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The Effect of Adding Ondansetron and Metoclopramide to Intravenous Acetaminophen on Pain Control and Post-operative Nausea and Vomiting: A Randomized Double-blind Clinical Trial

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Abstract

Background: Pain and postoperative nausea and vomiting (PONV) are two common complications of laparoscopic cholecystectomy, highlighting the particular importance of increasing satisfaction among patients undergoing this surgery.

Aim: This study was performed aimed to evaluate the effect of adding ondansetron and metoclopramide to intravenous acetaminophen on pain control and postoperative nausea and vomiting of patients undergoing laparoscopic cholecystectomy.

Method: This double-blind clinical trial study was conducted in 2019 on 83 patients in the central operating room of Ghaem Hospital in Mashhad, Iran. The patients were randomly assigned to three groups. The first and second groups received intravenous acetaminophen with ondansetron at doses of 4 and 8 mg, respectively, and the third group received intravenous acetaminophen with metoclopramide. Pain and PONV scores were measured postoperatively. Data were analyzed by SPSS (version 25.0) and GEE model, Chi-square, ANOVA and Kruskal-Wallis tests. $P<0.05$ was considered statistically significant.

Results: Patients in the first and second groups experienced more pain than those in the third group at the time of entering the recovery, leaving the recovery, and 6 h after the surgery ($P<0.001$). However, the PONV scores were not significantly different among the three groups ($P=0.812$).

Implications for Practice: The co-administration of metoclopramide and acetaminophen was more effective than acetaminophen and ondansetron in controlling postoperative pain of laparoscopic cholecystectomy.

Keywords: Acetaminophen, Metoclopramide, Ondansetron, Pain control, PONV

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Introduction

Although laparoscopic surgery causes less postoperative pain than open surgery, however, the pain at the site of the laparoscopic port incision and in the shoulder and upper abdomen are the main complaints. Moreover, since postoperative nausea and vomiting (PONV) is the other complaints of these patients, it is important to adopt measures to address this issue (1-5).

Today, acetaminophen is one of the most widely used analgesics due to its efficacy, safety, low side effects, and rare drug interactions (5, 6). Acetaminophen has different mechanism of actions that some of them have not been identified yet. It controls pain by preventing the production of prostaglandin E2, indirectly activating the cannabinoid receptor type 1, inhibiting the nitric oxide system by involving N-methyl-D-aspartate and substance P, and directly by stimulating descending serotonergic pathways that hinder pain signals transmitted by the spinal cord. Serotonin 5-Hydroxytryptamine (5-HT_3) receptor antagonists, such as ondansetron, are at the front line of PONV treatment (7, 8). Furthermore, use of intravenous acetaminophen can also reduce PONV and the rate of antiemetic consumption (9-12). PONV is a common complication with a prevalence rate of 20-30% (3, 10). Ondansetron is the selective 5-HT_3 antagonist which is effective in the prevention of PONV particularly if administered prior to the onset (3). In laparoscopic cholecystectomy, ondansetron administration can reduce the incidence of PONV in the first 4 h after the surgery (1). Ondansetron, in addition to triggering zone chemoreceptor in the medulla oblongata, affects the 5-HT_3 receptor in the spinal cord on the pathway that modulates pain transmission signals. Some studies proposed that since ondansetron has antagonistic effects on 5ht3 receptors, it can reduce analgesic effects of acetaminophen. Therefore, ondansetron may be present at the 5-HT3 receptor of acetaminophen antagonist since the two medications have opposite effects on the 5-HT3 pathway (7).

However, other studies have not concluded that co-administration of 5ht3 antagonists such as ondansetron and tropisetron could reduce the analgesic effects of acetaminophen. Moreover, review of literature showed one study which claimed direct analgesic effects for 5-HT_3 antagonists (7, 12-17). Metoclopramide is another medication used to control PONV, and some studies reported the analgesic effects of this medication (18-22). Khazaei et al. and Karacabey et al. examined the effect of metoclopramide on migraine headaches and confirmed the results of previous studies regarding the positive effect of metoclopramide in reducing such headaches (19, 20). Ceyhan and colleagues conducted an experimental study on male rats and reported that metoclopramide could reduce incisional pain (22).

Contrary to the laboratory results, the findings of some clinical studies have indicated that ondansetron did not reduce or even increased the analgesic effect of acetaminophen; however, the results of some studies have reported the blockage or reduction of this effect. According to our researches, there was no study on analgesic effect of co-administration of metoclopramide and acetaminophen and comparing its analgesic effect with ondansetron; therefore, this study was performed aimed to evaluate the effect of adding ondansetron and metoclopramide to intravenous acetaminophen on pain control and postoperative nausea and vomiting of patients undergoing laparoscopic cholecystectomy.

Methods

This double-blind clinical trial study with a parallel design was conducted in 2019 on patients undergoing laparoscopic cholecystectomy in the central operating room of Ghaem Hospital in Mashhad, Iran. According to the study by Koyunco et al. (7), the sample size was estimated to be 25 patients in each group by confidence level of 95% and power of 80%; finally, considering the possibility of 10% drop, 28 patients were considered in each group The study population consisted of all patients undergoing laparoscopic cholecystectomy. Participants were selected by Convenience Sampling method and entered the study after obtaining the written informed consent. The subjects were randomly allocated to three groups using the selection of sealed envelopes by the researcher. The first group (group A) received 1 g of intravenous acetaminophen by infusion 30 minutes before the end of surgery plus 4mg of ondansetron at the end of procedure. The second group (group B) was administered 1 g of intravenous acetaminophen by infusion 30 minutes before the end of surgery plus 8 mg of ondansetron at the end of procedure. The third group (group C) took 1 g of intravenous acetaminophen by infusion 30 minutes before the end of surgery plus 10 mg of metoclopramide at the end of procedure. Postoperative pain was measured as a primary outcome using the Numeric Rating

Scale (NRS) after transferring the patient to the recovery room when patients' consciousness returned, before leaving the recovery room and 6 h after the operation in the ward. According to this scale, patients were asked to score their pain from a score of 0= no pain to 10= the most pain they have ever experienced. The validity and reliability of this scale have been investigated in various studies (23,24). Analgesic drug (other than acetaminophen) was injected for patients who had NRS score of > 4.

Demographic data, including age, weight, gender, and the duration of surgery were also recorded. The severity of nausea and vomiting before leaving the recovery was assessed by the PONV scale, which was developed by Wengritzky et al., who also evaluated its validity and reliability. In this 4-item scale, the highest score of items one or two is multiplied by the scores of items three and four to render the PONV score in the first 6 h after surgery (25).

The inclusion criteria were: class I and II ASA age of 18-64 years, ability to communicate, no drug addiction, no analgesic administration in the last 24 h, no ondansetron or metoclopramide intake in the last 24 h, no chronic pain, and no history of sensitivity to acetaminophen, ondansetron, and metoclopramide.

The exclusion criteria were: unusual and severe side effects of anesthesia, such as a severe drop (more than 50% of the baseline) in systolic blood pressure and heart rate that doesn't respond to initial treatment, surgical complications which turned the procedure into an open surgery or despite managing the surgery with the closed approach, the operation lasted for more than 50% of the average of other operations, and the incidence of PONV, which required treatment with any of the medications in the family of 5-hydroxytryptamine inhibitors.

All participants were completely monitored. General anesthesia was induced with propofol 2.5 mg/kg, atracurium 0.5 mg/kg, fentanyl 2 mcg/kg, and midazolam 20 mcg/kg. Maintenance of anesthesia was continued with propofol at a dose of 100-200 mcg/kg/min and remifentanil at a dose of 0.2-0.3 mcg/kg/min. The laparoscopic procedure and employed equipment were identical for all patients.

In addition to the patients and the statistical analyzer, the person completing the NRS and PONV scales was also blinded to the groups. Kolmogorov-Smirnov test was applied to assess the normal distribution of quantitative variables. Qualitative variables were expressed in the form of frequency and percentage, quantitative variables in the form of mean (standard deviation), or with median (1st and 3rd quarters) in the case of a non-normal distribution. Chi-square and Fisher's exact test were used to evaluate the equality of proportions of qualitative variables among the three groups. Analysis of variance was used to compare the mean of quantitative normal variables in the three groups. The marginal model of generalized estimate equations (GEE) was used for intragroup and intergroup comparisons. Bonferroni's post hoc test was used for pairwise comparisons. Data was analyzed using SPSS software (version 25.0). $P< 0.05$ was considered statistically significant.

Ethical considerations

This research was approved by the Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran (Ir.mums.medical.rec.1397.593) and registered in the Iranian Registry of Clinical Trials (IRCT20160516027925N4). Informed consent was obtained from the patients before entering the study. All the conditions, the possibility of study withdrawal and how to access the results were explained to the participants orally and in written form. The data of this study can be obtained by sending an email request to the corresponding author while maintaining the confidentiality of the patients' information.

Results

A total of 84 individuals participated in this study, among them 1 case in the third group was excluded due to surgical complications leading to open surgery (Figure 1). In the acetaminophen + ondansetron 4mg (group A), acetaminophen + ondansetron 8mg (group B), and acetaminophen + metoclopramide (group C), 77.8%, 75.0%, and 74.1% of the patients were female, respectively. According to the Analysis of variance, Chi-square and Kruskal Wallis tests, all three groups were homogeneous in terms of gender (P=0.947), age (P>0.802), weight (P=0.724), and the duration of surgery (P>0.99). The summary of demographic information and the duration of surgery were presented in Table 1.

The patients' PONV mean scores in the acetaminophen + ondansetron 4mg (group A), acetaminophen + ondansetron 8mg (group B), and acetaminophen + metoclopramide (group C) groups were

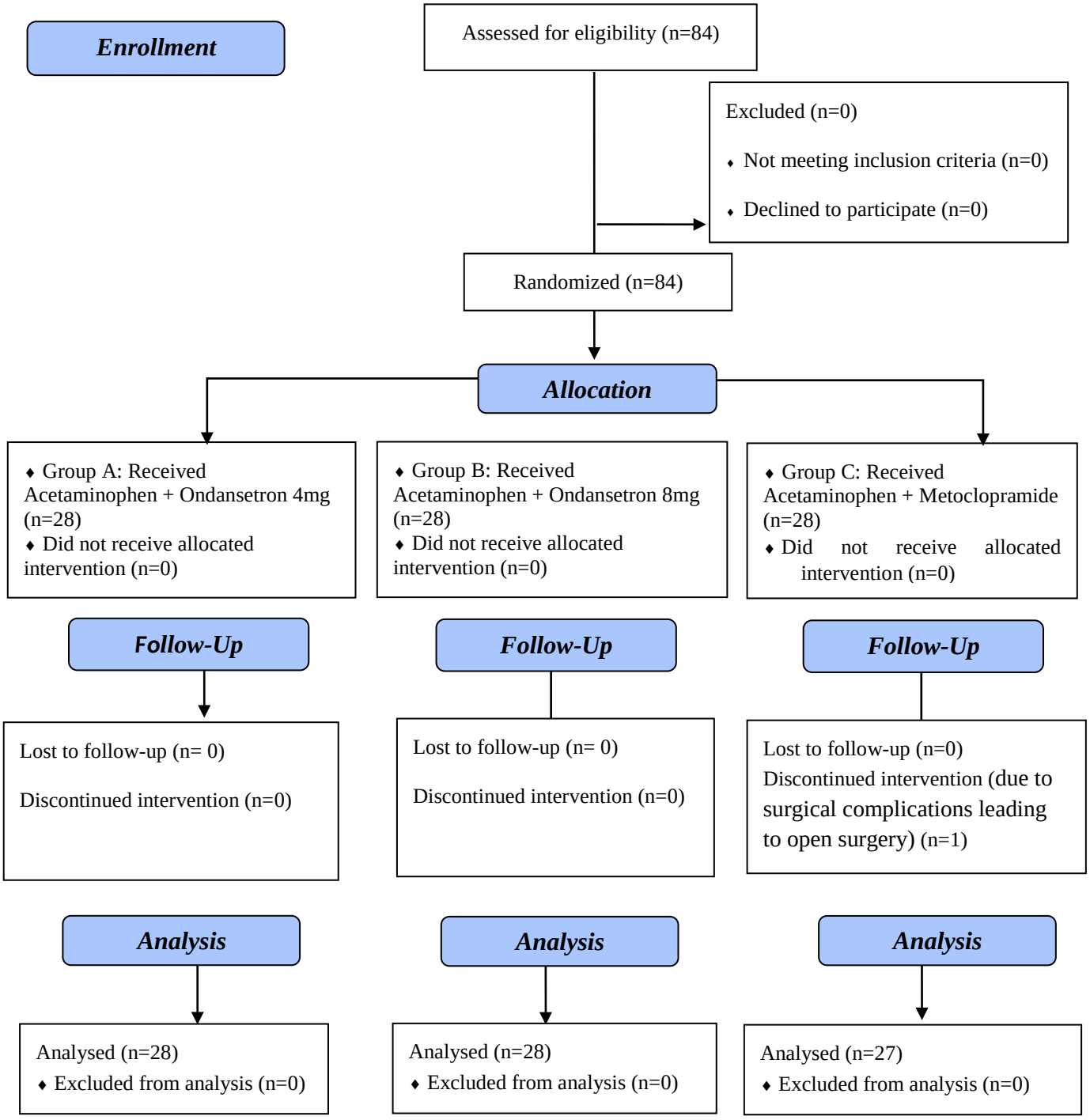

Figure 1. CONSORT flow diagram of the study

calculated at 160.61±241.31, 127.39±206.19, and 137.15±214.23, respectively. Kruskal-Wallis test showed no significant difference among the three groups in terms of PONV mean scores (P=0.812). A summary of the main findings was provided in Table 2.

The mean of the interval between the end of surgery and the first analgesia injection were obtained at 2.14±1.18, 1.79±0.74, and 3.76±1.22 h in the A, B and C groups, respectively. Kruskal-Wallis test showed significant difference among the three groups in this regard (P<0.001). The results of Bonferroni's post hoc test revealed no significant difference between the A and C groups (P>0.999); however, significant differences were observed between the A and B groups (P<0.001) and the B and C groups (P<0.001).

Table 1. The patients' characteristics according to gender, weight, age and duration of surgery in three groups

Variable		intervention1	intervention2	control	Statistic P-value
Gender[a]	Male	6 (22.2)	7 (25.0)	7 (25.9)	$\chi2$=0.109 P =0.947[*]
	Female	21 (77.8)	21 (75.0)	20 (74.1)	
Age (years)[b]		45.75±12.16	45.75±12.16	43.74±14.33	F=0.221 P=0.802[**]
Weight (kg)[b]		62.14±4.58	62.21±4.63	61.22±5.95	F=0.324 P=0.724[**]
Duration of surgery (minutes)[c]		59.11±9.43 60 (50 , 65)	59.11±9.43 60 (50 , 65)	59.07±9.61 60 (50 , 65)	H=0.000 P>0.999[***]

[a] was expressed in frequency (percentage), [b] mean±standard deviation, [c] mean±standard deviation with median (1st quarters, 3rd quarters) in the case of a non-normal distribution.
[*] Chi-square [**] ANOVA [***] Kruskal-Wallis

The mean of pain score at the time of the first analgesia injection were estimated at 6.54±1.07, 6.79±0.83, and 7.04±8.60 in the A, B and C groups, respectively. Kruskal-Wallis test showed no significant difference among the three groups in this regard (P<0.001). The results of Bonferroni's post hoc test showed no significant difference between the A and B groups (P=0.958); nevertheless, significant difference was found between the A and C groups (P<0.001) and the B and C groups (P<0.001).

This difference was also observed in the pain score at the time of the second analgesic injection. The pain scores in the acetaminophen + ondansetron 4mg (A) and acetaminophen + ondansetron 8mg (B) groups were significantly different from those of the acetaminophen + metoclopramide (C) group (P<0.002 and P<0.001, respectively). Kruskal-Wallis test did not show a significant difference in the mean score of the interval between the first and second analgesic injections (P=0.794).

Figure 2 indicated that the mean scores of postoperative pain scores after return of consciousness,

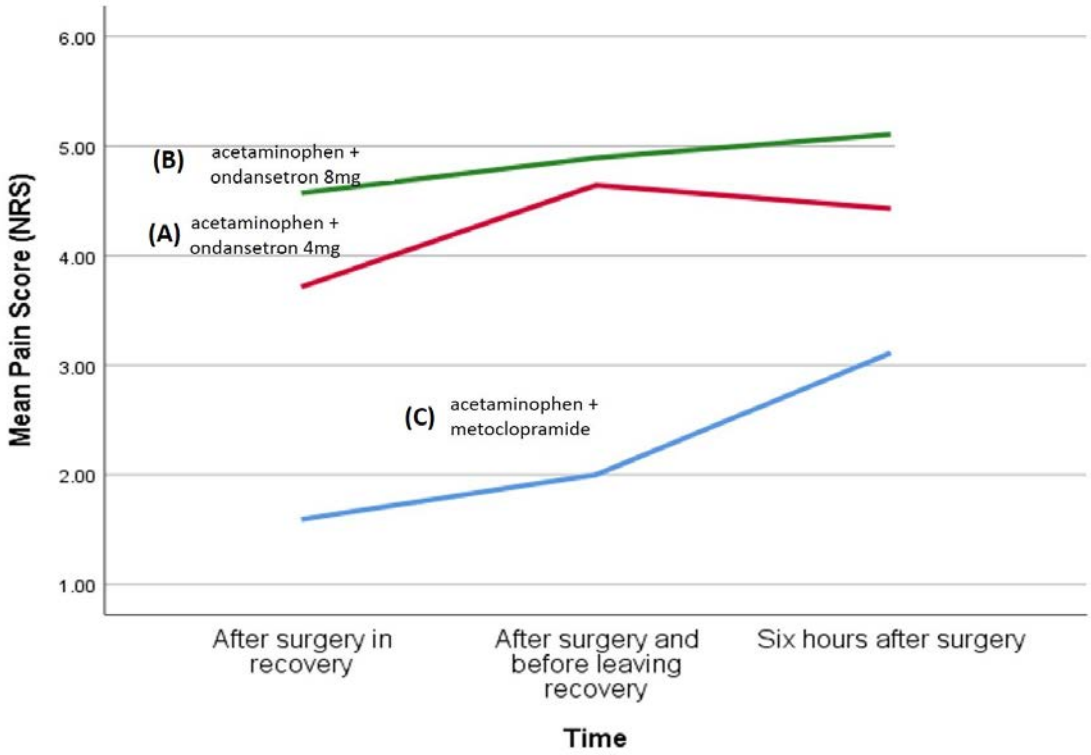

Figure 2. Mean pain score during three time points in the three groups

Table 2 .Mean of the time interval between surgery and injection of painkillers, pain score, and nausea and vomiting in three groups

Variable	Group	N	Mean±SD Median (Q1, Q3)	Statistic P-value	Pairwise Comparisons
Pain score at the time of first time painkiller injection	acetaminophen + ondansetron 4mg (A)	28	6.54±1.07 7 (6, 7)	H=25.034 P<0.001*	A vs C P<0.001* B vs C P<0.001* A vs B P=0.958
	acetaminophen + ondansetron 8mg (B)	28	6.79±0.83 7 (6, 7)		
	acetaminophen + metoclopramide (C)	27	7.04±8.60 5.00 (5.00, 6.00)		
Pain score at the time of second time painkiller injection	acetaminophen + ondansetron 4mg (A)	18	6.00±0.34 6 (6, 6)	H=19.410 P<0.001*	A vs C P=0.002* B vs C P<0.001* A vs B P=0.436
	acetaminophen + ondansetron 8mg (B)	20	6.25±0.44 6 (6, 6.75)		
	acetaminophen + metoclopramide (C)	6	5.17±0.41 5 (5, 5.25)		
The time interval between surgery and the first injection of painkillers	acetaminophen + ondansetron 4mg (A)	28	2.14±1.18 2 (1.25, 2.75)	H=34.678 P<0.001*	A vs C P>0.999 B vs C P<0.001* A vs B P<0.001*
	acetaminophen + ondansetron 8mg (B)	28	1.79±0.74 2 (1, 2)		
	acetaminophen + metoclopramide (C)	27	3.76±1.22 4.00 (3.00, 4.00)		
The time interval between surgery and the second injection of painkillers	acetaminophen + ondansetron 4mg (A)	18	5.72±0.46 6 (5, 6)	H=461 P=0.794	-
	acetaminophen + ondansetron 8mg (B)	20	5.80±0.41 6 (6, 6)		
	acetaminophen + metoclopramide (C)	6	5.83±0.41 6 (5.75, 6)		
PONV Score	acetaminophen + ondansetron 4mg (A)	28	160.61±241.31 9 (6, 300)	H=0.417 P=0.812	-
	acetaminophen + ondansetron 8mg (B)	28	127.39±206.19 10 (6.5, 275)		
	acetaminophen + metoclopramide (C)	27	137.15±214.23 8.00 (3.00, 300)		

* Kruskal-Wallis test

leaving the recovery, and 6 h after the end of surgery were different in the three groups. According to the GEE model, the NRS score was significantly different in the three groups (Table 3) (P<0.001). Bonferroni's post hoc test indicated that the acetaminophen + ondansetron 4mg (A) and the acetaminophen + ondansetron 8mg (B) groups were significantly different from the acetaminophen + metoclopramide (C) group (P<0.001 and P<0.001, respectively).

In the intragroup analysis for three time points, only the acetaminophen + metoclopramide (C) group had a significant difference (P<0.001). According to Bonferroni's post hoc test, the difference was observed at the time of leaving recovery and six hours after surgery (P<0.001), and the time of entering recovery and six hours after surgery (P<0.001). The results of the GEE model (Table 3) showed more details.

Table 3. The results of the GEE model of the studied variables on pain score after surgery

Group	Time	Mean±SD Median (Q1 , Q3)	Pairwise Comparisons
acetaminophen + ondansetron 4mg (A)	After surgery in recovery (1)	3.71±2.48 3 (2 , 6.75)	1 vs 2 p= 0.512
	After surgery and before leaving recovery (2)	4.64±2.08 4 (3 , 6.75)	1 vs 3 p= 0.368
	Six hours after surgery (3)	4.43±1.83 6 (3 , 6)	2 vs 3 p>0.999
acetaminophen + ondansetron 8mg (B)	After surgery in recovery (1)	4.57±2.06 3 (3 , 7)	1 vs 2 p>0.999
	After surgery and before leaving recovery (2)	4.89±2.02 4 (3 , 7)	1 vs 3 p= 0.441
	Six hours after surgery (3)	5.11±1.57 6 (3 , 6)	2 vs 3 p>0.999
acetaminophen + metoclopramide (C)	After surgery in recovery (1)	1.59±1.67 2 (0 , 2)	1 vs 2 p= 0.275
	After surgery and before leaving recovery (2)	2.00±1.00 2 (2 , 3)	1 vs 3 p<0.001
	Six hours after surgery (3)	3.11±1.78 3 (2 , 5)	2 vs 3 p<0.001
Tests of Model Effects	Time (Wald Chi-Square: 17.858; P-value<0.001) Group (Wald Chi-Square: 77.874; P-value<0.001)		
Pairwise Comparisons	Control vs Intervention 1<0.001 Control vs Intervention 2<0.001 Intervention 1vs Intervention 2: 0.198		

Discussion

According to the results of the present study, the patients in the A and B groups who received ondansetron at doses of 4 and 8 mg with acetaminophen, respectively, experienced more pain than the group C who were administered 10 mg of metoclopramide with acetaminophen. Although the group B received a higher dose of ondansetron but had higher mean pain scores than the group A. The results of the study conducted by Ramirez et al. on the interaction and analgesic effect of I.V acetaminophen with 5-HT_3 antagonists showed that the pain score in the acetaminophen and ondansetron group was not significantly different from the acetaminophen plus droperidol group, which is a dopamine antagonist similar to metoclopramide. Nevertheless, the administration of morphine in the ondansetron group was 3 times higher, which could indicate the contradictory effect of the 5-HT_3 antagonist with acetaminophen (14). In the present study, the time of the first analgesia injection in acetaminophen + ondansetron 8mg (B) group was sooner than acetaminophen + ondansetron 4mg (A) group that could show the contradictory effect of the 5-HT3 antagonist with acetaminophen.

Some discrepancy between the results of the mentioned study and the present study can be explained by the different time intervals for assessing the pain scores. Ramirez et al. also investigated this interaction in tonsillectomy among children and suggested the necessity of further studies in other surgeries (14). The findings of other studies indicate a reduction in the analgesic effect of acetaminophen when used concomitantly with 5-HT_3 antagonists (7, 15). In the study performed by Koyuncu et al. on patients with abdominal hysterectomy, the postoperative pain scores were higher I those receiving acetaminophen plus ondansetron than those who received acetaminophen alone (7).

In some studies, the concomitant use of acetaminophen and 5-HT_3 antagonist not only did not reduce the analgesic effect of acetaminophen but also increased its analgesic effect (12, 13). Bhosale et al. reported that the co-administration of ondansetron and paracetamol did not decrease the analgesic effect of paracetamol (13). Based on the results of the above mentioned study, after taking acetaminophen, the concentration of serotonin will be increased, which is one of the mechanisms that acetaminophen inserted its analgesic property, however, 5-HT_3 antagonists, such as ondansetron, can

block it; nonetheless, their investigation has concluded differently when examined in clinical studies. This differences in the results can be attributed to two reasons; firstly, the mentioned study was performed on patients with local anesthesia and secondly, a small sample size (n=20) may be the effect of other analgesic mechanisms of acetaminophen other than increased serotonin. Furthermore, the findings of the studies by Bhosale et al. and Tiippana et al. have reported the independent analgesic effects of 5-HT_3 antagonist (13,17).

Another similar study was performed by Akhondi et al. on patients who underwent upper extremity fracture surgery, and the results revealed that the concomitant use of Apotel (I.V Acetaminophen) and ondansetron could reduce pain more than the administration of Apotel alone. One of the reasons for this difference in the results of their research with those of other studies could be related to the different types of surgery and methods of medication injection. In the present study, the medications were given to the patients in the forms of bolus and infusions for 30 min, but in the mentioned study, 4 ml/h of Apotel and ondansetron (4 mg ondansetron + 2 g Apotel + 100 ml normal saline) was infused during 25 h using a patient-controlled analgesia pump (12).

The results of the mentioned study also indicated that the difference between the doses of pethidine administered as an analgesic after the surgery was not significant in the control and intervention groups, which was inconsistent with the assumption that Apotel with ondansetron leads to more analgesia than Apotel alone. In the present study, although the dose of ondansetron was increased from 4 mg to 8 mg and the mean pain scores were lower in patients receiving a lower dose of ondansetron, the results of the Kruskal-Wallis test showed no statistically significant differences. Nevertheless, in the acetaminophen + metoclopramide (C) group, metoclopramide not only controlled PONV (none of the three groups showed a statistically significant difference in PONV score regardless of the intervention), but also reduced pain more than the other medication administered in the other two groups.

Regarding the higher analgesic effect of acetaminophen in the presence of metoclopramide in the acetaminophen + metoclopramide (C) group, it can be stated that in addition to the fact that this increase might be due to the lack of blocking effect of acetaminophen on increasing serotonin compared to ondansetron, a reduction in pain could also be due to the analgesic effects of metoclopramide. Various studies have been performed to investigate the analgesic effects of metoclopramide. Mecklem et al. compared the effect of concomitant injections of Propofol plus lidocaine with metoclopramide plus Propofol. They concluded that the pain scores were similar in both groups and metoclopramide could be effective in controlling pain at the time of Propofol injection, as the same as lignocaine (21). An experimental study carried out by Ceyhan et al. revealed that the analgesic effect of metoclopramide on skin incisions was similar to that of tramadol (22).

Moreover, numerous studies have been performed to examine the effect of metoclopramide on reducing nausea and migraine headaches, the results of which were indicative of the positive effect of metoclopramide on reducing patients' pain scores (19, 20).

Considering that the acetaminophen + metoclopramide (C) group experienced less pain in all three time points than the acetaminophen + ondansetron 4mg (A) and acetaminophen + ondansetron 8mg (B) groups, this finding revealed that the analgesic effect of metoclopramide with acetaminophen was at its highest level when the patient regained full consciousness, while over time, patients' pain increased as the clinical effect of the drug decreased.

Implications for practice

Considering the equal efficacy of metoclopramide and ondansetron (5-HT_3 antagonist) in reducing PONV and the greater efficacy of co-administration of metoclopramide and acetaminophen in controlling postoperative pain after laparoscopic cholecystectomy, it seems that the concomitant use of metoclopramide and acetaminophen is more logical for controlling PONV and pain after laparoscopic cholecystectomy.

One of the limitations of the present study was related to the high prevalence of PONV after laparoscopic cholecystectomy, it was immoral to consider a group without receiving anti-nausea as a control. Other limitation was confounding effect of variables on pain that was tried to be controlled by random allocation of cases in three groups, injected analgesic drugs after surgery for patients with NRS score >4, and the same conditions of surgical procedure and anesthesia drugs during surgery.

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Conflicts of interest
The authors declared no conflict of interest.

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