

Effect of Ondansetron and Dexamethasone as antiemetics on postoperative pain and nausea

Postoperative pain and nausea

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Abstract

Aim: The aim of this study was to investigate the effect of the use of ondansetron and dexamethasone as an antiemetic in laparoscopic cholecystectomy surgery on postoperative tramadol consumption.

Material and Method: This prospective, randomized, double-blind study included 90 ASA I-II patients, aged 18-60 years who had planned to undergo laparoscopic cholecystectomy surgery. The patients' ECG, blood pressure, cardiac rate, and peripheral oxygen saturation were monitored. Prior to anesthesia induction, an injection was administered from two syringes, which had been prepared with medications by another person. Intravenous injection of 4 mg of ondansetron (2 ml) and saline (2 ml) was administered to Group O (n=25), injection of 8 mg of dexamethasone (2 ml) and saline (2 ml) was administered to Group D (n=25) and injection of 4 mg of ondansetron (2 ml) and 8 mg of dexamethasone (2 ml) was administered to Group OD (n=25). Standard anesthesia induction was performed on all patients and was maintained with 1-2% sevoflurane, 50% nitrogen protoxide, and 50% oxygen. Immediately after the gall bladder was removed, a patient-controlled analgesia (PCA) device was loaded with 1.5 mg/kg tramadol. The PCA device was set to a bolus dose of 30 mg with a locked period of 10 min. In all of the groups, hemodynamic changes, pain scores (numeric rating scale -NRS), analgesia consumption (mg), potential side-effects of nausea and vomiting and sedation scores were evaluated at postoperative 5, 15, 30, 45 and 60 minutes in the recovery room and at 4, 8, 12 and 24 hours in the ward. **Results:** No statistically significant difference was determined with respect to the heart rate, mean arterial pressure and oxygen saturation values in the 24-hour postoperative follow-up period ($p>0.05$). The consumption of total tramadol was lower compared to that of ondansetron ($p=0.002$). In patients who received both dexamethasone and ondansetron, the pain scores and total tramadol consumption were statistically significantly lower from the postoperative 45th minute onwards compared to other groups ($p<0.001$).

Discussion: The combination of ondansetron and dexamethasone was more effective in preventing severe problems of nausea, vomiting, and pain following laparoscopic cholecystectomy compared to the use of ondansetron or dexamethasone alone.

Keywords

Nausea; Vomiting; Pain; Ondansetron; Dexamethasone

DOI: 10.4328/ACAM.20158 Received: 2020-03-10 Accepted: 2020-04-13 Published Online: 2020-04-20 Printed: 2021-01-01 Ann Clin Anal Med 2021;12(1):60-64

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Introduction

Nausea and vomiting are often observed following laparoscopic cholecystectomy surgery with a reported incidence of 53%-72%. This results in the aspiration of gastric contents increased intraocular pressure and psychological stress, which then delays recovery and discharge from the hospital [1,2]. Thus, antiemetics are used alone or in combination for nausea and vomiting prophylaxis [1,2]. Frequently used medications include droperidol, metoclopramide, diphenhydramine, dexamethasone, propofol, oxygen, and ondansetron. In recent years, there has been an increasing number of studies demonstrating the use of dexamethasone alone or in combination with a serotonin receptor antagonist, such as ondansetron, which has been effective in postoperative nausea and vomiting prophylaxis [1,2]. However, the antiemetics used may have an interaction with the analgesia used for postoperative pain, and the anti-nociceptive effects may be antagonized [3-5].

Tramadol is an analgesic that is known to be centrally effective. In addition to a mild opioid effect, it inhibits the presynaptic reuptake of noradrenaline and serotonin and stimulates serotonin expression at the level of the spinal cord. With regard to the role of spinal serotonin receptors in pain transmission, it is thought that the efficacy of serotonin selective antagonists, such as ondansetron, may be reduced [4,5]. Several studies have shown that postoperative tramadol consumption is increased with the use of ondansetron, which is often used in the treatment of nausea and vomiting associated with surgery or tramadol [3-5]. However, although dexamethasone alone is known to be effective in acute visceral pain and has a synergistic interaction with tramadol, to the best of our knowledge, no studies have examined the interaction of tramadol with the combination of ondansetron and dexamethasone for nausea and vomiting prophylaxis.

The aim of this study was to investigate the effect of ondansetron and dexamethasone used together as an antiemetic in laparoscopic cholecystectomy surgery on postoperative tramadol consumption.

Material and Methods

This study consisted of 90 ASA 1-II patients, aged 24-60 years, who had planned to undergo laparoscopic cholecystectomy surgery. Patients with severe coronary, renal and liver disease, stone retention, or a previous history of postoperative nausea and vomiting; those who would not be able to use the patient-controlled analgesia device; epileptic patients who are dependent on medication; patients with a history of peptic ulcer; patients who received antidepressant therapy; and patients with an allergy to ondansetron, dexamethasone or tramadol were excluded from the study. Approval for the study was granted by the Local Ethics Committee, and informed consent was obtained from all of the patients.

All patients were verbally informed about the patient-controlled analgesia pump system (Abbott Pain Management Provider-USA), which was used to evaluate pain using the Numerical Rating Scale (from 0 = no pain to 10 = intolerable pain). In the operating room, the ECG; systolic, diastolic and mean blood pressures; heartbeat rate; and peripheral oxygen saturation were monitored. In all of the patients, an intravenous route was

opened preoperatively on the dorsal hand, and saline infusion of 5-10 ml/kg was initiated. Prior to anesthesia induction, an injection was administered from two syringes that had been prepared with medications by another person. An intravenous injection of 4 mg of ondansetron (2 ml) and saline (2 ml) was administered to Group O (n=30), an injection of 8 mg of dexamethasone (2 ml) and saline (2 ml) was administered to Group D (n=30), and an injection of 4 mg of ondansetron (2 ml) and 8 mg of dexamethasone (2 ml) was administered to Group OD (n=30). Anesthesia induction consisting of 4-6 mg sodium thiopental, 0.1 mg/kg, vecuronium bromide, and 2-3 mcgr/kg fentanyl was administered to all patients and maintained with 1-2% sevoflurane, 50% nitrogen protoxide, and 50% oxygen. Immediately after the gall bladder was removed, a patient-controlled analgesia (PCA) device was loaded with 1.5 mg/kg tramadol. The PCA device was set to a bolus dose of 30 mg with a locked period of 10 min. At the end of the operation, the effect of the muscle relaxant was antagonized with 0.01 mg/kg atropine sulfate and 0.05 mg/kg neostigmine, and tracheal extubation was performed. In the recovery room, the patients were determined to be awake when they could correctly state their birthdate, and the PCA control button was then given to the patient. In all of the groups, hemodynamic changes, pain scores (NRS), analgesia consumption (mg), potential side-effects of nausea and vomiting and sedation scores were evaluated at postoperative 5, 15, 30, 45 and 60 minutes in the recovery room and at 4, 8, 12 and 24 hours in the ward.

Statistical Analysis

The data obtained in the study were analyzed using the SPSS (Statistical Package for Social Sciences) 11.5 software program. In a comparison between the groups of obtained measured values, which showed a normal distribution, ANOVA was performed, and repeated-measures ANOVA was performed for comparison within the groups. For the values that are not normally distributed, the Kruskal Wallis test was performed between groups and the Friedman test was performed within groups. In the comparison of numerical data between groups, the categorical data frequency table Chi-square test was used.

Results

No statistically significant difference was determined between groups in terms of age, weight, height, gender distribution, duration of anesthesia or duration of the operation (Table 1).

No statistically significant difference was determined between groups in terms of heart rate, mean arterial pressure and oxygen saturation values at different postoperative time points ($p>0.05$).

No significant difference was determined between groups with respect to nausea and vomiting 5 minutes postoperatively in Group D, which was at a significantly higher level compared to Group O and Group OD ($p=0.04$).

No statistically significant difference was determined between groups with respect to the starting amount of tramadol. There was no difference between groups at 5 and 15 minutes in terms of tramadol consumption or from 30 minutes onwards, and a statistically significant difference was determined at these time points. Tramadol consumption in Group OD at 30 minutes was statistically significantly lower compared to Group O, and

at subsequent time points, it was statistically significantly lower compared to both Group O and Group D ($p=0.003$, $p=0.01$, $p=0.001$, $p<0.001$, $p<0.001$, $p<0.001$) (Table 2).

In the evaluation between groups at 5, 15, 30, 45 and 60 minutes and at 8, 12 and 24 hours, the NRS values in Group OD were statistically significantly lower compared to Group O and in Group D ($p=0.002$) (Table 5). At 30 minutes, there was a statistically significant difference between Group D and Group O, with lower values in Group D. Although the NRS values of Group OD were significantly lower compared to the Group O, they were similar to those of Group D at hour 4 (Table 3).

Table 1. Demographic Data (mean ± SD)

	Group D (n=30)	Group O (n=30)	Group OD (n=30)	P-value
Age (years)	44.3±10.6	49.5±10.2	48.8±9.2	P=0.09
Weight (kg)	76.1±12.2	76.7±11.5	77.5±11.5	P=0.89
Height (cm)	164.7±7.5	162.3±8.3	162.7±7.5	P=0.46
Gender F/M	19/11	22/8	23/7	P=0.47
Duration of anesthesia (min)	66.1±9.4	64.8±9.9	66.6±10.7	P=0.76
Duration of operation (min)	48.5±10.1	46.6±8.1	49.3±10.4	P=0.55

Table 2. Total tramadol consumption at different postoperative time points (mg)

	Group D (n=30)	Group O (n=30)	Group OD (n=30)	P-value
5 th min	114.1±17.4	118.0±20.1	119.3±19.7	0.557
15 th min	131.1±25.6	135.0±27.4	125.3±26.6	0.368
30 th min	156.5±39.2	161.0±29.7	139.3±30.8	0.03
45 th min	173.1±30.0	183.0±37.4	152.3±34.3	0.003*
60 th min	195.1±38.1	198.0±45.0	169.3±42.2	0.017*
4 th hr	269.1±60.7	303.5±93.8	231.0±63.1	0.001*
8 th hr	323.1±73.0	370.5±111.4	270.0±89.8	<0.001*
12 th hr	370.1±98.8	423.8±121.0	275.0±88.2	<0.001*
24 th hr	393.1±100.0	437.8±110.5	280.0±86.6	<0.001*

*P<0.001 is statistically significant.

Table 3. NRS values at different postoperative time points (median ± min-max)

	Group D (n=30)	Group O (n=30)	Group OD (n=30)	P-value
5 th min	2.0±1-3	2.0±1-4	2.0±1-3	0.0021*
15 th min	2.5±1-4	3.0±1-5	2.0±1-3	<0.0001*
30 th min	2.0±1-4	3.0±1-5	2.0±1-3	<0.0001*
45 th min	3.0±1-4	3.0±1-5	2.0±1-3	0.0001*
60 th min	3.0±1-4	3.0±1-4	2.0±1-4	0.0074*
4 th hr	2.5±2-4	3.0±1-4	2.0±1-4	0.0094
8 th hr	2.0±1-4	3.0±0-4	2.0±1-4	0.0040*
12 th hr	2.0±1-3	2.0±0-4	1.0±0-2	0.0009*
24 th hr	1.0±1-2	2.0±0-3	1.0±0-2	0.0103*

*P<0.001 is statistically significant.

Discussion

In this study, the effect of ondansetron and dexamethasone as antiemetics in laparoscopic cholecystectomy surgery on postoperative tramadol consumption was investigated.

Consistent with similar studies, it was determined that dexamethasone used for nausea prophylaxis resulted in a lower total tramadol consumption compared to ondansetron ($p=0.002$). In addition, in patients who were given the combination of ondansetron and dexamethasone for postoperative nausea and vomiting prophylaxis, the pain scores and total tramadol consumption were statistically significantly lower compared to other groups from the postoperative 45th minute onwards ($p<0.001$). Elective laparoscopic cholecystectomy is performed as a routine day procedure. The incidence of nausea and vomiting following laparoscopic cholecystectomy has been reported to be 53%-72% [1-4]. Nausea and vomiting as a response to specific warnings is a protective reflex against the absorption of toxins. In addition, postoperative nausea and vomiting are a significant block to discharging patients on the same day [1]. Despite new technologies and medications, the incidence of postoperative nausea and vomiting remains at 20%-30%. Postoperative nausea and vomiting can result in serious complications, such as aspiration, dehydration, electrolyte deficiency and opening of the wound site. Extending the hospital stay and re-admittance for a day-procedure surgery results in increased costs.

In this study, the postoperative efficacy of ondansetron, dexamethasone and the combination of ondansetron-dexamethasone as antiemetics in laparoscopic cholecystectomy patients was investigated, and the effect on tramadol consumption applied as patient-controlled analgesia for the treatment of postoperative pain was examined. There are many reasons for postoperative nausea and vomiting, including pharyngeal stimulation, gastrointestinal distension, abdominal distension, abdominal surgery, anesthetic agent, pain, opioids, hypotension, hypoxia, vestibular impairments, and psychological factors. There are specific factors that predispose patients to nausea and vomiting, such as age (more common in children), gender (female), a history of nausea and vomiting, holding of the device, lengthy operation, depth of anesthesia, carbon dioxide retention, inexperienced anesthetist, type of surgery and the number of visitors during recovery.

In the current study, there was no difference between groups with respect to the factors of type of surgery, gender, age, duration of operation and depth of anesthesia, all of which may lead to nausea and vomiting in patients. To reduce the personal risk factors, patients with a history of nausea and vomiting after previous operations and those who would not be able to hold the device were excluded from the study. In all of the operations, the carbon dioxide insufflation pressure applied and amount were similar between the groups. The skill of the surgeon and anesthetist could create a personal predisposition, and thus, the utmost care was taken for the operations to be performed by the same surgical and anesthesia team. All of the operations were shorter than 12 hours, which is the length of time required to increase the incidence of nausea and vomiting for all patients.

The anesthesia technique and depth may affect postoperative incidence, and thus, the same anesthesia technique and depth

were maintained in all patients. The use of opioids (fentanyl), nitrogen protoxide and cholinesterase inhibitor, which could induce nausea and vomiting, was similar between the groups. These efforts and the removal of factors may reduce the rate of nausea and vomiting in the patients in this study.

Pharmacological interventions to reduce postoperative nausea and vomiting have been evaluated in several randomized controlled studies. Most of the drugs used have been compared with a placebo. The use of serotonin receptor antagonists, low-dose dexamethasone, droperidol, and metoclopramide have been reported to reduce the incidence of postoperative nausea and vomiting and the need for additional antiemetics [1,2,4-15]. Cruz et al. [16] examined the effect of the timing of the use of ondansetron on postoperative nausea and vomiting and showed that administration 30 min prior to the completion of long surgical procedures was more effective than application before anesthesia induction. The antiemetic property of ondansetron, which is a 5-HT₃ receptor antagonist, is based on blockade of 5-HT₃ receptors in the chemoreceptor trigger zone and enteric neurons.

Used preoperatively, there are analgesic and antiemetic effects of glucocorticoids. Because genomic effects begin slowly, the preoperative use of glucocorticoids is recommended.

In a study performed by Wang et al. [17], dexamethasone was used to prevent nausea and vomiting in laparoscopic cholecystectomy patients, and it was reported that dexamethasone significantly reduced the incidence of nausea and vomiting after laparoscopic cholecystectomy.

Although the etiology of high nausea and vomiting after laparoscopic surgery is not fully understood, there are combined risk factors, including carbon dioxide insufflation, peritoneal distension, diaphragmatic irritation, and visceral organ irritation and manipulation. Nausea and vomiting in laparoscopic surgery are multifactorial and none of the existing antiemetics can antagonize all of the neurotransmitter systems. Thus, multiple interventions are recommended for patients at high risk of postoperative nausea and vomiting, including antiemetic medication of two or more different classes [18]. Independent of the patient-related risks of postoperative nausea and vomiting, the application of total intravenous anesthesia with propofol with either ondansetron or dexamethasone will reduce postoperative nausea and vomiting to the same degree [18]. The combination of ondansetron and dexamethasone has attracted attention because ondansetron is highly effective against early vomiting, while dexamethasone is effective for nausea and vomiting at both early and late stages (2-24 hours) [19]. However, the late-stage effect of dexamethasone is more evident [20].

In a study by Bano et al. [21], dexamethasone and the combination of ondansetron and dexamethasone were evaluated for the prevention of nausea and vomiting following laparoscopic cholecystectomy, and it was reported that the combination of ondansetron and dexamethasone provided a better prophylaxis than the use of dexamethasone alone.

Although the optimum prophylactic dose of ondansetron is 4-8 mg [19] and dexamethasone is widely used at a dose of 8-10 mg [20], it has been reported that smaller doses are effective in laparoscopic day surgery [22]. The doses applied to the patients in the current study were similar to those recommended in the

literature.

Because dexamethasone requires a period of time for the antiemetic effect to start, ondansetron, dexamethasone and the combination of ondansetron and dexamethasone used in the current study were administered prior to anesthesia induction. It is thought that the high rate of vomiting observed in the dexamethasone group in the early period was due to the late onset of the effect of dexamethasone.

Postoperative pain and nausea and vomiting are undesirable events in the postoperative period. One in three patients undergoing laparoscopic cholecystectomy suffers from severe pain. The use of opioids, such as tramadol in the treatment of postoperative pain is one of the most important factors in creating susceptibility to postoperative nausea and vomiting. Tramadol, which is widely used in the treatment of moderate pain, can be used together with antiemetics to prevent nausea and vomiting postoperatively. However, the combined use of these medications can create a different effect to the value of the research. The severity of postoperative pain in patients administered with ondansetron, dexamethasone and the combination of ondansetron and dexamethasone in this study was measured using NRS. At all time periods, the NRS values of the patients who received the combination of ondansetron and dexamethasone were lower compared to patients who received ondansetron or dexamethasone alone. When the use of ondansetron and dexamethasone alone was evaluated, the NRS values of the dexamethasone group were lower than those of the ondansetron group at 30 minutes and 4 hours.

Tramadol consumption was lower in the ondansetron-dexamethasone combination group after the 30th minute postoperatively compared to the ondansetron group and after 45 minutes compared to the dexamethasone group.

In a study by De Witte et al. [23], 1 mg/kg tramadol with 0.1 mg/kg ondansetron and placebo were administered 15 min before anesthesia induction, and ondansetron reduced the activity of tramadol. However, 4 mg of ondansetron administered at anesthesia induction did not reduce the incidence of nausea and vomiting in 24 hours postoperatively.

In another study by Arcioni et al. [24], the interaction of the combined use of ondansetron and tramadol was investigated, and it was found that ondansetron most likely blocked spinal 5-HT₃ receptors, and the analgesic effect of tramadol was reduced. Used together with ondansetron to provide effective analgesia in the postoperative period, the required tramadol dose and the use of ondansetron alone, which cannot be well-controlled, increased emetic stimulation. Thus, when tramadol was used for postoperative pain, ondansetron should be the first choice of medication as an antiemetic.

Glucocorticoids are widely used medications in inflammatory diseases. The mechanism underlying this effect is the interaction of gene transcription modulation, which resulted in intranuclear glucocorticoid receptors. Gene expression induced by steroids is modulated at the protein level 2-3 hours after medication use. The glucocorticoid genomic anti-inflammatory effects are the means of reduction in prostaglandin synthesis. In addition, glucocorticoids inhibit hyperalgesia induced by inflammatory mediators, such as TNF α , interleukin-1- β , and interleukin-6 [24]. In addition, the rapid initiation of analgesic

and anti-hyperalgesic effects has been shown in human pain models [24].

The interactions between opioids and glucocorticoids have been reported to be involved in a variety of physiological responses, including pain. The interaction in nociception of glucocorticoids and opioids is debatable, as both additive and antagonist effects have been reported. Serotonin plays an important role in the mechanisms of pain control and affects nociception due to various receptors consisting of 5-HT_{1A}-D, 5-HT_{2A}-C, 5-HT₃ and 5-HT₄. In a study by Dürsteler et al., the interaction of dexamethasone and tramadol was investigated in an acute visceral pain model in rats, and it was reported that the combination of tramadol and dexamethasone could be useful in the treatment of pain in humans [25]. The results of the current study showed that dexamethasone used for nausea prophylaxis caused less total consumption of tramadol compared to ondansetron, which is consistent with the previously described information. Interestingly, the postoperative pain was less and the total tramadol consumption was reduced in patients who had experienced postoperative nausea and vomiting prophylaxis with the combination of ondansetron and dexamethasone. The addition of dexamethasone to ondansetron for nausea and vomiting prophylaxis prevented the probable increase in total tramadol consumption.

Because laparoscopic cholecystectomy is a day procedure, it is widely applied. In addition, despite the application of new technology and medications, postoperative nausea and vomiting and pain remain to be two unwanted events that still occur at high rates [1-4].

Nausea and vomiting in laparoscopic surgery are multifactorial, and none of the current antiemetics can antagonize all neurotransmitter systems. Thus, multiple interventions are recommended for patients at high risk of postoperative nausea and vomiting, including antiemetic medication of two or more different classes [19,20]. However, antiemetics used for the treatment of postoperative pain may interact with the analgesics used and may antagonize anti-nociceptive effects [3-5].

In conclusion, the combination of ondansetron-dexamethasone was more effective in the prevention of severe nausea and vomiting and pain following laparoscopic cholecystectomy compared to the use of ondansetron or dexamethasone alone. In addition, dexamethasone in the combination eliminated the negative effect between ondansetron and tramadol. It is thought that in the absence of a fully defined non-genomic mechanism, dexamethasone in the combination eliminated the negative effect between ondansetron and tramadol, thereby preventing a potential increase in total tramadol consumption.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: None

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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How to cite this article:

İsa Şen, Oya Kılıcı, Eyüp Horasanlı, Serpil Deren, Dilşen Örnek, Nermin Göğüş. Effect of Ondansetron and Dexamethasone as antiemetics on postoperative pain and nausea. *Ann Clin Anal Med* 2021;12(1):60-64