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Optimization of anesthesia antiemetic measures versus combination therapy using dexamethasone or ondansetron for the prevention of postoperative nausea and vomiting

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Abstract
Background More than half of the patients undergoing laparoscopic cholecystectomy experience postoperative nausea and vomiting (PONV). This condition is related to the surgical, anesthetic, and patient factors. Volatile anesthetics, nitrous oxide, and opioids are known anesthetic risk factors for PONV, and thus preventive measures are justified. Propofol-based total intravenous anesthesia (TIVA), ondansetron, and dexamethasone each are reported to reduce PONV by approximately 30%. Avoiding or reducing perioperative narcotic analgesics, use of an 80% oxygen concentration, and proper intravenous fluid administration also reduce PONV. The anesthetic antiemetic measures have been studied separately. This study aimed to test the efficacy of these anesthetic antiemetic measures collectively with or without ondansetron or dexamethasone in preventing PONV among patients undergoing laparoscopic cholecystectomy.
Methods For this study, 160 patients undergoing laparoscopic cholycestectomy (33 males and 147 females) were randomized into one of three groups. Group O received 4 mg of ondansetron; group D received 8 mg of dexamethasone; and group P received normal saline immediately after induction of anesthesia. All the patients received propofol-based TIVA, 80% oxygen concentration, 20 ml/kg of Hartman's solution, and 1.5 mg/kg of tramadol. Opioids, nitrous oxide, and volatile anesthetics were not used for any patient. Episodes of PONV were recorded at 0- to 4-h and 4- to 24-h intervals.
Results The incidences of PONV were 32% in the ondansetron group, 30% in the dexamethasone group, and 33% in the saline group. There were no significant differences among the groups ($p > 0.05$).
Conclusion Ondansetron or dexamethasone added to collective anesthetic antiemetic measures does not further decrease the incidence of PONV after laparoscopic cholycestectomy.

Keywords Dexamethasone · Laparoscopic cholecystectomy · Nausea · Ondansetron · Propofol · Vomiting

Postoperative nausea and vomiting (PONV) occurs in 20–30% of surgical procedures after general anesthesia [1], and the incidence is as high as 50–70% after laparoscopic cholecystectomy [2]. Patients report PONV as a major cause of their fear and discomfort [3]. The risk factors for PONV include female gender, nonsmoking status, and a history of PONV or motion sickness [4].

The use of intraoperative and postoperative opioids, volatile anesthetic agents, or nitrous oxide is reported to be an anesthetic risk factor for PONV [5–8]. Although many antiemetic drugs and techniques have been used, no universal prophylaxis exists that can prevent PONV completely [9]. Ondansetron, a 5-hydroxytryptamine (5-HT3) receptor antagonist, and dexamethasone have been found to reduce PONV significantly after laparoscopic cholecystectomy compared with placebo [10–12].

Apfel and Korttila [13] reported that substituting propofol for volatile anesthetics reduced the risk of PONV by

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19% and that substituting nitrogen for nitrous oxide reduced the risk by 12%. These authors also stated that combining the two anesthetic strategies (i.e., total intravenous anesthesia [TIVA]) is as effective as a single antiemetic drug. The intraoperative use of an 80% oxygen concentration and proper intravenous fluid administration intraoperatively also are reported to reduce PONV.

To date, most studies have compared these anesthetic techniques separately either with or without antiemetic medications. This study therefore was designed to evaluate the hypothesis that the combination of anesthetic antiemetic measures (TIVA, 80% oxygen concentration, 20 ml/kg of intravenous fluid hydration, and avoidance of perioperative opioids) and either ondansetron or dexamethasone is more effective than the anesthetic antiemetic measures alone in preventing PONV for patients undergoing laparoscopic cholecystectomy.

Patients and methods

After scientific and institutional review board approval, the study enrolled 196 American Society of Anesthesiologists (ASA) grades 1 and 2 patients ages 18–70 years scheduled for elective laparoscopic cholecystectomy under general anesthesia in the Department of Anesthesia and Intensive Care at the University of Jordan, Amman, Jordan between November 2007 and March 2008. Informed written consent was obtained from all the patients recruited to the study protocol.

The exclusion criteria specified all patients who had received antiemetics or cortisone within 48 h before surgery and those who required opioids before and after surgery. We also excluded pregnant, breastfeeding ladies or any patient with a body mass index (BMI) exceeding 34 kg/m^2. Patients with gastrointestinal, hepatic, renal, mental, or psychiatric illnesses and those with a history of motion sickness also were excluded from the study protocol.

The patients were admitted to the operating room after premedication with 5 mg of oral diazepam 2 h before induction of anesthesia. Institution of routine monitoring was done, and the patients were randomly assigned to one of three groups. Group O received 4 mg of ondansetron; group D received 8 mg of dexamethasone; and group P received normal saline. The drugs were prepared in 2-ml syringes and administered immediately after induction of anesthesia. The syringes were prepared by the pharmacist in the operating room before induction of anesthesia and administered according to a table of randomized numbers. The anesthetists, surgeons, and nurses managing these patients were blinded to the study drugs.

The same anesthetics and techniques were used for all the patients. Anesthesia was induced with 2 mg/kg of propofol and 3 mg of midazolam through a 20-gauge cannula inserted at the back of the hand. Intubation of the trachea was facilitated with 0.5 mg/kg of atracurium, and the patient's lungs were ventilated with 0.8 oxygen in air to achieve normocapnia. Analgesia was preemptively administered intravenously by 1 g of paracetamol and 1.5 mg/kg of tramadol.

Anesthesia was maintained with propofol at 4–10 mg/kg/h. Nitrous oxide, volatile anesthetics, and other narcotics were not used during the study. Propofol infusion was adjusted to maintain an adequate depth of anesthesia as indicated by the bispectral index monitor (Aspect Medical Systems, Natick, MA, USA), clinical signs, and hemodynamic monitoring. Boluses of 5- to 10-mg atracurium were given when indicated.

After the start of controlled ventilation, a nasogastric tube was inserted to empty the stomach of air and other gastric contents. Electrocardiogram, blood pressure, and oxygen saturation were monitored. The patients were positioned in the anti-Trendelenburg position with the right side tilted up. The peritoneal cavity was insufflated with carbon dioxide (CO_2) gas at an intraabdominal pressure of 10–16 cm of water.

Laparoscopic cholecystectomy was performed under video guidance, and all surgeries were performed by the same surgeon. The four laparoscopy entry sites were infiltrated with a total 0.5% plain bupivacaine dose of 20 ml for intra- and postoperative pain control. A Hartman's solution total of 20 ml/kg was administered to all the patients.

At the end of surgery, the patients were positioned in the Trendelenburg position. An attempt was made to empty the remaining insufflated gas completely by abdominal shaking while the trocars were still in place. The nasogastric tube was aspirated and removed slowly before extubation. Reversal of the residual muscle relaxant effect was accomplished by neostigmine 70 μg/kg with atropine 15 μg/kg. The trachea then was extubated, and the patients were transferred to the postanesthesia recovery room (PACU).

The durations of anesthesia, surgery, and CO_2 insufflation were recorded. The incidence of PONV was observed for 24 h after surgery. Nausea and vomiting were recorded at intervals of 0–4 h and 4–24 h after surgery and treated with a rescue of 10 mg metoclopromide when necessary. This was administered if nausea was intractable and lasted for at least 15 min or at the patient's request anytime.

A visual analog pain score (VAS) also was recorded 4 and 24 h after surgery. The patients were asked to rate their pain on 10-cm visual analogue scale ranging from 0 (no pain) to 10 (the most severe pain). Postoperative pain in the recovery room was treated with an intramuscular injection

of 75 mg diclofenac when the VAS was four or higher at the request of the patient. The pain then was reassessed, and if VAS persisted at more than four, a subsequent 2-mg dose of morphine was given, and the patient was excluded from the study.

After discharge from the recovery, postoperative analgesia was provided with an intramuscular injection of 75 mg diclofenac, not to exceed 150 mg during a maximum use of 24 h, as required with a regular intravenous paracetamol (Perfalgan) at a dose of 1 g every 6 h.

For all the patients, we used the Apfel score to predict the occurrence of PONV [4]. This score includes the risk factors of female gender, history of PONV or motion sickness, nonsmoking status, and the use of postoperative opioids for pain relief. Apfel and Korttila [13] demonstrated that the incidence of PONV was 10% with none of the mentioned risk factors present, 21% with one risk factor, 39% with two risk factors, 61% with three risk factors, and 79% with four risk factors present.

The postoperative data collection was performed by an anesthesia resident blinded to the study groups. The data were collected before the patients were transferred to the floor, and then every 4 h until 24 h by direct interview of the patient and review of his or her medication sheets.

Several studies have found the average postlaparoscopic cholecystectomy nausea and vomiting incidence under general anesthesia to be in the range of 60–70% (i.e., without any intervention or antiemetics). A sample size of 50 patients in each group was determined to be adequate for demonstrating a 35% reduction in the incidence of PONV from 65 to 42% ($a = 0.05$, $b = 0.95$). In our study, we increased the sample size to 60 patients in each group to increase the power of the study further.

The means of the three groups were compared using analysis of variance (ANOVA), in which multiple-range tests with Fisher's least significant difference were used to compare the means to detect any significant differences between the three groups at a 95% confidence interval. For the values expressed as numbers and percentages, the chi-square test was used to compare percentages. A p value of 0.05 or less was considered significant. Statistical analysis was carried out using Statgraphics Centurion XV professional statistical software, version 15.1.02 (Statpoint, Inc. 2006, USA).

Results

Of the 196 patients who consented to participate in the study, 180 (60 in each group; 147 females and 33 males) completed the study, and 16 who received morphine for postoperative analgesia were excluded. Data from the 180 study patients were analyzed. There were no significant statistical differences in demographic data among the groups (Table 1). The patient-related risk factors, Apfel score, and surgically related risk factors (duration of surgery and gas insufflation) for PONV were similar between the groups (Table 1).

The predicted incidence of PONV according to the Apfel score for our patients was estimated to be approximately 60%. During the entire 24-h study period, PONV was experienced by 18 patients (30%) in the dexamethsone group, 19 patients (32%) in the ondansetron group, and 20 patients (33%) in the normal saline group. Statistical analysis of these results showed no significant differences among the three groups ($p > 0.05$). Rescue antiemetics were needed by four patients in group D (7%), five patients in group O (8%), and seven patients in group P (12%), with no significant difference observed between the groups ($p > 0.05$) (Table 2). The postoperative pain scores at 4 and at 24 h also were similar among the three groups (Table 3).

Table 1 Patients' demographic and operative characteristics

Variable	Group D Dexamethasone	Group O Ondansetron	Group P Saline	p Value
n	60	60	60	
Age (years)	45.1 ± 14.1	43.6 ± 13.3	44 ± 14.9	0.832
Weight (kg)	76.1 ± 12.0	76.4 ± 13.2	76 ± 15.7	0.983
Sex (F/M)	50/60	44/60	53/60	.091
Diabetes mellitus	4	1	2	0.112
Hypertension	4	5	9	0.129
Previous history of PONV	5	1	3	0.404
Smokers	2	4	2	0.760
Apfel score	2.80 ± 0.58	2.84 ± 0.66	2.85 ± 0.61	0.89
Duration of surgery (min)	44.5 ± 18.1	41.2 ± 13.4	43.1 ± 13.0	0.479
Duration of anesthesia (min)	59.9 ± 18.8	57.9 ± 14.5	60.3 ± 16.5	0.685
Duration of gas insufflation (min)	34.1 ± 15.3	33.1 ± 13.8	33.5 ± 12.5	0.951

Values are n or mean ± standard deviation. There are no significant differences among the groups

PONV postoperative nausea and vomiting

Table 2 Evaluation of postoperative nausea and vomiting associated with laparoscopic cholecystectomy

Time (h)	Variable	Group D Dexamethasone *n* (%)	Group O Ondansetron *n* (%)	Group P Saline *n* (%)
	n	60	60	60
0–4	Nausea alone	6	12	7
	Nausea and vomiting	3	4	6
4–24	Nausea alone	7	0	3
	Nausea and vomiting	2	3	4
0–24	Nausea alone	13	12	10
	Nausea and vomiting	5	7	10
	Total PONV	18 (30)	19 (32)	20 (33)
	Rescue antiemetics	4 (7)	5 (8)	7 (12)

There are no significant differences among the groups at the 95% confidence level

PONV postoperative nausea and vomiting

Table 3 Postoperative visual analog pain score (VAS) for the three groups at 4 and 24 h

Time (h)	Group D Dexamethasone	Group O Ondansetron	Group P Saline	*p* Value
4	3.5 ± 1.4	2.9 ± 1.5	3.3 ± 1.4	0.677
24	3.1 ± 1.1	3.1 ± 1.4	2.8 ± 1.3	0.344

Values are expressed as mean ± standard deviation. There are no significant differences among the groups at the 95% confidence level

Discussion

Although PONV is described as a minor side effect after laparoscopic surgery, it is considered to be a major cause of patients' fear and dissatisfaction [2]. The etiology of PONV after laparoscopic cholecystectomy is multifactorial, including patient, surgical, and anesthetic factors.

Piper et al. [14] reported that nitrous oxide increases PONV significantly compared with oxygen in air. The use of a supplemental inspired concentration of oxygen was found to reduce the incidence of this side effect [15]. Apfel et al. [6] found that volatile anesthetics are the main cause of PONV in the first 2 h postoperatively. Opioids are known risk factors for nausea and vomiting by direct stimulation of a chemoreceptor trigger zone and by a decrease in stomach and intestinal motility [5].

The use of combined paracetamol and tramadol was proved to exploit well-established complementary pharmacokinetics. The combination of these drugs was found to demonstrate a genuine synergy, rapid onset of efficacy, and a prolonged effect [16]. The use of this combination together with adjuvant infiltration of the wound sites by a local anesthetic was found to be effective in accomplishing adequate relief of our patients' perioperative pain. When this was supplemented with postoperative regular intravenous paracetamol and declofinac sodium, the patients had satisfactory postoperative pain relief.

Of our 196 patients, 16 experienced inadequate pain relief in the postoperative period, which was not relieved by declofinac sodium, necessitating the administration of intravenous morphine. These 16 patients were excluded from the study protocol due to the known ematogenic effect of morphine.

Perioperative generous hydration also was shown to reduce the incidence of thirst and vomiting in ambulatory patients undergoing general anesthesia [17]. Accordingly, 20 ml/kg of Hartman's solution was administered to all the patients in our study.

On the other hand, propofol-based TIVA was found to be associated with a lower incidence of PONV than inhalational anesthetics [18]. Its action seems related to the direct reduction of 5-HT3 levels in the area postrema [19]. Kim et al. [20] found that subhypnotic doses of propofol for patient-controlled antiemesis was effective in reducing the incidence of PONV with a high level of satisfaction. The analysis of Apfel and Korttila [13] indicated that substituting propofol for a volatile anesthetic reduced the risk of PONV by 19%, that substituting nitrogen for nitrous oxide reduced the risk by 12%, and that the combination of these two anesthetic management strategies (TIVA) thus reduced the risk of PONV as much as any single antiemetic.

The multifactorial etiology of PONV necessitates increased interest in using a combination of antiemetic measures. This approach, previously proved to have improved efficacy, has been advocated for patients with high risk factors [21]. Based on these facts, we proposed that the incidence of PONV will be reduced more if antiemetic drugs such as ondansetron or dexamethasone are added to propofol-based TIVA and other anesthetic measures the same as if a multimodal antiemetic technique is used.

The anesthetic technique in our study was based on the maximum prophylactic measures we could offer, from avoiding inhalational anesthetic agents, nitrous oxide, and

opioids to the use of multimodal analgesic therapy and high inspired oxygen concentration with good hydration and adequate gastric suctioning.

The results of this study demonstrate that the addition of dexamethasone or ondansetron to the aforementioned anesthetic measures did not further reduce the incidence of PONV after laparoscopic cholecystectomy. A possible explanation for this finding is that propofol, dexamethasone, and high intraoperative oxygen concentration all may act by reducing the release of 5-HT3, an emetogenic substance that stimulates 5-HT3 receptors in the chemoreceptor trigger zone, which in turn stimulates the vomiting center. Therefore, little benefit will be obtained when dexamethasone is added to TIVA.

Ondansetron also reduces the release of 5-HT3. Again, little benefit will be obtained by adding ondansetron to TIVA because the level of 5-HT3 already is low by the effect of propofol and the high inspired oxygen concentration. This principle was demonstrated earlier when it was found that an inspired oxygen fraction of 0.8 compared with 0.4 did not further reduce postoperative nausea and vomiting in dolasetron-treated patients undergoing laparoscopic cholecystectomy [14].

The results in our study are in accordance with those of Apfel and Korttila [13], who showed the small further antiemetic effects gained when two interventions were used compared with one intervention. Moreover, other authors have shown no benefits of increased inspired oxygen concentration in reducing PONV [14]. In our study, ondansetron had a weak effect over nausea in the 0- to 4-h study period compared with its antivomiting effect. This accords with other studies showing that ondansetron is more effective against vomiting than against nausea [22].

On the other hand Habib et al. [23] showed that the multimodal antiemetic strategy using propofol-based TIVA and 50% oxygen in air (no nitrous oxide) with a combination of droperidol and ondansetron is superior to propofol-based TIVA with 50% oxygen in air alone. The authors found that the patients in the first group had a significantly less frequent incidence of nausea, had lower nausea scores, required fewer rescues, and were more satisfied with the PONV management in both the immediate and postdischarge periods.

The contradiction between the aforementioned study and ours can possibly be explained by the strategies applied. Habib et al. [23] used fentanyl for all their patients, which may explain the difference in the incidence of PONV among their groups. Moreover, we did not use a combination of two antiemetic drugs in our study, which may explain the lack of difference in PONV among our patients. We did not observe major side effects of the study medication that may have affected patients during anesthesia or in the recovery period. In addition, we observed no significant difference in the postoperative pain scores between the groups that may have affected the results of our study.

In summary, ondansetron or dexamethasone separately did not further decrease PONV when added to a comprehensive anesthesia regimen that comprised TIVA, avoidance of perioperative opioids, and the use of high oxygen concentration and generous intravenous fluids for patients undergoing laparoscopic cholecystectomy. However, further studies are needed to find suitable interventions added to optimum anesthetic measures for further reduction of postoperative nausea and vomiting.

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