local infiltration was performed.

All the patients were shifted to post anesthetic care unit (PACU) and then to surgical ward. The intensity of clinical pain experienced was evaluated using a standardised 10cm Visual Analogue Scale (VAS) 2, 6, 12 and 24 hrs post surgery (0 = no pain, 10 = worst pain imaginable). If patient noted presence of pain, the patient was asked to describe the type of pain: visceral (abdominal) pain or shoulder-tip pain.

A common protocol for rescue analgesia was followed. Patients with VAS score ≥ 4 or who specifically requested pain relief, were given intravenous Ketorolac (30 mg) as a first line rescue analgesia. If muscle pain had continued after 30 minutes in spite of treatment with acetaminophen/ketorolac, the second line of rescue drug was intravenous Tramadol 50 mg. The interval between the end of anesthesia and the time of the first rescue request for analgesia was considered the pain-free interval. A total of doses administered within 24 hrs and associated opioid side effects (nausea, vomiting, dizziness) were reported.

The primary outcome measures of the following were collected at 2, 6, 12, and 24 hours postoperatively: (1) VAS pain score, (2) first request for rescue analgesia,

(3) total opioid consumption during the 24 hours after surgery, and (4) number of opioid-related adverse events. Secondary outcomes were patient satisfaction and local anesthetic related complications.

Data analysis was done through the use of Statistical Package for the Social Sciences (SPSS) version 26.0. Normality of continuous variables was determined by Shapiro-Wilk test. Data from continuous variables such as age, weight, BMI, pain scores, time to analgesia were presented as mean ± standard deviation. For categorical data (gender, comorbidities, adverse events), this data was presented as mean, frequency and percentage. T test (independent samples t test) for continuous variables was used to make between group comparisons. Pearson X2 test or Fisher's exact test was used to compare categorical variables as necessary. Female and male subjects were then split into four age-groups and unit of intervention efficacy within each stratum was assessed. All p-values of ≤0.05 (two-tailed test) were statistically significant.

RESULTS

The total number of patients that were included and entered in the study were 150 patients. Study protocol adherence was 100% without any drop-out. All of the baseline characteristics were balanced between the treatment groups and demonstrated successful randomization. The mean age of the study population was 41.5 years ± 9.3 years. Among the 150 participants, 102 were female (68.0%) and 48 were male (32.0%). The mean BMI was 25.4 ± 3.1 kg/m² which was in the normal to overweight range for most of the patients. There was no difference between the groups with respect to age, sex, BMI, ASA (Table 1), operative time or intra-abdominal pressure during pneumoperitoneum.

Table 1. Baseline demographic and intraoperative data (n=150)

Variable	Group A (n=75)	Group B (n=75)	p-value
Age (years) Mean ± SD	41.1 ± 9.1	41.9 ± 9.5	0.602
Gender n (%) Male	23 (30.7%)	25 (33.3%)	0.865
Gender n (%) Female	52 (69.3%)	50 (66.7%)	
Body Mass Index (kg/m²)	25.2 ± 2.9	25.6 ± 3.3	0.434
Operative Time (minutes)	44.8 ± 8.2	46.1 ± 7.9	0.325
Pneumoperitoneum Pressure (mmHg)	12.1 ± 0.7	12.0 ± 0.8	0.573

The following summary of the main findings showed that postoperative pain was extremely significantly reduced in the intraperitoneal bupivacaine group. The VAS score of the Group A was significantly lower than the Group B at 2 hours after surgery (3.1 ± 0.8 vs. 5.4 ± 1.2, p < 0.001). This analgesic advantage persisted through the intermediate recovery period: at 6 hours (2.8 ± 0.7 vs. 4.6 ± 0.9, p < 0.001) and at 12 hours (2.4 ± 0.6 vs. 3.8 ± 0.8, p = 0.003). At 24 hours the difference between groups was not significant (VAS scores: 2.1 ± 0.5 vs. 2.3 ± 0.6, p = 0.120), meaning that by this point in time the analgesic effect had worn off (Table 2).

Table 2. Postoperative Visual Analogue Scale (VAS) Pain Scores

Time Point	Group A (n=75)	Group B (n=75)	p-value
VAS at 2 hours	3.1 ± 0.8	5.4 ± 1.2	<0.001*
VAS at 6 hours	2.8 ± 0.7	4.6 ± 0.9	<0.001*
VAS at 12 hours	2.4 ± 0.6	3.8 ± 0.8	0.003*
VAS at 24 hours	2.1 ± 0.5	2.3 ± 0.6	0.120

Analgesia requirement: Pain free interval was significantly longer in the bupivacaine group. The mean time to first request for rescue analgesia was 7.4 ± 1.8 hours in Group A compared to 3.2 ± 0.9 hours in Group B (p < 0.001), which is a 2.3 fold difference in time to first request for rescue analgesia. Therefore, 29.3% (n=22) of patients in Group A needed more than one dose of rescue analgesia during 24 hours, while 72.0% (n=54) of patents in control group required more than one dose rescue analgesia during 24 hours (p < 0.001). Overall postoperative opioid consumption was decreased by 38.5% in Group A (p < 0.001).

Table 3. Rescue Analgesia Requirements and Opioid-Related Adverse Events

Variable	Group A (n=75)	Group B (n=75)	p-value
Time to first rescue analgesia (hours)	7.4 ± 1.8	3.2 ± 0.9	<0.001*
Required >1 rescue dose n (%)	22 (29.3%)	54 (72.0%)	<0.001*
Postoperative nausea/vomiting n (%)	9 (12.0%)	21 (28.0%)	0.014*
Dizziness/sedation n (%)	4 (5.3%)	12 (16.0%)	0.033*

The decrease in opioid-related adverse effects was highly correlated with a decrease in opioid consumption. The incidence of postoperative nausea and vomiting was 12.0% (n=9) in the bupivacaine group and 28.0% (n=21) in controls (p = 0.014). Dizziness and sedation were reported in 5.3% (n=4) of Group A patients versus 16.0% (n=12) in Group B (p = 0.033). There were no reports of local anesthetic toxicity or bradycardia, hypotension or secondary peritonitis in either group.

Subgroup analyses based on gender and age showed comparable efficacy of interventions within the subgroups. The pain reduction at 2 hours postoperatively was significant for both female (3.0 ± 0.7 vs. 5.5 ± 1.1, p < 0.001) and male participants (3.3 ± 0.9 vs. 5.2 ± 1.3, p = 0.002). Analogous data (Table 4) demonstrated maintained efficacy in both age groups of participants (<40 years and ≥40 years), suggesting that the lesions in the study of efficacy of the intraperitoneal bupivacaine administration were not restricted to certain age groups of individuals. (Table 4).

Table 4. Post-Acute Pain scores using VAS were performed and analyzed at 2 hours POST-OP by stratified analysis.

Stratum	Group A	Group B	p-value
Female (n=102)	3.0 ± 0.7	5.5 ± 1.1	<0.001*
Male (n=48)	3.3 ± 0.9	5.2 ± 1.3	0.002*
Age <40 years (n=70)	2.9 ± 0.6	5.3 ± 1.0	<0.001*
Age ≥40 years (n=80)	3.2 ± 0.8	5.6 ± 1.2	<0.001*

DISCUSSION

Intraperitoneal instillation of bupivacaine indicates that it significantly decreases postoperative pain intensity, markedly increases pain-free interval and significantly reduces opioid consumption after laparoscopic cholecystectomy in this randomized-controlled trial. A clinically and statistically significant effect on visceral pain blockade with direct application of bupivacaine to subhepatic and subdiaphragmatic peritoneal surfaces was found that remained for 12 hours postoperatively which is more than adequate to cover the critical early postoperative period in the setting of minimally invasive surgery.

The significant difference between VAS score at 2 h (5.4 to 3.1) shows that the mechanism behind this pain reduction is the interception of the visceral afferent nociceptive pathway before the central sensitization takes place in this model (15,16). The reduction in the measured VAS score (from 5.4 to 3.1 at 2 h) was approximately 43% less pain, demonstrating the effectiveness of interruption of visceral afferent pain pathways in this experimental model of laparoscopic surgery. The important implication of this early and pertinent pain reduction clinically is that it is directly translated to patients' postoperative comfort in the important immediate post-surgical period.

The longer it lasts with bupivacaine (7.4 hours) versus those without (3.2 hours), is of importance clinically. This prolonged analgesia (12,13) is associated with a reduction in rescue opioid requirements by 38.5% in our study 11,14, which is similar to how other regional anesthetic techniques have shown to reduce opioid use by 30-50% in laparoscopic surgery, thereby reducing the sedative and emetogenic effects of systemic opioids which results in earlier tracheal extubation, improved GI function, enhanced ability to mobilize, early onset of oral intake, and faster functional recovery – all of which can help meet enhanced recovery after surgery (ERAS) goals and maximize resource usage in the hospital (5,7).

The reductions in postoperative nausea and vomiting (PONV) were 28.0% to 12.0% and in dizziness, 16.0% to 5.3% in the bupivacaine group, and those will directly match the decrease in opioid use (5,11). PONV and sedation due to systemic opioids are common well-known problems that impact significantly on patient satisfaction and recovery; this is especially important with ambulatory or day surgery in which nausea and vomiting may prolong discharge . The ability to achieve the latest enhanced recovery principles as well as improve patient satisfaction is due to the refined safety characteristics and the decrease in side effects.
Stratified analyses showed a similar effect of analgesics on pain across gender and age groups; these analyses provided additional evidence that our results are generalizable. This analgesic effect was still statistically significant and clinically meaningful when comparing the women against the men, or comparing the younger against the older patients. Due to this consistency, we believe that ip bupivacaine to be a powerful tool in our health care context that is effective on a variety of patient types and does not need differential dosing based on patient attributes.

Several major strengths of this study are the utilization of a double-blinded randomized controlled study design, a consistent surgical team without differences in surgical technique, thorough pain measures taken at precisely declared timepoints, and clearly established inclusion and exclusion criteria providing the opportunity to reproduce this study. The study

followed the CONSORT guidelines to report RCT and process of allocation concealment was maintained throughout.

But some shortcomings need to be recognized. First, it was a single-center study in an urban setting in a military tertiary care hospital, and may not be applicable to all resource-limited and peripheral healthcare areas in Pakistan. Second, we did not directly measure the serum concentrations of bupivacaine or directly assess systemic toxicities to quantify local anesthetic absorption. Third, no dose-response or comparisons to other local anesthetic agents (ropivacaine or levobupivacaine) that may offer other efficacy profiles were made. Fourth, there was no evaluation of the longer term outcome such as chronic post-surgical pain or patient functional status beyond the immediate post-surgical timeframe.

Future multicenter studies may be conducted on varying concentration and volume of the local anesthetic used, different combination of local anesthetics including Epinephrine which can be used to make local anesthetic block more effective perhaps to prolong its overall effect, and studies may be done in various hospital and clinics of different areas of Pakistan. Also, future research could provide results on longer-term outcomes such as return to normal activity, functional recovery indices and health related QoL measures to facilitate its wide scale implementation in healthcare institutions of Pakistan.

CONCLUSION

This study showed 0.5% bupivacaine instilled in the peritoneum is simple, safe and effective postoperative add on injection for pain management in LC. The technique successfully diminishes early postoperative visceral pain; substantially prolonged pain-free period following the operation and noticeably reduced request for rescue systemic opioids and related complications. With its excellent safety record, low cost, ease of use, and effectiveness shown in this randomized controlled trial, instillation of I.P. local anesthetic should be determined a valuable technique for use in a multimodal approach to anesthesia in laparoscopy-based general surgery. If this technique is incorporated in everyday surgical procedures it can help improve patient satisfaction, better postoperative recovery and better optimal utilization of resources in tertiary-care hospitals all over Pakistan.

LIST OF ABBREVIATIONSASA: American Society of Anesthesiologists

- CMH: Combined Military Hospital
- ERAS: Enhanced Recovery After Surgery
- FCPS: Fellow of College of Physicians and Surgeons
- IRB: Institutional Review Board
- PNTR: Pakistan National Trial Registry
- PONV: Postoperative Nausea and Vomiting
- RCT: Randomized Controlled Trial
- SD: Standard Deviation
- SPSS: Statistical Package for the Social Sciences
- VAS: Visual Analogue Scale
- WHO: World Health Organization

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CONFLICT OF INTEREST

None

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None

ETHICAL APPROVAL

The protocol was duly approved from the Institutional Review Board and Ethics Committee Combined Military Hospital Lahore (IRB: CMH/GS/2024-045). The trial has been registered at the Pakistan National Trial Registry (PNTR202401000456). All procedures were conducted in keeping with the ethical principles laid down in the Declaration of Helsinki. All participants provided written informed consent prior to signing up..

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