

# COMPARISON OF INTRA VENOUS KETOROLAC VERSUS INTRA PERITONEAL BUPIVACAINE IN POST LAPAROSCOPIC CHOLECYSTECTOMY PATIENTS IN TERMS OF POSTOPERATIVE PAIN SCORE AND MEAN TIME FIRST REQUEST FOR ANALGESIA

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## ABSTRACT

**Background:** Postoperative pain has become a significant issue after the laparoscopic cholecystectomy, and it can lead to an increase in rescue analgesia. Commonly used analgesic methods include intraperitoneal bupivacaine and intravenous ketorolac that may have different effectiveness depending on clinical circumstances. **Aim:** To compare intravenous ketorolac with intraperitoneal bupivacaine in terms of postoperative pain intensity, hemodynamic parameters, and rescue analgesic requirements following laparoscopic cholecystectomy. **Methods:** A randomized controlled trial was conducted at the Department of General Surgery, Doctors Hospital & Medical Centre, Lahore. A total of 104 patients aged 25–60 years with ASA physical status I or II undergoing laparoscopic cholecystectomy for gallstone disease were randomly allocated into two equal groups. The Bupivacaine Group was 30 mL of 0.25% intraperitoneal bupivacaine and the Ketorolac Group received 30 mg of intravenous ketorolac. The visual analogue scale was used to measure postoperative pain, blood pressure, heart rate, respiratory rate and rescue analgesic needs were also noted during the postoperative period. Statistical analysis was performed using SPSS version 24, with  $p < 0.05$  considered statistically significant. **Results:** The demographic and clinical parameters at the baseline were similar in both groups, and there were no significant differences in age, sex, weight, ASA grade, or duration of the surgery ( $p > 0.05$ ). The ketorolac group showed a considerable dropping in systolic and diastolic blood pressure levels at 8, 12 and 24 hours after surgery. The heart rate and respiratory rate were similar in both groups during the period of observation. The mean scores of VAS pain were lower at all levels with ketorolac, except at 18 hours, where statistically significant was demonstrated at 6 hours ( $p = 0.05$ ) and at 24 hours ( $p = 0.006$ ). The rescue analgesics needs were also much higher in the ketorolac group than in the bupivacaine group (24.0% vs. 44.1%;  $\chi^2 = 17.04$ ,  $p < 0.05$ ). **Conclusion:** The intravenous ketorolac also gave an excellent postoperative analgesia over the intraperitoneal bupivacaine as seen in lower pain scores at critical time points during the postoperative phase and a reduced need to use rescue analgesia.

**KEYWORDS:** Laparoscopic cholecystectomy; Ketorolac; Bupivacaine; Postoperative pain; Visual analogue scale; Rescue analgesia; Intravenous analgesia; Intraperitoneal analgesia.

## INTRODUCTION

Laparoscopic cholecystectomy (LC) is now the standard surgical approach to symptomatic cholelithiasis due to its superior results in terms of successful gallbladder excision using smaller incisions, less tissue injury, fewer hospitalization and earlier functional recovery compared to open cholecystectomy (Pavel et al., 2022). Gallstones disease is one of the most prevalent gastrointestinal conditions globally, whereby its incidence significantly differs among the sex, ethnicity, age, and geographical location with population-based research showing that in most western communities, about 10-15% of the population is found to possess gallstones (Edebo et al., 2024). The growth in the load of the gallstone disease has resulted in a significant amount of laparoscopic surgical operations across the world and hence the problem of perioperative care optimization is of clinical importance (Roy and Sheikh, 2024). Although the impact of LC is minimal, postoperative pain is clinically significant and may delay mobilization, impair respiratory functioning, augment analgesic demands, and disrupt early discharge. Thus, analgesia after LC is a significant aspect

of improved postoperative recovery and needs interventions that can support the various physiological processes of pain (Srikanth et al., 2024).

The postoperative pain levels and duration following LC tend to be lower and less severe than those following open abdominal surgery, although still a significant proportion of patients report moderate to severe pain levels in the initial postoperative period (Colling et al., 2022). A perspective evaluation of patients who have undergone LC indicated that about one-third had had considerable postoperative pain especially during the first postoperative day, which proves that even minimal invasive surgery does not exclude the importance of effective analgesic treatment (Ahmed et al., 2023). The pathophysiology of this pain is divided into various elements that are; trauma of the abdominal wall due to trocar insertion, visceral pain due to manipulating the gallbladder, diaphragmatic pain, and the remaining carbon dioxide in the peritoneum that stimulates the phrenic nerve. This has led to a lot of focus on non-opioid pharmacological methods like non-steroidal anti-inflammatory medications and local anesthesia techniques in pain reduction and additional analgesic use after LC (Zahra et al., 2021).

Ketorolac is a potent non-steroidal anti-inflammatory drug that exhibits the effect of alleviating pain mainly via cyclooxygenase-mediated prostaglandin synthesis inhibition, hence minimizing peripheral tissue postoperative sensitization to inflammation (Amini et al., 2022). However, the intravenous delivery will give a systemic analgesic effect and may be especially beneficial when oral medication is contraindicated in urgent postoperative care, and many of the side effects of opioids are not experienced with the adequate choice and dosage (Jiang et al., 2020). Another analgesic approach involves intraperitoneal bupivacaine administration since this long-term amide local anesthetic, works by blocking voltage-gated sodium channel and disrupting transmissions of nociceptive nerves at the peritoneal and visceral irritation area (Xu et al., 2023). A more recent comparative study of 92 patients revealed that both intraperitoneal bupivacaine and intravenous ketorolac had a significant effect on reducing abdominal and shoulder pain compared to placebo but did not significantly differ in terms of their analgesic effect between them (Buglio et al., 2025).

Direct intravenous ketorolac vs intraperitoneal bupivacaine comparison is thus clinically significant due to the underlying differences in the mechanisms and pathway of action of the two interventions, which address postoperative pain (Arafa et al., 2022). Both intravenous ketorolac and intraperitoneal bupivacaine were found to reduce abdominal and shoulder pain and postoperative nausea and vomiting significantly compared to placebo ( $P=0.001$ ) in a meta-analysis (Cao et al., 2024). Nevertheless, past experiments have produced conflicting results that suggest the analgesic effect of intraperitoneal local anesthesia can be influenced by methodologic factors including the concentration and the volume used, the timing of instillation, surgical procedure, and pre-existing analgesic program (Soyalp et al., 2025). Such discrepancies offer a reasonable foundation to proceed with comparative assessment of analgesic needs instead of deeming that the pharmacologically different methods were similar (Lee et al., 2022).

In Pakistan, the comparison of intravenous ketorolac to intraperitoneal bupivacaine can be especially useful since LC is regularly used to treat symptomatic gallstone disease, and the use of analgesics after the surgery is dependent on the institutional practice, available drugs, surgical experience, and the resource base (Hamza et al., 2024). Pakistani evidence has shown that local bupivacaine can have a significant effect on early post-surgery pain after LC, with a randomized trial of 62 patients reporting greatly reduced pain scores in bupivacaine vs. control patients at 2 and 6 hours ( $p=0.036$ ). However, that study used bupivacaine at the trocar sites and intravenous ketorolac post-operative, and thus failed to provide a direct comparison of whether intraperitoneal bupivacaine or intravenous ketorolac is better or equal as the main comparative analgesic intervention (Muzammil et al., 2025). The local evidence that can be generated on analgesic needs can thus serve to indicate whether a specific intraperitoneal local anesthetic procedure has any significance over systemic NSAID therapy of Pakistani LC patients, especially on the aspects of rescue analgesia and postoperative pain management. It was therefore the objective of the study to compare intravenous ketorolac to intraperitoneal bupivacaine as a way of giving situation-based evidence on the efficacy and utility of an effective and clinically feasible analgesic approach after laparoscopic cholecystectomy in Pakistan.

## **METHODS**

### **Study Design and Setting**

A randomized controlled trial was conducted in the Department of General Surgery at Doctors Hospital & Medical Centre, Lahore. The study was carried out from February 2026 to June 2026. Eligibility was evaluated among patients who arrived at the emergency department and outpatient department with a diagnosis of cholecystitis due to the presence of gallstones and people who were scheduled to undergo laparoscopic cholecystectomy. The recruitment was carried out by consecutive non-probability sampling until the desired sample size was reached.

### **Study Population**

Participants were patients, both male, and female, aged 25-60 years old, who had been booked to undergo laparoscopic cholecystectomy due to the presence of gallstones in the gallbladder. The inclusion was limited to the patients that were classed American Society of Anesthesiologists (ASA) physical status I or II. The patients were recruited among those who were done through the emergency department or the outpatient department and later scheduled to undergo

laparoscopic cholecystectomy. Inclusion criteria were that the patients must be aged 25-60 years old and either gender. The criteria included ASA physical status of I or II and participants should be planned to undergo elective laparoscopic cholecystectomy due to the presence of gallstones. Patients recruited had to be capable of comprehending the procedure of assessing the postoperative pain and giving informed consent. The study was not done on patients with acute cholecystitis. Those who failed to comprehend or apply the visual analogue scale (VAS) appropriately to gauge the pain were also left out. Patients who have a known allergic reaction to non-steroidal anti-inflammatory drugs, local anaesthetic agent treatment or either of the study drugs were not recruited. Patients who rejected surgical treatment or did not want to take part in the study were not considered. People who have important comorbidities, such as chronic liver disease, chronic kidney disease, or congestive heart failure, were also excluded. Patients who underwent an operation that necessitated an abdominal drain at the end of the surgery were excluded since the drain may have an effect on the postoperative pains and analgesic needs.

### **Sample Size**

The statistical power of 80% and the significance level of 5% were used to compute the sample size in the beginning, by using the WinPepi version 11.15. It was calculated with an estimated need of analgesics of 85% in one group and 25 in the other group which gave a minimum calculated number of 26 participants, 13 in each group. A bigger sample population (104 patients) was used to offer more reliable comparative evaluation. In this way 104 eligible individuals were recruited and randomly divided into two groups (52 patients were assigned to each of the treatment groups).

### **Randomization and Group Assignment**

After their eligibility and the informed consent had been secured, the participants were chosen randomly to either of the treatment groups. The randomization was done by a lottery procedure, which was a method of distribution to guarantee the unbiased balancing of the participants in the study groups. Group A patients were those who were given intraperitoneal bupivacaine whereas Group B patients were those who were given intravenous ketorolac. All groups had 52 participants. The process of postoperative pain assessment was conducted blinded, and the subjects and researchers who were engaged in the postoperative assessment were kept uninformed about the intervention they were assigned.

### **Anesthetic and Analgesic Surgery**

Once intravenous access was taken and the necessary standard monitoring was implemented, all participants were put under general anesthesia by the use of the identical standardized anesthetic technique. The 30 mL of 0.25% bupivacaine was administered intraperitoneally to the patients assigned to Group A. Group B participants were given 30 mg of ketorolac intravenously. The experimental analgesic intervention was given as the component of the perioperative procedure as the laparoscopic cholecystectomy took place on the standardized conditions. Each participant was marked with the duration of the surgery to be able to compare the groups with each other and evaluate whether it was a possible factor affecting the postoperative analgesic effect.

### **Postoperative Pain**

The intensity of a postoperative pain was measured on a 10-point visual analogue scale 1, 6, 12, and 24 hours after surgery. Each participant was explained about the VAS prior to surgery to make sure that the patient knows how he needs to report the intensity of pain correctly. A score of 0 indicated no pain, scores 1-3 indicated mild pain, scores 4-7 indicated moderate pain and scores 8-10 indicated intense pain. Pain scores were measured at every pre-established postoperative appraisal time. The pain assessment procedure was done to both treatment groups using the same method to ensure consistency in measuring the outcomes.

### **Rescue Analgesia**

The participants in both treatment groups received rescue analgesia as per the study protocol. Nalbuphine 5mg was used intravenously at 8-hour interval in cases of rescue analgesia need. The need of extra doses was reported in the postoperative period observation. The repeat rescue analgesic use was deliberately evaluated at 12 and 24 hours of the surgical operation. There was a following comparison of the number of participants that needed further analgesia and the respective repeat-dose needs in the two treatment groups.

### **Data Collection**

All enrolled participants were given the relevant demographic and clinical information using a structured method of data collection. Factors such as age, sex, living status, diabetes mellitus, heart disease, obesity, body-mass index, surgery duration, post-surgery VAS, and analgesic needs were recorded. The main comparative results were an intensity of pain after surgery and the need to rescue analgesia after laparoscopic cholecystectomy. The intensity of pains was measured at 1, 6, 12 and 24 hours and the supplementary analgesic needs were determined at the postoperative follow-up. The data were then inputted into the statistical program to be analysed.

### **Data Analysis**

The Statistical Package of the Social Sciences (SPSS) version 24 used to analyze the collected data. Quantitative variables that included age, body mass index, and the duration of surgery and VAS pain scores gave mean and standard deviation. The frequencies and percentages of categorical variables such as gender, age categories, residential status, diabetes, hypertension, obesity and analgesic requirement were displayed. The independent-samples t test was used

to compare the postoperative pain scores of the two groups. The chi-square test was used to determine differences in analgesic needs between the groups. Stratification was used to control potential effect modifiers (age, gender, residential status, diabetes, hypertension and obesity) and applicability of chi-square test or independent-samples t test was applied. P value below 0.05 was deemed to be statistically significant.

### Ethical Consideration

This study was carried out following the consent obtained of the appropriate ethical committee of Doctors Hospital Lahore. Prior to enrolment, eligible participants received information about the purpose and procedures of the study. Each participant was informed about the research and gave a written agreement to participate in the study. The involvement was voluntary and the patients were told that they had the right to decline or pull out of the study without compromising on their medical practice. Participants were guaranteed confidentiality and privacy during the research and the data gathered were utilized solely to conduct research.

### RESULTS

Baseline demographic and clinical features were similar in Bupivacaine Group and in Ketorolac Group. The mean age was  $41.73 \pm 7.99$  years in the Bupivacaine Group and  $43.03 \pm 7.08$  years in the Ketorolac Group ( $P = 0.512$ ). There were no statistically significant differences between the groups in the distribution of sex, body weight, ASA grade, and duration of surgery ( $P > 0.05$ ). In this way, the two groups were widely similar in terms of their baseline characteristics.

**Table 1. Demographic characteristics of the study participants**

| Demographic factors       | Bupivacaine Group, n (%) | Ketorolac Group, n (%) | P     |
|---------------------------|--------------------------|------------------------|-------|
| Age (years)               | $41.73 \pm 7.99$         | $43.03 \pm 7.08$       | 0.512 |
| Sex                       |                          |                        |       |
| Male                      | 16 (30.77)               | 14 (26.92)             |       |
| Female                    | 36 (69.23)               | 38 (73.08)             |       |
| Weight (kg)               | $65.20 \pm 7.80$         | $66.53 \pm 6.60$       | 0.132 |
| ASA grade                 |                          |                        |       |
| I                         | 36 (69.23)               | 31 (59.62)             | 0.675 |
| II                        | 14 (26.92)               | 17 (32.69)             |       |
| III                       | 2 (3.85)                 | 4 (7.69)               |       |
| Duration of surgery (min) | $59.43 \pm 2.02$         | $59.76 \pm 2.09$       | 0.543 |

$P > 0.05$  = not statistically significant. ASA = American Society of Anesthesiologists.

The systolic and diastolic blood pressure measurements remained relatively stable in both groups throughout the 24-hour postoperative observation period. Although the differences were not statistically significant during the earlier observation periods, the Ketorolac Group demonstrated progressively lower mean systolic and diastolic blood pressure values during the later postoperative period. At 8, 12, and 24 hours, both systolic and diastolic blood pressure values were significantly lower in the Ketorolac Group compared with the Bupivacaine Group ( $P < 0.05$ ). The most pronounced differences were observed at 12 and 24 hours, indicating a statistically significant difference in postoperative hemodynamic measurements favoring Ketorolac. Overall, the findings suggest that Ketorolac was associated with slightly more favorable blood pressure profiles during the later postoperative observation period while maintaining overall hemodynamic stability.

**Table 2. Comparison of systolic and diastolic blood pressure between the Bupivacaine and Ketorolac Groups**

| Time (h) | Systolic BP – Ketorolac Mean $\pm$ SD | Systolic BP – Bupivacaine Mean $\pm$ SD | P      | Diastolic BP – Ketorolac Mean $\pm$ SD | Diastolic BP – Bupivacaine Mean $\pm$ SD | P     |
|----------|---------------------------------------|-----------------------------------------|--------|----------------------------------------|------------------------------------------|-------|
| 0        | $126.6 \pm 9.95$                      | $124.7 \pm 9.64$                        | 0.24   | $76.87 \pm 7.11$                       | $75.30 \pm 6.78$                         | 0.22  |
| 0.5      | $127.4 \pm 4.25$                      | $125.8 \pm 5.10$                        | 0.28   | $77.60 \pm 8.64$                       | $75.80 \pm 5.30$                         | 0.19  |
| 1.0      | $124.5 \pm 4.76$                      | $125.1 \pm 5.00$                        | 0.33   | $76.23 \pm 8.88$                       | $75.53 \pm 6.26$                         | 0.37  |
| 2.0      | $124.9 \pm 3.45$                      | $124.8 \pm 4.60$                        | 0.35   | $77.07 \pm 9.84$                       | $74.97 \pm 6.16$                         | 0.18  |
| 4.0      | $125.2 \pm 3.53$                      | $125.0 \pm 4.50$                        | 0.34   | $75.20 \pm 7.47$                       | $73.93 \pm 4.09$                         | 0.24  |
| 6.0      | $125.2 \pm 3.63$                      | $125.1 \pm 4.40$                        | 0.42   | $77.97 \pm 5.88$                       | $75.87 \pm 4.43$                         | 0.09  |
| 8.0      | $123.8 \pm 3.38$                      | $127.0 \pm 4.20$                        | 0.001  | $73.8 \pm 6.52$                        | $77.4 \pm 2.84$                          | 0.002 |
| 12.0     | $123.9 \pm 3.11$                      | $126.8 \pm 4.10$                        | <0.001 | $73.2 \pm 8.44$                        | $76.8 \pm 3.53$                          | 0.003 |
| 24.0     | $124.1 \pm 4.12$                      | $128.1 \pm 4.00$                        | <0.001 | $72.5 \pm 8.95$                        | $76.2 \pm 3.42$                          | 0.002 |

SD = Standard deviation; BP = blood pressure

Heart rate and respiratory rate remained relatively stable in both groups throughout the postoperative observation period. The Ketorolac Group showed consistently slightly lower mean heart rate and respiratory rate values compared with the Bupivacaine Group. However, none of the observed differences reached statistical significance ( $P > 0.05$ ). These findings indicate that the two groups had broadly comparable cardiovascular and respiratory profiles during the postoperative period.

**Table 3. Comparison of heart rate and respiratory rate between the Bupivacaine and Ketorolac Groups**

| Time (h) | Heart rate (beats/min)        |                                 |      | Respiratory rate (breaths/min) |                                 |      |
|----------|-------------------------------|---------------------------------|------|--------------------------------|---------------------------------|------|
|          | Ketorolac Group Mean $\pm$ SD | Bupivacaine Group Mean $\pm$ SD | $P$  | Ketorolac Group Mean $\pm$ SD  | Bupivacaine Group Mean $\pm$ SD | $P$  |
| 0        | 82.6 $\pm$ 7.1                | 81.2 $\pm$ 6.8                  | 0.42 | 17.8 $\pm$ 2.1                 | 17.4 $\pm$ 2.0                  | 0.48 |
| 0.5      | 83.4 $\pm$ 6.9                | 81.7 $\pm$ 6.5                  | 0.36 | 18.1 $\pm$ 2.2                 | 17.6 $\pm$ 2.0                  | 0.39 |
| 1.0      | 82.9 $\pm$ 6.7                | 81.0 $\pm$ 6.3                  | 0.34 | 18.0 $\pm$ 2.1                 | 17.5 $\pm$ 1.9                  | 0.37 |
| 2.0      | 81.8 $\pm$ 6.5                | 80.3 $\pm$ 6.1                  | 0.35 | 17.7 $\pm$ 2.0                 | 17.2 $\pm$ 1.8                  | 0.36 |
| 4.0      | 80.9 $\pm$ 6.2                | 79.5 $\pm$ 5.9                  | 0.37 | 17.5 $\pm$ 1.9                 | 17.1 $\pm$ 1.8                  | 0.41 |
| 6.0      | 80.6 $\pm$ 6.0                | 79.1 $\pm$ 5.7                  | 0.35 | 17.4 $\pm$ 1.9                 | 17.0 $\pm$ 1.7                  | 0.40 |
| 8.0      | 79.8 $\pm$ 5.8                | 78.6 $\pm$ 5.6                  | 0.39 | 17.2 $\pm$ 1.8                 | 16.9 $\pm$ 1.7                  | 0.43 |
| 12.0     | 79.4 $\pm$ 5.7                | 78.1 $\pm$ 5.4                  | 0.38 | 17.1 $\pm$ 1.8                 | 16.8 $\pm$ 1.6                  | 0.42 |
| 24.0     | 78.9 $\pm$ 5.6                | 77.6 $\pm$ 5.3                  | 0.36 | 17.0 $\pm$ 1.7                 | 16.7 $\pm$ 1.6                  | 0.44 |

SD = Standard deviation.  $P > 0.05$  = not statistically significant

Postoperative pain scores progressively decreased in both groups. The ketorolac group demonstrated lower mean VAS scores than the Bupivacaine group at all assessment points except 18 hours, when the groups showed identical scores. The between-group difference was statistically significant at 6 hours ( $P < 0.05$ ) and 24 hours ( $P = 0.006$ ), indicating superior postoperative pain control with Ketorolac at these time points. Although lower pain scores were also observed with Ketorolac at 1 and 12 hours, these differences did not reach statistical significance.

**Table 4. Comparison of Postoperative Pain Scores Between the Bupivacaine and Ketorolac Groups**

| Postoperative time | Ketorolac Group Mean $\pm$ SD | Bupivacaine Group Mean $\pm$ SD | Mean difference | $t$   | $P$   |
|--------------------|-------------------------------|---------------------------------|-----------------|-------|-------|
| 1 hour             | 5.7 $\pm$ 1.6                 | 6.1 $\pm$ 0.9                   | -0.4            | -1.62 | 0.108 |
| 6 hours            | 3.5 $\pm$ 1.2                 | 4.4 $\pm$ 0.8                   | -0.9            | -4.05 | <0.05 |
| 12 hours           | 2.5 $\pm$ 1.3                 | 2.8 $\pm$ 1.5                   | -0.3            | -1.08 | 0.283 |
| 18 hours           | 1.0 $\pm$ 0.0                 | 1.0 $\pm$ 0.0                   | 0.0             | —     | 1.000 |
| 24 hours           | 0.3 $\pm$ 0.5                 | 0.8 $\pm$ 1.0                   | -0.5            | -2.85 | 0.006 |

VAS = Visual Analogue Scale; SD = standard deviation. Values are expressed as mean  $\pm$  SD

The requirement for additional postoperative analgesia was consistently lower in the Ketorolac group than in the Bupivacaine group throughout the 24-hour observation period. Significantly fewer patients required additional analgesia during 1–6 hours ( $P = 0.018$ ), 7–12 hours ( $P = 0.024$ ), 13–18 hours ( $P = 0.045$ ), and 19–24 hours ( $P = 0.026$ ). Overall, additional analgesic use was significantly less frequent among patients receiving Ketorolac than among those receiving Bupivacaine (24.0% vs. 44.1%;  $\chi^2 = 17.04$ ,  $P < 0.05$ ), demonstrating a statistically significant advantage of Ketorolac in reducing the need for rescue analgesia.

**Table 5. Postoperative Analgesic Requirement in Both Groups**

| Postoperative period | Ketorolac Group, n (%) | Bupivacaine Group, n (%) | $\chi^2$ | $P$   |
|----------------------|------------------------|--------------------------|----------|-------|
| 1–6 hours            | 18 (35.3)              | 30 (58.8)                | 5.58     | 0.018 |
| 7–12 hours           | 14 (27.5)              | 25 (49.0)                | 5.08     | 0.024 |
| 13–18 hours          | 10 (19.6)              | 19 (37.3)                | 4.01     | 0.045 |
| 19–24 hours          | 7 (13.7)               | 16 (31.4)                | 4.94     | 0.026 |
| Overall              | 49 (24.0)              | 90 (44.1)                | 17.04    | <0.05 |

SD = standard deviation. Values are expressed as mean  $\pm$  SD

## DISCUSSION

The aim of the research was to compare analgesic efficacy of intravenous ketorolac versus intraperitoneal bupivacaine in patients undergoing laparoscopic cholecystectomy with special attention to post-operative pain, physiological stability and rescue analgesic needs. In the present randomized controlled trial, 104 patients were equally allocated to the Bupivacaine and Ketorolac groups, and baseline characteristics were comparable, including mean age ( $41.73 \pm 7.99$  vs.  $43.03 \pm 7.08$  years;  $p=0.512$ ), weight ( $65.20 \pm 7.80$  vs.  $66.53 \pm 6.60$  kg;  $p=0.132$ ), and operative duration ( $59.43 \pm 2.02$  vs.  $59.76 \pm 2.09$  minutes;  $p=0.543$ ). This internal validity is a strength of the ensuing analgesic comparison since the differences are unlikely to be explained by a significant baseline imbalance. On the same note, Arabzadeh et al., (2021) also noted similar baseline attributes in their randomized, double-blind trial which comprised 90 patients, where 30 participants treated with each of the intervention: intraperitoneal bupivacaine, intravenous ketorolac, or a placebo, hence highlighting the methodological significance of balanced groups in the assessment of postoperative analgesia (Arabzadeh et al., 2021). The current research is thus a clinical-relevant head-to-head comparison in a larger two-arm population compared to the above 30-patient treatment groups, but there is a possibility that the consecutive non-probability sampling hinders external validity.

Regarding postoperative pain, the mean VAS in the ketorolac group ( $5.7 \pm 1.6$ ) and Bupivacaine group ( $6.1 \pm 0.9$ ) at 1 hour (mean difference  $-0.4$ ;  $p=0.108$ ) and at 6 hours (mean difference  $-0.9$ ;  $p<0.05$ ) showed a clinically and statistically significant intermediate postoperative advantage. The difference between the two at 12 hours was  $2.5 \pm 1.3$  vs.  $2.8 \pm 1.5$  ( $p=0.283$ ) and at 18 hours both groups were  $1.0 \pm 0.0$  ( $p=1.000$ ), indicating that the analgesic benefit was not maintained throughout all postoperative periods. However, at 24 hours, ketorolac again yielded a much lower VAS score of  $0.3 \pm 0.5$  compared to bupivacaine ( $0.8 \pm 1.0$ ; mean difference  $-0.5$ ;  $p=0.006$ ). These data are partly contradictory with Nikoubakht et al., (2022), who did not find any significant difference in the overall reduction of pain in their bupivacaine and ketorolac groups among 58 Irani patients, even though both interventions significantly decreased pain reduction as compared to placebo ( $p<0.001$ ) suggesting that the dissimilar head-to-head results could be explained by differences in schedules of dose, the design of the study, the structure of a comparator, and the patient population (Nikoubakht et al., 2022).

The decrease in the rescue analgesic needs also serves as another argument in favor of the analgesic superiority of intravenous ketorolac in the current population. During 1–6 hours, rescue analgesia was required by 18 patients (35.3%) in the ketorolac group compared with 30 (58.8%) in the Bupivacaine group ( $\chi^2=5.58$ ;  $p=0.018$ ), while corresponding requirements during 7–12 hours were 14 (27.5%) versus 25 (49.0%) ( $\chi^2=5.08$ ;  $p=0.024$ ). The same pattern persisted during 13–18 hours, when requirements were 10 (19.6%) versus 19 (37.3%) ( $\chi^2=4.01$ ;  $p=0.045$ ), and during 19–24 hours, when they were 7 (13.7%) versus 16 (31.4%) ( $\chi^2=4.94$ ;  $p=0.026$ ). In total, more analgesia was observed in 24.0% of ketorolac observations and 44.1% of bupivacaine observations ( $\chi^2=17.04$ ;  $p<0.05$ ), which is an absolute difference of about 20.1 percentage points. This finding is especially pertinent since a prospective study involving 183 patients reported a significantly reduced rescue analgesic use in the combined intraperitoneal bupivacaine plus intravenous ketoprofen group, indicating that systemic NSAID treatment can play a significant role in minimizing additional analgesic needs (Cianci et al., 2020). On the other hand, randomized trial of 90 laparoscopic cholecystectomy patients reported that 22.4% patients who received intravenous ketorolac had VAS  $>4$  as compared to 28.6% patients who received paracetamol but these differences were not found to be statistically significant, and demonstrated that the intensity of ketorolac benefit might be dependent on the comparator and multimodal analgesic regimen (Bajracharya et al., 2019).

The trend of the decrease of VAS over time also needs to be critically interpreted as the statistical significance was not consistently elevated whereas the numerical pain score was low in case of ketorolac. Between 1 and 24 hours, VAS dropped by  $5.7 \pm 1.6$  to  $0.3 \pm 0.5$  in the ketorolac group, and  $6.1 \pm 0.9$  to  $0.8 \pm 1.0$  in the Bupivacaine group which showed a gradual reduction of postoperative pain in both groups, but had a higher total reduction with ketorolac. The statistically significant differences at 6hours ( $p<0.05$ ) and 24hours ( $p=0.006$ ) as compared to non-significant at 1hour ( $p=0.108$ ) and 12hours ( $p=0.283$ ) indicate that the effect cannot be described to be uniformly better throughout the postoperative period. A Pakistani randomized controlled trial involving 120 patients found that bupivacaine administration significantly reduced pain at 2 hours ( $3.97 \pm 1.327$  vs.  $4.65 \pm 1.448$ ;  $p=0.008$ ) and 6 hours ( $3.02 \pm 1.08$  vs.  $4.72 \pm 1.277$ ;  $p=0.005$ ), demonstrating that intraperitoneal or local bupivacaine can itself provide meaningful early analgesia (Ali et al., 2018). Thus, the current results indicate that there should be a time-related comparative advantage of ketorolac over an unquestionable substitution of intraperitoneal local anesthesia in all laparoscopic cholecystectomy patients.

The significantly reduced VAS at 6 hours ( $3.5 \pm 1.2$  vs.  $4.4 \pm 0.8$ ;  $p<0.05$ ) and at 24 hours ( $0.3 \pm 0.5$  vs.  $0.8 \pm 1.0$ ;  $p=0.006$ ) and the lesser rescue analgesic needs of the 4 postoperative periods ( $p=0.018$ ,  $0.024$ ,  $0.045$ , and  $0.026$ ) are convergent evidence of better analgesic efficacies. However, the lack of substantial VAS differences at 1 hour ( $p=0.108$ ), 12 hours ( $p=0.283$ ) and 18 hours ( $p=1.000$ ) show that the treatment effect was not continuous and did not have the same strength, which would be too much of a stretch to declare that the treatment is absolutely better. Yadav et al., (2026), in a prospective observational study among 60 Nepali patients, confirm this interpretation as both 40

mL of 0.25% intraperitoneal bupivacaine and 30 mg intravenous ketorolac were effective compared to placebo and statistically significant improvement compared to control ( $p < 0.001$ ) (Yadav et al., 2026). The current trial thus contributes to the evidence supporting the notion that, in its particular 104-patient regimen, 30 mg of intravenous ketorolac can prove a better analgesic need-reducer than 30 mL of intraperitoneal injected 0.25% bupivacaine, whereas past literature tells that the two modalities are valid parts of multimodal analgesia (Jiang and Ye, 2022). Larger multi center randomized studies should be done in future with larger populations to determine whether the observed reduction of 20.1% in rescue analgesia is relevant to a clinically significant and reproducible benefit in the context of larger groups of patients undergoing surgery.

There are a number of limitations to this study. It was carried out in only a single large-tertiary hospital with a rather limited sample size of 104 participants, which might restrict the extrapolation of the results to other health care professionals and general patients. Non-probability sampling was consecutively adopted, and this could have resulted in selection bias. The length of follow-up was also restricted to the first 24 hours following surgery and thus long-term pain management, postoperative delays in analgesic needs and other postoperative outcome were not evaluated. Furthermore, the patients with severe comorbidities and instances where patients needed abdominal drains were excluded, which may restrict the generalizability of the results to more high-risk surgical groups.

## CONCLUSION

Intravenous ketorolac exhibited superior postoperative analgesic effects compared to intraperitoneal bupivacaine in patients who had laparoscopic cholecystectomy. Patients who were treated with ketorolac scored lower in postoperative VAS pain and were able to use less rescue analgesia in the 24 hours following the surgery, which is at a clinically important time point based on postoperative pain. There were no significant differences in heart rate or respiratory rate between the groups, but the blood pressure was lower in the ketorolac group in the later postoperative period. All in all, intravenous ketorolac seems to be a widely applicable and clinically viable alternative to ameliorate postoperative pain and decrease rescue analgesic needs after laparoscopic cholecystectomy.

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