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Preventing Postoperative Nausea and Vomiting After Laparoscopic Cholecystectomy: A Prospective, Randomized, Double-Blind Study

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ABSTRACT

BACKGROUND: Postoperative nausea and vomiting (PONV) are potential complications in patients after laparoscopic cholecystectomy (LC). Combination antiemetic therapy often is effective for preventing PONV in patients undergoing LC, and combinations of antiemetics targeting different sites of activity may be more effective than monotherapy.

OBJECTIVE: The aim of this study was to compare the administration of a subhypnotic dose of propofol combined with dexamethasone with one of propofol combined with metoclopramide to prevent PONV after LC.

METHODS: Sixty adult patients scheduled for LC were randomly assigned to 1 of 2 treatment groups. The patients in group 1 received 0.5 mg/kg propofol plus 8 mg dexamethasone, and those in group 2 received 0.5 mg/kg propofol plus 0.2 mg/kg metoclopramide. The number of patients experiencing nausea and vomiting at 0 to 4, 4 to 12, and 12 to 24 hours postoperatively and as well as additional use of rescue antiemetics were recorded.

RESULTS: The total PONV rates up to 24 hours postanesthesia were 23.3% and 50% for group 1 and group 2, respectively. Comparisons of the data revealed that at 0 to 4 hours, the number of patients experiencing vomiting was 6 (20%) in group 1 and14 (46.7%) in group 2 ($P = 0.028$). The frequency of vomiting in group 1 was significantly lower than that for group 2 ($P = 0.028$), and the rate of rescue antiemetic use in group 2 was higher than that in group 1 (20% vs 46.7%; $P = 0.028$). In the evaluation of PONV based on the nausea and vomiting scale scores, the mean PONV score was 0.4 (0.2) in group 1 compared with 1.0 (0.2) in group 2 ($P = 0.017$). There were no significant differences between the values at 4 to 12 hours and at 12 to 24 hours. The frequency of adverse reactions (respiratory depression: 1.3%, 1.3%; laryngospasm: 1.3%, 0%; cough: 1.3%, 0%; hiccup: 1.3%, 0%;) was not significantly different in the 2 groups.

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CONCLUSIONS: Administration of a subhypnotic dose of 0.5 mg/kg propofol plus 8 mg dexamethasone at the end of surgery was more effective than administration of 0.5 mg/kg propofol plus metoclopramide in preventing PONV in the early postoperative period in adult patients undergoing LC. (*Curr Ther Res Clin Exp.* 2011; 72:1-12)

KEY WORDS: dexamethasone, laparoscopic cholecystectomy, metoclopramide, postoperative nausea and vomiting, propofol.

INTRODUCTION

Postoperative nausea and vomiting (PONV) are the most common symptoms affecting patients after surgery under general anesthesia, with an incidence of approximately 30%.[1]

The true incidence of PONV is difficult to determine because of the lack of a single stimulus of onset as well as the range of possible etiologies (medical, surgical, and patient and anesthesia associated). In the absence of antiemetic treatment, the incidence of PONV is estimated to be 25% to 30% for all surgical interventions and patient populations.[2] However, the incidence rate of PONV after laparoscopic cholecystectomy (LC) is higher than that after other types of surgery.[3,4] A rate of 46% to 75% has been reported for patients who did not receive antiemetic treatment after LC.[3–5]

Propofol was first reported to be an effective antiemetic at low doses in patients undergoing chemotherapy for cancer.[6] Song et al[7] have shown that intravenous (IV) administration of 0.5 mg/kg propofol, a low dose, at the end of surgery was effective in preventing nausea and vomiting after LC.

The use of propofol to maintain anesthesia also reduces PONV. Patients administered propofol to induce anesthesia have a lower incidence of PONV after LC than do those administered thiopentone/halothane for anesthesia. Further, it has been shown that propofol possesses direct antiemetic properties that are not attributable to the lipid in the emulsion formulation of the drug, as once hypothesized.[8]

Dexamethasone may offer additional benefits over traditional antiemetics in improving surgical outcomes. Several studies have shown that dexamethasone, a corticosteroid, is an effective antiemetic for PONV prophylaxis,[9–11] and Holte and Kehlet[9] reported that dexamethasone produces antiemetic effects in various types of surgery. Compared with placebo, dexamethasone, 8 mg IV given 90 minutes before LC, has been reported to reduce PONV significantly.[12] Dexamethasone is inexpensive and effective, with minimal adverse effects after single-dose administration.[13]

Metoclopramide is a central D_2-receptor antagonist and a prokinetic agent that hastens esophageal clearance, accelerates gastric emptying, and shortens bowel transit time.[14] As an antiemetic, metoclopramide is widely used in clinical practice.[2,15] Prophylactic IV administration of metoclopramide, 10 to 20 mg, reduces the incidence of PONV after LC and is as effective as ondansetron, 4 to 8 mg.[16,17] At higher doses (0.2 mg/kg), metoclopramide is associated with extrapyramidal reactions such as akathisia and motor restlessness.[2,15] None of the antiemetics currently available is entirely effective, perhaps because most of them act through the blockade of 1

receptor. Combination antiemetic therapy often is effective for preventing PONV in patients undergoing LC,[8,18,19] and agents with different sites of activity may be more effective than a single drug.[8]

Although reports on propofol and steroid combination therapy are available, no evidence was uncovered regarding the effects of a combination of propofol plus metoclopramide and propofol plus dexamethasone for the prevention of PONV. A MEDLINE literature search (inception–2009) using the terms *PONV*, *antiemetic*, *propofol*, *metoclopramide*, and *dexamethasone* did not identify any studies regarding the effects of a combination of propofol plus metoclopramide and propofol plus dexamethasone for the prevention of PONV.

This prospective, randomized, double-blind study aimed to evaluate the effectiveness and tolerability of a low dose of propofol plus 8 mg dexamethasone and a low dose of propofol plus metoclopramide for the prevention of PONV in patients undergoing LC.

METHODS

This randomized, double-blind, controlled clinical study was carried out at the Yüksek İhtisas Hospital in Kırıkkale,Turkey. Approval was obtained from the Ethics Committee at Kirikkale University Medical School, Kirikkale, Turkey. All patients provided written informed consent. Sixty patients scheduled for LC (aged 25 to 55 years; 48 women) with an American Society of Anesthesiologists (ASA) physical status classification system risk of 1 or 2 were randomly assigned to 1 of 2 groups: the propofol plus 8 mg dexamethasone group (group 1) and the propofol plus 0.2 mg/kg metoclopramide group (group 2). Patients were assigned using a computer-generated random number table. Indications for LC in this clinical trial were symptomatic cholelithiasis, chronic cholecystitis, and cholecystic polyp. Exclusion criteria included history of hepatic, renal, or cardiovascular diseases; chronic obstructive pulmonary disease; hematologic or gastrointestinal disorders, or both; hypersensitivity to propofol or to any other drug; history of vertigo or motion sickness; previous postoperative emesis; pregnant, breastfeeding, or menstruating women; use of an antiemetic agent within 24 hours before surgery; and laparoscopy replaced by laparotomy. All LC procedures were performed by the same team of anesthesiologists and surgeons. Different anesthesiologists carried out the data collection and treating roles in this study.

Patients fasted for 8 hours before surgery, and no one was premedicated. In the operation room, heart beat rate (HBR), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), and peripheric oxygen saturations (Spo_2; Datascope Passport 2, Datascope Corp, Mahwah, New Jersey) were monitored. Anesthesia for all patients in both groups was induced with thiopentone 5 mg/kg (IV bolus dose) followed by remifentanil infusion at 0.2 μg/kg/min and sevoflurane inspiration at 1% to 2 % concentration. After patients received vecuronium (0.1 mg/kg), all were ventilated mechanically with O_2/air (50%/50%), 4 L/min end tidal carbon dioxide ($ETco_2$) 35 to 40 mm Hg through orotracheal intubation (TMS Maxi 2200 M, Penlon AV 900, Oxford, United Kingdom). The maintenance

doses of remifentanil and sevoflurane were adjusted for hemodynamic stability. Throughout surgery, hydration was maintained with an infusion of isotonic or Ringer's lactate solution at a rate of 3 mL/kg to 5 mL/kg. Hemodynamic parameters and Spo_2 measures were recorded before and after the infusion, every 5 minutes for 30 minutes after intubation, in 15-minute intervals thereafter, and every 30 minutes for the remainder of the 24-hour postoperative period.

Before induction of anesthesia and at the time of skin closure, patients in group 1 were given 0.5 mg/kg of propofol (IV bolus dose; propofol 1%) plus 8 mg dexamethasone Deksamet® amp, Osel, Istanbul, Turkey (8 mg/2 mL). Group 2 patients were given 0.5 mg/kg propofol (IV bolus; propofol 1% Primperan® amp, Biofarma, Istanbul, Turkey) plus 0.2 mg/kg metoclopramide IV (10 mg/2mL) before skin incision closure. All syringes—propofol plus dexamethasone and propofol plus metoclopramide—were prepared by the same investigator. Patients in each group received 2 syringes, 1 active and 1 placebo. Patients, the anesthesiologist attending during surgery, and the anesthesiologist who collected postoperative data were all blinded to the randomization process and the identity of the study drugs.

At the time of the last surgical suture, all anesthetic maintenance agents were terminated and the time was recorded. The lungs were manually ventilated with 100% oxygen (4 L/min) until spontaneous respiration was achieved. Residual muscle relaxation was antagonized with 0.03 mg/kg neostigmine and 0.02 mg/kg atropine, and the patients were appropriately extubated. Time of extubation; eye opening; response to verbal stimulation; and orientation to place, time, and people were recorded.

All patients were removed to postoperative recovery and remonitored after extubation. Patients remained for evaluation of potential postoperative complications and recovery for at least 1 hour.

The primary end point of this study was the total PONV rate up to 24 hours postanesthesia. The secondary end points were incidence of nausea, incidence of vomiting, severity of nausea, use of rescue antiemetic drugs, and occurrence of side effects for 24 hours postanesthesia. All episodes of PONV (nausea or vomiting), whether in the care unit or in the general ward, were recorded during the first 24 hours after anesthesia in 3 time periods (0 to 4, 4 to 12, and 12 to 24 hours postanesthesia).

The degree of PONV was scored using the nausea-vomiting scale (NVS) (**Table I**) at 0 to 4, 4 to 12, and 12 to 24 hours. Additional antiemetics (10 mg metoclopropamide) were administered intravenously when the NVS score was ≥ 3. Patients were observed for 24 hours postoperatively, and nausea and vomiting times and times of additional antiemetic and analgesic administration were recorded.

Statistical analyses were performed by SPSS statistical package for Windows (Chicago, Illinois). Parametric values were evaluated with the Student *t*-test. Nonparametric values were compared using the Mann-Whitney U test. Side effects, gender, and ASA status were compared using χ^2 and Fisher exact tests. A $P < 0.05$ was considered statistically significant.

Table I. Nausea vomiting scale.

NVS	Severity
0	No complaints
1	Mild nausea
2	Moderate nausea
3	Frequent vomiting (4 times)
4	Severe vomiting (continuous)

NVS = nausea vomiting scale.

RESULTS

A total of 64 patients were approached for study inclusion, 4 of whom were excluded based on criteria described previously. Sixty patients (mean [SD] age, 42.15 [8.85] years; height, 165.85 [7.6] cm; and weight, 71.65 [9.1] kg) completed the study (**Table II**). No statistically significant between-group differences were found in the patients' demographic and clinical characteristics.

The total PONV rates up to 24 hours postanesthesia were 23.3% and 50% in groups 1 and 2, respectively.The comparisons of the groups for the number of patients with nausea showed a significant difference at 0 to 4 hours, whereas there were no statistically significant differences at 4 to 12 and at 12 to 24 hours. The incidence of nausea at 0 to 4 hours was 7 patients (23.3%) in group 1, 15 (50%) in group 2 ($P = 0.032$). The incidence rate of vomiting in group 1 was statistically significantly lower than that in group 2 (20% vs 46.7%; $P = 0.028$). The comparisons of the groups for the incidence of vomiting at 0 to 4 hours revealed a rate of 6 patients (20%) in group 1 and 14 patients (46.7 %) in group 2 (**Table III**).

Comparison of groups regarding number of patients with nausea ($P = 0.032$), vomiting ($P = 0.028$), and need for extra antiemetics ($P = 0.028$) uncovered a

Table II. Demographics characteristics.

Parameters	Group 1 (n = 30)	Group 2 (n = 30)	*P*
Age, y	42.8 (9.9)	41.5 (7.8)	0.787
Weight, kg	72.8 (10.1)	70.5 (8.1)	0.895
Height, cm	165.3 (7.0)	166.4 (8.2)	0.916
Smoking, no. (%)	11 (36.7)	9 (30)	0.584
ASA (I/II), no. (%)	24 (80.0%)/6 (20.0)	25 (83.3%)/5 (16.7)	0.739
Gender (F/M), no. (%)	23 (76.7%)/7 (23.3)	25 (83.3%)/5 (16.7)	0.519
Duration of operation, min	105.5 (11.0)	110.5 (10.5)	0.625

ASA = American Society of Anesthesiologists. Data are mean (SD) unless otherwise indicated.

Table III. Number of patients experiencing nausea or vomiting (n[%]).

Nausea/Vomiting	Group 1 (n = 30)	Group 2 (n = 30)	*P*
Nausea			
0–4 h	7 (23.3)	15 (50.0)*	0.032
4–12 h	6 (20.0)	7 (23.3)	0.754
12–24 h	0 (0)	0 (0)	–
Vomiting			
0–4 h	6 (20.0)	14 (46.7)*	0.028
4–12 h	2 (6.7)	4 (13.3)	0.671
12–24 h	0 (0)	0 (0)	–

*$P < 0.05$, compared with group 1.

significant difference at 0 to 4 hours but no significant differences at 4 to 12 and at 12 to 24 hours. There were significant differences between groups in the need for additional antiemetics; 6 patients (20%) in group 1, and 14 patients (46.7%) in group 2 required additional antiemetics ($P = 0.028$) (Table IV).

The mean (SD) NVS score was 0.4 (0.2) in group 1 and 1.0 (0.2) in group 2 ($P = 0.017$) (Table IV). The amount of additional antiemetics used was significantly higher in group 2 than in group 1 ($P = 0.016$). There were no differences between groups for postoperative use of metamizole and nonsteroidal antiinflammatory drugs ($P > 0.05$); however, a significant difference was found between group 1 and group 2 for additional antiemetic use (group 1, 6 [20%] and group 2, 14 [46.7%]; $P = 0.028$).

No significant differences were found between groups for eye opening; time to response to verbal stimulation; and orientation to place, time, and people (Table V).

Side effects are presented in Table VI. There were no differences between groups for cough, laryngospasm, urinary retention, respiratory depression, or hiccup (Table VI).

Table IV. The number of patients subjected to NVS, additional antiemetics, and additional antiemetics.

	Group 1 (n = 30)	Group 2 (n = 30)	*P*
Additional antiemetics patients, no. (%)	6 (20)	14 (46.7)*	0.028
NVS, mean (SD)	0.4 (0.2)	1.0 (0.2)*	0.017
Additional antiemetics, mean (SD), mg	2.0 (0.9)	6.3 (1.4)*	0.016

NVS = nausea vomiting scale.
*$P < 0.05$ compared with group 1.

Table V. Recovery periods. Data are mean (SD) unless otherwise indicated.

Parameters	Group 1 (n = 30)	Group 2 (n = 30)	*P*
Opening eyes in response to verbal commands (min)	2.1 (1.5)	1.8 (1.4)	0.486
Opening eyes spontaneously (min)	4.0 (3.1)	2.8 (1.8)	0.267
Orientation to place (min)	6.5 (3.9)	4.7 (3.2)	0.202
Orientation to time (min)	7.2 (4.3)	5.4 (3.4)	0.233
Orientation to people (min)	6.9 (3.9)	5.4 (3.4)	0.305

Data are mean (SD) unless otherwise indicated.

DISCUSSION

In our study, patient demographics, type of surgical procedure, and anesthetic administered were similar between groups. In addition, patients with a history of motion sickness or previous postoperative emesis had been excluded from the study; thus, the difference in incidence of PONV between groups was likely attributable to variation in antiemetic drugs.

Our findings indicated that effectiveness of the combination of propofol plus dexamethasone was significantly better than the combination of propofol plus metoclopramide.

Numerous agents have been used to treat PONV at varying dosages and time intervals.[2,20–25] Parameters such as nausea and vomiting scores for 4 hours in the early postoperative period or in the postoperative 24 hours, number of episodes and severity of vomiting, number of antiemetics required, amount of antiemetics used, hospitalization time, and problems caused by nausea and vomiting are studied to evaluate the effectiveness of these agents. In our study, the severity of nausea and vomiting was measured using the NVS for the postoperative 24 hours, and the number of patients with nausea, vomiting, or need for additional antiemetics was compared for postoperative hours 0 to 4, 4 to 12, and 12 to 24 hours; the results were expressed in percentages. We determined that the immediate postoperative bolus

Table VI. Incidence of adverse reactions.

Adverse Reactions	Group 1 (n = 30)	Group 2 (n = 30)	*P*
Cough	0 (0%)	1 (3.3%)	0.5
Laryngospasm	0 (0%)	1 (3.3%)	0.5
Urinary retention	0 (0%)	0 (0%)	–
Respiratory depression	1 (3.3%)	1 (3.3%)	–
Hiccup	0 (0%)	1 (3.3%)	0.5

dose of 0.5 mg/kg of propofol plus 8 mg dexamethasone was more effective than the bolus dose of 0.5 mg/kg propofol plus 0.2 mg/kg metoclopramide for control of PONV during the first 4 postoperative hours.

PONV develops as a complication after anesthesia, and if not prevented, recovery and hospitalization time can be prolonged,[2,25] leading to unpleasant hospital experiences and increased health care costs.[2] Prolonged vomiting may result in electrolyte imbalance (hypocalcemia, hypochloremia, hyponatremic metabolic alkalosis) and dehydration, Mallory-Weis tears, esophageal rupture, wound opening, and hematoma formation under skin flaps after abdominal, vascular, eye, or plastic surgery.[2,20,22]

The effect of intraperitoneal insufflation of carbon dioxide (CO_2) on residual stretching and irritation of the peritoneum[23] and duration of surgery[15,26] are other factors that affect PONV after LC. In our study, however, treatment groups were similar for patient demography, types of LC, anesthetics administered, and analgesics used postoperatively. Patients with a history of motion sickness, previous PONV, or both and women who were menstruating were excluded from the study because they have a remarkably high risk for PONV.[15,26,27]

Propofol used as an induction agent or continuously administered for maintenance was found to cause less PONV compared with other induction agents and anesthesia techniques.[25,28] Despite a much lower incidence of PONV with the use of propofol, in total IV anesthesia, high cost constitutes a negative aspect on its use for this purpose.[29–31] The antiemetic mechanism of propofol is not clearly known. This characteristic has been attributed to either its sedative effect or modulation of subcortical pathway[21,32] and possibly due to its weak serotonin antagonist effect.[21,33]

The use of propofol for maintenance of anesthesia has a positive effect on PONV reduction. Song et al[7] have determined that low doses (0.5 mg/kg) of propofol infused at the end of surgery in patients who have undergone LC under general anesthesia reduce the incidence of PONV. Fujii and Nakayama[34] have determined that low doses of propofol plus dexamethasone at the end of surgery in patients who have undergone LC under general anesthesia reduce the incidence of PONV.

Fujii et al[35] showed that a low dose (0.5 mg/kg) of propofol combined with 8 mg of dexamethasone was more effective than propofol alone for the prevention of PONV in adult Japanese patients having general anesthesia for extractions of third molars.

In our study, low-dose (0.5 mg/kg) propofol combined with dexamethasone (8 mg) was administered; the prevention of PONV was comparable with that reported in similar studies.[18,34,35]

Numazaki and Fujii[33] have reported that the minimum dose of propofol for effective prevention of PONV is 0.5 mg/kg given intravenously at the end of surgery; when used at a dose of 0.25 mg/kg, its effect is no different from that of placebo. These authors have also concluded that at doses of 0.5 mg/kg and 0.75 mg/kg, propofol has similar effects; doses under 1 mg/kg yield less sedation, dysphoria, and extrapyramidal signs, so 1 mg/kg is not recommended.[33] Based on this information, we used 0.5 mg/kg propofol (bolus dose).

Dexamethasone may offer additional benefits over traditional antiemetics in improving surgical outcomes. Compared with placebo, dexamethasone 8 mg IV given

90 minutes before LC has been reported to significantly reduce PONV.[12] Although 8 mg IV is probably the most commonly used dose of dexamethasone for preventing PONV in adults, the optimal dose has yet to be defined. One dose-finding study reported 2.5 mg to be the minimum effective dose for preventing postoperative vomiting in patients undergoing major gynecological surgery,[36] whereas subsequent studies reported 5 mg to be the minimum effective dose in patients undergoing thyroidectomy.[10] Dexamethasone is most effective in preventing PONV when it is administered immediately before induction of anesthesia rather than near the end of unconsciousness.

The long-term administration of dexamethasone causes adverse effects, such as an increased risk for infection, glucose intolerance, delayed wound healing, superficial ulceration of gastric mucosa, and adrenal suppression.[37] In our study, however, these adverse effects were not related to a single dose of dexamethasone. Adverse effects observed in our study were not clinically important in any of the groups.

Metoclopramide is one option for conventional antiemetic treatment. Generally, IV use of 10 mg or 0.2 mg/kg metoclopramide is recommended.[23,38] Adverse effects of metoclopramide include sedation, dizziness, and drowsiness. Extrapyramidal symptoms are not common but can occur and include feelings of weakness, anxiety, agitation, and motor restlessness.[39] Slow IV administration of metoclopramide and administration of a preoperative anxiolytic sedative are important strategies for reducing the risk of akathisia from the administration of IV metoclopramide.[40]

In earlier studies, the incidence of PONV associated with administration of nitrous oxide (N_2O) was high. N_2O is known to cause nausea and vomiting when administered as the sole anesthetic agent. N_2O can also cause PONV due to changes in middle ear pressure and bowel distention due to diffusion into closed cavities.[41] Gan et al[26] have recently reported consensus guidelines for managing PONV and concluded that the use of N_2O during maintenance of anesthesia should be avoided. In our study, therefore, we did not use this anesthetic gas.

It is known that positive pressure ventilation, a full stomach, and opioids and anticholinergics used in premedication lead to increased PONV in anesthesia induction.[2,42] In our study, no premedication was carried out. We tried to avoid strong positive pressure ventilation; before extubation, we performed gastric aspiration, decreasing the effect of such factors that increase nausea and vomiting in the preoperative period.

To reduce the effect of patient- and anesthesia-specific factors, we homogenized study groups for age, body weight, height, ASA group, sex, duration of operation, and anesthesia. Such differences may account for differences observed in some studies.

Our study had potential limitations. First, the use of anticholinesterase and atropine was not avoidable. Second, these data may not be applicable to different surgical procedures or anesthetic techniques. Third, no prestudy power analysis was performed. Fourth, the original design included a placebo control group; however, the institutional review board at our center decided that this would not be ethical because the patients studied were at high risk for developing PONV.

In conclusion, subhypnotic bolus doses of propofol plus dexamethasone used at the end of LC were significantly more effective than propofol plus metoclopramide in preventing PONV in this patient population. Additional studies are needed to compare the effectiveness of subhypnotic doses of propofol with other antiemetics.

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