Original Article

Comparing the Efficacy and Side Effects of Intravenous Ibuprofen and Acetaminophen in Pain Control Following Laparoscopic Cholecystectomy

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ABSTRACT

BACKGROUND

The importance of using effective postoperative analgesia is widely accepted. Systemic opioids are the gold standard for reducing severe pain after surgery, but the side effects have limited the use of adequate doses. We aimed to evaluate the effect of adding intravenous acetaminophen and intravenous ibuprofen to fentanyl on patient-controlled analgesia.

METHODS

In this randomized clinical trial study in Ardabil city hospital at 2019, 90 patients undergoing elective laparoscopic cholecystectomy were randomly divided into three groups. The control group (n=30) received normal saline, the acetaminophen group (n=30) received 1g intravenous acetaminophen, and the ibuprofen group (n=30) received 800 mg intravenous ibuprofen. All patients received a pain control by intravenous pump containing fentanyl (15µ/ml). The drugs were injected intravenously after surgery. Shoulder and abdominal pain scores, sedation rate, nausea and vomiting, satisfaction, and the doses of fentanyl and meperidine were recorded in SPSS software within 24 h after surgery.

RESULTS

The mean abdominal pain scores in ibuprofen (3.02) and acetaminophen (2.89) groups were not significantly different (P=0.719) but were significantly lower than in the control group (5.10) (P<0.001). The severity of shoulder pain, nausea and vomiting, sedation, and fentanyl intake were not significantly different in the ibuprofen and acetaminophen groups but were significantly lower than in the control group.

CONCLUSION

The use of both intravenous acetaminophen and ibuprofen in pain control after surgery can reduce the need for opioid use. Acetaminophen can also be a suitable alternative for postoperative pain control in patients that are unable to use NSAIDs.

KEYWORDS

Intravenous ibuprofen; Intravenous acetaminophen; Postoperative pain control; Cholecystectomy

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INTRODUCTION

Pain is considered the fifth vital sign because of its importance and requires to be controlled to prevent mortality and complications after surgery[1,2]. Pain causes adverse consequences by various mechanisms that drive fundamental changes in the metabolism of susceptible individuals.It cancause hypertension, heart ischemia, respiratory, digestive, renal, and even increase mortality in patients. In addition, delay in patient movement after surgery increases hospital stay and treatment costs[3-5]. Although postoperative pain is a predictable problem, controlling it is a difficult challenge for physicians. Despite scientific progress in recognition of pain receptors and pharmacology, over 80% of patients experience moderate pain after surgery, and 31-37% experience severe pain[6,7]. Currently, the use of narcotic analgesics is one mainstay of treatment. However,it may lead to side effects such as respiratory depression, sedation, drowsiness, itching, skin rash, urinary retention, delayed onset of bowel activity, and nausea/vomiting[8].

Narcotic analgesics play a key role in pain management by acting on the central nervous system, but cannot block the inflammatory aspect of pain[9,10]. Eliminating the inflammatory response may reduce the need for opioids and strengthen the control of postoperative processes[11,12]. Non-steroidal analgesics such as ibuprofen and other analgesics such as acetaminophen have long been used to block pain and inflammation in a variety of conditions. These agents prevent the stimulation of pain receptors in response to injury by inhibiting the conversion of arachidonic acid to prostaglandins[13]. Therefore, for pain control, the use of different mechanisms can reduce the required dose of drugs and their side effects resulting in better pain control (multimodal analgesia)[14].

In this study, we aimed to introduce non-narcotic drugs that are effective in pain control as an alternative to narcotic drugs to better control the pain after surgery.

MATERIALS AND METHODS

This study wasa three-blind clinical trial. The study population included patients aged 20 to 60 yr who underwent laparoscopic cholecystectomy with a diagnosis of cholecystitis. It included 90 patients randomly divided into three groups of 30 patients. The exclusion criteria were pregnancy, patients with asthma or chronic lung disease, patients with heart diseases, patients with renal failure and dialysis, a history of gastrointestinal bleeding, high blood pressure, a history of anemia, consumption of warfarin, concomitant use of furosemide and angiotensin-converting enzyme (ACE) inhibitors, drug dependence, allergy to ibuprofen and NSAIDs, and age less than 20 yr or over 60 yr.

Ninety patients with ASA (American Society of Anesthesiologists) grade I&II with an age range of 20 to 60 yr were included. These patients were candidates for laparoscopic cholecystectomy at Imam Khomeini Medical Center, Ardabil University of Medical Sciences, Ardabil, Iran at 2019.

The study method was explained to patients and written informed consent was obtained from the patients before the study. All patients underwent the same procedure (laparoscopic cholecystectomy) with the same anesthesiologists. The same protocol was used for all the patients.

Premedication with midazolam 20 µg/kg and, for anesthesia, fentanyl 2-4 µg/kg and propofol 2-3 mg/kg, atracurium 0.5 mg/kg of patient weight were injected. After 3 min, endotracheal intubation was performed with tube sizes of 7.5 to 8 mm. Isoflurane, along with nitrous oxide and oxygen 50/50, was administered for the maintenance of anesthesia. All patients were anesthetized in the same way and the duration of anesthesia and recovery time was the same for all patients. Patients were randomly divided into three groups of 30 using a sealed envelope. Ninety sealed envelopes containing 3 predetermined codes, representing the study groups, were prepared with 30 of each code. For each patient who entered the operating room for surgery, an envelope was randomly chosen and the code was recorded. The patients were unaware of the drug being injected. The healthcare professionals that injected the drugs and the researchers that recorded their information did not know the type of drug. The individual who analyzed patient information did not also know the type of drug that the patients had received.

The patients were divided into three groups of 30 cases. Group A received fentanyl as a bolus dose of 30 µg/ml as a patient control analgesia. The drugs were injected through PCA (Zhejiang Fert; Pouyan Tajhiz Teb of Asia Co. Ltd, China). This device had 1 ml bolus-dosing, 15-min lockout time, and none infusion rate with 100 mL reservoir

volumes pump with the placebo drug. The placebo comprised intravenous normal saline with a volume equal to that of other groups. Group B received fentanyl (with similar conditions to group A) and intravenous ibuprofen 800 mg. Group C received fentanyl (with similar conditions to group A) and intravenous acetaminophen 1g (acetaminophen elixir). Intravenous ibuprofen, acetaminophen, and placebo were injected three times (during the operation, 8 h after the operation, and 16 h after the operation). Fentanyl was given as a pain pump (viathe PCA method) for all patients. This helped to give the patients the drug by pushing a button if they felt pain after surgery. The pain pump was adjusted in the amount of 1 ml bolus and the locking time was 15 min. At the time of pain, patients received 1 ml of a solution containing fentanyl intravenously by pressing the button for the pain pump (PCA method).

Severe pain at the site of surgery and shoulder was measured based on VAS, nausea, and vomiting based on N/V Score, sedation based on Ramsay score, and the volume of received fentanyl were recorded. These data were documented and analyzed every 6 to 24 h after surgery with SPSS software(Chicago, IL, USA). Insufficient drug doses that did not control the patients' pain (VAS> 3) were detected and confirmed with the patient symptom evaluator. In these cases, meperidine (0.5 mg/kg) was administered intravenously and the required dose in each drug group was recorded within 24 h. For cases that had nausea and vomiting, 10 mg of metoclopramide was administered slowly and intravenously. Additionally, the patients were asked to assign a score from 1 (= least satisfaction) to 4 (= most satisfaction) on their analgesia response to evaluate patient satisfaction with the specific analgesia method. The candidates of this study would receive a form that contained information on how the research would be conducted and they would be included in the study if they were satisfied. During the study, they were excluded from the study if they were reluctant to continue to cooperate for any reason. In addition, all patient information was kept confidential.

The Ethics Committee of Ardabil University of Medical Sciences, Ardabil, Iran approved this study (Ethics Committee Code: IR.ARUMS.REC.1395.89). This study is registered in the Iranian Registry of Clinical Trials (Clinical Trial Code: IRCT20161024030479N2).

Statistical analysis

The SPSS software (Chicago, IL, USA) was used for statistical analysis. Frequency and percentage were used to present quantitative variables and the mean standard deviation was used to present qualitative variables. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

The flowchart of the study is shown in Figure 1. The final sample included 90 participants that were randomly allocated to three groups of equal size. Of the total sample, 24.4% were male, with 7-8 male individuals in each intervention group. The age was significantly different among the three groups (P=0.009). The mean age of each group included 36.16±9.67 for the group that received acetaminophen, 43.53±10.13 for the group that received ibuprofen, and 43.56±11.51 for the group that received placebo.

The profiles of different factors and outcomes of interest in the studied groups are shown in Figure 2. The findings on the effect of ibuprofen and acetaminophen on surgical site pain showed that the average pain intensity of patients significantly decreased at different times. The mean pain intensity of the acetaminophen group was not significantly different compared to the ibuprofen group (P=0.719). However, the pain intensity in these two groups was significantly different compared to the control group (P<0.001). The mean pain intensity in the ibuprofen, acetaminophen, and placebo groups was 3.02, 2.89, and 5.10, respectively. This shows that the patients in the acetaminophen and ibuprofen groups experienced 43.4% and 40.79% less pain, respectively, compared to the control group.

The findings of our study on shoulder pain showed that the mean pain intensity in the ibuprofen group (0.667) was not significantly different from the acetaminophen group (0.300) (P= 0.123). However, the control group with the mean pain intensity (1.092) differed significantly from the acetaminophen group. The control group experienced shoulder pain (72.48%) with more intensity compared to the acetaminophen group (P<0.001). There was no significant difference between ibuprofen and control groups (P= 0.074). This is because this drug use causes many side effects such as nausea and vomiting, sedation, and ileus.

In addition, the mean sedation rates in the

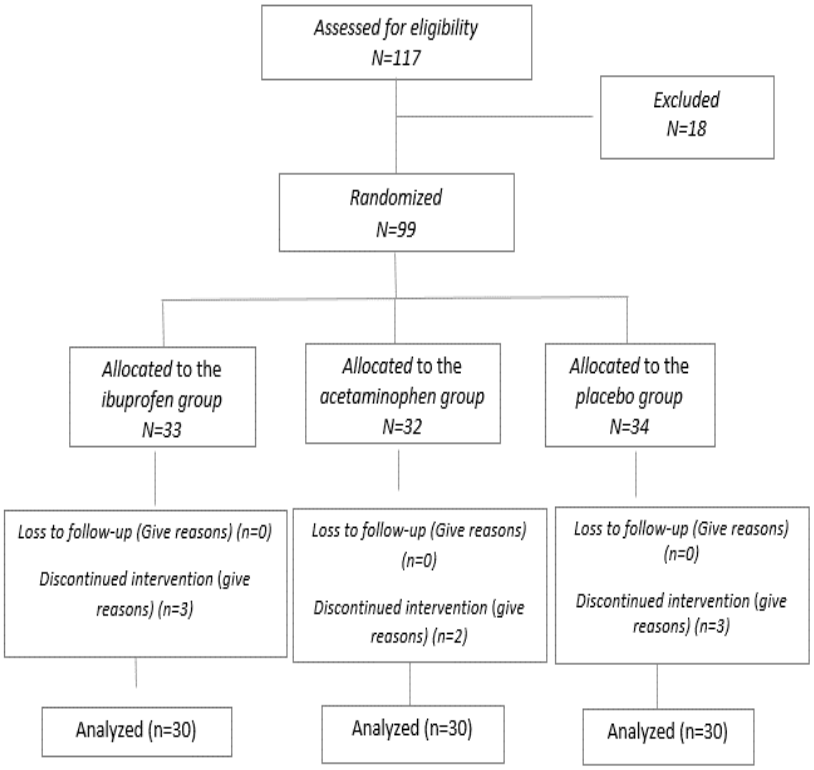

Figure 1: Flow diagram of the study population

acetaminophen, ibuprofen, and control groups for conscious and oriented were 61.6% (score 0), 65.83% (score 0), 51.6% (score 0), respectively. There was no significant difference between the two groups of acetaminophen and ibuprofen. However, the rate of sedation was significantly higher in the control group compared to the two drug groups. The control group experienced less consciousness with a 20.7% difference compared to the acetaminophen group and a 29.48% difference to the ibuprofen group.

Furthermore, the rate of nausea and vomiting in the three groups showed no nausea and vomiting in the drug groups as the following: acetaminophen: 59.16% (score 1), ibuprofen: 51.6% (score 1), and control group: 26.6% (score 1). The acetaminophen group experienced 55.05% more nausea and vomiting than the placebo group and 46.92% of the subjects required one or more drugs. The ibuprofen group experienced 48.45% more nausea and vomiting compared to the placebo group, 57.01% of the patients required one or more drugs, and the difference between the two groups was significant. The rate of nausea and vomiting in the first 6 h in the ibuprofen group was higher than acetaminophen (P=0.032).

The average volume of fentanyl consumption showed that the volume of fentanyl consumption in the ibuprofen group was 37.6 ml and was not significantly different from the acetaminophen group with 34.8 ml (P=0.673). However, there was a significant difference compared to the control group with 74.7 ml (P<0.001). In addition, patients in the acetaminophen group (53.42%) (opioid-sparing effect) and the ibuprofen group (49.63%) needed fewer opioids than the placebo group.

The total good and excellent satisfaction scores in the acetaminophen group were 93.3%. This parameter was 80% in the ibuprofen group and 50% in the control group. This resulted in a difference of 37.5% of the total good and excellent satisfaction scores between ibuprofen and placebo groups and a 43.3% difference between the acetaminophen and placebo groups. Satisfaction was not significantly different in the two groups of acetaminophen and ibuprofen (P=0.219). In addition, it was not significantly different in the control group compared to the ibuprofen group (P=0.075). However, satisfaction was significantly different compared to the acetaminophen group (P=0.001).

If the pain was not controlled with the prescribed drugs,(a fentanyl (pain control) pump was used) meperidine was administered to the patients.

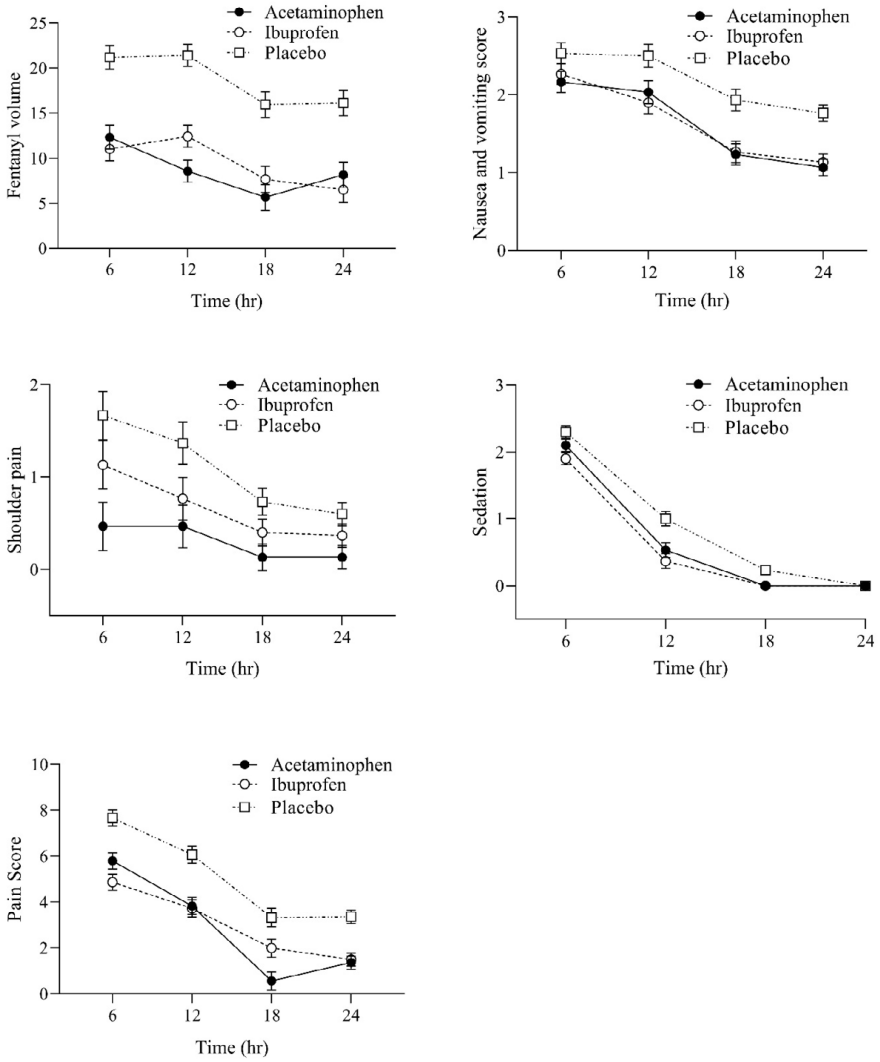

Figure 2: Profiles of outcomes in the three groups under study over time

Table 1: Descriptive statistics

Outcome	Variable	Ibuprofen group	Acetaminophen group	Placebo group
Fentanyl consumption		43.3	53.3	80
Nausea and vomiting Score (%)		51.6	59.6	26.6
Pain score mean VAS		3.02	2.89	5.10
Shoulder pain score mean VAS		0.667	0.3	1.092
SedationScore1 %		65.83%	61.6%	51.6%

The control group (80%) had the highest need for meperidine compared to 53.3% of the patients in the acetaminophen group and 43.3% of the patients in the ibuprofen group. The mean doses that were required were 55.00 mg in the control group, 18.33 mg in the acetaminophen group, and 14.16 mg in the ibuprofen group. 66.67% of patients in the acetaminophen and 74.25% of patients in the ibuprofen groups required less meperidine at 6 h after surgery, respectively, compared to the placebo group (significantly different in the two groups). However, at 18 and 24 h after surgery, the difference in pain intensity was not significant.

During the study, all patients were monitored for side effects related to ibuprofen (such as gastric ulcer, gastrointestinal bleeding, and allergic reactions) and acetaminophen (such as blood disorders, skin rash, and acute pancreatitis) (Table 1).

Table 2: Results of repeated measures ANOVA for variables and outcomes of interest

Outcome	Variable	F(df1, df2)	*P*-value	Partial η^2
Fentanyl consumption				
	Time	F (2.61, 226.70)= 45.39	<0.001	0.34
	Group	F (2, 87)= 21.22	<0.001	0.33
	Time×Group	F (5.21, 226.70)= 4.54	<0.001	0.09
Nausea and vomiting				
	Time	F (2.54, 221.06)= 54.23	<0.001	0.38
	Group	F (2, 87)=13.47	<0.001	0.24
	Time×Group	F (5.08, 221.06)= 0.92	0.47	0.02
Abdominal Pain score				
	Time	F(2.66, 231.85)= 155.21	<0.001	0.64
	Group	F (2, 87)= 22.63	<0.001	0.34
	Time×Group	F (5.338, 231.85)= 3.21	0.007	0.07
Shoulder pain score				
	Time	F (1.8, 156.67)= 22.96	<0.001	0.21
	Group	F (2, 87)= 5.67	0.005	0.11
	Time×Group	F (3.6, 156.67)= 1.85	0.13	0.04
Sedation				
	Time	F (2.48, 215.89)= 686.18	<0.001	0.89
	Group	F (2, 87)= 10.24	<0.001	0.19
	Time×Group	F (4.96, 215.89)= 4.8	<0.001	0.10

Table 3: The comparison of meperidine dose and patient satisfaction in the three studied groups

	Acetaminophen	Ibuprofen	Placebo		*P*-value
Meperidine dose(mg)	18.33±22.67	14.16±19.34	55.0±41.21	F(2, 54.62)= 12.1	<0.001
Patient satisfaction	3.43±0.62	3.13±0.73	2.60±0.85	F(2, 87)= 9.68	<0.001

The results of repeated measures and ANOVA related to the profiles in Figure 1 are shown in Table 2. Overall, all the outcomes significantly decreased over time (*P*=0.001). Furthermore, the mean of variables was significantly different among the three groups, where the placebo group had higher values relative to the intervention groups (*P*=0.001). The effect of the intervention groups was moderate to large, indicating noticeable differences among the three groups. The interaction between time and group (the Time×Group effect) was significant for fentanyl consumption, abdominal pain score, and sedation. The mean dose of meperidine and patient satisfaction with pain control among the three groups are compared in Table 3. Acetaminophen and ibuprofen had similar averages in both outcomes (*P*>0.26). However, both groups gave more desirable results than the placebo group (*P*<0.001).

DISCUSSION

Currently, the use of narcotic analgesics is one of the best approaches to control pain[8]. Narcotic analgesics affect the central nervous system, but they cannot block the inflammatory component of pain[9,10]. Eliminating the inflammatory response may reduce the need for opioids and strengthen the control of postoperative processes[11,12]. In this study, patients' mean age and sex in all the groups were not significantly different.

One of the important objectives of this study was to investigate whether the use of drugs such as ibuprofen and acetaminophen, as pain-ameliorating agents, could reduce the patient's need for narcotic drugs and, in turn, reduce the side effects of drug use. In addition, the rate of nausea/vomiting, sedation, surgical site pain, and shoulder pain decrease over time regardless of the group's drug effect.

Saryazdi et al. examined the effect of the intravenous prodrugs ketorolac and paracetamol on analgesia after abdominal surgery. The pain intensity in the paracetamol group was higher than in the ketorolac group. In addition, during the recovery period, 12.5% of the paracetamol group and 37.5% of the ketorolac group experienced nausea and vomiting, which was significantly different between the two groups. However, satisfaction was not significantly different between the two groups. Ketorolac caused less than

20.28% pain experience compared to paracetamol in the recovery phase. However, it caused 66.6% more nausea and vomiting than paracetamol[15]. In the present study, the severity of pain, nausea and vomiting, and satisfaction were not significantly different between the two groups. The reason for the difference between the results of these two studies could be because of the time of drug injection and the time of indicator measurement. Amrimaleh et al. investigated the analgesic effect of intravenous paracetamol and meperidine with meperidine alone. The rate of meperidine injection was less in the paracetamol group. The pain intensity was significantly higher immediately after surgery and 12 h later in the control group. In this study, the paracetamol group experienced 22.87% less pain than the control group and 53.94% had less need for meperidine[16]. This result was similar to the result of the present study in which the administration of intravenous acetaminophen significantly reduced the need for opioids. Furthermore, Imani et al. evaluated the effect of adding intravenous acetaminophen to fentanyl. The acetaminophen group had 20.83% less pain, 67% less nausea and vomiting, and 48% more satisfaction compared to the control group. They reported that 10% of the control group and 3.3% of the acetaminophen group required medication to control them. The rate of good and excellent satisfaction was 46.8% in the control group and 90% in the acetaminophen group, which was also a significant difference[17]. The results of our study were completely consistent with this study.

On the other hand, Naghibi et al. [18]evaluated the effect of intravenous ibuprofen. All patients received morphine if they felt pain. The mean volume of morphine consumption was 43.5 mg in the ibuprofen group and 0.54 mg in the control group, which was a significant reduction of 19.4% in the ibuprofen group. There was no significant difference between nausea and vomiting in ibuprofen and control groups. These findings were similar to our study in terms of reducing the severity of pain and the need for opioids in the ibuprofen group. In addition, Menhinick et al. evaluated the effectiveness of ibuprofen and its combination with acetaminophen in pain control. The rate of pain reduction over time was 71% in the placebo, 76% in the ibuprofen, and 96% in the two-drug groups. There was no significant difference between ibuprofen and placebo in terms of pain intensity. The level of satisfaction in the three groups was also not significantly different[19].

Limitations

This study has some limitations. The weight and height of the patients were not recorded. The duration of anesthesia was not evaluated. In addition, complications such as ileus and constipation were not assessed. Furthermore, it would have been possible to record results that are more comprehensive if the patients had been followed for a longer time.

Suggestions

Clinical trials with larger sample sizes are recommended to get more accurate results, assess more complications, and record and evaluate the height, weight, and complications (such as ileus). We also suggest that a group of healthcare professionals, such as physicians, students, and nurses, work in a regular and coordinated manner during research. This will decrease the errors and facilitate achieving results more rapidly.

CONCLUSION

The use of both intravenous acetaminophen and ibuprofen in pain control after surgery can reduce the need for opioid use. Acetaminophen can also be a suitable alternative for postoperative pain control in patients that are unable to use NSAIDs.

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CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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