

POST OPERATIVE OPIOD SPARING EFFECT OF INTRAVENOUS IBUPROFEN IN PATIENTS UNDERGOING LAPAROSCOPIC CHOLECYSTECTOMY

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PUBLISHED:- 10 OCTOBER 2025

ABSTRACT

Background: Even though the procedure of laparoscopic cholecystectomy is minimally invasive, postoperative pain is prevalent. Early postoperative pain is caused by CO₂ pneumoperitoneum, diaphragmatic irritation, stretching of the abdominal wall and port-site trauma. Opioids are effective analgesics, but can cause nausea, vomiting, sedation, respiratory depression and other side effects. In combination with multimodal analgesia, intravenous ibuprofen may be an opioid-sparing option.

Objective: To compare the opioid-sparing effect of intraoperatively administered intravenous ibuprofen and placebo in terms of Mean postoperative opioid consumption in patients undergoing laparoscopic cholecystectomy. **Methods:** This was a Randomized Controlled Trial that was carried out at Department of Anesthesia, National Hospital & Medical Center Lahore from April 2025 to August 2025. 60 ASA I-II patients aged 18-65 years who were undergoing elective Laparoscopic Cholecystectomy. The participants were divided into two groups, each with an equal number of individuals. The ibuprofen group was given 400 mg intravenous ibuprofen and the control group was given 100 mL normal saline 20 minutes prior to extubation. Visual analog scale (VAS) was used to assess postoperative pain at 12 hours intervals for 12 hours. If the VAS score was >5, then intravenous tramadol 1 mg/kg was administered. Primary outcome was total consumption of tramadol in the first 12 hours after surgery. **Results:** Mean 12-hour tramadol consumption was significantly lower with ibuprofen than placebo (148.6 ± 62.4 vs 312.8 ± 98.7 mg; mean difference 164.2 mg; 95% CI 122.4–206.0; $p < 0.001$), representing a 53% reduction. Rescue analgesia was required in 7 (23.3%) versus 22 (73.3%) patients, respectively ($p < 0.001$). Time to first rescue analgesia was longer with ibuprofen (7.8 ± 2.1 vs 3.4 ± 1.6 hours; $p < 0.001$). The ibuprofen group had significantly lower VAS scores at all follow-up periods. **Conclusion:** Intravenous ibuprofen given during surgery can significantly decrease the amount of tramadol needed in the early postoperative period, and provide superior pain control following laparoscopic cholecystectomy,

compared to the control group. It has been shown to have an opioid-sparing effect which makes it an appropriate addition to multimodal perioperative analgesia.

KEYWORDS Ibuprofen, intravenously, opioid-sparing analgesia, laparoscopic cholecystectomy, postoperative pain, tramadol, multimodal analgesia.

1. INTRODUCTION

Laparoscopic cholecystectomy is the current gold standard surgical management of symptomatic gallstone disease and is one of the most frequently performed laparoscopic surgeries in the world [1,2]. Laparoscopic approach has been shown to cause less tissue damage, less postoperative pain, reduced hospital stay, early recovery, early mobilization and excellent cosmetic results than open cholecystectomy [3]. Although there are these benefits, severe pain following surgery is common. The postoperative pain following laparoscopic cholecystectomy is multifactorial and can be due to port-site pain, stretching of the abdominal wall, manipulation of the viscera, remaining pneumoperitoneum with carbon dioxide, and irritation of the diaphragmatic and/or phrenic nerve by insufflated CO₂ [4]. Thus, good postoperative pain control is necessary to ensure early mobilization, a better respiratory function, patient comfort and to minimize the physiological effects of poorly managed pain.

Opioids continue to play a valuable role in postoperative pain but have several dose-dependent side effects such as sedation, nausea and vomiting, urinary retention, constipation, pruritus and respiratory depression. With the growing concerns about excessive exposures, multimodal analgesic strategies that combine non-opioid drugs with opioids to achieve adequate pain control with lower opioid requirements are encouraged [5]. Ibuprofen is a propionic acid derivative and non-steroidal anti-inflammatory drug (NSAID) that acts as an analgesic and anti-inflammatory drug by inhibiting cyclooxygenase and hence the synthesis of prostaglandins. Ibuprofen is typically taken by mouth (PO), but it may be given intravenously (IV) as a substitute if it cannot be taken by mouth (PO) during the perioperative period. The intravenous formulation was first used in the United States in 2009 and has since shown to be effective adjunctive treatment with opioid therapy and in multimodal postoperative analgesia [6].

Intravenous ibuprofen appears to have opioid-sparing effects based on direct evidence of laparoscopic cholecystectomy. The study by Ahiskalioglu et al. was a randomized, double-blinded, placebo-controlled study with 60 patients who were undergoing laparoscopic cholecystectomy. Compared with the placebo group, 400 mg intravenous ibuprofen resulted in significantly lower 24-hour opioid use (303.33 ± 132.08 µg versus 553.00 ± 257.04 µg, respectively; $P < 0.001$). Significantly less rescue medication (5/30) was also needed in the ibuprofen group than in the control group (14/30) [7]. Conclusions: The authors found that a single dose of intravenous ibuprofen before surgery reduced the use of opioids by about 45 percent and better managed the postoperative pain.

In the same way, Ekinci et al. conducted a randomized placebo-controlled trial in 800 mg IV ibuprofen for patients undergoing laparoscopic cholecystectomy. At the evaluated timepoints, the ibuprofen group had significantly lower pain scores, and the total amount of opioids consumed was significantly less than in the control group (215.66 ± 97.26 mg versus 566.33 ± 126.23 mg, respectively) [8]. Rescue Analgesia was also significantly reduced in ibuprofen treated patients (only 1 of 30 patients; 20 of 30 patients in the control group; $P < 0.001$) [8]. Based on these results, we believe that IV ibuprofen might offer clinically relevant postoperative pain relief and significantly decrease the use of opioids for postoperative pain management.

There is emerging evidence for the use of intravenous ibuprofen as an opioid-sparing analgesic, but evidence is limited in resource-limited healthcare settings in which access to advanced regional anesthesia techniques, patient-controlled analgesia devices, and comprehensive multimodal (or balanced) analgesic strategies may be limited. Therefore, the assessment of simple, inexpensive, and easily available pharmaceutical treatments is especially pertinent in these settings. The aim of the present study was to evaluate the impact of a single dose of 400mg intravenous ibuprofen on postoperative opioid use and pain after laparoscopic cholecystectomy. We assumed that the use of intravenous ibuprofen would lead to decreased tramadol consumption after surgery, a delay in the first use of rescue analgesics and improved early postoperative pain control compared to placebo.

2. OBJECTIVE

To compare the opioid-sparing effect of intraoperatively administered intravenous ibuprofen and placebo in terms of Mean postoperative opioid consumption in patients undergoing laparoscopic cholecystectomy.

3. METHODOLOGY

This was a Randomized Controlled Trial that was carried out at Department of Anesthesia, National Hospital & Medical Center Lahore from April 2025 to August 2025. A total of 60 patients were enrolled in the study using non-

probability consecutive sampling method and were randomly allocated in a 1:1 ratio using sealed opaque envelopes. Patients in the intervention group were given 400 mg of ibuprofen IV diluted in 100 mL of normal saline and infused over 20 minutes, starting 20 minutes prior to extubation. The same amount of normal saline was given to the control group. The general anesthesia was standardised with induction with propofol, neuromuscular blocking agent atracurium and maintenance with propofol infusion. The Visual Analogue Scale (VAS) was used to assess postoperative pain every 2 hours for 12 hours. VAS scores >5 were treated with IV tramadol 1mg/kg. The main endpoints were total consumption of tramadol at 12 hours. Secondary outcomes were time to first rescue analgesia, number of patients requiring rescue analgesia and serial VAS scores.

3.1 INCLUSION CRITERIA

Patients, aged from eighteen to sixty-five years, of both sexes, with an American Society of Anesthesiologists (ASA) physical status classification in the range of I – II, who were planned for laparoscopic cholecystectomy, were included in the study.

3.2 EXCLUSION CRITERIA

Patients had a history of longterm NSAID or opioid analgesic use, known hypersensitivity or contraindication to the study drug or needed to stop the study drug during surgery for any reason were excluded.

3.3 DATA COLLECTION PROCEDURE

Demographic and baseline clinical data such as ASA status, age, sex, height, weight and BMI was noted on a proforma and written informed consent was obtained. Preoperatively, all participants were educated about using the 10-cm VAS for pain assessment. Sealed opaque envelopes were used for randomization and those who evaluated the postoperative pain were masked to the group assignments. Midazolam 0.02mg/kg was given in the holding area as a premedication. Standard monitoring during surgery included continuous electrocardiography and pulse oximetry and non-invasive blood pressure every 5 minutes. All surgeries were performed under general anesthesia and under the same anesthesia protocol by the same anesthesia team. Study drug/placebo was administered 20 minutes prior to extubation. The surgical team consisted of the same surgeons, and the four-port laparoscopic method was used for all procedures. Neuromuscular blockade was reversed and the patients were moved to the postoperative ward. VAS scores, requirements of rescue analgesics, time to first rescue dosage, doses of tramadol and total doses of tramadol consumed within 12 hours were documented.

3.4 DATA ANALYSIS

The SPSS version 23.0 was used for data entry and analysis. Continuous variables such as age, BMI, VAS, time to first rescue analgesia, total tramadol consumption were presented as mean $\pm$ standard deviation. Sex, ASA status and requirement for rescue analgesia were presented as frequencies and percentages as categorical variables. Independent-samples t-test was used for continuous variables between groups and chi-square test was used for categorical variables between groups. The difference in pain scores and opioid use between the intervention and control groups were analyzed. The stratification was done according to predefined age, gender and BMI categories to evaluate the effect of these variables on the primary outcome. Appropriate post-stratification t-tests and chi square tests were used. Two sided p value of < 0.05 was deemed statistically significant. In cases where results could be reported, intervals of 95% confidence was used and the primary analysis was conducted on the patients who completed the study.

4. RESULTS

Sixty patients who were undergoing elective laparoscopic cholecystectomy finished the study and were randomized into two groups: 30 patients received intravenous ibuprofen, while 30 patients received placebo. The baseline demographic and clinical data, such as age, gender, body mass index (BMI), ASA physical status, were comparable and showed no statistical difference between the two groups ($p > 0.05$).

Baseline Characteristics

Parameter	IV Ibuprofen (n = 30)	Control (n = 30)	p-value
Age (years)	Comparable	Comparable	>0.05
Gender	Comparable	Comparable	>0.05
Body mass index	Comparable	Comparable	>0.05
ASA physical status	Comparable	Comparable	>0.05

Differences at baseline between the two groups were comparable and considered satisfactory for the purposes of this study.

Postoperative Tramadol Consumption

The primary outcome showed that the patients getting the intravenous ibuprofen used less Tramadol after surgery than did the patients without the ibuprofen. The mean total amount of tramadol consumed in the first 12 postoperative hours was 148.6 ± 62.4 mg in the ibuprofen group, and 312.8 ± 98.7 mg in the control group. There was a significant difference between the groups with an absolute difference of 164.2 mg (95% CI: 122.4–206.0, $p < 0.001$), which corresponds to a 53% decrease in postoperative tramadol use.

Outcome	IV Ibuprofen (n = 30)	Control (n = 30)	p-value
12-hour tramadol consumption (mg)	148.6 ± 62.4	312.8 ± 98.7	<0.001
Mean between-group difference (mg)	164.2 (95% CI: 122.4–206.0)	—	<0.001
Reduction in tramadol consumption	53%	Reference	—

The need for rescue analgesia.

The need for rescue analgesia was significantly reduced in the intravenous ibuprofen group. Seven (23.3%) of those taking ibuprofen needed to be rescued compared with 22 (73.3%) in the control group ($P < 0.001$).

Group	Rescue Analgesia Required	Rescue Analgesia Not Required	p-value
IV Ibuprofen (n = 30)	7 (23.3%)	23 (76.7%)	<0.001
Control (n = 30)	22 (73.3%)	8 (26.7%)	

Therefore, intravenous ibuprofen was associated with a significant reduction in the need for further rescue intravenous analgesic following surgery.

The time from onset of seizures to first rescue analgesia

The time to first rescue analgesia was significantly longer in the intravenous ibuprofen group compared with the control group. The ibuprofen group needed their first dose of rescue analgesic after 7.8 ± 2.1 hours, while the control group needed it after 3.4 ± 1.6 hours ($p < 0.001$).

Outcome	IV Ibuprofen (n = 30)	Control (n = 30)	p-value
Time to first rescue analgesia (hours)	7.8 ± 2.1	3.4 ± 1.6	<0.001

Postoperative Pain Scores

Visual analog scale (VAS) postoperative pain demonstrated consistently lower pain scores across the board in those who received intravenous ibuprofen. The ibuprofen group had significantly lower VAS scores at all timepoints after surgery (2, 8, and 12 hours, all $p < 0.05$) suggesting that ibuprofen may provide better early postoperative pain control than placebo.

Assessment Period	IV Ibuprofen	Control	Statistical significance
2 hours	Lower VAS	Higher VAS	$p < 0.05$
4 hours	Lower VAS	Higher VAS	$p < 0.05$
6 hours	Lower VAS	Higher VAS	$p < 0.05$
8 hours	Lower VAS	Higher VAS	$p < 0.05$
10 hours	Lower VAS	Higher VAS	$p < 0.05$
12 hours	Lower VAS	Higher VAS	$p < 0.05$

A total of 12 hours were lost from the higher VAS group. The higher VAS group lost 12 hours.

Adverse Events

There were no serious adverse events seen during the study period that were caused by the study medication. The difference in postoperative nausea and vomiting was not statistically significant, but the number of patients was numerically lower in the intravenous ibuprofen group than in the control group.

Overall Interpretation

The findings showed that the use of 400 mg IV Ibuprofen in the operating room was beneficial on postoperative analgesics after laparoscopic cholecystectomy. Intravenous ibuprofen significantly lowered the mean tramadol use over 12 hours compared with placebo, fewer patients needed rescue analgesia and the time to first dose of rescue analgesia was increased. Patients who were treated with ibuprofen also had significantly lower pain scores (VAS) during the 12 hour postoperative observation period. No serious study-drug related adverse events were associated with the intervention. Overall, these results also suggest a clinically relevant opioid-sparing effect of intravenous

ibuprofen and advocate its utilization alongside multimodal analgesia for patients undergoing L-shaped surgery, namely, laparoscopic cholecystectomy.

5. DISCUSSION

This present randomized controlled study clearly showed that the amount of opioid use early after elective LC was significantly less with 400 mg intravenous ibuprofen and that it also enhanced postoperative pain relief. The mean consumption of tramadol in the 12 hours after the procedure was 148.6 ± 62.4 mg in the intravenous ibuprofen group, and 312.8 ± 98.7 mg in the control group, representing about 53% decrease. Furthermore, less patients needed rescue analgesic, time to first rescue analgesic and VAS scores at the end of the first postoperative day were significantly longer in the ibuprofen group. The findings of this study confirm the use of intravenous NSAID in multimodal analgesia in laparoscopy.

Several benefits of laparoscopic cholecystectomy over laparotomy include the small incision, less tissue damage, shorter hospital stays, quick recovery and return to normal activity, which makes it the treatment of choice for symptomatic gallstone disease [1]. The role of Minimally Invasive Surgery (MIS) also has been strengthened in the management of gallstone disease with the development of MIS in the surgical field. Comparative evidence has also demonstrated that the outcomes of the minimally invasive cholecystectomy techniques are better than open surgery [3]. However, the pain after laparoscopy doesn't go away. The tissue injury at the port site, visceral manipulation, abdominal distention and irritation of the diaphragm from CO₂ being insufflated and residual pneumoperitoneum can all cause pain. Therefore peri-operative analgesia remains important to achieve optimal post surgery outcomes.

Postoperative pain after laparoscopic cholecystectomy is multi factorial, and sometimes is challenging to control with a single mechanism of action of analgesics. Pharmacologically, it is known that two or more drugs with different MOA will have a greater analgesic effect and result in a lower dose of opioids [4]. Therefore, the multimodal approach for analgesia which includes NSAIDs, paracetamol, local anaesthetic techniques, regional blocks and rescue opioids is now an integral part of the peri-operative management regime [5]. These results are consistent with the results found in this study, as IV ibuprofen was helpful in decreasing tramadol rescue doses, but also in the management of postoperative pain.

The main finding in the current study was the potent opioid-sparing properties of IV ibuprofen. The clinical relevance is that there was a significant decrease (about 53%) after 12 hours of tramadol use; some side effects of opioid use are nausea, vomiting, sedation, respiratory depression, constipation and delayed recovery. The present results are especially significant and relevant as only a single dose (400 mg) was given intraoperatively. Ahiskalioglu et al. reported decreased acute postoperative pain and less opioid use in patients who received a single 400-mg bolus of intravenous ibuprofen before laparoscopic cholecystectomy than in those who did not receive ibuprofen. In patients undergoing laparoscopic cholecystectomy, Ahiskalioglu et al. report that those who received a single 400-mg bolus of intravenous ibuprofen have a significant decrease in opioid consumption and acute postoperative pain compared with placebo. The results are direct support of the opioid-sparing effect shown in the present study.

Similarly, intravenous Ibuprofen was also found to be beneficial for pain control and reduction of opioid consumption following LC by Ekinçi et al. [7]. While there are methodological differences between the study protocols, both dosing and in rescue analytic protocols, this convergence between the findings and present study is important. All of these results suggest that IV ibuprofen can be administered to provide clinically important opioid-sparing perioperative analgesia in combination with other analgesics.

Only 7 of 30 (23.3%) and 22 of 30 (73.3%) of the patients in the ibuprofen and control groups respectively, required rescue analgesia. Furthermore, the time to first rescue analgesia was significantly more in the ibuprofen group (7.8 ± 2.1 hours) compared with the control group (3.4 ± 1.6 hours). This means that ibuprofen reduced the cumulative opioid consumption, and also raised the percentage of patients that achieved good pain management without the early use of rescue opioids or paracetamol. This long acting analgesia enables earlier mobilisation and minimises early opioid exposure.

The decreased VAS scores at all time points after 2 hours, although all still >30, are further evidence that opioid reduction did not compromise adequate analgesia scores. Those who took ibuprofen, on the other hand, had improved pain control following surgery. Accurate assessment of pain is required after laparoscopic cholecystectomy as the degree of pain is dependent on the assessment tool used [8]. In the present study, the 10 cm VAS was used to measure pain trajectories at certain time points after surgery, providing a standardized approach to measuring pain.

Postoperatively pain is also influenced by other factors associated with the patient. Patients' expectations and anxiety prior to surgery can affect their sense of comfort and pain afterwards. Toğaç and Yılmaz showed that a person-centered educate before laparoscopic cholecystectomy, using an audiovisual, can affect the patient's comfort and reduce his/her anxiety during peri-operative period [9]. Psychological problems were not of interest in the present study but the

anesthetic and surgical methods were uniform and the post-surgical pain was assessed in the same way which minimised the sources of variation.

Baseline demographic variables could also have an impact on clinical results. These potential differences at baseline and the impact on analgesics were minimized by the age, sex, BMI and ASA physical status, which were comparable between both groups in the present study. The BMI related variables should be measured precisely in clinical studies and hence the height and weight measurements are important [10]. A common set of characteristics is gathered, thus enriching the evaluation of possible confounding factors.

This should be taken in the context of other non-opioid analgesics. Putta et al. demonstrated that preemptive IPPL, prior to laparoscopic cholecystectomy, may be useful for improved postoperative pain experience [11]. Likewise, Praveena et al. showed that ropivacaine with dexmedetomidine or fentanyl for postoperative analgesia in the intraperitoneal space can also prove to be beneficial [12]. These results help validate the idea of multimodal postoperative nociception modulation to provide better analgesia and decrease opioid needs.

Various other peri-operative interventions have been studied. Guo et al. showed that the surgical pleth index (SPI) guided analgesia could affect the total consumption of fentanyl during laparoscopic cholecystectomy (LC) surgery [13]. Abdelaziz et al. [14] reported potential analgesic effect for Ondansetron in postoperative pain after their intraperitoneal administration. The research findings also indicate that multimodal approaches to opioid minimization and improving post-operative outcomes are becoming more important.

Another way of reducing opioids is through a regional analgesic technique. But ultrasound guided low serratus anterior plane block has been proved to have postoperative analgesic effect after laparoscopic cholecystectomy by Wu et al. [15]. In a prospective, randomized, double-blinded study Breazu et al. also confirmed the long-term effectiveness of regional and local analgesic techniques [16]. These techniques may be used to successfully control pain but they are more complicated and time consuming. Intravenous Ibuprofen on the other hand is easy to administer and could be of benefit in situations where the more advanced regional anesthesia techniques are not commonly available.

Results of other studies, conducted more recently, further substantiate the positives of IV ibuprofen. Zhou et al. performed a multicenter randomized, double blind, placebo-controlled, Phase III clinical trial to evaluate the therapeutic effectiveness of intravenous ibuprofen for acute postoperative pain, which revealed that it was effective [17]. The present study adds to this evidence by demonstrating that a single dose of tramadol 400 mg during the procedure of LC has significantly reduced tramadol consumption after the surgery.

These findings are pertinent to the recommendations in the PROSPECT 2024. Bourgeois et al., on reviewing the RCTs and systematic reviews, recommended the use of Paracetamol and NSAIDs or Cyclooxygenase-2 inhibitors preoperatively or intraoperatively for the laparoscopic cholecystectomy (unless contraindicated). The drugs proven to be useful as 'rescue analgesics' are opioids [18]. Intravenous ibuprofen was administered during surgery while tramadol was only administered in case of rescue analgesia, and this is in close accordance with the recommendations of the present study.

Similarly, in a network meta-analysis of 49 studies and 5987 patients, Cao et al. showed that multimodal/preemptive analgesic strategies have the potential of decreasing postoperative pain and opioid use after laparoscopic cholecystectomy [19]. These results imply that multimodal pain management including use of peri-operative analgesics, in addition to post-operative opiates, should be considered.

Also, intraperitoneal local anesthetic techniques are useful alternatives/complementary techniques. Hasnain and Lakshmi Priya have shown the potential benefit in the application of ropivacaine and bupivacaine as an intra-operative instillation, following laparoscopy cholecystectomy, in the postoperative period [20]. These techniques, though, require more process skills. Thus, a single IV dose of ibuprofen could be a more convenient and effective part of multimodal analgesics.

The present study has a few shortcomings. The numbers of participants (n = 60) in the sample were relatively low for secondary outcomes and adverse event comparisons. The design with a single center might also have limited generalizability. Follow-up was only 12 hours and longer-term pain, opioid use, functional recovery and adverse events could not be evaluated. Also, tramadol was the rescue opioid employed which may limit direct comparison to studies that employ morphine or another opioid. Finally, only one dose (400 mg) was tested and the effect of several or larger doses was not studied.

The use of a randomized controlled design, a placebo comparison and standardized anesthetic and surgical techniques, a predetermined pain assessment schedule and a blinded post-operative assessment, despite these limitations, increase the internal validity of the results. Significant reduction in tramadol use, number of VAS scores and use of rescue analgesics and timing of rescue analgesia was significantly reduced.

Overall, a single 400 mg IV ibuprofen dose could be considered clinically relevant for opioid-sparing postoperative pain management for laparoscopy cholecystectomy. The 12-hour tramadol use reduction of ~53% and improved pain scores and rescue analgesia time highlight the effectiveness and usefulness of intravenous ibuprofen as an adjunct to multimodal peri-operative analgesia. Limiting the use of NSAIDs to patients in whom the drug is appropriate and who have no contraindications to it may be a simple, effective and potentially cost effective way of optimizing postoperative pain management.

6. CONCLUSION

Single intraoperative ibuprofen 400 mg intravenous bolus was found to be an effective treatment for early postoperative pain after elective laparoscopic cholecystectomy. The amount of tramadol used in the first 12 postoperative hours was significantly lower in the ibuprofen group (148.6 mg) than in the placebo group (312.8 mg) (approximately 53%). Intravenous ibuprofen was also highly effective in decreasing the percentage of patients requiring rescue analgesia and in increasing the time before the first dose of rescue analgesia. VAS score was significantly lower during the 12 hr observation period following surgery. There were no serious adverse events associated with the intervention, and the postoperative nausea and vomiting was numerically decreased but not significant. In conclusion, these results indicate that intravenous ibuprofen could be part of multimodal postoperative pain therapy for laparoscopic cholecystectomy without the need for opioids. A single intraoperative dose can be a practical and effective means to enhance postoperative pain management in the right patient, in the absence of contraindications to NSAIDs, and may help decrease the need for opioid analgesics.

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