Egyptian Journal of Anaesthesia (2013) **29**, 117–123

Egyptian Society of Anesthesiologists

Egyptian Journal of Anaesthesia

www.elsevier.com/locate/egja
www.sciencedirect.com

Research Article

Postoperative nausea and vomiting prophylaxis: The efficacy of a novel antiemetic drug (palonosetron) combined with dexamethasone

Emad E. Mansour *

Department of Anesthesia, Ain Shams University, Egypt

Received 25 September 2012; accepted 12 November 2012
Available online 8 December 2012

KEYWORDS

Postoperative nausea and vomiting;
Antiemetics;
Dexamethasone;
Metoclopramide;
Palonosetron

Abstract *Background:* Palonosetron is a new, potent, and long-acting 5HT3-receptors antagonist that had been approved by the FDA for use in postoperative nausea and vomiting (PONV) prophylaxis. This study is designed to evaluate its efficacy combined with dexamethasone in PONV prophylaxis in highrisk patients scheduled for laparoscopic surgeries.

Methods: In this double-blind, active-controlled study, 150 patients aged 20–55 years, ASA I–II, and with Apfel's PONV score 2–4 were equally randomized to receive dexamethasone 8 mg before anesthesia induction and saline 30 min before the end of surgery (group D + S), dexamethasone 8 mg before anesthesia induction and metoclopramide 25 mg 30 min before the end of surgery (group D + M), or dexamethasone 8 mg combined with palonosetron 0.075 mg before anesthesia induction and saline 30 min before the end of surgery (group D + P). Incidences of early and late PONV, complete response, adverse events from antiemetics used, and overall patients' satisfaction were recorded.

Results: The incidence of PONV was comparable in the three groups 0–6 h postoperatively. Palonosetron–dexamethasone and dexamethasone–metoclopramide combination therapies significantly reduced the incidence of PONV at 6–12 h postoperatively compared to dexamethasone monotherapy (12% and 16%, vs. 36%, respectively, with $P < 0.05$). Moreover, palonosetron–dexamethasone combination therapy significantly reduced the incidence of PONV at 12–24 h postoperatively compared to both dexamethasone monotherapy (16% vs. 48%, $P < 0.01$), and dexamethasone–metoclopramide combination therapy (16% vs. 40%, $P < 0.05$). The incidence

* Address: King Fahd Military Medical Complex, PO Box 946, Dhahran 31932, Saudi Arabia. Tel.: +966 567320660; fax: +966 38440000.
E-mail address: emad.mansour@gmail.com.

Peer review under responsibility of Egyptian Society of Anesthesiologists.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.egja.2012.11.001

of adverse drug effects was comparable in the three groups. The overall patients' satisfaction was significantly higher in palonosetron–dexamethasone combination therapy compared to other groups.

Conclusion: Palonosetron–dexamethasone combination is effective and safe in PONV (early and late) prophylaxis in high-risk patients undergoing laparoscopic surgeries with known high-risk of PONV.

1. Introduction

Postoperative nausea and vomiting (PONV) is often the most common complication following anesthesia and surgery [1] with subsequent adverse consequences including delayed recovery, patient dissatisfaction, unexpected hospital admission, and delayed return to work [2]. The incidence of PONV is influenced by many factors including age, gender, smoking status, history of PONV or motion sickness, preoperative anxiety, type and duration of surgery, volatile anesthetics, nitrous oxide, postoperative use of opioid analgesics, and ambulation [1,3–5]. In high-risk patients, the incidence of PONV can reach up to 80%, indicating the importance of prophylaxis and control of this distressing complication [6].

Several pharmacological therapies (butyrophenones, antihistmincs, and dopamine receptor antagonists) have been tried in PONV prophylaxis [7,8]. No single antiemetic drug has proved to be a universal solution to PONV. In general, multimodal combination therapy has superior efficacy for PONV prophylaxis compared with monotherapy [9,10]. Dexamethasone was recommended as the first line drug, as it is safe and cheap [11,12]. Metoclopramide had been used as an antiemetic for more than 40 years (yr) in PONV Prophylaxis, and is cheap. Because of its triple action (central dopaminergic (D_2) receptors – central and peripheral 5-HT_3 receptors peripheral 5-HT_4 receptors), it is a potentially interesting drug for PONV prophylaxis [13].

Palonosetron is the latest potent and selective second generation 5-HT_3 receptor antagonist. It is the only drug of its class approved for prophylaxis against both acute and delayed chemotherapy-induced nausea and vomiting (CINV). Far higher receptor affinity and a much longer half-life (approximately 40 h) than other 5-HT_3 antagonists confer a prolonged duration of action [14,15]. Its use for PONV prophylaxis was approved by the Food and Drug Administration (FDA) in March 2008 following successful Phase III clinical trials [2].

The objective of this study is to compare the efficacy of palonosetron combined with dexamethasone vs. dexamethasone used alone and in combination with metoclopramide as prophylactic regimens for the prevention of PONV after laparoscopic surgical procedures with known high-risk of PONV.

2. Patients and methods

This study was conducted in the period from April 2012 to August 2012 at King Fahd Military Medical Complex (Dhahran, Saudi Arabia) after getting approval of institutional ethical committee and signed, informed, written consent from each patient. One hundred and fifty patients, aged 20–55 yr, with American Society of Anesthesiologists (ASAs) physical status I or II and scheduled for elective laparoscopic surgical procedures with known high-risk of PONV were included in this prospective, randomized, double-blind, active-controlled study. These laparoscopic surgical procedures included cholecystectomy, herniorraphy, and gynecological procedures. A simplified risk score implemented by Apfel et al. [6] for predicting PONV was used to identify appropriate patients for enrollment in this study. Risk factors were female gender, nonsmoking status, history of PONV or motion sickness, and postoperative opioids. Each risk factor was given a score of one. Only patients who had at least two risk factors (risk score 2–4) were enrolled. Patients aged > 60 yr, with ASA $\geqslant$ III, their body mass index (BMI) $\geqslant$ 35 kg m^{-2}, received a prophylactic antiemetic within 24 h of surgery, concomitant administration of steroids or psychotropic drugs, having a contraindication to the use of corticosteroids (glaucoma, severe hypertension, heart disease, renal failure, peptic ulcer disease, diabetes mellitus, adrenal insufficiency, immunosuppression, recent tuberculosis), pregnant or lactating women, had a condition requiring chronic opioid use, or were allergic to any of the study drugs were excluded and replaced by other patients.

Patients were randomly allocated into three equal groups (randomization was performed with the use of sealed envelopes) to receive one of three prophylactic regimens: group D + S (dexamethasone + saline group; $n = 50$), received intravenous (IV) dexamethasone 8 mg before induction of anesthesia and placebo (normal saline) 30 min before the expected end of surgery; group D + M (dexamethasone + metoclopramide group; $n = 50$) received IV dexamethasone 8 mg before induction of anesthesia and 25 mg metoclopramide IV 30 min before the expected end of surgery; group D + P (dexamethasone + palonosetron group; $n = 50$) received 0.075 mg of palonosetron (Emecad®) combined with dexamethasone 8 mg IV before induction of anesthesia (combination is known to be physically and chemically compatible) and saline placebo 30 min before the expected end of surgery. For proper blinding, the study drugs were prepared by the operating room (OR) pharmacy in the morning of operation. They were prepared in two identical 5 ml syringes and labeled; study drug 1 and 2. Study drug 1 was given immediately before induction of anesthesia (dexamethasone in groups D + S and D + M, and combination of dexamethasone and palonosetron in group D + P) and study drug 2 was given 30 min before the expected end of surgery (metoclopramide in group D + M, and normal saline in groups D + S and D + P) by the attending anesthesiologist who was blinded to the study. In the preoperative visit, all patients were taught to rate the degree of their perceived preoperative anxiety and pain using verbal analog scale (VAS). VAS is a verbal numerical rating scale from 0 to 10 where zero represents one extreme (not

anxious, or no pain) and the 10 representing the other extreme (anxious as can be, or the worst possible pain). Also, they were taught to use the patient-controlled analgesia (PCA) pump.

Immediately before surgery, all patients were assessed for anxiety. The anesthetic technique was standardized for all patients. Standard monitors were attached namely; 5-leads electrocardiography (ECG), Pulse oximetry (SpO_2), and non-invasive blood pressure monitor (NIBP). After obtaining baseline vital signs, the study drug 1 was given slowly IV, then anesthesia was induced with fentanyl 2 μg kg^{-1} IV and propofol 2–3 mg kg^{-1} IV. Endotracheal intubation was facilitated by the use of atracurium besylate at a dose of 0.5 mg kg^{-1} IV. General anesthesia was maintained with sevoflurane 2–3% in oxygen/air mixture (FiO_2 = 0.6). 30 min before the expected end of surgery, study drug 2 was given slowly IV. Immediately before the end of surgery, sevoflurane was discontinued and all patients were given 1 g paracetamol by IV drip for postoperative analgesia. At time of emergence, residual neuromuscular block was reversed by 0.05 mg kg^{-1} of neostigmine IV and 0.02 mg kg^{-1} of atropine IV. Anesthesia time (from start of induction to discontinuation of sevoflurane), the time of surgery (from the surgical incision to the placement of surgical dressings), and recovery times (from discontinuation of sevoflurane until the patient can grasp his or her hand on command) were recorded.

At the postanesthesia care unit (PACU) standard monitors were connected (ECG–SpO_2–NIBP) and all patients were given oxygen by face mask at a rate of 4 L min^{-1}. The patients were assessed for pain using VAS and if VAS is >4, rescue analgesia was given in the form of 1 g paracetamol given by IV drip and PCA protocol was initiated. The time of nausea and vomiting episodes were collected from the nursing chart upon arrival to PACU, at 6, 12 and 24 h postoperatively. Nausea was defined as the subjective sensation of an urge to vomit with absence of expulsive muscular movements. Vomiting was defined as forcible expulsion of gastric contents through the mouth, and retching was defined as an unproductive effort to vomit. An emetic episode was defined as a single attack of vomiting or retching, or any number of continuous vomiting or retches (one emetic episode should be separated from another by an absence of vomiting or retching for at least 1 min). Rescue antiemetic (ondansetron 4 mg IV) was given if patient experienced continuous nausea for more than 15 min or two or more emetic episodes whilst in hospital. The treatment was repeated if necessary. Complete response (CR) of the drug was defined as no PONV and no administration of rescue antiemetic during the study period.

The PCA device (Graseby 3300 PCA pump, Smiths Group, UK) was primarily adjusted without background infusion to deliver a demand dose of 1 ml (10 μg fentanyl) with a lockout interval of 10 min and, rescue bolus doses of 2 ml (20 μg), and 4-h limit of 200 μg. Those settings could be readjusted according to the patient's VAS in the postoperative period. The total opioid analgesic consumption was recorded by the acute pain service nurse in charge who was blinded to the study. Adverse effects were also recorded including headache, dizziness, myalgia, constipation, and extrapyramidal manifestations. At 24 h postoperatively, the overall patients' satisfaction with the PONV prophylactic regimens was assessed using a three-point scale, in which a score of 1 indicates "totally dissatisfied"; 2, "neutral"; and 3, "totally satisfied".

The incidence of PONV in laparoscopic surgeries is 75% if no prophylaxis is given with an anticipated reduction in the incidence of PONV up to 25% in D + S group which was the therapeutic outcome for dexamethasone when given as the sole prophylactic agent in a previous study established by power analysis [16]. Based on that, the group size necessary to detect a clinically relevant difference of 25% in the incidence of PONV in groups D + P and D + M in relation to the group D + S was estimated to be 50 patients per group to give a power of 0.8 at a level of $P = 0.05$ (α error = 0.05; β error = 0.1).

Data were presented as mean ± standard deviation (SD), median (range), or absolute number (percentage) as appropriate. Groups were compared to each other using the parametric or the nonparametric versions of analysis of variance (ANOVA) followed by the appropriate post hoc analysis if significance was detected. Nominal data were compared using Chi-square (χ^2) test or alternatively by Fisher's exact test if the expected frequencies were < 5.0. P values < 0.05 were considered significant. Statistical software package (Graph Pad In Stat® version 3.00 for Windows, Graph Pad Software Inc., San Diego, California, USA) was used for data analysis.

3. Results

In this randomized, double-blind, active-controlled study, one hundred and fifty patients were randomly allocated into three groups: group D + S (dexamethasone + saline; $n = 50$), group D + M (dexamethasone + metoclopramide; $n = 50$), and group D + P (dexamethasone + palonosetron; $n = 50$). All patients completed the study.

Groups were comparable with regard to demographic data (age, gender, BMI, ASA physical status), risk factors for PONV, and times of anesthesia; recovery; and PACU stay (Table 1).

Effects of the three antiemetic regimens on PONV are shown in Table 2. At 0–6 h postoperatively, the incidence of PONV, rescue antiemetic therapy, and CR was comparable among the three groups. At 6–12 h postoperatively, the incidence of PONV and rescue antiemetic therapy started to be significantly lower in groups D + P and D + M compared with the active-control group. Moreover, the number of patients who showed CR to antiemetic prophylactic therapy was significantly higher in groups D + P and D + M compared with D + S group [44 (88%) and 42 (84%) vs. 32 (64%), respectively, with estimated P value < 0.05] (Table 2). At 12–24 h postoperatively, the incidence of PONV and rescue antiemetic therapy was significantly lower in D + P group in comparison with the other two groups (Table 2). Furthermore, the incidence of CR was significantly higher in D + P group in comparison with D + S, and D + M groups being 84% vs. 52%, and 60%, respectively, with estimated P value < 0.01 for D + S group and $P < 0.05$ for D + M group (Table 2). The overall incidence of PONV and rescue antiemetic therapy over the 24 h study period was significantly lower in D + P group in comparison with other groups (Table 2). Also, the number of patients who exhibited CR was significantly higher in D + P group in comparison with D + S, and D + M groups being 42 (84%) vs. 24 (48%), 29 (58%), respectively, with estimated P value < 0.01 (Table 2).

Table 1 Demographic data, times (anesthesia, surgery, recovery, PACU stay), and risk factors.

	Group D + S (n = 50)	Group D + M (n = 50)	Group D + P (n = 50)	P value
Age (yr)	33.4 ± 8.6	35.7 ± 9.2	34.9 ± 9.5	0.442
BMI (kg m^{-2})	25.6 ± 6.4	26.9 ± 7.1	27.1 ± 6.2	0.466
ASA class I/II	30/20	23/27	26/24	0.484
Risk factors:				
Female gender	29 (58)	23 (46)	28 (56)	0.436
Nonsmoking status	43 (86)	42 (84)	38 (76)	0.387
History of PONV or motion sickness	17 (34)	19 (38)	15 (30)	0.700
Apfel's risk score: (2/3/4)	6/26/18	4/30/16	7/23/20	0.698
Surgeries performed:				
Laparoscopic cholecystectomy	33 (66)	34 (68)	31 (62)	0.814
Laparoscopic hernia repair	8 (16)	6 (12)	7 (14)	0.847
Gynecologic laparoscopy	9 (18)	10 (20)	12 (24)	0.752
Duration of surgery (min)	66.7 ± 13.4	62.6 ± 12.7	65.1 ± 11.9	0.268
Duration of anesthesia (min)	92.6 ± 19.4	99.8 ± 20.2	98.7 ± 21.4	0.166
Recovery time (min)	11.2 ± 3.1	11.8 ± 2.6	11.6 ± 3.4	0.607
PACU stay time (min)	33.2 ± 5.3	34.7 ± 6.2	32.9 ± 5.1	0.225
Preoperative anxiety (VAS)	3.5 (1–5)	3.0 (1–6)	3 (0–6)	0.174
Fentanyl consumption by PCA (mg)	0.46 ± 0.08	0.0.50 ± 0.15	0.49 ± 0.13	0.245

Group D + S = dexamethasone + saline; group D + M = dexamethasone + metoclopramide; group D + P = dexamethasone + palonosetron; n = number; yr = years; BMI = body mass index; PONV = postoperative nausea and vomiting; PACU = post-anesthesia care unit; Y/N = yes/no; min = minutes; VAS = visual analog scale; PCA = patient-controlled analgesia; mg = milligrams.
Data are expressed as mean ± SD, median (range), number (percentage), or absolute number.
$P < 0.05$ was considered significant.

Regarding the incidence of recorded adverse events of the antiemetic regimens, the three groups were comparable (Table 3). At the end of the 24 h study period, the number of patients who were totally satisfied with the antiemetic regimens was significantly higher in D + P group in comparison with D + S, and D + M groups being 44 (88%) vs. 24 (48%), and 31 (62%), respectively, with estimated P value < 0.01 (Table 3).

4. Discussion

The main findings in the current study are: (1) Dexamethasone monotherapy effectively reduced the incidence of early PONV (0–6 h postoperatively) down to 24% and failed to significantly reduce the incidence of late PONV (6–24 h postoperatively) in relation to the other two combination therapy groups, (2) Metoclopramide–dexamethasone combination therapy effectively reduced the incidence of PONV 0–12 h postoperatively down to 16% with significant difference at 6–12 h postoperatively in relation to dexamethasone monotherapy group, and failed in reducing PONV in the rest of the 24 h study period in relation to palonosetron–dexamethasone and (3) Only palonosetron–dexamethasone prophylactic regimen effectively and significantly reduced the incidence of PONV over the whole 24 h postoperative period down to 16% with significantly greater patients' satisfaction in relation to the other two groups.

PONV is unpleasant and distressing sensation and many patients consider it to be as debilitating as the pain associated with surgery [17]. PONV may cause electrolyte disturbances and may affect the surgical outcome, with unexpected hospital admission and consequent higher health care costs. PONV is multifactorial, the important factors being age, sex, smoking status, history of PONV or motion sickness, type and duration of surgery, inhalation anesthetics and use of nitrous oxide, postoperative pain, opioid requirements, and inadequate IV fluid therapy [4,18]. In the current study, all these factors were considered in patients' enrollment and only patients with two or more risk factors (Apfel's risk score = 2–4) were enrolled in the study. Additional risk factors were also included as the type of surgery and only laparoscopic surgeries with known high-risk of PONV were included namely; cholecystectomy, herniorraphy, and gynecological procedures.

Aspinall and Goodman [19] have suggested that placebo-controlled trials in patients at high risk of PONV may be unethical if active drugs are available and for that reason, a placebo-control group was not included in the current study. Dexamethasone 8 mg IV, given before induction of anesthesia, was used instead as an active-control group. The dose of 25 mg IV of metoclopramide was used in dexamethasone–metoclopramide combination therapy group according to Wallenborn et al. [13], who concluded in their large multicentric study that 25 mg or 50 mg metoclopramide added to the basic intervention of 8 mg dexamethasone is effective and safe way to prevent PONV. Palonosetron in a dose of 0.075 mg in palonosetron–dexamethasone combination therapy group was used according to Kovac et al. [20], who demonstrated that 0.075 mg of IV palonosetron is the more effective dose in prevention of PONV than 0.025 mg and 0.05 mg.

Dexamethasone, a long-acting glucocorticoid, has been reported to have an effective prophylactic effect on PONV in adults undergoing laparoscopic surgery. It has a long biological half-life of 36–48 h and excellent side-effects profile after a single dose of 8 mg IV given before anesthesia induction [21]. The precise mechanism of action is not well understood, but may be due to prostaglandin antagonism, serotonin inhibition in the gut and the release of endorphins that elevate mood and stimulate appetite [22]. In the current study, no difference observed in prevention of PONV in the early postoperative

Table 2 Incidence of PONV, rescue antiemetic treatment, and complete response.

Time intervals	Patients with	Group D + S (n = 50)	Group D + M (n = 50)	Group D + P (n = 50)	P value
0–6 h	Nausea	7 (14)	5 (10)	4 (8)	0.613
	Vomiting	6 (12)	4 (8)	2 (4)	0.337
	Nausea and vomiting	12 (24)	8 (16)	5 (10)	0.169
	Rescue treatment	3 (6)	2 (4)	2 (4)	0.861
	Complete response	38 (76)	42 (84)	45 (90)	0.169
6–12 h	Nausea	13 (26)	8 (16)	6 (12)	0.172
	Vomiting	11(22)	1 (2)**	1 (2)**	< 0.01
	Nausea and vomiting	18 (36)	8 (16)*	6 (12)*	< 0.01
	Rescue treatment	10 (20)	1 (2)**	1(2)**	< 0.01
	Complete response	32 (64)	42 (84)*	44 (88)*	< 0.01
12–24 h	Nausea	17 (34)	12 (24)	6 (12)*	0.034
	Vomiting	13 (26)	9 (18)	2 (4)**	< 0.01
	Nausea and vomiting	24 (48)	20 (40)	8 (16)**a	< 0.01
	Rescue treatment	14 (28)	10 (20)	1(2)**a	< 0.01
	Complete response	26 (52)	30 (60)	42 (84)**a	< 0.01
0–24 h	Nausea	21 (42)	18 (36)	8 (16)**a	0.013
	Vomiting	16 (32)	10 (20)	2 (4)**a	< 0.01
	Nausea and vomiting	26 (52)	21 (42)	8 (16)**a	< 0.01
	Rescue treatment	15 (30)	12 (24)	2 (4)**b	< 0.01
	Complete response	24 (48)	29 (58)	42 (84)**b	< 0.01

Group D + S = dexamethasone + saline; group D + M = dexamethasone + metoclopramide; group D + P = dexamethasone + palonosetron; PONV = postoperative nausea and vomiting; n = number; h = hours.
Data were presented as number (percentage).
* $P < 0.05$ when compared with the active-control D + S group.
** $P < 0.01$ when compared with the active-control D + S group.
[a] $P < 0.05$ when compared with D + M group.
[b] $P < 0.01$ when compared with D + M group.

period (0–6 h) among the three groups and the three regimens were effective in controlling PONV evidenced by high incidence of CR in the three groups being 76%, 84%, and 90% in dexamethasone monotherapy, dexamethasone–metoclopramide, and dexamethasone–palonosetron combination therapies, respectively (P = 0.169). The difference was only found in late postoperative period (6–24 h) and the incidences of PONV and rescue antiemetic treatment were significantly frequent in dexamethasone monotherapy group compared to the other groups (reaching 36% for PONV and 20% for rescue treatment at 6–12 h, and 48% for PONV and 28% for rescue treatment at 12–24 h postoperatively).

Henzi et al. [12] in their systematic review of the prophylactic effect of dexamethasone on PONV concluded that a single dose of 8 mg dexamethasone is an effective prophylactic antiemetic in prevention of early, and late PONV, late efficacy being most pronounced. These conclusions are consistent with the findings in the current study in that the incidence of early (0–6 h) PONV in dexamethasone monotherapy group was 24% with 51% reduction in the reported incidence of PONV after laparoscopic surgery as a placebo-control group was not included in the current study for ethical issues. Furthermore, the incidences of PONV at 6–12 h and 12–24 h postoperatively were 36% and 48%, respectively, with 39% and 27% reductions, respectively, in the reported incidence of PONV after laparoscopic surgery. Opposite to conclusions of Henzi et al., late efficacy of dexamethasone was less pronounced and the higher incidence of PONV for 6–24 h postoperatively was most likely related to the emetic effect of postoperative fentanyl and it is evident that combination antiemetic therapy was more effective in controlling this problem. This explanation is supported by a previous study conducted by Apfel et al. [22] who concluded that postoperative opioid consumption is one of the main predictors of PONV in the late postoperative period.

Metoclopramide is still used widely in clinical practice; however, the dose-responsiveness of metoclopramide in PONV prophylaxis has never been established [12]. When used in doses of 10 mg, it was found to be ineffective [23] and larger dosages were as effective as ondansetron or droperidol when added to dexamethasone [11]. Metoclopramide in a dose of 50 mg IV has been shown to significantly reduce late PONV, but the side-effects profile is unsatisfactory [13]. Other studies also found that 20 mg metoclopramide was ineffective, possibly because of the small sample sizes [10,24,25]. The timing of antiemetic prophylaxis seems to influence efficacy. In most of the studies, metoclopramide was given immediately after induction of anesthesia, irrespective of its time of maximum effect and short half-life. The results of those previous studies justify the dose of metoclopramide chosen in the current study (25 mg IV), and its timing of administration (30 min before the expected end of surgery) to get the maximal beneficial effect and avoid its undesirable adverse effects. It was also combined to the standard IV dexamethasone 8 mg which was given immediately before anesthesia induction.

Results of the current study revealed that dexamethasone–metoclopramide combination therapy effectively reduced the incidence of early (0–6 h) and late (only up to 12 h) PONV down to 16% compared to 36% incidence in dexamethasone monotherapy group at 6–12 h postoperatively. However, this

Table 3 Incidence of complications and patients' satisfaction.

	Group D + S (n = 50)	Group D + M (n = 50)	Group D + P (n = 50)	P value
Complications				
Extrapyramidal symptoms	0 (0)	0 (0)	0 (0)	–
Headache	1 (2)	2 (4)	2 (4)	0.813
Dizziness	1 (2)	3 (6)	1 (2)	0.437
Constipation	0 (0)	2 (4)	1 (2)	0.360
Myalgia	1 (2)	3 (6)	2 (4)	0.594
Patients' satisfaction				
Totally satisfied	24 (48)	31 (62)	44 (88)[**a]	<0.01
Neutral	2 (4)	7 (14)	4 (8)	0.202
Totally dissatisfied	24 (48)	12 (24)	2 (4)[**a]	<0.01

Group D + S = dexamethasone + saline; group D + M = dexamethasone + metoclopramide; group D + P = dexamethasone + palonosetron; n = number.
Data were presented as number (percentage).
[**] $P < 0.01$ when compared with the active-control D + S group.
[a] $P < 0.01$ when compared with D + M group.

prophylactic regimen failed to significantly reduce the incidence of PONV at 12–24 h postoperatively being 40% and was comparable to 46% incidence in dexamethasone monotherapy group. This failure may be attributed to the short half-life of metoclopramide and to the emetic effect of postoperative fentanyl given by PCA to control postoperative pain. The dose of 25 mg metoclopramide was found to be safe evidenced by absence of extrapyramidal manifestations and the incidence of other adverse events was comparable in the three prophylactic regimens. These results are consistent with the multicentric study conducted by Wallenborn et al. [13] who found that 25 mg metoclopramide combined to the standard 8 mg dexamethasone was effective in preventing PONV and the need for rescue drugs up to 12 h postoperatively with high safety profile.

Palonosetron had been approved by FDA for PONV prophylaxis in March 2008. Afterward multiple clinical researches were conducted to prove its efficacy. Candiotti et al. [26] conducted a study in a large series of patients scheduled for outpatient abdominal or gynecological laparoscopy and found that the incidence of CR from 0 to 24 h was 43%, and nausea severity was markedly decreased. Similarly, Kovac et al. [20] in their multicentric study found that 56% of the study population had CR from 0 to 24 h. Results of the current study revealed that combination therapy of 0.075 mg palonosetron and 8 mg dexamethasone given at the time of anesthesia induction effectively reduced incidence of PONV and 84% of this study population had CR from 0 to 24 h postoperatively. This incidence of CR was significantly higher compared with other the regimens used, being 58% in dexamethasone–metoclopramide combination and 48% in dexamethasone monotherapy with estimated $P < 0.01$.

The higher incidence of CR in palonosetron–dexamethasone combination therapy group was comparable to the reported incidences in other studies. Bhattacharjee et al. [27] found the incidence of CR to be 90% during 0–48 h postoperatively when palonosetron 0.075 mg was given IV prior to induction of anesthesia to female patients scheduled for laparoscopic cholecystectomy. More recently, Ghosh et al. [28] observed that the incidence of CR during 0–48 h postoperatively was 83.33% in palonosetron monotherapy and 86.66% when dexamethasone was combined to palonosetron in patients undergoing laparoscopic cholecystectomy. These findings support the fact that palonosetron has prolonged protective effect against PONV; especially when combined with dexamethasone as it binds to the allosteric site of 5-HT_3 receptors with positive cooperativity and prevents serotonin from binding to the orthosteric site of 5-HT_3 receptors [29]. This explains the long half-life of palonosetron (approximately 40 h) and its high binding affinity for 5-HT_3 receptors that is markedly different from older 5-HT_3 receptor antagonists. Additionally, there is a cross-talk between neurokinin-1 (NK-1) and 5HT_3 receptors signaling pathways and substance P (NK-1 receptors agonist) was shown to potentiate 5-HT_3 receptors-mediated inward current. Palonosetron inhibits the cross-talk between 5-HT_3 and NK-1 receptor pathways in dose and time-dependent fashions [30].

The adverse events related to palonosetron administration were minimal in this study. This observation contributed to the greatest patients' satisfaction in palonosetron–dexamethasone combination therapy reported in the current study as the percentage of patients who were totally satisfied in that group was 88% compared to 48% and 62% in dexamethasone monotherapy and dexamethasone–metoclopramide combination therapy groups, respectively ($P < 0.01$).

In conclusion, palonosetron 0.075 mg when combined with dexamethasone 8 mg and given immediately before anesthesia induction is effective and safe regimen in prevention of early (0–6 h) and late (6–24 h) PONV in high-risk patients scheduled for laparoscopic surgeries with known high-risk of PONV. Moreover, palonosetron–dexamethasone combination therapy is superior to dexamesathone–metoclopramide combination and dexamethasone monotherapy with regard to the overall outcome of PONV prophylaxis over 24 h postoperatively, evidenced by significantly lower incidence of PONV, higher incidence of CR, and greater overall patients' satisfaction.

References

[1] Watcha MF, White PF. Postoperative nausea and vomiting. Its etiology, treatment, and prevention. Anesthesiology 1992;77:162–84.
[2] Muchatuta NA, Paech MJ. Management of postoperative nausea and vomiting: focus on palonosetron. Ther Clin Risk Manage 2009;5:21–34.

[3] Gan TJ. Risk factors for postoperative nausea and vomiting. Anesth Analg 2006;102:1884–98.
[4] Sinclair DR, Chung F, Mezei G. Can postoperative nausea and vomiting be predicted? Anesthesiology 1999;91:109–18.
[5] Kenny GNC. Risk factors for post-operative nausea and vomiting. Anaesthesia 1994;49(Suppl.):S2–5.
[6] Apfel CC, Läärä E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting. Anesthesiology 1999;91:693–700.
[7] White PF, Watcha MF. Postoperative nausea and vomiting: prophylaxis versus treatment. Anesth Analg 1999;89:1337–9.
[8] Gan T, Sloan F, Dear Gde L, El-Moalem HE, Lubarsky DA. How much are patients willing to pay to avoid postoperative nausea and vomiting? Anesth Analg 2001;92:393–400.
[9] Habib AS, Gan TJ. Combination therapy for postoperative nausea and vomiting – a more effective prophylaxis? Ambul Surg 2001;9:59–71.
[10] Eberhart LH, Morin AM, Bothner U, Georgieff M. Droperidol and 5-HT3-receptor antagonists, alone or in combination, for prophylaxis of postoperative nausea and vomiting. A meta-analysis of randomized controlled trials. Acta Anaesthesiol Scand 2000;44:1252–7.
[11] Apfel CC, Korttila K, Abdalla M, Kerger H, Turan A, Vedder I, et al. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. New Engl J Med 2004;350: 2441–51.
[12] Henzi I, Walder B, Tramer MR. Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systematic review. Anesth Analg 2000;90:186–94.
[13] Wallenborn J, Gelbrich G, Bulst D, Behrends K, Wallenborn H, Rohrbach A, et al. Prevention of postoperative nausea and vomiting by metoclopramide combined with dexamethasone: randomised double blind multicentre trial. BMJ 2006;333:324–7.
[14] Wong EHF, Clark R, Leung E, Loury D, Bonhaus DW, Jakeman L, et al. The interaction of RS 25259-197. A potent and selective antagonist, with 5-HT3 receptors, in vitro. Brit J Pharmacol 1995;114:851–9.
[15] Soltz R, Cyong J, Shah A, Parisi S. Pharmacokinetic and safety evaluation of palonosetron, a 5-hydroxytryptamine-3 receptor antagonist, in US and Japanese healthy subjects. J Clin Pharmacol 2004;44:520–31.
[16] Darkow T, Gora-Harper ML, Goulson DT, Record KE. Impact of antiemetic selection on postoperative nausea and vomiting and patient satisfaction. Pharmacotherapy 2001;21:540–8.
[17] Klockgesthes-Radke A, Piorek V, Corzier TC, Kettler D. Nausea and vomiting after laparoscopic surgery: a comparison of propofol and thiopentone/halothane anaethesia. Eur J Anaesth 1996;13:3–9.
[18] Maharaj CH, Kallam SR, Malik A, Hassett P, Grady D, Laffey JG. Preoperative intravenous fluid therapy decreases postoperative nausea and pain in high risk patients. Anesth Analg 2005;100:675–82.
[19] Aspinall RL, Goodman NW. Denial of effective treatment and poor quality of clinical information in placebo controlled trials of ondansetron for postoperative nausea and vomiting: a review of published trials. BMJ 1995;311:844–6.
[20] Kovac Al, Eberhart L, Kotarski J, Clerici G, Apfel C. A randomized double-blind study to evaluate the efficacy and safety of three different doses of palonosetron versus placebo for preventing postoperative nausea and vomiting over a 72 h period. Anesth Analg 2008;107:439–44.
[21] Wang JJ, Ho ST, Liu YH, Lee SC, Liu YC, Liao YC, et al. Dexamethasone reduces nausea and vomiting after laparoscopic cholecystectomy. Brit J Anaesth 1999;83:772–5.
[22] Apfel CC, Kranke P, Katz MH, Goepfert C, Papenfuss T, Rauch S, et al. Volatile anaesthetics may be the main cause of early but not delayed postoperative vomiting: a randomized controlled trial of factorial design. Brit J Anaesth 2002; 88:659–68.
[23] Rowbotham DJ. Current management of postoperative nausea and vomiting. Brit J Anaesth 1992;69(S1):46–59.
[24] Piper SN, Suttner SW, Rhm KD, Maleck WH, Larbig E, Dolasetron Boldt J. but not metoclopramide prevents nausea and vomiting in patients undergoing laparoscopic cholecystectomy. Can J Anesth 2002;49:1021–8.
[25] Quaynor H, Ræder JC. Incidence and severity of postoperative nausea and vomiting are similar after metoclopramide 20 mg and ondansetron 8 mg given by the end of laparoscopic cholecystectomies. Acta Anaesthesiol Scand 2002;46: 109–13.
[26] Candiotti KA, Kovac AL, Melson TI, Clerici G, Gan TJ. A randomized, double-blind study to evaluate the efficacy and safety of three different doses of palonosetron versus placebo for preventing postoperative nausea and vomiting. Anesth Analg 2008;107:445–51.
[27] Bhattacharjee DP, Dawn S, Nayak S, Roy PR, Acharya A, Dey R. A comparative study between palonosetron and granisetron to prevent postoperative nausea and vomiting after laparscopic cholecyatectomy. J Anaesth Clin Pharmacol 2010;26:48–53.
[28] Ghosh S, Pal A, Acharya A, Biswas C, Ghosh TR, Ghosh S. Palonosetron and palonosetron plus dexamethasone to prevent postoperative nausea and vomiting in patients undergoing laparscopic cholecystectomy: a prospective, randomized, double-blind comparative study. Anesth Essays Res 2011; 5(20):134–7.
[29] Rojas C, Stathis M, Thomas AG, Massuda EB, Alt J, Zhang J, et al. Palonosetron exhibits unique molecular interactions with the 5-HT_3 receptor. Anesth Analg 2008;107:469–78.
[30] Rojas C, Li Y, Zhang J, Stathis M, Alt J, Thomas AG, et al.. The antiemetic 5-HT3 receptor antagonist palonosetron inhibits substance P-mediated responses in vitro and in vivo. Pharmacol Exp Ther 2010;335:362–8.