



Effect of Ondansetron and Dexametasone on Post-Operative Nausea and Vomiting in Patients Undergoing Laparoscopic Cholecystectomy

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ABSTRACT

Background: Post-operative nausea and vomiting (PONV) are the most common unpleasant experiences following laparoscopic surgeries.

Objectives: In the current research, compared the effect of dexamethasone and ondansetron combined and separately on preventing nausea and vomiting in the patients undergone elective surgery with general anesthetic using laparoscopic cholecystectomy procedure.

Patients and Methods: One hundred fifty patients with ASA class I and II aged between 20-65 years voluntarily participated in this double-blind randomized prospective study. The patients were randomly divided into three groups of 50. All the participants faced general anesthetic procedure whereas each group received different treatment regimen as follow: the O-group, 4 mg ondansetron, the D-group, 8 mg dexamethasone, and the OD-group, combination of 4 mg of ondansetron plus 8 mg dexamethasone. Every episode of PONV and the need for antiemetic drug were evaluated 6 hours following the operation and then every 6 hours up to 24 hours after the operation. The complete response was defined as the case with no episode of PONV within the 24 hours and the need for anti-vomiting cases was defined as the failure in prophylaxis.

Results: The complete response was observed in 62.2, 68.2 and 89.6 percent of O, D, and OD groups, respectively. The frequency of complete response was significantly lower in OD-group ($P = 0.011$ vs. the D and $P = 0.005$ vs. the O group). The need for the antiemetic drug in groups O, D, and OD was 28.3, 22.8, and 6.2, respectively. The incidence of vomiting and failure in prophylaxis was observed in D-group during the first six hrs. The highest need for the anti-vomiting drug within the 6 to 24 hours of post operation was observed in group O compared to the group OD ($P = 0.012$).

Conclusions: Combination of dexamethasone and ondansetron is more effective than the treatment of PONV by each of these drugs separately following the laparoscopic cholecystectomy. The application of dexamethasone alone in preventing premature PONV is less effective than the application of ondansetron or the combination of these two drugs. In addition, ondansetron alone is less effective than the combination of these two drugs in preventing PONV.

► Implication for health policy/practice/research/medical education:

Patients undergoing general anesthesia for laparoscopic cholecystectomy have a high incidence of post-operative nausea and vomiting (PONV). Combination of dexamethasone and ondansetron is more effective than the treatment of PONV following the laparoscopic cholecystectomy.

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1. Background

Laparoscopic surgery has reduced the morbidity rate following a Cholecystectomy and the procedure is considered as a preferred method for signed Cholecystitis cases (1, 2). Despite this fact, 53-72% of operations are reported to have post-operative nausea and vomiting (PONV) (3-5). Severe nausea and vomiting can cause dehydration, imbalance in electrolytes and consequently delay the discharge of the patients from the hospital. In addition, PONV causes the risk of aspiration, dehiscence of wound (6), and prolonged bleeding from the operation site, venous hypertension, hematoma, esophagus rupture and blindness (7, 8). The condition is so critical for the patients that preventing PONV is more important than the pain control following the operation and they are even willing to pay \$100 for an effective treatment of vomiting (9). In summary, PONV is one of the most unpleasant experiences of the patients following the surgery and constitute the most common cause of complaints by the patients (10). Thus, reducing the incidence of PONV by applying various animating drugs enhances the satisfactions of patients and reduces the recovery time and discharge from the hospital (11, 12). It is possible to control PONV, but it is not possible to completely eliminate it. The main etiology of this problem is multifactorial. There are several contradictory causes of PONV and despite the availability of treatments; still the preferred treatment is unclear for the majority of physicians (9, 13). Ondansetron, is a 5 hydroxytryptamin type 3 receptor (5-HT₃) that has anti vomiting effects on surgery patients (14, 15). Dexamethasone is also another glucocorticoid drug with the minimum side effects used in the patients undergoing chemotherapy as an anti-vomiting drug (16). The anti PONV of this drug is recognized (17). As indicated earlier, in laparoscopic cholecystectomy surgeries, when no drug is used, the incidence of PONV is approximately 53-72% and following the use of 4mg of dexamethasone, the rate drops to 20% and following the prescription of 4mg of ondansetron, it decrease to about 43% (18). In another clinical research, the incidence of PONV was compared with the prescription of combination of dexamethasone and ondansetron, and using each of these drugs separately. The results showed that the incidence of PONV after using both drugs was 11% while the incidence rate after the prescription of dexamethasone and ondansetron separately were 34% and 40%, respectively (19).

2. Objectives

Considering the significance of the PONV, this double-blind clinical trial was designed to examine the safety and effectiveness of using the combined dose of 8mg dexamethasone and 4mg of ondansetron versus a single dose of 8 mg of dexamethasone and 4 mg of ondan-

setrone alone to prevent PONV in patients undergoing laparoscopic cholecystectomy

3. Patients and Methods

In this study, participants were 150 ASA class I and II patients aged between 20 to 65 years who underwent laparoscopic cholecystectomy under general anesthesia at Shahid Beheshti Hospital of Kashan. Following the completion of human consent forms recommended by the ethic committee of the university, the operations were performed. The patients who had the history of nausea or vomiting or consumed H₂ blocker 48 hours prior to the operation were excluded. Also the patients who had a history of allergy to drug or were addicted to narcotics were excluded. In addition, the patients who were pregnant at the time or were in menstruation period or faced kidney problems with high level of BUN or Cr or had history of movement disorders were excluded from the study. At the time of entry to the operation room, the routine monitoring including base NIBP, HR, O₂sat was recorded and ET CO₂, (end-tidal carbon dioxide or capnograph) and EKG was set. The patients were randomly assigned into three groups of equal size (n = 50). One group received venous injection of 4mg ondansetron combined with 8 mg of dexamethasone- the OD-group. The second group was given venous injection of 8 mg of dexamethasone- the D-group. For the third group, 4 mg of endanestron was administered- the O-group. The checklist was prepared according to the table of random numbers prior to the start of anesthetic state. The syringe containing the treatment regiments for the three groups was injected by an experienced nurse who was not participating in the research. The preparations were made by using normal saline set to 5cc volume and injected. For all the patients in the study, similar anesthetic regime was applied. The Anesthetic state was induced with midazolame 0.05 mg/kg + fentanyl 2 mg/kg + thiopental 5 mg/kg + atracurium 0.5 mg/kg that after 3 minutes were tracheal intubated and connected to the ventilator. Maintaining anesthetic state was managed by applying nitric oxide 67%, oxygen 33% and halothane 0.8%. Atracurium repetition was performed according to the monitoring of muscle, nerve, and fentanyl repetition was performed based on heart rate change or blood pressure increase ($P > 20\%$). Continuation of halothane was managed by monitoring the depth of anesthetic state ($P < 60$). The patients received 5 mg of diazepam 6 hours prior to the start of surgery. Ventilation of the patients was performed by CMV in such a way that ET CO₂ was maintained for approximately 30-35 mmHg. Suction of air was done through a nasogastric tube (NGT), and stomach content was removed after inserting a tube. Abdomen was insufflated with carbon dioxide (CO₂) at a flow rate of 0.2 l/min, and intra-abdominal pressure (IAP) was maintained below 15 mmHg throughout surgery. The patients were

kept in terendelenberg reverse position and tilted mildly toward the left. The surgery was guided through video display through three punctures on the abdomen. At the end of surgery procedure, it was checked to make sure that the abdomen was completely desufflated and suction was performed on NGT. Anatomization was carried on remaining muscle nerve block by applying 0.04 mg/kg Neostigmine and 0.02 mg/kg Atropine. The trachea was intubated once the patient awakened. No other sedative, analgesic or antiemetic drug was administered. The variables of interest that were recorded during the study included the duration of surgery and anesthesia, volume of the venous liquids prescribed, the amount of drugs used, hemodynamic signs and any hemodynamic instability.

The patients were monitored carefully for 24 hours, following the operation. Monitoring in recovery was performed by the recovery room personnel and in wards by trained nurses. In all the stages, the double blind approach was maintained. The first dose of analgesia was introduced by 1 mg/kg of meperidine intramuscular (IM) based on the need of the patient. This prescription was repeated every 8 hours based on the patients demand and in case the pain did not subside, Diclofenac Na. suppository was used. The incidence of PONV was counted and recorded in the recovery room according to the patients complaints as follow:

0 = no nausea or vomiting

1 = nausea only

2 = retching or/and vomiting

In case the score for PONV reached 2 or the patient clearly demanded antiemetic drug, 10 mg of venous metoclopramide was prescribed and if needed, the prescription was repeated with 8 hour intervals. The complete response was defined as the cases with no episode of PONV observed after 24 hours of awakening. Failure of prophylaxis was defined for the cases when the antiemetic drug was needed within the 24 hour period after the operation. The feeding of patients started 8 hours after the termination of the surgery or with the start of

bowel sound. The cases of PONV with 0 to 6 hours were coded as the early PONV and other incidences after this period were labeled as the late PONV so that the effectiveness of treatment could be compared at various times. The incident rate of PONV and the need for animating drug between the three groups were compared. To determine the sample size, the power of the tests were set to 80% and $\alpha = 0.05$. To analyze the data, statistical tests such as Anova, Kolmogorov-Smirnov, t-test, Kruskal-wallis, Mann-Whitney and Levene tests were employed. The significance level was set to $P \leq 0.05$.

4. Results

Out of 150 patients participating in the research, 13 cases needed open cholecystectomy and thus they were excluded from the study. Therefore, 138 complete cases were available for the evaluation. The results of analysis by comparing the individual characteristics of the patients and factors related to the surgery and anesthesia showed no significant difference among the three groups ($P > 0.05$, Table 1). In addition, the first request for meperidine and the amount of consumed meperidine in all groups was similar (Table 1). Complete response was observed in 89.6 percent of the patients who consumed the combination of dexamethasone and ondansetron (group OD). In this regard, 68.2 percent of the patients received dexamethasone (group D), and 62.2 percent of the patients received ondansetron. This difference was statistically significant compared to the OD group ($P < 0.05$, Table 2). The incidence of nausea in - O-group was significantly higher than the OD-group ($P < 0.05$), but no such difference was present between the D and OD-group ($P > 0.05$, Table 2). The incidence of vomiting in D-group was 18.2 percent within the first 24 hours. This rate was 13.1% and 4.2% for the O and OD-groups respectively and this difference was statistically significant compared with the OD-group ($P < 0.05$). The total PONV incidence within the first 24 hours in group O and D was 14 (31.8%) and 16 cases (34.9%), respectively. This rate in group OD was 5 (10.4%) cases, the difference was statistically significant ($P < 0.05$). The rate of need for an-

Table 1. Descriptive Statistics for Demographic, Surgery and Anesthetic Factors According to the Treatment Group

	Group O	Group D	Group OD	P value
Patients, No.	46	46	44	
Age, y, Mean \pm SD	40.65 \pm 9	40.06 \pm 8.2	41.18 \pm 7.51	0.81
Gender, No.				
Female	42	40	42	0.81
Male	4	4	6	
Duration of anesthesia, min, Mean \pm SD	104.26 \pm 7.97	105.47 \pm 9.83	107.79 \pm 9.58	0.169
Duration of surgery, min, Mean \pm SD	80.06 \pm 5.51	81.84 \pm 6.94	82.25 \pm 7.44	0.251
Total volume of liquid used, ml, Mean \pm SD	14.86.3 \pm 105.12	505.9 \pm 107.29	1490 \pm 117.91	0.672
Total amount of meperidine, mg, Mean \pm SD	50.97 \pm 11.62	51.02 \pm 10.26	51.97 \pm 10.19	0.825
First meperidine demand, min, Mean \pm SD	134.47 \pm 11.58	133.86 \pm 11.8	133.70 \pm 10.98	0.717
24 hr after receiving meperidine, mg, Mean \pm SD	190.54 \pm 35.13	91.25 \pm 31.64	183.7 \pm 34.27	0.330

Table 2. Frequency of Patients According to PONV and Need for Receiving Anti Vomiting Drug During the 24 Hours Interval

	Group O	Group D	Group OD	P value		
				O/D	O/OD	D/OD
Patients, No.	46	44	48	-	-	-
Complete score, No., (%)	30 (62.2)	30 (68.3)	43 (89.6)	0.82	0.005 ^a	0.019 ^a
Nausea, No. (%)	10 (21.8)	6 (13.6)	3 (6.2)	0.41	0.03 ^a	0.3
Vomiting, No. (%)	6 (13.1)	8 (18.2)	2 (4.2)	0.5	0.15	0.04
Total PONV, No. (%)	16 (34.9)	14 (31.8)	5 (10.4)	0.82	0.005 ^a	0.01 ^a
Need antiemetic drug, No. (%)	13 (28.3)	10 (22.7)	3 (6.3)	0.64	0.005 ^a	0.03 ^a

Abbreviation: PONV, post-operative nausea and vomiting

^aSignificant Difference**Table 3.** Frequency of Incidence of Nausea, Vomiting and the Need for Receiving Anti Vomiting Drug at Various Time Intervals After the Operation

	Interval, hr	Nausea, No. (%)	Vomiting, No. (%)	PONV, No. (%)	Need Antiemeting, No. (%)
Group O (n = 46)					
	0 - 6	2 (4.3)	2 (4.3)	4 (8.6)	3 (6.5)
	6 - 24	8 (17.3)	4 (8.6)	12 (26)	10 (21.8)
Group D (n = 44)					
	0 - 6	4 (9.1)	6 (13.6)	10 (22.7)	8 (18.2)
	6 - 24	2 (4.5)	2 (4.5)	4 (9.1)	2 (4.5)
Group OD (n = 48)					
	0 - 6	1 (2.1)	0 (0)	1 (2.1)	1 (2.1)
	6 - 24	2 (4.2)	2 (4.2)	4 (8.4)	2 (4.2)
P value (0 - 6)					
	O/D	0.42	0.26	0.08	0.047 ^a
	O/OD	0.6	0.23	0.19	0.6
	D/OD	0.18	0.01 ^a	0.003 ^a	0.01 ^a
P value (6 - 24)					
	O/D	0.09	0.6	0.09	0.056
	O/OD	0.046 ^a	0.4	0.025 ^a	0.012 ^a
	D/OD	1	1	0.7	1

Abbreviation: PONV, post-operative nausea and vomiting

^aSignificant Different

tiemetic drug within 24 hours was significantly less in OD group compared to those of the other two groups. Only 6.3 percent of the patients in OD-group needed antiemetic drug compared to 10 (22.7%) in D-group and 13 (28.3%) in O-group, respectively (Table 2). The results of analysis following the various time intervals after the operation, during the first six hours, showed that the frequency of vomiting in the group that received dexamethasone was significantly higher than the group that received the combination dose ($P < 0.05$). In addition, the incidence of premature PONV and need for antiemetic drug was significantly higher in group D ($P < 0.05$). In this time interval, the need for the antiemetic drug was higher for the D-group (Table 3). Within 6 to 24 hours after the operation, the incidence of vomiting was significantly higher in group O than the OD-group ($P = 0.012$), but no such difference existed between the O and D groups ($P = 0.056$, Table 3).

5. Discussion

Laparoscopic cholecystectomy is the treatment of choice for gallbladder stone. It decreases the rate of morbidity and the length of hospitalization. (2, 20). There is a high incidence of PONV in patients undergoing general anesthesia for laparoscopic cholecystectomy which is due to various reasons including prolonged Co2 insufflations, residual pneumoperitoneum, gallbladder surgery, isoflurane and glycopyrolat application, hypotension during the operation, history of movement disorders and PONV (4, 21). In the current study, the incidence of PONV in patients undergoing laparoscopic cholecystectomy who received different antiemetic treatments was compared. Considering the fact that PONV is inevitable during the laparoscopic cholecystectomy, no placebo drug was applied due to the ethical reasons. The dosage applied in

the research was based on the prescription used in other studies (15, 22). In this research, a number of risk factors during the anesthesia and surgery, the volume of liquid, and meperidine prescribed during the surgery for the three groups were similar. Thus, the difference in the incidence of PONV in this study is assumed to be due to the prescription of different antiemetic drugs. Corticosteroid exerts its effects on specific reception protein and regulates the expression of Corticosteroid-responsive genes. A time sequence for the occurrence of this change in gene expression and protein synthesis is necessary. For this reason, the majorities of the corticosteroids effects do not appear immediately but instead they occur several hours later. This condition can explain the latency of antiemetic effects of dexamethasone. In addition, the prolonged anti vomiting effect of dexamethasone can be attributed to the prolonged half-life of this drug (36 to 72 hr) (23). Dexamethasone is a glucocorticosteroid that has severe antiemetic effects for PONV. The recommended dose for adult patients is 5-10 mg (17). The antiemetic effect of this drug may be attributed to prostoglandin antagonism, peripheral or central control of serotonin, increase in releasing endorphine and change in penetrability of CSF blood barrier in relation to serum proteins (18, 23, 24). Ondansetron is selective 5-HT₃ antagonist that is used for its effect in nausea and vomiting due to chemotherapy and radio therapy in addition to surgery operation (22, 25, 26). This medicine has minor side effects such as headache, flushing, vertigo and constipation. After 24 hours post operation. The incidence of PONV and the need to antiemetic drug in patients who used combination of dexamethasone and ondansetron was significantly less than the patients who used one of these drugs. The use of either one of these drugs had similar antiemetic effect. In a study conducted by McKenzie and associates (27), similar results were found. In addition, Lopez-Olando *et al.* (28) reported that 84 percent of the patients who used combination of dexamethasone and ondansetron had complete response. However, no significant differences in the incidence of PONV were found between the groups that received dexamethasone or ondansetron alone. In the current study during the first six hours post operation, The incidence of vomiting and the need for antiemetic drug in the group that received dexamethasone was significantly higher than the group that received either ondansetron or a combination of dexamethasone and ondansetron with no significant difference in the premature incidence of PONV. This result indicates that the use of dexamethasone is not sufficient to prevent the premature vomiting in patients who undergo surgery (29). Thomas and Jones demonstrated that 28.3 percent of the patients who use dexamethasone faced failure in prophylaxis within the first 3 hours after the operation. This rate for ondansetron alone or combination of ondansetron - dexamethasone was 22 and 8.6 percent, respectively. Rajeeva *et al.* (30) showed that the

combination of ondansetron - dexamethasone controls the late PONV more effectively than the premature PONV. In this study, within the 6 to 24 hours post operation, the patients who used ondansetron after the operation needed more antiemetic drug than the patients who received the combination dose ($P = 0.012$), however, no significant difference was found between the group that received dexamethasone compared to the patients who received ondansetron ($P = 0.05$). The shorter duration of effectiveness for ondansetron compared to dexamethasone is an indication of late prophylaxis failure for ondansetron. The half-life of endoctrine is between 4 to 9 hours (24-26). Subramaniam and Madan (31) showed that the incidence of premature PONV (in the first 6 hour after the operation) in children who receive dexamethasone is 24.4 percent. For the children who receive ondansetron, this rate was 17.8 percent. These authors also demonstrated that the incidence of late PONV (within 6 to 12 hours) was significantly less in the dexamethasone group compared to the ondansetron group (6.67% vs. 24.4% respectively) Similar results were reported in patients undergoing ambulatory surgery (14, 17). In addition, it was shown that dexamethasone had stronger effect than ondansetron in preventing delayed nausea and vomiting following chemical therapy (32). In summary, despite all the advances in medical sciences and anesthesiology, the so called simple subject like PONV remains a challenge. Some patients have a history of severe PONV and some surgery operations are associated with the high risk of PONV. Many researches are underway to examine the preferred treatment in this regard. This is despite the fact that some of these procedures do not look very promising. The limitations of this study included not counting the frequency, severity, length and duration of nausea and vomiting in addition to follow-up recording of the variables of interest after 24 hours past the operation. Also, the length of hospitalization and possible side effects were not examined. However, the results of this study clearly demonstrated that the patients who face PONV and are treated by combined drug prophylactic approach need less antiemetic drug than the patients who receive one drug.

More researches with less limitation are needed to identify the most effective and economic treatment for the surgery operations. According to the findings of the current study, the treatment of PONV is more effective by the combination of ondansetron and dexamethasone than the use of either one of these two in laparoscopic cholecystectomy. More specifically, dexamethasone alone is not very effective to prevent the premature PONV. In addition, using ondansetron alone is less effective in preventing late PONV comparing to the combination use of ondansetron and dexamethasone.

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Authors' Contribution

Mohammad Eidy (study design), Hamid Reza Vafaei (study design and article writing), Mehdi Rajabi (data collection), Mahdi Mohammadzadeh (data collection), Abdolreza Pazouki (data collection).

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