COMPARATIVE EVALUATION OF ANALGESIC OUTCOMES OF INTRAPERITONEAL VERSUS SUBCUTANEOUS ADMINISTRATION OF BUPIVACAINE FOR LAPAROSCOPIC CHOLECYSTECTOMY PATIENTS

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ABSTRACT

OBJECTIVES

This study aimed to compare the analgesic efficacy and recovery outcomes of intraperitoneal versus subcutaneous administration of bupivacaine in patients undergoing laparoscopic cholecystectomy.

METHODOLOGY

This was a comparative clinical study conducted at the Department of Anesthesiology, Rawalpindi Medical University, and at Allied Hospitals. A total of 86 ASA class I patients undergoing elective laparoscopic cholecystectomy were divided into two groups: intraperitoneal bupivacaine (n=43) and subcutaneous port-site infiltration (n=43). Post-operative pain was assessed using the Visual Analog Scale (VAS) at 1, 2, 4, 6, 12, and 24 hours. Time to first rescue analgesia, total analgesic consumption, number of rescue doses, recovery parameters, and complications were recorded. Repeated measures ANOVA, independent sample t-test, and chi-square test were applied, with $p \leq 0.05$ considered statistically significant.

RESULTS

Intraperitoneal bupivacaine significantly reduced post-operative VAS scores at all time intervals ($p < 0.001$). Repeated-measures ANOVA demonstrated significant effects of time ($p < 0.001$) and group ($p < 0.001$), indicating consistently lower pain scores in the intraperitoneal group. Time to first rescue analgesia was longer (211.1±44.1 vs 120.0±44.9 min), and total analgesic consumption was lower (82.7±24.4 vs 125.4±21.1 mg) compared with subcutaneous infiltration ($p < 0.001$). Patients demonstrated earlier ambulation, earlier oral intake, shorter hospital stay, and higher satisfaction ($p < 0.001$). Shoulder tip pain was significantly reduced (11.6% vs 46.5%), while other complications were comparable between groups.

CONCLUSION

Intraperitoneal bupivacaine was associated with improved post-operative analgesia, an enhanced recovery profile, and reduced shoulder tip pain, without increasing complications, compared with subcutaneous infiltration; however, these findings should be interpreted cautiously due to the non-randomized study design.

KEYWORDS: *Laparoscopic Cholecystectomy, Pain, Analgesia, Anesthesia, Outcomes*

INTRODUCTION

Laparoscopic cholecystectomy is the standard treatment for symptomatic gallstone disease and is widely preferred due to reduced tissue trauma, shorter recovery time, and decreased hospital stay compared with open surgery.[1,2] Despite its minimally invasive nature, post-operative pain remains a significant clinical concern affecting patient comfort, early mobilization, and discharge readiness. Post-operative pain following laparoscopic surgery is multifactorial, involving visceral pain due to peritoneal stretching and gallbladder bed manipulation, somatic pain from trocar incisions, and referred shoulder tip pain caused by diaphragmatic irritation and retained carbon dioxide.[3] Effective post-operative analgesia is essential to facilitate early mobilization, reduce opioid consumption, and improve overall recovery outcomes.[4] Various strategies have been proposed, including systemic analgesics, regional anesthesia techniques, and local anesthetic infiltration. Although port-site infiltration is widely used due to its simplicity and safety, it primarily targets somatic pain and does not adequately address visceral and diaphragmatic components. In contrast, intraperitoneal instillation of local anesthetic directly acts on peritoneal nociceptors and may reduce pneumoperitoneum-induced irritation, thereby providing more comprehensive analgesia.[5,6] Bupivacaine, a long-acting amide local anesthetic, is commonly used for post-operative pain management due to its prolonged duration of action and

favorable safety profile at recommended doses.[7] Several recent studies have evaluated intraperitoneal administration of local anesthetics in laparoscopic surgeries; however, findings regarding its superiority over conventional techniques remain inconsistent.[8,9] Furthermore, most previous studies have relied on limited statistical methods, and there is a lack of robust analyses incorporating longitudinal pain assessment and effect-size estimation, particularly in local populations. Therefore, this study aimed to compare the analgesic efficacy and post-operative recovery outcomes of intraperitoneal versus subcutaneous administration of bupivacaine in patients undergoing elective laparoscopic cholecystectomy.

METHODOLOGY

This study was a prospective, non-randomized, comparative clinical study conducted in the Department of Anesthesiology, Rawalpindi Medical University and Allied Hospitals, Rawalpindi, over a period of 2 months from November 2025 to January 2026. Due to the non-randomized allocation in routine clinical practice, the study is observational, and causal inferences should be interpreted with caution. Patients undergoing elective laparoscopic cholecystectomy under general anesthesia were followed and divided into two groups based on the analgesic technique used in routine departmental practice. Patients were allocated to two equal groups based on the analgesia administered at the end of surgery. The intraperitoneal group received intraperitoneal instillation of bupivacaine, while the subcutaneous group received port-site infiltration of bupivacaine. Allocation was based on routine anesthetic practice without randomization or allocation concealment, which may introduce selection bias and confounding by indication**.** A blinded observer performed post-operative assessment to reduce assessment bias; however, patients and anesthesiologists were not blinded, introducing a potential risk of performance bias. All surgeries were performed using a standardized four-port laparoscopic cholecystectomy technique by experienced surgeons. General anesthesia was induced using intravenous propofol (2 mg/kg), fentanyl (2 µg/kg), and atracurium (0.5 mg/kg), followed by endotracheal intubation and maintenance with isoflurane in an oxygen-air mixture with intermittent atracurium boluses. After surgery, patients in the intraperitoneal group received 20 ml of 0.25% bupivacaine injected into the gallbladder bed and the subdiaphragmatic space, while those in the subcutaneous group received 20 ml of 0.25% bupivacaine infiltrated at all trocar sites. No additional local anesthetic was administered. Ethical approval was obtained from the Institutional Research Forum and Research and Ethical Committee of Rawalpindi Medical University and Allied Hospitals (Ref No. 688/IREF/RMU/2025 dated 26-11-2025). Written informed consent was obtained from all participants. Confidentiality was ensured through anonymization, and the study was conducted in accordance with the principles of the Declaration of Helsinki. The sample size was calculated using a formula for comparison of two means, assuming an expected difference in post-operative VAS score of 1.5 units with a standard deviation of 2.0 based on previous literature, at a 95% confidence level and 80% power, resulting in a total sample size of 86 patients (43 per group).[8] Inclusion criteria comprised patients aged 18-65 years of either gender, classified as ASA physical status I, undergoing elective laparoscopic cholecystectomy, and willing to participate. Exclusion criteria included hypersensitivity to local anesthetics, ASA class II or higher, pregnancy, chronic opioid use, psychiatric illness, conversion to open surgery, or refusal to participate. Baseline demographic and perioperative variables, including age, gender, body mass index, duration of surgery, duration of anesthesia, history of acute cholecystitis, and previous abdominal surgery, were recorded. Post-operative pain intensity was assessed using the Visual Analog Scale (VAS; 0-10) at 1, 2, 4, 6, 12, and 24 hours. Observers were trained prior to data collection to ensure consistency in VAS assessment, although formal inter-rater reliability was not statistically measured. Intravenous tramadol (50 mg) was administered as rescue analgesia when VAS ≥4. Time to first rescue analgesia, total analgesic consumption within 24 hours, and number of rescue doses were documented. Recovery parameters included sedation score, time to ambulation, time to oral intake, duration of hospital stay, and patient satisfaction score. Sedation was assessed using a 4-point scale (1 = alert, 4 = deeply sedated), while patient satisfaction was measured using a 5-point Likert scale (1 = very dissatisfied to 5 = very satisfied). Post-operative complications within 24 hours, including shoulder tip pain, nausea, vomiting, bradycardia, hypotension, urinary retention, local anesthetic toxicity, and allergic reactions, were recorded. Data were collected using a structured pro forma by an anesthesia resident who was not involved in administering the intervention. Three consultant anesthesiologists reviewed the data collection tool to ensure content validity. Confounding was minimized through standardized anesthesia protocols, consistent drug dosages, and uniform surgical techniques; however, residual confounding cannot be excluded due to the non-randomized design. Data were analyzed using SPSS version 26 (IBM Corp., USA). Quantitative variables were expressed as mean ± standard deviation, and categorical variables as frequency and percentage. A repeated-measures ANOVA was applied to assess differences in VAS clinically meaningful and sustained analgesic advantage.

The intraperitoneal group demonstrated significantly scores over time between groups, with appropriate post hoc analyses. An independent-samples t-test was used to compare continuous variables, while chi-square or Fisher's exact test was used for categorical variables. Effect sizes and 95% confidence intervals were calculated where appropriate to enhance statistical interpretation. A p-value ≤0.05 was considered statistically significant. The study was reported in accordance with the TREND (Transparent Reporting of Evaluations with Non-randomized Designs) guidelines.

RESULTS

The two groups were comparable with respect to demographic and perioperative characteristics. There was no statistically significant difference in age, BMI, duration of surgery, duration of anesthesia, gender distribution, presence of acute cholecystitis, or history of previous abdominal surgery ($p>0.05$), indicating baseline homogeneity between the groups. All patients belonged to ASA class I, ensuring comparable anesthetic risk. Table 1 demonstrates that both groups were well matched at baseline with no statistically significant differences in demographic or clinical variables. This minimizes confounding and strengthens the validity of group comparisons. Repeated-measures ANOVA showed a significant effect of time on post-operative pain ($F = 129.35$, $p < 0.001$, partial $\eta^2 = 0.606$), indicating that pain decreased over time in both groups. However, the interaction between time and group was not significant ($F = 0.661$, $p = 0.653$), suggesting that both groups improved in a similar pattern. A highly significant group effect was observed ($F = 361.82$, $p < 0.001$, partial $\eta^2 = 0.812$), indicating consistently lower pain scores in the intraperitoneal group. Although the interaction between time and group was not statistically significant, the consistently lower VAS scores across all time points in the intraperitoneal group indicate a lower VAS scores at all time points ($p < 0.001$). The mean difference ranged from -1.39 to -1.74 with narrow confidence intervals, indicating strong statistical precision. Effect size analysis showed very large effects (Cohen's $d = 1.55$-2.12), confirming strong clinical significance. The intraperitoneal group showed significantly prolonged time first to rescue analgesia and reduced total analgesic consumption and rescue doses ($p < 0.001$). These findings indicate improved pain control and reduced opioid requirement. The intraperitoneal group showed significantly better recovery outcomes, including earlier ambulation, earlier oral intake, a shorter hospital stay, and higher satisfaction ($p < 0.001$). Shoulder tip pain was significantly lower ($\chi^2 = 12.69$, $p < 0.001$) with a moderate effect size (Cramér's $V = 0.384$). Other complications were not statistically different. Regression analysis showed the model was significant ($F = 18.82$, $p < 0.001$, $R^2 = 0.541$). Group was the only significant predictor ($\beta = 0.670$, $p < 0.001$), indicating that treatment type independently influenced pain outcomes. The intraperitoneal group consistently demonstrated lower mean VAS scores at all postoperative time points compared with the subcutaneous group, indicating an improved and sustained analgesic effect.

Table 1: Baseline Characteristics of Patients (n = 86)

Variable	Intraperitoneal (n=43)	Subcutaneous (n=43)	Test statistic	p-value
Age (years)	38.9 ± 11.7	42.2 ± 12.9	t(84) = -1.245	0.217
BMI (kg/m²)	27.6 ± 3.22	27.6 ± 3.05	t(84) = 0.017	0.986
Duration of Surgery (min)	60.2 ± 11.2	60.6 ± 10.3	t(84) = -0.175	0.862
Duration of Anesthesia (min)	82.1 ± 11.3	82.1 ± 10.3	t(84) = -0.008	0.994
Male	21 (48.8%)	25 (58.1%)	$\chi^2 = 0.748$	0.387
Female	22 (51.2%)	18 (41.9%)	_	_
Acute cholecystitis	07 (16.3%)	13 (30.2%)	$\chi^2 = 2.345$	0.126
Previous surgery	03 (7.0%)	5 (11.6%)	$\chi^2 = 0.551$	0.458

Table 2: Comparison of Post-operative Pain Scores (VAS) with CI and Effect Size

Time	Intraperitoneal	Subcutaneous	Mean Difference (95% CI)	p-value	Effect Size (d)
1 hr	3.35 ± 0.93	4.74 ± 0.82	-1.39 (-1.77 to -1.02)	<0.001	1.59
2 hr	3.58 ± 0.91	5.06 ± 0.72	-1.48 (-1.83 to -1.13)	<0.001	1.80
4 hr	4.17 ± 0.83	5.72 ± 1.14	-1.55 (-1.98 to -1.12)	<0.001	1.56
6 hr	3.81 ± 0.88	5.28 ± 0.95	-1.47 (-1.86 to -1.07)	<0.001	1.60
12 hr	2.48 ± 0.97	4.26 ± 1.02	-1.78 (-2.21 to -1.36)	<0.001	1.79
24 hr	1.00 ± 0.85	2.74 ± 0.78	-1.74 (-2.09 to -1.39)	<0.001	2.12

Table 3: Post-operative Analgesic Requirements

Variable	Intraperitoneal	Subcutaneous	Mean Difference	p-value
Time to rescue (min)	211.1 ± 44.1	120.0 ± 44.9	+91.1	<0.001
Total analgesia (mg)	82.7 ± 24.4	125.4 ± 21.1	-42.7	<0.001
Rescue doses	0.65 ± 0.61	1.81 ± 0.66	-1.16	<0.001

Table 4: Recovery Outcomes and Complications

Variable	Intraperitoneal	Subcutaneous	Test	p-value
Sedation	1.21 ± 0.56	1.35 ± 0.57	t	0.256
Ambulation (hrs)	7.72 ± 2.01	9.92 ± 1.85	t	<0.001
Oral intake (hrs)	6.47 ± 2.06	9.10 ± 1.99	t	<0.001
Hospital stay (hrs)	19.1 ± 3.4	25.6 ± 3.9	t	<0.001
Satisfaction	4.15 ± 0.66	3.10 ± 0.83	t	<0.001
Shoulder pain	11.6%	46.5%	χ^2=12.69	<0.001
Nausea	14.0%	27.9%	χ^2	0.112
Vomiting	9.3%	20.9%	χ^2	0.132
Bradycardia	2.3%	2.3%	Fisher	1.000
Hypotension	2.3%	7.0%	Fisher	0.616

Table 5: Multivariate Regression Analysis (VAS at 24 hours)

Variable	Beta (β)	95% CI	p-value
Group	0.670	1.08 – 2.09	<0.001
Age	0.010	NS	0.894
BMI	-0.021	NS	0.780
Surgery duration	-0.022	NS	0.772
Total analgesia	0.089	NS	0.408

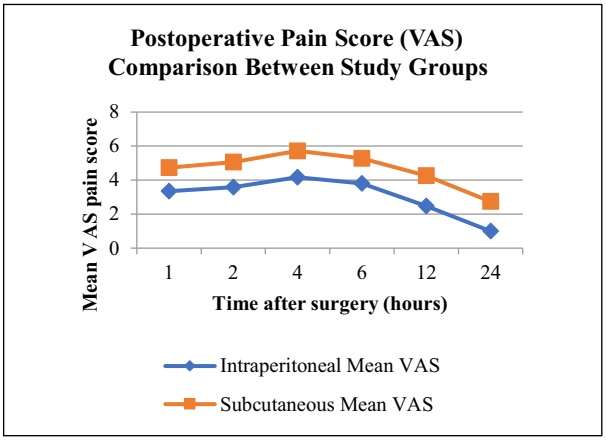

Figure 1: Comparison of post-operative pain intensity (VAS score) between intraperitoneal and subcutaneous bupivacaine groups over 24 hours following laparoscopic cholecystectomy.

DISCUSSION

Intraperitoneal bupivacaine was found to be more effective than subcutaneous (port-site) infiltration in patients undergoing laparoscopic cholecystectomy. Despite comparable baseline characteristics (Table 1), the intraperitoneal group demonstrated significantly lower VAS scores at all post-operative time points (1-24 hours), with the greatest difference observed in the early post-operative phase (Table 2). Unlike many previous studies that relied solely on simple comparative statistics, the present study incorporates repeated-measures ANOVA, effect size estimation, and multivariate regression, providing a more robust and clinically interpretable assessment of analgesic effectiveness. Furthermore, repeated-measures ANOVA demonstrated a significant effect of time ($p < 0.001$). However, a non-significant interaction between time and group ($p = 0.653$), indicating that although both groups improved over time, the intraperitoneal group consistently maintained lower pain scores across all time points. The large effect sizes observed (Cohen's d >1.5) indicate that the differences are not only statistically significant but also clinically substantial. Although the interaction between time and group was not statistically significant, the consistently lower VAS scores ac ross all time points, supported by large effect sizes (Cohen's d = 1.55-2.12), indicate a clinically meaningful and sustained analgesic advantage. This finding aligns with contemporary evidence suggesting that intraperitoneal local anesthetics effectively target visceral pain by acting on peritoneal nociceptors and reducing diaphragmatic irritation. Similar findings have been reported in recent randomized controlled trials and systematic reviews.[10,11,12,13] The clinical relevance of enhanced pain management is further supported by our findings on analgesic requirements. The intraperitoneal group showed a significantly longer time to first rescue analgesia and reduced total analgesic consumption and number of rescue doses (Table 3). The magnitude of reduction in analgesic requirement reflects not only statistical significance but also clinical importance, suggesting reduced opioid dependence and improved patient comfort. These findings are consistent with previous studies demonstrating that intraperitoneal administration reduces post-operative analgesic demand by providing broader peritoneal coverage and minimizing nociceptive transmission.[3,14,15] In addition to improved pain control, the intraperitoneal group exhibited earlier ambulation, earlier oral intake, shorter hospital stay, and higher patient satisfaction (Table 4). These findings are clinically significant as they support enhanced recovery pathways and align with modern ERAS (Enhanced Recovery After Surgery) principles. Recent evidence has similarly shown that improved analgesia contributes to early mobilization, reduced hospital stay, and better overall patient outcomes.[4,16] One important finding of this study was a significant reduction in shoulder tip pain in the intraperitoneal group (Table 4). Shoulder tip pain following laparoscopic surgery is primarily attributed to diaphragmatic irritation due to residual carbon dioxide. The targeted delivery of local anesthetic to the subdiaphragmatic region likely explains the reduction observed in this study. This finding is supported by previous studies demonstrating that intraperitoneal interventions effectively reduce referred shoulder pain by minimizing peritoneal irritation and residual gas effects.[15,17,18,19] The safety profile of intraperitoneal bupivacaine in this study was comparable to that of subcutaneous infiltration. No cases

of local anesthetic toxicity or allergic reactions were observed, and other complications such as nausea, vomiting, bradycardia, and hypotension were not significantly different between groups. These findings are consistent with recent systematic reviews confirming that intraperitoneal local anesthetics are safe when used within recommended dosage limits.[13,20] A major strength of this study is the use of advanced statistical methods, including repeated-measures ANOVA, confidence intervals, effect size estimation, and multivariate regression. The regression analysis demonstrated that group allocation remained an independent predictor of post-operative pain ($p < 0.001$), even after adjusting for potential confounders, thereby strengthening the internal validity of the findings.

LIMITATIONS

This was a prospective, non-randomized study, and allocation based on routine clinical practice, without randomization or allocation concealment, introduces potential selection bias and limits causal inference. Although baseline comparability and regression adjustment were performed, residual confounding cannot be excluded. The study was conducted at a single center with a relatively small sample size, limiting generalizability. Post-operative pain assessment using the Visual Analog Scale is subjective and influenced by individual perception, despite observer training aimed at minimizing variability. Additionally, formal inter-rater reliability was not statistically assessed, which may affect measurement precision. Finally, the follow-up period was limited to 24 hours, restricting evaluation of long-term analgesic outcomes and chronic pain prevention.

CONCLUSION

Intraperitoneal bupivacaine was associated with significantly improved postoperative analgesia and recovery outcomes compared with subcutaneous infiltration; however, these findings should be interpreted cautiously due to the non-randomized study design. Patients in the intraperitoneal group experienced lower pain scores at all post-operative time intervals, delayed need for rescue analgesia, reduced total analgesic consumption, and fewer rescue doses. Improved recovery parameters, including earlier ambulation, earlier oral intake, shorter hospital stay, and higher patient satisfaction, were also observed, along with a marked reduction in shoulder tip pain without increased adverse effects. These findings suggest that intraperitoneal bupivacaine is a safe, effective, and clinically beneficial technique that may be incorporated into routine post-operative pain management protocols for elective laparoscopic cholecystectomy to enhance recovery and patient comfort.

CONFLICT OF INTEREST: None

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AUTHORS CONTRIBUTION

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The authors accept responsibility for all aspects of the work and will ensure that any concerns regarding the accuracy or integrity of any part are properly investigated and resolved.