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Comparison of Analgesic Effects of Paracetamol and Ibuprofen After Laparoscopic Cholecystectomy

Laparoskopik Kolesistektomi Sonrası Parasetamol ve İbuprofenin Postoperatif Analjezik Etkilerinin Karşılaştırılması

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ABSTRACT Objective: Non-steroid anti-inflammatory drugs (NSAIDs) and paracetamol (P) are frequent constituents of multimodal postoperative analgesia. The aim of this study was to compare analgesic effects of intravenous (IV) paracetamol and ibuprofen (IB) administered intraoperatively and in repeated doses postoperatively to the patients who underwent laparoscopic cholecystectomy. **Material and Methods:** A total of 40 patients with class of American Society of Anesthesiologists (ASA) I-III who underwent laparoscopic cholecystectomy were randomized into Groups-P and IB in this randomized, prospective and double-blind study. After anesthesia induction and initiation of the surgery, Group-P patients received 1 g IV paracetamol and Group-IB patients received 800 mg IV ibuprofen. At skin closure, 1.5 mg/kg of IV tramadol was administered. For postoperative analgesia, a patient-controlled analgesia (PCA) pump with tramadol was used. During the first 24h postoperatively, Group-P patients received 1 g of IV paracetamol and Group-IB patients received 400 mg of IV ibuprofen at every 6h. Patients with visual analog pain scale (VAS) scores ≥ 4 received rescue analgesia. The groups were compared for postoperative first 24h VAS scores, PCA demand, total tramadol dose, and rescue analgesic requirement. **Results:** Compared with Group-P, Group-IB had significantly lower VAS-awakening, VAS-post-anesthesia care unit (PACU) and VAS-6th h scores. Postoperative rescue analgesic requirement was lower in Group-IB than in Group-P at all timepoints, most notably in the PACU. **Conclusion:** Compared with paracetamol, intraoperative and repeated postoperative doses of ibuprofen substantially decreased the pain scores and rescue analgesic requirement. As a component of multimodal analgesia, IV ibuprofen is an effective option for postoperative pain management.

Keywords: Ibuprofen; postoperative pain; analgesia; laparoscopic cholecystectomy; paracetamol

ÖZET Amaç: Non-steroid anti-inflamatuar ilaçlar (NSAİİ) ve parasetamol multimodal postoperatif ağrı tedavisinde sıklıkla kullanılan ilaçlardır. Bu çalışmanın amacı, laparoskopik kolesistektomi operasyonu geçiren hastalarda intraoperatif ve postoperatif dönemde tekrarlanan dozlarda uygulanan intravenöz (IV) parasetamol ve ibuprofen'in analjezik etkilerinin karşılaştırılmasıdır. **Gereç ve Yöntemler:** Randomize, prospektif, çift-kör olan bu çalışmada laparoskopik kolesistektomi geçiren ASAI-III toplam 40 hasta Grup-P ve Grup-IB olarak randomize edildi. Anestezi indüksiyonu sonrası cerrahi başlangıcında Grup-P'deki hastalara 1 g parasetamol ve Grup-IB'deki hastalara 800 mg ibuprofen IV olarak uygulandı. Cilt sutürlerine geçildiğinde 1,5 mg/kg IV tramadol verildi. Postoperatif analjezide tramadol ile hazırlanmış hasta kontrollü analjezi cihazı (HKA) kullanıldı. Postoperatif ilk 24 saat boyunca Grup-P'deki hastalara 1gr parasetamol, Grup-IB'deki hastalara 400mg ibuprofen 6 saat arayla IV olarak uygulandı. VAS skorları ≥ 4 olan hastalara kurtarıcı analjezik uygulandı. Gruplar postoperatif ilk 24 saat VAS skorları, HKA kullanım miktarı, toplam tramadol miktarı, kurtarıcı analjezik gereksinimi açısından karşılaştırıldı. **Bulgular:** Grup-P ile karşılaştırıldığında Grup-IB'de VAS- uyanma, VAS-anestezi sonrası bakım ünitesi ve VAS-6.saat değerleri belirgin olarak düşüktü. Postoperatif kurtarıcı analjezik gereksinimi özellikle anestezi sonrası bakım ünitesinde olmak üzere tüm dönemlerde anlamlı olarak düşüktü. **Sonuç:** Parasetamol ile karşılaştırıldığında intraoperatif ve postoperatif tekrarlayan dozlarda IV ibuprofen uygulaması, postoperatif dönemde ağrı skorlarını ve kurtarıcı analjezik gereksinimini belirgin olarak düşürmektedir. Multimodal analjezinin bir parçası olarak IV ibuprofen postoperatif ağrı tedavisinde etkili bir analjezik seçeneğidir.

Anahtar Kelimeler: İbuprofen; postoperatif ağrı; analjezi; laparoskopik kolesistektomi; parasetamol

Effective analgesia is a principal component of postoperative care. Insufficient or excessive analgesia can result in increased myocardial ischemia and possibly lead to myocardial infarction, thromboembolic or pulmonary complications, chronic postoperative pain, impaired quality of life, damaged immune system, and delayed discharge from the hospital.[1] Modern postoperative analgesia focuses on early mobilization and discharge. High doses of opioid analgesics are restricted by their side effects, including respiratory depression, nausea/vomiting, gastrointestinal dysfunction, and urinary retention.[2] Consequently, a balanced or multimodal analgesia using adjuvant medications has recently been developed. Neural blockade, epidural analgesia, wound infiltration with local anesthetics, and non-opioid intravenous (IV) drugs alone or in combination with opioid analgesics have increasingly been used for avoiding high opioid doses and their side effects.[3] Nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol (acetaminophen) have been used for this purpose.[4] Paracetamol is frequently used as an analgesic and antipyretic in adult and pediatric patients. Its effect on the central nervous system is caused by prostaglandin inhibition via the cyclooxygenase (COX) pathway. IV paracetamol is used alone or in combination with opioids for perioperative pain management.[4,5]

Ibuprofen which is an NSAID is a propionic acid derivative with anti-inflammatory, antipyretic, and analgesic properties. Its oral form is widely used worldwide. With the introduction of its IV form, ibuprofen has increasingly been used in multimodal analgesia. Moreover, IV ibuprofen has been shown to be safe and effective for intraoperative and postoperative use in orthopedic, gynecological, and abdominal surgeries, thereby, decreasing the use of opioids in these settings.[5-7]

Several factors play a role in development of pain after laparoscopic cholecystectomy. Phrenic nerve irritation from carbon dioxide insufflation into the peritoneal cavity, abdominal distention, trocar site incisions, tissue trauma following gallbladder removal, and individual factors contribute to the emergence of postoperative pain.[8] The aim of the present study was to compare the analgesic effects and side effects of IV paracetamol and ibuprofen administered intraoperatively and in repeated doses postoperatively to patients who underwent laparoscopic cholecystectomy.

MATERIAL AND METHODS

This randomized prospective study was conducted in University of Health Sciences Fatih Sultan Mehmet Health Research and Application Center between January 2017-January 2018 according to the principles of the Declaration of Helsinki 2008. After approval by the local ethics committee of the university (No: 2016/83) and obtaining informed consent, the study was conducted with 40 patients aged between 18 and 65 years with American Society of Anesthesiologists (ASA) physical status scores of I–III and who underwent laparoscopic cholecystectomy. The exclusion criteria were use of NSAIDs during the recent 12 h; ongoing use of oral anticoagulants, lithium, ACE inhibitors, furosemide, and aspirin; hemoglobin levels < 10 mg/dL; platelet count < 80.000; body mass index (BMI) > 35; known allergy to ibuprofen or paracetamol; and history of bleeding disorders, gastrointestinal bleeding, heart failure, renal failure, or hepatic failure.

The study protocol along with information on postoperative use of the visual analog pain scale (VAS) and patient-controlled analgesia (PCA) device were explained to the patients preoperatively. Using the sealed envelope technique, patients were randomized into those who were administered paracetamol (Group P, n=20) or ibuprofen (Group IB, n=20).

Heart rate, noninvasive blood pressure, peripheral oxygen saturation (SpO_2), and bispectral index (BIS) were monitored and recorded preoperatively as well as at every 5 min throughout the operation. All patients received 2-2.5 mg/kg of propofol, 2 mcg/kg of fentanyl, and 0.6 mg/kg of rocuronium as standard anesthesia induction throughout the surgery. After sufficient muscle relaxation and when the BIS levels were <60, orotracheal intubation was performed.

After intubation, anesthesia was maintained with 1.5%-2% of sevoflurane and 0.2-0.5 mcg/kg/min of remifentanyl. The depth of anesthesia was monitored based on BIS with target levels of 40-60. After creating a pneumoperitoneum at a fixed pressure of 14 mmHg in all patients and initiating surgery, Group P patients received 1 g of paracetamol IV (Parol 10 mg/ml, ATABAY, Istanbul, Turkey) and Group IB patients received 800 mg of ibuprofen (Intrafen 800 mg/8 ml, GEN İLAÇ, Ankara, Turkey) in 200 ml of saline; both drugs were to be delivered in 30-min infusions. At skin closure, 1.5 mg/kg of IV tramadol and 0.1 mg/kg of IV ondansetron were administered. All surgeries were conducted by the same surgical team and with the same technique. At the end of the surgery, muscle relaxants were antagonized with 0.03-0.05 mg/kg of neostigmine and 0.01-0.02 mg/kg of atropine. When the extubation criteria were met, the patients were extubated and transferred to the post-anesthesia care unit (PACU). The surgical and anesthetic durations were recorded.

The PCA device was prepared with tramadol, set up with 15-mg bolus and 15-min lockout periods, and without a basal infusion before leaving the operation room. As explained preoperatively, the patient was asked to press the button whenever pain was felt. In the first 24 h postoperatively, Group P patients received 1 g of IV paracetamol at every 6 h, whereas Group IB patients received 400 mg of IV ibuprofen in 100 mL of saline at every 6 h.

One anesthesiologist administered the study drugs in the operating room and during the postoperative period. Another anesthesiologist, who was blinded to the groups, recorded the study parameters in the intraoperative and postoperative periods. Visual analogue scale (VAS) scores using a 10-cm VAS line (0 for no pain; 10 for the most intense pain), heart rate, blood pressure, dyspnea, nausea, vomiting, bleeding, headache, pruritus, and urinary retention in the patients were recorded on awakening in the operation room; at 30-min postoperatively in the PACU; and at the 6th, 12th, and 24th h postoperatively. Patients with VAS scores ≥ 4 in the postoperative period received 20 mg IV meperidine as rescue analgesia. PCA demand and supply amounts, total tramadol dose (in mg), and rescue analgesic requirement were recorded.

STATISTICS

Sample Size

The primary endpoint of the study was the VAS score at the time of awakening. In our pilot study, which included five patients in each group, the calculated mean±standard deviation (SD) of VAS scores were 1.6±1.5 in Group P and 0.4±0.95 in Group IB. Sample size calculations suggested that 20 patients/group are sufficient for detecting differences of 1.2 as significant at $p<0.05$ with at least 80% power.

Statistical Analysis

All statistical analyses were performed with IBM SPSS ver.23.0. The Shapiro–Wilk test was used for testing normality. Descriptive statistics were expressed as mean ± SD. Continuous variables were compared using the Student's t-test and Mann–Whitney U-test when data were not normally distributed. Categorical variables were compared using the Pearson's chi-square test and Fisher's exact test. Friedman test was used for in-group comparisons. A p value of <0.05 was considered to be significant.

RESULTS

Demographic data of the patients are shown in Table 1. There was no significant difference between the groups in terms of age, sex, weight, BMI, ASA scores, duration of surgery, and duration of anesthesia. Among all recordings, heart rate, mean arterial pressure, and SpO_2 levels were similar for both groups.

When the VAS scores were analyzed, VAS-awakening, VAS-PACU, and VAS-6th h scores of Group IB were lower than those of Group P. No significant difference was observed between VAS-12th and -24th h scores. Within each group, the VAS-PACU scores were higher than the VAS scores at the other time points (Table 2).

There was no significant difference between the groups in terms of PCA demand, supply, and

TABLE 1: Demographic data of the patients.

Variables	Group P (n = 20)	Group IB (n = 20)	p
Sex M/F	5/15	7/13	0.490[a]
Age (years)	50.2 ± 9.3	46.7 ± 10.81	0.279[b]
ASA			
1	6 (30%)	12 (60%)	0.069[c]
2	12 (60%)	8 (40%)	
3	2 (10%)	0 (0%)	
Weight (kg)	75.5 ± 10.06	80.4 ± 9.45	0.121[b]
BMI (kg/m^2)	28.6 ± 2.54	28.6 ± 3.3	1.000[b]
Duration of surgery (min)	45.25 ± 11.79	45.1 ± 13.46	0.970[b]
Duration of anesthesia (min)	52.85 ± 10.66	53.65 ± 13.12	0.785[d]

Values are presented as number (%) or mean ± standard deviation.
[a]Pearson's chi-square test,
[b]Student's t-test,
[c]Fisher's exact test (Fisher–Freeman–Halton), dMann–Whitney U-test.
*p < 0.050
ASA: American Society of Anesthesiologist physical status, BMI: body mass index.

total tramadol doses. Postoperative rescue analgesic requirement was significantly lower in Group IB than in Group P at all periods, most notably in the PACU (Table 3). During the postoperative period, two patients in each group had nausea and one patient in Group P had vomiting. Dyspnea, bleeding, headache, urinary retention, or pruritus was not observed in any of the patients. There was no difference between the groups in terms of the incidence of postoperative side effects.

DISCUSSION

We aimed to compare postoperative effects of IV ibuprofen and paracetamol in patients who underwent laparoscopic cholecystectomy based on VAS scores, PCA demand, rescue analgesic requirement, and side effects. Upon comparing two groups, VAS scores of Group IB patients at the first 6h postoperatively were prominently lower than those of Group P patients. Although the PCA demand and total tramadol amount did not differ between the groups, the number of patients who required rescue analgesia was lesser in Group IB. The groups did not exhibit any differences with respect to side effects.

TABLE 2: Comparison of VAS scores at different postoperative time points.

Variables	Group P (n = 20)	Group IB (n = 20)	p
VAS-Awakening	2.6 ± 1.96	0.45 ± 0.94	<0.001¶[b]
VAS-PACU	4.3 ± 1.56*[a]	3.2 ± 1.44 **[a]	0.026¶[b]
VAS-6th	2.7 ± 1.69	1.5 ± 1.32	0.017¶[b]
VAS-12th	1.75 ± 1.65	1.05 ± 1.32	0.146
VAS-24th	0.9 ± 1.07	0.8 ± 0.95	0.757
P	<0.001*[a]	<0.001**[a]	

Values are presented AS mean ± standard deviation.
[a]Friedman test, [b]Mann-Whitney U-test.
¶p < 0.050.
PACU: Post anesthesia care unit, VAS: visual analog scale.

TABLE 3: Comparison of the postoperative rescue analgesic requirement and PCA use between the groups.

Variables	Group P (n = 20)	Group IB (n = 20)	p
Rescue analgesic requirement at the PACU	14 (70%)	5 (25%)	0.010*[a]
Rescue analgesic requirement in the ward (6, 12, and 24 h)	5 (25%)	0 (0%)	0.047*[b]
Rescue analgesic requirement at all timepoints	15 (75%)	5 (25%)	0.002*[a]
PCA demand (number)	21.05 ± 28.15	16.85 ± 12.78	0.718[c]
PCA supply (number)	9.70 ± 6.13	9.15 ± 5.71	0.799[c]
Total amount of tramadol (mg)	144 ± 93.91	136 ± 83.61	0.820[c]

Values are presented as number (%) or mean ± standard deviation.
[a]Pearson's chi-square test, [b]Fisher's exact test, [c]Students's t-test
*p < 0.050
PACU: Post anesthesia care unit, PCA: Patient controlled analgesia.

Laparoscopic cholecystectomy has its advantages over open surgery with reduction in tissue damage and postoperative pain and shorter hospital stay and time to return to normal physical activity.[9] Nevertheless, following laparoscopic cholecystectomy, moderate pain arises, which peaks in the first postoperative hour and then gradually reduces after 24-72 h.[10] Saadati et al. have reported that VAS scores after laparoscopic cholecystectomy at the 6th, 18th, and 24th h were 2.5, 2.1, and 1.7, respectively.[11] In our study, VAS scores were higher than these scores in both groups, particularly those taken in the PACU. The VAS scores of both groups decreased throughout the 6th, 12th, and 24th postoperative h.

Pain is an important factor that can delay hospital discharge after laparoscopic cholecystectomy.[11] Various combinations of drugs, routes of administration, and preferred times of administration are the factors to consider during pain management. Opioids and NSAIDs are frequently used for alleviating pain after laparoscopic cholecystectomy; in particular, IV paracetamol infusion, alone or in combination with tramadol, is safe and effective.[12-15] For acute pain management, a combination of tramadol with NSAIDs is superior to their individual use at the same doses.[16]

The analgesics used in our study were ibuprofen, paracetamol and for patient controlled analgesia a synthetic, weak opioid, tramadol. The effect of ibuprofen on postoperative pain following laparoscopic cholecystectomy has been studied. Ahıskalıoglu et al noted a decrease in the 24-h opioid use, pain scores, and rescue analgesic requirement with a single dose of 400 mg ibuprofen preoperatively.[17] Another study on patients who had undergone laparoscopic cholecystectomy reported similar results with administration of 800 mg ibuprofen in addition to pregabalin preoperatively.[18] In this study, we administered ibuprofen intraoperatively and in repeated doses at every 6 h in the first 24 h postoperatively.

Ibuprofen is a NSAID that inhibits prostaglandin synthesis through non-selective COX inhibition. Furthermore, COX-2 inhibition has analgesic, antipyretic, and anti-inflammatory properties, whereas COX-1 inhibition is responsible for the undesired renal and gastrointestinal effects. With a COX-1: COX-2 inhibition ratio of 2.5:1, ibuprofen carries a lesser risk of bleeding and gastrointestinal side effects than other NSAIDs (ketorolac, which has a COX-1: COX-2 inhibition ratio of 330:1).[5] For analgesia, IV ibuprofen is administered at 400-800 mg at every 6 h, whereas for fever, it is administered IV at an initial dose of 400 mg, with repeated doses at 100-200 mg at every 4 h. IV administration results in quicker peak plasma concentration times and faster absorption. The terminal elimination half-life (t½β) of ibuprofen is 2.2 h for 400 mg and 2.4 h for 800 mg, and the maximum recommended daily dose is 3,200 mg.[19] In our study, Group IB patients received 800 mg of IV ibuprofen at the start of the surgery and continued doses of 400 mg every 6 h, i.e., a cumulative dose of 2,400 mg in 24 h.

Several studies have evaluated the efficacy of ibuprofen for postoperative analgesia with such regimen. In their study on patients who had undergone orthopedic and abdominal surgery, Southworth et al. showed that administration of ibuprofen at skin closure resulted in lower pain scores and morphine demand in the first 24 h with an 800-mg dose and a decrease in pain scores without a difference in morphine demand with a 400-mg dose.[20] Xintong Liu et al. reported that administration of 800 mg of IV ibuprofen intraoperatively and every 6 h postoperatively substantially decreased pain scores and morphine demand in the first 24 hours in the patients who had undergone radical cervical cancer surgery.[21] A similar study conducted with the patients who had undergone abdominal surgery reported a decrease in morphine demand on day one, resting VAS score, and rescue analgesic requirement with 800 mg of IV ibuprofen administered at skin closure and at every 6 h postoperatively.[22]

In our study, the VAS scores were significantly lower in Group IB than in Group P, particularly during the first 6 h. The total tramadol dose was lower in Group IB (136±83.61 mg) than in Group P (144 ± 93.91), although the difference was not significant ($p>0.05$). The number of the patients who

required rescue analgesia in the PACU (p=0.01) and wards (p<0.05) were smaller in Group IB than in Group P. The PCA-delivered tramadol dose was similar despite different rescue analgesia requirement between the groups. This may be explained by the lockout periods of the PCA device, which did not meet the demands for tramadol during the early postoperative period.

Several studies have compared analgesic efficacies between NSAIDs and paracetamol. A study on patients who had undergone laparoscopic cholecystectomy concluded that the 24-h postoperative pain management was better with perioperative paracetamol than that with perioperative diclofenac administration.[23] Another study on patients who had undergone cesarean section reported similar postoperative pain scores with preoperative 1 g of IV paracetamol and 400 mg of oral ibuprofen.[24] IV ibuprofen (800 mg) is more effective than IV paracetamol (1 g) in reducing renal colic pain.[25] To the best of our knowledge, a study that compared analgesic effects of IV ibuprofen and paracetamol in repeated doses after laparoscopic cholecystectomy has not yet been reported.

Intravenous ibuprofen is well-tolerated when used for treating pain and fever.[20-22] However, its most frequent side effects requiring immediate treatment are nausea, vomiting, headache, and urinary retention. Pruritus is the most important side effect that results in cessation of treatment and is observed in < 1% of patients.[19] The other possible side effects of ibuprofen are similar to those of the other NSAIDs. In our study, the side effects observed were nausea (Group P, n=2/20; Group IB, n=2/20) and vomiting (Group P, n=1/20; Group IB, n=0/20). There was no significant difference between the groups in terms of side effects.

Our study had some limitations. First was the small sample size, which was likely because only patients who underwent a single type of surgery by the same surgical team were included to prevent confounders that could emerge from the type of surgery or variance of surgeons. Another limitation was the lack of a placebo group that did not receive ibuprofen nor paracetamol; this could have improved the analysis of the efficacy of ibuprofen as a postoperative analgesic.

CONCLUSION

In patients who had undergone laparoscopic cholecystectomy, intraoperative and repeated postoperative doses of IV ibuprofen reduced postoperative pain scores and rescue analgesic requirement more prominently than those of paracetamol. Therefore, ibuprofen is a more effective postoperative analgesic than paracetamol. We believe that IV ibuprofen as a constituent of multimodal analgesia is an effective analgesic drug option in postoperative pain management.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

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