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Original Article

Efficacy of intravenous ibuprofen and acetaminophen on postoperative pain and tramadol consumption in laparoscopic cholecystectomy: prospective, randomized, double-blinded clinical trial

Laparoskopik kolesistektomide intravenöz ibuprofen ve asetaminofenin postoperatif ağrı ve tramadol tüketimi üzerine etkinliği: prospektif, randomize, çift kör klinik çalışma

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Abstract

Aim: Many techniques, including multimodal analgesia, have been used to manage postoperative pain after laparoscopic cholecystectomy (LC). Although the number of studies using intravenous (IV) ibuprofen is still limited, ibuprofen has been shown to have a potential role in managing postoperative pain. The primary outcome of this study is to evaluate and compare the impact of IV forms of ibuprofen and acetaminophen on 24-hour postoperative opioid consumption and pain management in patients undergoing LC. The second outcome of the study is to evaluate the impact of ibuprofen and acetaminophen on opioid-related adverse events (ORAE).

Materials and Methods: This study was a prospective, randomized, double-blind clinical trial. Following ethical committee approval, 70 patients aged 18 to 65, American Society of Anesthesiology (ASA) score I- II, and those scheduled for LC were enrolled in the study. Patients were randomly divided into two groups. The control group (n=35) received 800 mg IV ibuprofen (group I) in 100 mL saline during surgery, while the acetaminophen group (n=35) received 1000 mg (group A). In the postoperative period, all patients received a patient-controlled analgesia (PCA) device with tramadol. The PCA device was set to a bolus dose of 10 mg and had a lockout time of 15 minutes. A blinded pain nurse assessed postoperative analgesia at the 1st, 2nd, 4th, 6th, 12th, and 24th hours using a numerical rating scale (NRS). The incidence of postoperative nausea and vomiting (PONV), total tramadol consumption, and the need for additional analgesics during the 24-hour postoperative period were recorded.

Results: Seventy patients who underwent LC participated in this study. The use of analgesic medications was statistically lower in group I than in the other group A. NRS scores between the IV ibuprofen and acetaminophen groups were statistically similar at the 1st, 2nd, 4th, 6th, 12th, and 24th hours postoperatively ($P>0.05$). 24-hour opioid consumption was statistically significantly higher in group A than in group I ($P<0.05$). PONV rates were similar in the ibuprofen and acetaminophen groups ($P>0.05$). ORAEs were similar between groups.

Conclusion: Ibuprofen as part of tramadol-based multimodal analgesia reduced tramadol consumption compared to acetaminophen during the first 24 hours postoperatively following elective LC surgery. The IV ibuprofen-tramadol combination appeared superior to an acetaminophen-tramadol combination. ORAEs were similar in both groups.

Keywords: Ibuprofen, acetaminophen, postoperative pain, analgesia, laparoscopic cholecystectomy

Abbreviations: ASA= American Society of Anesthesiologists, IV= intravenous, NRS= Numerical rating scale, PCA= patient-controlled analgesia, PONV= postoperative nausea and vomiting syndrome, ORAE= opioid-related adverse events

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Öz

Amaç: Laparoskopik kolesistektomi (LC) sonrası postoperatif ağrıyı yönetmek için multimodal analjezi de dahil olmak üzere birçok teknik kullanılmıştır. İntravenöz (IV) ibuprofen kullanan çalışmaların sayısı hala sınırlı olsa da, ibuprofenin postoperatif ağrı yönetiminde potansiyel bir rolü olduğu gösterilmiştir. Bu çalışmanın birincil amacı, LC uygulanan hastalarda IV ibuprofen ve asetaminofen formlarının postoperatif 24 saatlik opioid tüketimi ve ağrı yönetimi üzerindeki etkisini değerlendirmek ve karşılaştırmaktır. Çalışmanın ikincil amacı, ibuprofen ve asetaminofenin opioidle ilişkili advers olaylar (ORAE) üzerindeki etkisini değerlendirmektir.

Gereç ve Yöntemler: Bu çalışma prospektif, randomize, çift kör bir klinik çalışmaydı. Etik kurul onayı alındıktan sonra yaşları 18 ile 65 arasında değişen, American Society of Anesthesiology (ASA) skoru I-II olan ve LC planlanan 70 hasta çalışmaya alındı. Hastalar rastgele iki gruba ayrıldı. Ameliyat sırasında kontrol grubu (n=35) 100 mL salin içinde 800 mg IV ibuprofen (grup I), asetaminofen grubu (n=35) 1000 mg (grup A) aldı. Postoperatif dönemde tüm hastalara tramadollü hasta kontrollü analjezi (HKA) cihazı verildi. PCA cihazı, 10 mg bolus dozuna ayarlandı ve 15 dakikalık bir kilitleme süresine sahipti. Kör bir ağrı hemşiresi, postoperatif analjeziyi sayısal derecelendirme ölçeği (NRS) kullanarak 1, 2, 4, 6, 12 ve 24. saatlerde değerlendirdi. Postoperatif 24 saatlik dönemde postoperatif bulantı ve kusma insidansı, toplam tramadol tüketimi ve ek analjezik ihtiyacı kaydedildi.

Bulgular: Bu çalışmaya LC uygulanan 70 hasta katıldı. Analjezik ilaç kullanımı grup I'de grup A'ya göre istatistiksel olarak daha düşüktü. İV ibuprofen ve asetaminofen grupları arasında NRS skorları postoperatif 1, 2, 4, 6, 12 ve 24. saatlerde istatistiksel olarak benzerdi (P>0.05) . 24 saatlik opioid tüketimi grup A'da grup I'e göre istatistiksel olarak anlamlı derecede yüksekti (P<0.05). POBK oranları ibuprofen ve asetaminofen gruplarında benzerdi (P>0.05). ORAE'ler gruplar arasında benzerdi.

Sonuç: Tramadol bazlı multimodal analjezinin bir parçası olarak ibuprofen, elektif LC cerrahisini takiben postoperatif ilk 24 saat boyunca asetaminofene kıyasla tramadol tüketimini azaltmıştır. IV ibuprofen-tramadol kombinasyonu, asetaminofen-tramadol kombinasyonundan avantajlı olarak izlendi. ORAE'ler her iki grupta da benzerdi.

Anahtar kelimeler: İbuprofen, asetaminofen, postoperatif ağrı, analjezi, laparoskopik kolesistektomi

Introduction

Laparoscopic cholecystectomy (LC) is the most common abdominal surgery in developed countries. It is the gold standard surgical technique for gallstone disease [1]. This procedure has less postoperative pain, better cosmetic outcomes, faster healing, and earlier mobilization [2].

Several factors are involved in the development of pain after LC. This pain is quite complex and is generally considered visceral. Factors involved in developing this pain include irritation of the phrenic nerve due to the insufflation of CO_2 into the abdominal cavity, distension of the abdomen, incisions at the ports, and trauma associated with removing factors [3].

Postoperative pain is an acute sensation associated with an inflammatory process associated with surgical trauma that decreases as the tissue heals. Successful postoperative analgesia is known to prevent most pain-related effects on the patient, such as the inability to breathe comfortably, increased workload on the cardiovascular system, thromboembolic events with delayed mobilization, and increased stress response with activation [4,5].

Opioids play a crucial role in pain management by acting on the central nervous system, but they cannot block the inflammatory aspect of pain [6]. Eliminating the inflammatory response can reduce the need for opioids and strengthen the control of postoperative processes [7,8]. Opioid use has been associated with severe adverse effects, including respiratory depression, postoperative pruritus, urinary retention, gastrointestinal events, sedation, and allergic reactions [9]. Combining nonsteroidal anti-inflammatory drugs (NSAIDs) with opioids may also reduce adverse effects and the required opioid dose [10-13]. The ASA Task Force on Acute Pain Management reports that opioids in combination with NSAIDs, COXIBs, or acetaminophen may be superior to opioid use alone [5].

Nonsteroidal analgesics such as ibuprofen and other analgesics such as acetaminophen have long been used to reduce pain and inflammation in various conditions. These agents prevent the stimulation of pain receptors in response to injury by inhibiting the conversion of arachidonic acid to prostaglandins [14].

The IV form of ibuprofen has been used in the United States since 2009 for treating mild and moderate pain and severe pain in combination with opioids [15,16]. Ibuprofen is a propionic acid derivative that like other NSAIDs, has anti-inflammatory, antipyretic, and analgesic effects. Compared with other NSAIDs, it has a lower side effect profile on the gastrointestinal tract and cardiovascular

system due to its balanced COX-1 and COX-2 inhibition [17]. Because of the inherent risk of bleeding during surgery, drugs inhibiting COX are generally accepted reluctantly [18].

Acetaminophen is the most commonly used analgesic, administered orally or intravenously. Because its gastrointestinal and cardiovascular side effects are few, it can be safely used in patient populations with other diseases in addition to the primary pathology leading to surgery. However, its lack of anti-inflammatory effect may not be sufficient to relieve inflammatory symptoms [19].

The present study aims to evaluate and compare the impact of IV forms of ibuprofen and acetaminophen on pain management and opioid consumption in patients undergoing surgery LC.

Material and Methods

Following ethical committee approval, 70 ASA stage I- II patients aged 18 to 65 who were scheduled for LC were enrolled in this prospective, randomized, double-blind study. Informed consent was obtained from all individual participants included in the study. Before surgery, patients were informed about the medications in the study, the NRS for pain assessment, and the use of the PCA device.

The same anesthetic protocol was used in both groups, and all LC surgeries were performed laparoscopically by the same surgical team using the same technique. Data collected included age (years), gender, height (cm), weight (kg), BMI, ASA score, duration of anesthesia (minutes), and duration of surgery (minutes). Patients with a score above ASA 3, with a history of renal, hepatic, and cardiovascular disease, gastrointestinal bleeding, peptic ulcer or inflammatory bowel disease, diabetes, or other neuropathic disease, patients with a weight of less than 40 kg, a BMI greater than 35, an allergy to acetaminophen, long-term use of NSAIDs and opioids, a history of oral anticoagulants, a platelet count < 80.000, inability to use a PCA device, and those who discontinued the medication required for the study for any reason, as well as those who were pregnant, were excluded from the study.

Patients were randomly divided into two groups. Group I (ibuprofen group, n = 35) received 800 mg IV ibuprofen, and group A (acetaminophen group, n = 35) received 1000 mg IV acetaminophen after intubation. The study drugs were administered in 100 mL saline. In all patients, a standardized general anesthesia protocol was performed by an experienced anesthesiologist. Electrocardiogram (ECG), heart rate (HR), peripheral oxygen saturation (SpO_2), and noninvasive blood pressure monitoring were performed in all cases, and all measurements were recorded at 5-minute intervals during surgery. After preoxygenation (100%, 4 L/min O_2 for 3 min), propofol (1-2 mg/kg), rocuronium (0.8mg/kg), and fentanyl (0.1 µg/kg) was administered during induction of anesthesia via IV at doses calculated according to ideal body weight. End-tidal carbon dioxide ($EtCO_2$) was monitored continuously after intubation. Tidal volume and ventilation rate were adjusted to maintain arterial blood $EtCO_2$ partial pressure at 35-45 mmHg, and 0.1-0.2 µg/kg fentanyl was titrated as needed for analgesia when HR and mean arterial blood pressure (MAP) increased 20% above baseline during surgery. Anesthesia was maintained with 2-3% sevoflurane in both groups. Inhalation in a 0.5 O_2 oxygen-air mixture was discontinued at the onset of skin suturing, and the fresh gas flow was changed to 1.5 L/min oxygen for both groups. Remifentanil IV infusion 0.05-0.2 µg/kg/min was administered to maintain anesthesia. Granisetron 10-20 µg/kg IV was administered to all groups approximately 10 min before the end of surgery. At the end of the surgery, 0.05-0.07 mg/kg neostigmine methyl sulfate and 0.02-0.03 mg/kg atropine sulfate were administered as antagonists of muscle relaxants. Tracheal extubation was performed when extubation criteria were fully met in the operating room, and the patient was then transferred to recovery room.

Postoperative Analgesia Management

Patients in two groups received their medications over a 24-hour period postoperatively. They were connected to a PCA device in the recovery room. The tramadol-prepared PCA device was programmed for a 15-minute lockout and a bolus dose of 10 mg without basal infusion, which was maintained for 24 hours. NRS scores for pain (NRS 0= no pain, NRS 10= worst possible pain) and tramadol doses consumed were recorded the 1st, 2nd, 4th, 6th, 12th, and 24th hours postoperatively. A blinded pain nurse performed a postoperative follow-up of the patients. The incidence of ORAE and bleeding related to protocol medications was analyzed. The adverse effects of ibuprofen, acetaminophen, and opioids were recorded.

Statistical Analysis

The study's sample size was calculated using the G*Power program (v3.1.9.2). We conducted a pilot study with five patients in our clinic. According to this pilot study, the postoperative opioid consumption in these patients was 83±22 mL, considered clinically significant. Therefore, a difference of 20 mL between the two groups was detected with a power of 80% and 0.05 error with 20 patients in each group. Considering a 20% failure rate, we included 35 patients in each group using the double-block randomization method.

Shapiro-Wilk test and QQ plots were evaluated to test normality. Comparisons of continuous variables for normal and non-normal distributed variables were run by using Student's t and Mann Whitney U tests between groups. To understand if the distributions of group factors categories are homogenous among categories of nominal variables, chi-square or Fisher's exact tests were used. The difference between the two groups, 6-time points, and the interaction of these two main effects

were tested with two-way repeated measures of ANOVA. The sphericity assumption was performed by using Mauchly's test sphericity. As a violation of this assumption, Wilk's Lambda statistic was used as multivariate test results. General descriptive statistics are summarized as median (minimum and maximum) for continuous variables. A "p" value of less than 0.05 was considered statistically significant, and IBM SPSS Statistics for Windows, Version 20.0. were used for all these statistical analyses.

Results

Each group in this study included 35 patients and the patient allocation is outlined in the consort flow diagram (Fig. 1). Baseline demographics, except for gender, duration of the operation and antiemetic consumption were similar between groups and showed no statistical difference (p>0.05) (Table 1). In particular, the doses of opioid consumption at 4, 12, and 24 hours were significantly higher in group A than in group I (Table 2) (Fig. 2). The cumulative doses of tramadol consumption according to PCA doses are higher in acetaminophen groups than ibuprofen group (Fig. 3). Pain scores (NRS) in group I and group A at the 1st, 2nd, 4th, 6th, 12th, and 24th hours were similar (p > 0.05). Only the 24-hour pain score was significantly higher in group I than in group A (p < 0.05) (Table 3).

From the 1st to the 24th hour, pain scores decreased radically in both groups, and the groups behaved in parallel in time. Although there was no statistical difference between the groups, the ibuprofen group was above the acetaminophen group from the 1st to the end of the 24th hour (Fig 4). The incidence of ORAEs and bleeding is similar in both groups (p>0.05) (Table 4).

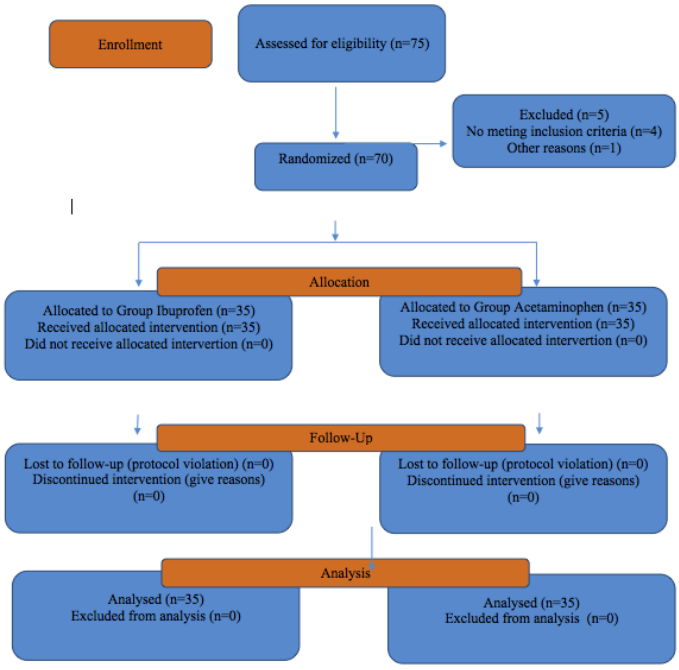

Figure 1. Consort flow diagram of the study

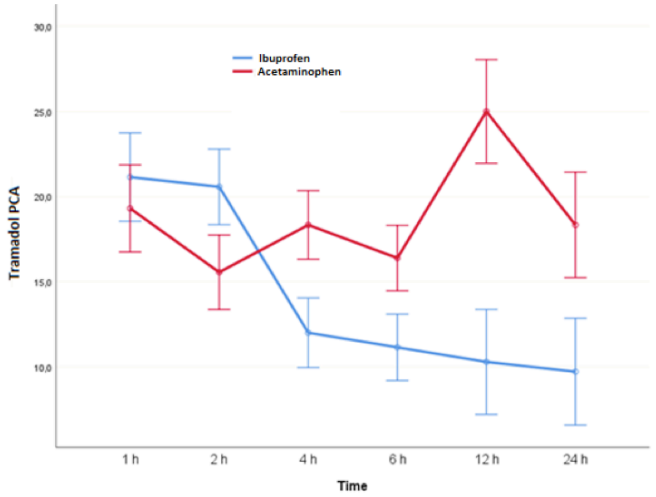

Figure 2. Time graph of tramadol patient control analgesia (PCA) use

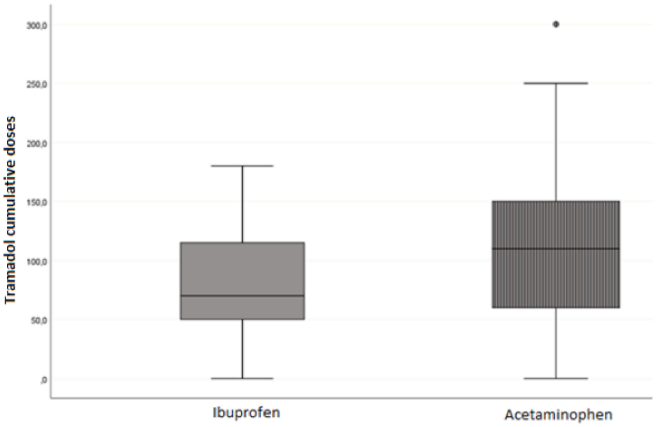

Figure 3. Tramadol cumulative doses of groups

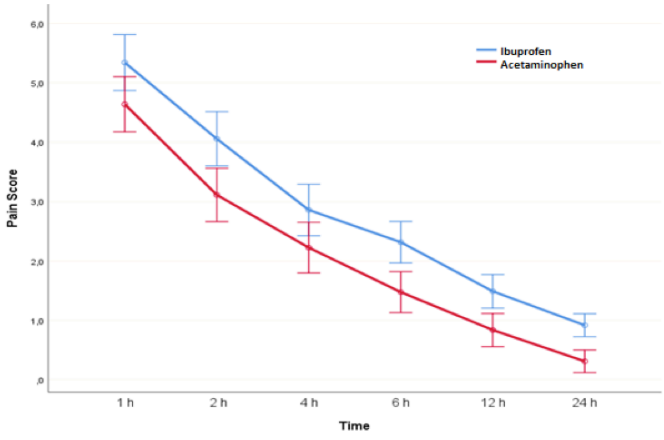

Figure 4. Pain scores of groups over time

Table 1. Demographic characteristic of study patients

	Group I (n=35)	Group A (n=35)	p
Age, year	50.09±13.38	46.92±11.04	0.280
Gender (M/F)	6/29	16/19	0.013#
Weight, kg	71.4±13.2	73.86±15.57	0.476
Height, cm	164.17±7.39	167.78±9.36	0.077
BMI (kg/m2)	26.51±4.77	25.99±3.53	0.604
ASA status (I/II)	11/24	8/27	0.560
Duration of the operation, min	81.29±28.24	74.86±15.65	0.418
Antiemetic consumption	0.86±1.24	0.97±1.28	0.878

ASA=American Society of Anesthesiologists, BMI=Body mass index
Independent t test results are expressed as mean ± standard deviation or as numbers of patients
#p< 0.05 independent t test

Table 2. Postoperative tramadol consumption of the patients with respect to the groups

Time	Group I (n=35)	Group A (n=35)	p
1 h	20(0-50)	20(0-70)	0.514
2 h	20(0-60)	10(0-40)	0.197
4 h	10(0-50)	15(0-50)	0.040
6 h	10(0-40)	10(0-50)	0.062
12 h	10(0-40)	20(0-120)	0.001
24 h	0(0-60)	10(0-70)	0.021
Cumulative doses	70(0-180)	110(0-300)	0.069

Mann Whitney U test results are expressed as median (min-max)

Table 3. The Pain Intensity of the Patients According to the Groups Based on the NRS

Time	Group I (n=35)	Group A (n=35)	p
1 h	6(0-9)	4(0-9)	0.242
2 h	5(0-10)	3(0-8)	0.186
4 h	2(0-8)	2(0-8)	0.534
6 h	2(0-8)	1(0-6)	0.216
12 h	1(0-8)	0(0-4)	0.182
24 h	0(0-6)	0(0-4)	0.033

NRS= Numerical Rating Scale.
Mann Whitney U test results are expressed as median (min-max)

Table 4. The comparison of the incidence of ORAE and bleeding between groups

	Group I (n=35)	Group A (n=35)	* p
Breathing depression	0	0	1.000
Confusion	0	0	1.000
Urinary retention	0	0	1.000
Nausea /Vomiting	20	19	0.712
Pruritus	0	0	1.000
Dyspepsia	0	0	1.000
Constipation	0	0	1.000
Bleeding	0	0	1.000

ORAE= Opioid-related adverse events
Values are expressed as numbers, *p> 0.05

Discussion

This study demonstrates that administering ibuprofen to treat postoperative pain in surgery LC reduces opioid consumption more than acetaminophen. Ibuprofen did not cause any serious adverse events, and it was well tolerated.

Several studies [23-25] recommend multimodal analgesic regimens. Multimodal analgesia reduces the dosage and adverse effects of analgesics, allowing safer pain management, improving the quality of analgesia, and leading to better functional outcomes [5]. IV acetaminophen and ibuprofen are essential options, either alone or in combination, for treating pain and fever and reducing opioid use. Furthermore, confirmed by the World Health Organization's pain ladder [26], which specifies the use of these medications and regional anesthesia as the first choice to relieve acute pain [19].

Many previous studies have favored IV acetaminophen and ibuprofen as part of multimodal analgesic treatment [24,25] for postoperative pain. Tramadol is an a typical opioid and affects both the μ-opioid receptor agonist and an inhibitor of monoamine neurotransmitter reuptake. Tramadol's analgesic and pharmacologic effects are similar to those of other opioids [11]. Because of the beneficial effects of tramadol, it was preferred as part of the multimodal analgesic protocol in this study. We also compared two different combinations of the drugs (IV ibuprofen-tramadol and IV acetaminophen-tramadol) for treating mild and moderate-to-severe pain as an adjunct to opioids. Results showed that total tramadol consumption after surgery was significantly lower in the ibuprofen group compared with the acetaminophen group [27]. The IV form of ibuprofen has been studied in patients undergoing orthopedic surgery, abdominal hysterectomy, or LC; it is reported to be relatively safe and effective [21,23,28].

Kayhan et al. [29] stated that the administration of 800 mg IV ibuprofen to treat postoperative pain in morbidly obese patients undergoing bariatric surgery did not significantly reduce opioid consumption compared with IV acetaminophens but resulted in lower pain intensity. In our study, opioid consumption was significantly reduced compared with acetaminophen infusion, but patients' pain scores did not differ between the two drug groups.

In contrast to our study, Sparber et al. found that preemptive administration of ibuprofen significantly decreased postoperative pain scores in patients undergoing laparoscopic inguinal hernias but did not affect opioid consumption [30].

In addition, Erdi et al. [31] demonstrated in their study of

patients undergoing LC that mean abdominal pain scores were not significantly different in the ibuprofen and acetaminophen groups but were significantly lower than in the control group.

The use of IV ibuprofen and acetaminophen was associated with a reduction in total morphine consumption compared with the control group, according to Akbas et al. study. Also, the use of IV ibuprofen significantly reduced total morphine consumption compared with control and acetaminophen [32]. The study by Ekinci et al. [33] has a control group besides the ibuprofen and acetaminophen group. They suggested that IV ibuprofen resulted in lower pain scores and opioid consumption compared with acetaminophen postoperatively in the first 24 hours in patients undergoing LC surgery. In addition, it reduced the need for rescue analgesics and ORAE. Therefore, IV ibuprofen may have a more potent analgesic effect than IV acetaminophen in postoperative pain management [33]. At the same time PONV and pruritus were more common in the control group than in other groups in terms of adverse effects. Notably, the group I had a lower incidence of nausea than group A. This study showed that the IV form of ibuprofen reduced pain scores and opioid consumption in the 24-hour postoperative period compared with acetaminophen. In addition, rescue analgesic utilization was significantly lower in those in the ibuprofen group [33].

Ahiskalioglu et al. [28] reported that a single preventive dose of IV ibuprofen significantly decreased VAS scores and the incidence of PONV by 45%, as well as the side effects of opioid use in LC patients. Because they compared the control group and ibuprofen in this study, they were able to calculate the effect on side effects. In our study, none of our patients had cardiac or renal side effects, respiratory depression, pruritus, confusion, or bleeding.

One limitation of the study is the absence of a control group. The second limitation is that we did not record anesthesia time. Another limitation, the study could have been performed with a larger sample size and as a multi-center study.

Conclusion

The administration of ibuprofen during surgery for the treatment of postoperative pain reduces opioid consumption more than acetaminophen. Ibuprofen was well tolerated, and no serious adverse events were observed; however, our sample size was too small to draw any definite conclusions. In patients requiring postoperative pain control in LC, ibuprofen may be a safe and valuable alternative to acetaminophen.

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Financial interest

None.

Ethical Statement

Institutional approval was obtained before article submission from Baskent University Institutional Review Board. Project no: KA15/346

Declaration of Competing Interest

No conflict of interest.

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