The Efficacy of Ibuprofen for Postoperative Pain Following Laparoscopic Cholecystectomy: A Randomised Controlled Study

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ABSTRACT

Objective: To compare the effects of intravenous (IV) ibuprofen and acetaminophen on pain perception and opioid consumption following laparoscopic cholecystectomy.

Study Design: Randomised-controlled study.

Place and Duration of the Study: Department of Anaesthesiology and Reanimation, Giresun University Training and Research Hospital, Giresun, Turkiye, from February to April 2024.

Methodology: The patients undergoing laparoscopic cholecystectomy were randomised into two groups: Group I (n = 35; administered 800 mg of ibuprofen) and Group A (n = 36; administered 1000 mg of acetaminophen). Demographic data, including gender, age, American Society of Anaesthesiologists (ASA) classification, body mass index (BMI), duration of anaesthesia and surgery, incidence of postoperative nausea and vomiting (PONV), length of hospital stay (LOS), visual analogue scale (VAS) scores, and opioid consumption, were recorded. To compare the two independent groups, the Student's t-test was used for parametric data, whereas the Mann-Whitney U-test was employed for non-parametric variables. A p-value <0.05 was considered statistically significant.

Results: Demographic data such as age, gender, BMI, and ASA scores were similar in both groups. The pain scores at recovery, 12, and 24 hours were lower in Group I (p <0.05). However, the VAS scores were similar at 2 and 6 (p >0.05). While the peak VAS scores were similar between the groups, the VAS scores at discharge were found to be significantly lower in Group I (p= 0.271, 0.001 respectively). In terms of total tramadol consumption, 24-hour consumption was lower in Group I (100 [0-300] and 0 [0-300] mg, respectively; p = 0.001).

Conclusion: The present study suggests that the IV administration of ibuprofen results in lower pain scores and reduced opioid consumption compared with the administration of acetaminophen postoperatively in patients undergoing laparoscopic cholecystectomy.

Key Words: *Intravenous ibuprofen, Acetaminophen, Laparoscopic cholecystectomy, Postoperative pain control, Analgesia, Anti-inflammatory agents.*

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INTRODUCTION

Cholecystectomy is generally performed using a laparoscopic technique and is known to be the most common abdominal surgery in developed countries.[1] In a study conducted by Soper *et al.* in 1992, which included 618 patients who successfully underwent laparoscopic cholecystectomy procedures, this method was defined as the gold standard.[2]

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Postoperative pain is an undesirable condition, and it has been reported that 80% of patients undergoing any surgical procedure complain of acute pain and that 75% of such patients report moderate-to-extreme pain.[3] Ineffectively controlled postoperative pain may result in postoperative complications, morbidity, and prolonged hospitalisation. Factors affecting the development of pain following laparoscopic surgery include phrenic nerve irritation caused by port-site incisions, CO_2 insufflation, trauma caused by the removal of gallbladder, and patients' sociocultural status.[4]

With respect to multimodal analgesia, including not only opioids but also non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen is strongly recommended for the effective control of postoperative pain.[5,6] In utilising multimodal analgesia, the aim is to reduce the opioid usage and, consequently, adverse events such as nausea, respiratory depression, vomiting, and sedation.[7]

Both acetaminophen and NSAIDs have analgesic and antipyretic effects; however, acetaminophen does not have anti-inflammatory effects.[8] Ibuprofen is a propionic acid with analgesic and anti-inflammatory effects and has a long history of use as an oral analgesic. Of note, ibuprofen has been used intravenously for more than ten years following the approval by the United States Food and Drug Administration in 2009. It is recommended that patients be given an intravenous dose of 400-800 mg of ibuprofen every 6 hours, with an upper limit of 3200 mg per day.[9]

This study aimed to determine the difference between ibuprofen and acetaminophen for postoperative pain at different time points and to examine the effectiveness of ibuprofen (800 mg, single dose) compared to acetaminophen in reducing postoperative opioid consumption.

METHODOLOGY

The effect size for the comparison of opioid consumption at 24 hours postoperatively was calculated to be 0.68. Assuming a statistical power of 90% and a significance level of 5%, the required sample size was determined to be 35 to 36 patients per group, yielding a total of 71 participants.

This study was approved by the Ethical Committee of Giresun Training and Research Hospital, Giresun, Turkiye (Approval No. KAEK-230; dated: 06/11/2023), and registered in the clinical trials database (Clinical Trials ID: NCT06127394). Informed consent was obtained from all included patients. The CONSORT guidelines were followed for the study.

The present study included patients aged between 18 and 65 years, American Society of Anaesthesiologists (ASA) grade I-II, scheduled for laparoscopic cholecystectomy from February to April 2024. Patients with a history of allergies or hypersensitivity to the aforementioned agents, renal, hepatic, or gastrointestinal disease, significant cognitive impairment, recent use of long-term nonsteroidal anti-inflammatory or opioids, oral anticoagulant use or known bleeding disorders, diabetes or other neuropathic diseases, and those who were pregnant or breastfeeding were excluded. Demographic data, ASA score, duration of surgery and anaesthesia (in minutes), length of hospitalisation (in hours) were recorded.

Randomisation of the patients was performed according to computer-generated random number tables, and allocation was performed with the envelope technique. The researcher who recorded patients' demographic and follow-up data was unaware of the type of medicine being administered.

Patients were informed of the study protocol and the visual analogue pain scale (VAS) one day prior to surgery. The ibuprofen group (Group I; n = 35) was administered 800 mg of ibuprofen, and the acetaminophen group (Group A; n = 36) received 1,000 mg of acetaminophen intravenously in 100 mL saline at the end of the surgery. All procedures were performed with the same anaesthesiology and surgery team. General anaesthesia was induced with 2-3 mg/kg of propofol, 0.6 mg/kg of IV rocuronium, and 2 µg/kg of fentanyl in both groups. Maintenance anaesthesia was established with 2% sevoflurane in an air-oxygen mixture.

During surgery, a 20% increase in patients' heart rate and mean arterial pressure compared to the baseline was interpreted as pain, and remifentanil was administered accordingly. Subsequently, 2 mg/kg of sugammadex was administered to antagonise the effects of rocuronium. Patients were extubated in the operating room and then taken to the recovery room. During the postoperative period, all patients continued to receive the routine application of acetaminophen at 8-hour intervals, and tramadol was given to those with a VAS score above 4, which is a standard practice in the general surgery ward.

Patients who reported a VAS score greater than 4 in the recovery room were given 100 mg of tramadol as rescue analgesia. Following surgery, all patients received acetaminophen every 8 hours during their stay in the ward. A blinded investigator, unaware of the specific medications administered, evaluated postoperative pain levels and monitored for adverse events. The pain intensity was evaluated by using the VAS, where 0 indicated no pain and 10 represented the worst imaginable pain. Any patient scoring above 4 on the VAS received 100 mg of tramadol. Pain scores along with vital signs were documented at 1, 2, 6, 12, and 24 hours after surgery. Additionally, the occurrence of postoperative nausea and vomiting (PONV) was tracked throughout the first 24 hours postoperatively.

Analyses were performed by using SPSS for Windows, version 23.0 (SPSS Inc., Chicago, IL, USA). The Shapiro–Wilk test was used for testing the assumption of normality in qualitative variables. Categorical variables were analysed using Pearson's Chi-square test or Fisher's exact test, depending on data characteristics and expected frequencies. To compare two independent groups, the Student's t-test was used for parametric data, whereas the Mann-Whitney U test was employed for non-parametric variables. A p-value <0.05 was considered statistically significant.

RESULTS

Three patients from Group A and two from Group I were excluded from the study due to conversion to open surgery or the need for intensive care unit (ICU) admission (Figure 1). Ultimately, 71 patients were included in the final analysis, with 35 receiving ibuprofen and 36 receiving acetaminophen.

Demographic variables, including age, gender, body mass index (BMI), and ASA scores, showed no statistically significant difference between the groups. Duration of anaesthesia or surgery was similar in the study ($p > 0.05$; Table I).

Mean arterial pressure (MAP) and heart rate were consistent across all follow-up intervals in both groups. However, peripheral oxygen saturation (SpO_2) was significantly higher in Group I at all-time points ($p < 0.05$).

Table I: Demographic characteristics of the patients.

Variables	Group A (n = 36)	Group I (n = 35)	p-values
Age (years), mean ± SD	53.97 ± 10.74	53.91 ± 12.14	0.708*
Gender (M/F)	28/8	24/11	0.43$^{\alpha}$
BMI (kg/m^2), median (min-max)	28.04 (21.67-34.89)	27.55 (21.3-37.39)	0.913**
ASA (I/II)	12/22	6/28	0.243$^{\beta}$
Duration of anaesthesia (min), median (min-max)	70 (50-200)	75 (45-130)	0.443**
Duration of surgery (min), median (min-max)	60 (40-185)	65 (30-120)	0.426**
PONV (Y/N)	7/29	4/31	0.514$^{\alpha}$
LOS (hours), median (min-max)	41 (20-101)	44 (19-51)	0.737**

*SD: Standard deviation; ASA, American Society of Anesthesiologists; LOS: Length of stay; PONV: Postoperative nausea and vomiting; BMI: Body mass index; $^{\alpha}$Pearson Chi-square; $^{\beta}$Fisher's exact test; *Student's t-test; **Mann-Whitney U test; p <0.05 is defined as statistically significant.*

Table II: Comparison of VAS values between Group A and Group I.

Variables	Group A (n = 36) Median (min-max)	Group I (n = 35) Median (min-max)	p-values
VAS at recovery	4 (1-9)	3 (2-6)	**0.002***
VAS at 2^{nd} hours	5 (3-7)	5 (3-6)	0.722
VAS at 6^{th} hours	3.5 (2-7)	3 (2-6)	0.355
VAS at 12^{th} hours	3 (0-5)	2 (0-4)	**<0.001***
VAS at 24^{th} hours	2 (0-4)	0 (0-3)	**0.008***
Peak VAS (0-24 hours)	5 (3-9)	5 (3-6)	0.271*
VAS at discharge	1 (0-3)	0 (0-2)	**<0.001***
Additional tramadol needed within 24 hours following surgery (mg)	100 (0-300)	0 (0-300)	**<0.001***

*Values are expressed as median (min-max); VAS: Visual analogue scale. *Mann-Whitney U test. p <0.05 is defined as statistically significant. The bold values indicate statistical significance.*

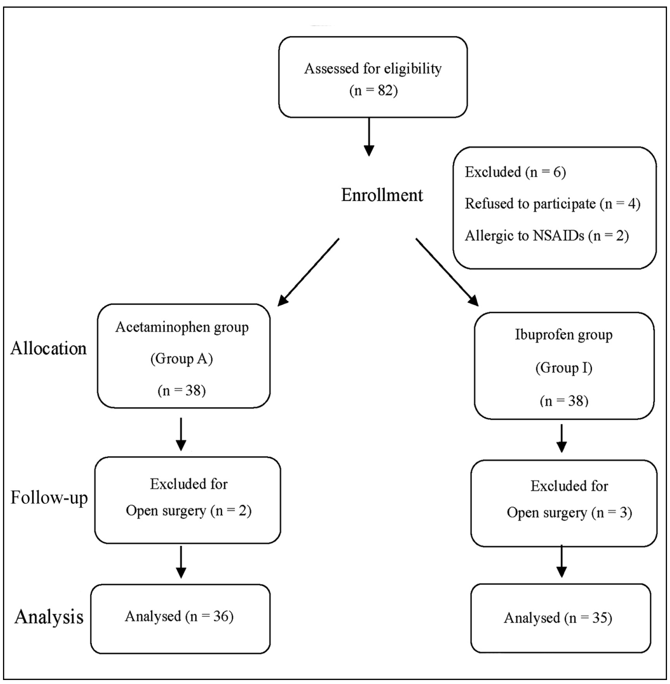

Figure 1: Patient flowchart.

VAS pain scores recorded in the recovery room, as well as at the 12^{th} and 24^{th} postoperative hours, were significantly lower in Group I (p <0.05). No significant difference was found between the groups at the 2^{nd} and 6^{th} hours postoperatively (p >0.05, Table II). Although peak postoperative pain scores were comparable, discharge VAS scores were significantly lower in Group I (p = 0.271 and 0.001, respectively).

Regarding analgesic consumption, total tramadol use over the first 24 hours was significantly lower in Group I [(0 (0-300) mg; p = 0.001, Table II)].

DISCUSSION

The study demonstrated that ibuprofen had similar pain scores in comparison to acetaminophen in the first six hours following surgery. However, the use of ibuprofen reduced patients' pain scores at 12 and 24 hours. Opioid consumption was also significantly lower on the first postoperative day in Group A. The incidence of PONV was similar in both groups.

Postoperative pain remains a common issue, with nearly three-quarters of patients reporting moderate to severe intensity within the initial 24-hour period post-surgery.[6] Pain can result in hypertension, myocardial ischaemia, respiratory and renal complications, delays in patient mobilisation, and resultantly, increased mortality. Moreover, postoperative pain can increase the length of hospitalisation and treatment costs. Although there is extensive information about the physiology and pharmacology of postoperative pain, a significant majority of patients still complain of moderate-to-severe pain.

At present, the use of narcotic analgesics is one mainstay of treatment by acting on the central nervous system without having an anti-inflammatory effect. If the inflammatory response can be eliminated, opioid use may be reduced. Ibuprofen, a commonly used NSAID, controls pain by interrupting the inflammatory process. Therefore, the use of different mechanisms can help to reduce the required drug dose and thus the impact of side effects.[10]

Well-controlled postoperative pain aims to facilitate the patient's functional recovery and accelerate the return to daily activities. Effective postoperative pain management increases patient comfort, enables early mobilisation, reduces the length of hospitalisation, and therefore decreases associated hospital costs. Lundy introduced balanced anaesthesia in 1926,[11] suggesting that the balanced administration of different agents and the application of various techniques could reduce the impact of complications arising from the use of a single anaesthetic agent. In 1993, Kehlet and Dahl described multimodal analgesia (MMA) in their study and recommended a multimodal approach for postoperative pain.[7] The aim of multimodal analgesia is to provide effective and sufficient analgesia for the patient while minimising the impact of side effects associated with drug administrations, especially opioids.

Owing to negative side effects, the popularity of opioid-based postoperative pain management has decreased among surgeons and anaesthesiologists. Despite this, it still remains a cornerstone of pain management. Extended hospitalisations and the potential for addiction reduce the appeal of opioid use in pain management. In contrast, NSAIDs have emerged as alternative agents, which represent a fundamental element of multimodal analgesia strategies in the management of postoperative pain.[4]

NSAIDs suppress the inflammatory response by inhibiting prostaglandin synthesis. COX-1 generates prostaglandins involved in the gastrointestinal mucosa; COX-2, in contrast, is induced to mediate pain and inflammation. Thus, while COX-2 inhibition contributes to pain control, COX-1 inhibition can cause gastrointestinal symptoms. NSAIDs contribute to gastrointestinal mucosal and operative bleeding as a result of COX-1 inhibition. In a meta-analysis published in 2014, the authors stated that the use of NSAIDs did not demonstrate an increased risk of bleeding.[12] In a study conducted on children undergoing tonsillectomy, a higher rate of severe bleeding in children receiving ibuprofen could not be excluded.[13] In a meta-analysis including 74 studies and 151,031 patients, the results demonstrated that NSAIDs were unlikely to be the cause of postoperative bleeding complications.[14]

Following the approval of IV ibuprofen by the FDA, the authors of many studies have demonstrated that it can aid in controlling pain and reducing opioid consumption up to 24 hours postoperatively.[15-19] Kim *et al*. reported results of the six studies comparing IV ibuprofen with a placebo in patients undergoing septorhinoplasty, laparoscopic cholecystectomy, pancreaticoduodenectomy, and thyroidectomy.[20] Despite there being heterogeneity in their meta-analyses and the limited number of included studies, they were able to demonstrate that ibuprofen reduces postoperative pain scores and opioid consumption.

Laparoscopic surgery, which causes less trauma, is superior to open surgery in terms of pain development; however, pain remains quite common following laparoscopic surgery. Moreover, in the first few postoperative hours, the level of pain reported by patients can even be similar to that reported following open surgery.[21] The combination of anaesthetic blocks with analgesic drugs as a part of multimodal analgesia is recommended to manage pain. Truncal blocks are commonly used for laparoscopic-guided cholecystectomy and many forms of abdominal surgery.[22] These blocks may be combined with opioid and non-opioid analgesic drugs to achieve targeted pain control.

In 2015, Moore *et al*. published a meta-analysis comparing the oral forms of ibuprofen and acetaminophen for the management of various painful conditions, such as acute postoperative pain, dysmenorrhoea, headache, osteoarthritis, back pain, cancer, and paediatric pain. They noted that neither agent is effective for every patient and that both are necessary in pain management. However, they also highlighted in their study that ibuprofen showed superiority in many painful conditions, suggesting that the role of acetaminophen as a first-line analgesic should be reconsidered.[23] In the present study, the superiority of ibuprofen in pain control within the first six hours following surgery could not be demonstrated; however, ibuprofen was significantly more effective than acetaminophen for pain control after 12 hours.

Intravenous (IV) ibuprofen was approved by the U.S. Food and Drug Administration (FDA) in 2009 for the treatment of mild-to-moderate pain and fever in adults. In 2015, its indications were expanded to include paediatric patients aged six months and older. IV ibuprofen is available in 400 mg and 800 mg formulations, with a recommended dosing interval of every 6 to 8 hours.[9]

The efficacy of IV ibuprofen in managing postoperative pain has been explored in various surgical settings, including laparoscopic procedures.[15-20] In a study conducted by Ekinci *et al*., ninety patients undergoing laparoscopic cholecystectomy were evaluated, and it was found that preoperative administration of 800 mg IV ibuprofen significantly reduced both postoperative pain scores and opioid requirements compared with acetaminophen.[15] Similarly, Ahiskalioglu *et al*. demonstrated that a single preoperative dose of 400 mg IV ibuprofen resulted in lower postoperative pain scores and reduced opioid consumption in a cohort of 60 patients undergoing the same procedure.[1]

In the current study, IV analgesics were administered at the conclusion of surgery. The postoperative pain outcomes observed were consistent with those reported in previous research, further supporting the effectiveness of IV ibuprofen in this context.

Ciftci *et al*. compared 800 mg of ibuprofen with 1,000 mg of acetaminophen in their study on patients undergoing laparoscopic sleeve gastrectomy cases. They showed that the VAS values for both ibuprofen and acetaminophen within the first 24 hours were lower than those of the Control group and noted a reduction in opioid consumption. Ibuprofen administration was associated with lower pain scores than acetaminophen administration during the first two post-operative hours.[6] In the present study, the VAS scores at 6 hours postoperatively were similar between both groups; however, at 12 and 24 hours postoperatively, as well as at discharge, ibuprofen administration resulted in lower VAS scores.

Gurkan *et al*. administered IV ibuprofen 30 minutes before the end of total hip replacement surgery and four times within the first 24 hours. They demonstrated that the 800 mg of IV ibuprofen every six hours helped reduce both pain scores and morphine consumption during the post-operative period.[16] Similarly, Mohammadian Erdi *et al*. administered ibuprofen (800 mg) and acetaminophen (1,000mg) intraoperatively, continuing administration at eight and 16 hours post-operatively. In their study involving patients undergoing laparoscopic cholecystectomies, they found ibuprofen to be superior to acetaminophen but noted that acetaminophen remains a suitable alternative for postoperative pain management.[17] In the present study, a single dose of ibuprofen (800 mg) at the end of surgery was administered, and postoperative pain was managed with acetaminophen and tramadol on the ward. Although the pain scores were similar in the first six hours postoperatively, there was a significant decrease in pain scores in Group I compared to Group A between 12 and 24 hours.

With the use of NSAIDs, concerns arise regarding side effects, such as gastric discomfort and bleeding. In a randomised controlled study investigating the side effects associated with ibuprofen and acetaminophen use, rates of sedation and PONV were found to be similar in the ibuprofen and acetaminophen groups.[17] In the present study, patients who showed any gastrointestinal symptoms were excluded, and the frequency of PONV was similar between the two groups.

The study has several limitations. Primarily, a single 800 mg dose of IV ibuprofen was administered. While the aim of the study was to assess the efficacy of a one-time dose for post-operative pain control, a more comprehensive evaluation could have been achieved by including an additional study arm receiving repeated doses at 6- to 8-hour intervals during the postoperative period. Secondly, the assessment of adverse events was limited to the incidence of PONV. Other common opioid-related side effects, such as pruritus, sedation, constipation, dyspepsia, and urinary retention, were not documented. Therefore, they should be considered in future research.

CONCLUSION

Compared with acetaminophen, a single-dose of IV ibuprofen was associated with significantly greater reductions in post-operative pain intensity and opioid consumption within 24 hours of following laparoscopic cholecystectomy. These findings suggest that IV ibuprofen may offer a more potent option for postoperative pain management in this patient population. Nonetheless, further studies involving different dosing regimens and various surgical procedures are warranted to better define the role of IV ibuprofen in post-operative analgesia.

ETHICAL APPROVAL:
Ethics approval was obtained from the Ethics Committee of Giresun Training and Research Hospital, Giresun, Turkiye (Decision No. KAEK-230; dated: 15.11.2023).

PATIENTS' CONSENT:
Written informed consent was obtained from all included patients.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
AB: Conception, design of the study, acquisition, data analysis, interpretation, and supervision.
FAB, IT: Data acquisition, analysis, and interpretation.
All authors approved the final version of the manuscript to be published.

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