Original Article

A Comparative Study of Palonosetron Versus Palonosetron and Dexamethasone for the Prevention of Postoperative Nausea and Vomiting in Subjects Undergoing Laparoscopic Surgeries: A Randomized Double-blind Control Study

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Abstract

Background: Palonosetron is an effective antiemetic that can be used for treating postoperative nausea vomiting which is a major problem in laparoscopic surgeries. **Aims:** The aim of this study was to find out whether addition of dexamethasone to palonosetron would be more effective than palonosetron alone in prevention of this problem in patients undergoing laparoscopic surgeries. **Settings and Design:** This study was conducted as a double blind study in MS Ramaiah hospital, Bangalore. **Materials and Methods:** Ninety patients with ASA grade 1 and 2 between 20-60 years of age undergoing elective laparoscopic surgery under general anaesthesia were randomised into two groups of 45 patients each. Group-P received 0.075 mg of palonosetron and Group-P+D received the same dose of palonosetron and 8 mg of dexamethasone before induction. The number of complete responders along with four point nausea and vomiting scores were recorded at 2, 6, 24, 48 hours post-operatively. **Statistical Analysis Used:** Difference in the number of complete responders in each of the groups were tested to be of statistical significance through Chi square test of significance. *P* value <0.05 was considered as statistically significant. *t*-test was used for categorical data assessment. **Results:** Complete responders recorded in group P+D were 34 (75.5%) and in group P were 35 (77.7%). Three patients in group P+D (6.7%) and 4 patients in group P (8.9%) required rescue anti-emetics. The *P* value obtained was 0.694 (>0.05) and hence not statistically significant. **Conclusion:** The addition of dexamethasone to palonosetron does not offer an added advantage over the usage of palonosetron alone as a single drug.

Key words: Dexamethasone, general anesthesia, laparoscopy, palonosetron, postoperative nausea and vomiting

Introduction

Postoperative nausea and vomiting (PONV) is a common occurrence after laparoscopic surgeries.[1] It is the second most common postsurgical complication after pain for which the incidence is 20–30% after general anesthesia using volatile anesthetics and raises up to 70% in high-risk patients.[2] The incidence of PONV in patients undergoing laparoscopy ranges from 40% to 75%.[3] Kapur had defined it as a "big little problem" following ambulatory surgeries.[4]

PONV is said to have a multifactorial etiology. During laparoscopic surgeries, carbon dioxide insufflation leads to the dilatation of intestinal loops which stimulates mechanoreceptors in the gut wall, leading to increased serotonin synthesis. This triggers the chemoreceptor trigger zone in the medulla which receives vagal afferents from various parts of the body and evokes an emetic response (PONV).[5]

Palonosetron is a newer generation 5 hydroxytryptamine (5HT3) receptor antagonist. It has a long half-life of 40 h and undergoes slower elimination from the body, thereby providing PONV relief for approximately 48 h after surgery.[6] Previous studies have shown that when dexamethasone is added to 5HT3 antagonist such as ondansetron, the efficacy is increased.[5,7,8]

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In this study, we intended to find out whether a combination of palonosetron and dexamethasone would be more effective than palonosetron alone in the prevention of PONV in patients undergoing laparoscopic surgeries under general anesthesia. The secondary objective was to see if the combination of two antiemetic drugs leads to any increase in the incidence of side effects.

Subjects and Methods

After ethical approval by our Institutional Ethics Committee, patients, aged 20–60 years, belonging to American Society of Anaesthesiologists (ASA) physical status 1 and 2 scheduled for elective laparoscopic surgery under general anesthesia were selected for the study after obtaining written informed consent. The period of study was from November 2012 to August 2014.

Based on the study carried out by Ghosh *et al*. in 2011,[5] it has been reported that complete response (no vomiting and no rescue medications) was observed as 83.33% in Group P (palonosetron alone) compared to 86.66% in Group P + D (palonosetron and dexamethasone), assuming equivalence of response rate. Adobe software nMaster (version 2.0, Adobe systems Inc.) was used for sample size estimation. Taking alpha error as 0.05 and keeping the power of the study at 80%, it was estimated that 45 patients in each group need to be recruited for the study. Thus, ninety subjects for both arms were included for the study. Inclusion criteria were age of 20–60 years, ASA Grade 1 and 2, and patients undergoing elective laparoscopic surgeries under general anesthesia. Exclusion criteria were gastrointestinal or renal disease/ongoing vomiting, cancer chemotherapy/radiotherapy within the past 4 weeks, experience of nausea, vomiting, or taken anti-emetic/steroid medication 24 h before surgery, pregnant patients/lactating mothers, a known allergy previously to the same drug/group, patients with no history or signs of increased intracranial pressure, and history of alcohol or drug abuse. Surgeries of duration <90 min were not included in the study.

After obtaining written informed consent, the patients were randomized by computer-generated random table numbers inserted into an envelope and assigned into two groups, Group P - palonosetron group and Group P + D palonosetron and dexamethasone group. To ensure blinding, both the group patients received the contents of 2 ml syringes. The patients assigned to *P* Group received palonosetron 0.075 mg diluted to 2 cc and the contents of another syringe containing 2 cc of normal saline. Patients assigned to P + D Group received 0.075 mg of palonosetron diluted to 2 cc and dexamethasone 8 mg in 2 cc syringe. The drugs were prepared by one of the authors. The drugs were given by an anesthetist who was conducting the case and was blinded to the contents of the syringe. The study drug was given just before induction in the operation theater. Patients of both the groups were induced under the same standard institutional protocol for general anesthesia.

All patients were subjected to overnight fasting and were premedicated with tablet pantoprazole 40 mg the previous night and on the morning of the surgery. Induction was done with injection fentanyl 2 μg/kg body weight, injection thiopentone 5 mg/kg body weight, and injection vecuronium 0.1 mg/kg body weight. Intubation was done with an oral-cuffed endotracheal tube of appropriate size. Anesthesia was maintained with air, oxygen, and sevoflurane with muscle relaxant and controlled ventilation. For pain relief, injection diclofenac 75 mg intravenous (i.v.) and injection paracetamol 1 g i.v. were given to all patients intraoperatively toward the end of the surgery. Monitoring of electrocardiogram, noninvasive blood pressure, pulse, oxygen saturation, and end-tidal carbon dioxide ($EtCO_2$) was done for all the patients. The intra-abdominal pressures were maintained between 10 and 12 mm Hg for upper abdominal surgeries and up to 15 mm Hg for lower abdominal surgeries. Ryle's tube was inserted at the request of the surgeons for upper abdominal laparoscopic surgeries and was removed for all patients before extubation. At the end of the surgery, carbon dioxide was removed by suction and manual compression of the abdomen. At the end of the surgery, patients were reversed with injection neostigmine 50 μg/kg and injection glycopyrrolate 10 μg/kg. They were extubated when $EtCO_2$ was in the normocarbic range and were sent to postoperative recovery room where they were given oxygen at 5 L/min by mask in the propped up position. Postoperative analgesia was given with i.v. boluses of 25 micrograms of injection fentanyl for the period of time the patients were kept in postanesthetic care unit (PACU), which was approximately 2 h for all the patients. The analgesic was given at a verbal numeric rating scale >4 (the scale ranged from 0 to 10.0 being no pain and 10 being the maximum pain). After the duration of PACU stay, the patients were shifted to the wards where they were given injection paracetamol 1 g intravenously sixth hourly and injection diclofenac 75 mg intravenously twice a day. The patients were asked about nausea, vomiting, retching, and any side effects at 2, 6, 24, and 48 h after tracheal extubation by the investigator. In our study, oral feeds were started 24 h after surgery. The nursing staff attending to the patient was instructed to note down any episode of nausea and vomiting in the intervening period and after starting the feeds.

Nausea was defined as a subjectively unpleasant sensation associated with awareness of the urge to vomit. Retching was defined as a labored, spastic, rhythmic contraction of the respiratory muscles without the expulsion of gastric contents. Vomiting was defined as the forced expulsion of stomach and gastrointestinal contents through the mouth/nose.

The severity of PONV was assessed on a 4-point scoring system (Ghosh *et al*.)[5]

Score 0 - no nausea and no retching
Score 1 - complaining of sickness and retching
Score 2 - vomiting once or twice in 30 min
Score 3 - vomiting >two times in 30 min.

Patients were evaluated for other side effects (headache, dizziness, and drowsiness) during the 48 h postoperative period.

The number of complete responders was recorded. Complete response was defined as; no nausea, vomiting or retching, and no need of rescue antiemetic medicine within the 48 h postoperative period. This corresponded to a PONV score of 0. Rescue antiemetic was given to patients with a PONV score of ≥2 or on the demand of the patient. The rescue antiemetic used was 10 mg i.v. injection metoclopramide.

Statistical analysis was done using SPSS software version 20. IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. Mean and standard deviation were estimated to describe the quantitative parameters such as age, weight, and duration of the surgery. Proportion of the subjects with complete response (no nausea, no retching, and no vomiting) to the medication was estimated in each group along 95% confidence interval. Differences in the proportions of complete responders in each of the groups were tested of statistical significance through Chi-square test of significance. $P < 0.05$ was considered statistically significant. *t*-test was used for categorical data assessment. Other variables that were recorded were – age (years), sex, weight (kilograms), duration of surgery (minutes), height (centimetres), type of laparoscopic surgery, intraoperative hemodynamics (pulse, systolic blood pressure, diastolic blood pressure, and mean arterial pressure), and need for postoperative analgesia.

Results

Demographic parameters in terms of age, body weight, height, and gender (male/female) along with their ASA status (I or II) were comparable in both the groups [Table 1]. In this study, it was observed that Group P + D had 18 males (40%) and 27 females (60%), whereas Group P had 22 males (48.9%) and 23 females (51.1%). In our study, both the groups had female predominance. The data were equally distributed in both the groups.

All the patients studied were nonsmokers. Statistically, both the groups were comparable according to ASA grading.

Table 2 shows the types of laparoscopic surgeries performed in our institution. The values are presented as numbers. The patients were equally distributed in both the groups.

Table 1: Demographic characteristics of patients in each group

Parameters	Group P+D (*n*=45)	Group P (*n*=45)	*P* value
Age (years)	40.8±12.7	40.4±13.7	0.873
Weight (kg)	65.2±11.5	64.2±13.1	0.688
Height (cm)	159.6±07.8	160.5±09.6	0.641
BMI	25.5±3.8	24.9±4.7	0.511
Duration of Surgery (min)	100.8±48.3	104.2±39.9	0.715
Duration of Anaesthesia (min)	117.3±48.8	122.8±40.2	0.560

Values are presented as mean±SD and analysed using x^2 test of significance

Table 2: Distribution of patients in various laparoscopic sugeries

Types of surgery	Group P+D (*n*=45)	Group P (*n*=45)
Upper abdominal surgeries		
Laparoscopic ventral hernia repair	3	3
Laparoscopic cholecystectomy	26	25
Lower abdominal surgeries		
Diagnostic laparoscopy	6	5
Laparoscopic appendectomy	7	10
Laparoscopic ovarian cystectomy	3	0
Laparoscopic vaginal hysterectomy	0	2

x^2: 0.349, P=0.349 The values are presented as number of patients of each type of surgery

Table 3: Changes in various parameters in both the groups

Baseline parameters	Group P+D (*n*=45)	Group P (*n*=45)	*P* value
Heart rate	85.2±16.1	85.0±15.6	0.947
Systolic blood pressure (SBP)	130.4±19.3	132.2±21.2	0.679
Diastolic blood pressure (DBP)	82.6±15.5	80.9±14.2	0.610
Mean arterial pressure (MAP)	98.5±15.5	98.0±15.0	0.389

Values are presented as mean±SD

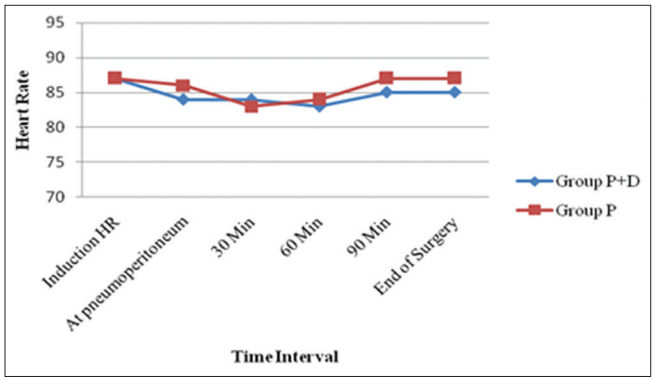

Figure 1: Trend in the variation of heart rate during surgery

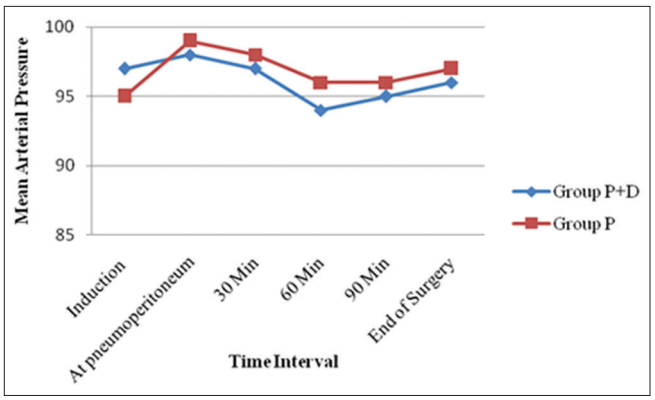

Figure 2: Variation in the trend of mean arterial pressure during surgery

All the baseline parameters were comparable in both the groups [Table 3, Figures 1 and 2].

The incidence of PONV was compared in both the groups at 2, 6, 24, and 48 h after surgery. The difference was comparable in both the groups and was not statistically significant at any point [Table 4 and Figures 3-6]. Thereafter, overall, the group was clubbed as people who had nausea and vomiting (PONV score of 1, 2, and 3) as compared to those who did not have nausea and vomiting (PONV score 0). The *P* value obtained was 0.803 [Table 5]. Therefore, we conclude that the incidence of PONV is not significant in both the groups. In the present study, it was observed that PONV in Group P + D was seen in 11 (24.4%) patients as compared to ten (22.2%) patients in Group P.

The need for rescue antiemetics was compared in both the groups. The *P* value obtained was 0.694 (nonsignificant). In the present study, it was seen that only three patients (6.7%) required antiemetic drugs in Group P + D as compared to four patients (8.9%) in Group P [Table 6].

In this study, it was observed that six patients (13.3%) in Group P + D required analgesics in postoperative period as compared to ten patients (22.2%) in Group P, and there was no correlation to the incidence of PONV at subsequent hours in patients who received fentanyl as the postoperative analgesic in the first 2 h.

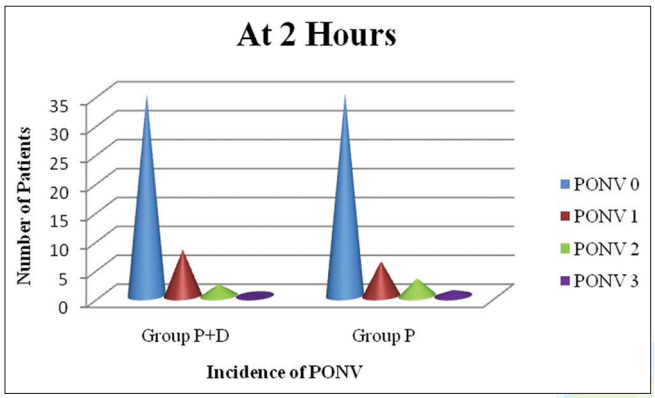

Figure 3: Incidence of postoperative nausea and vomiting at 0–2 h

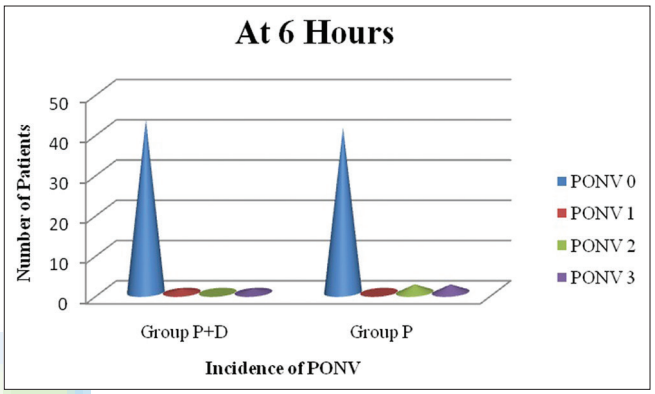

Figure 4: Incidence of postoperative nausea and vomiting at 2–6 h

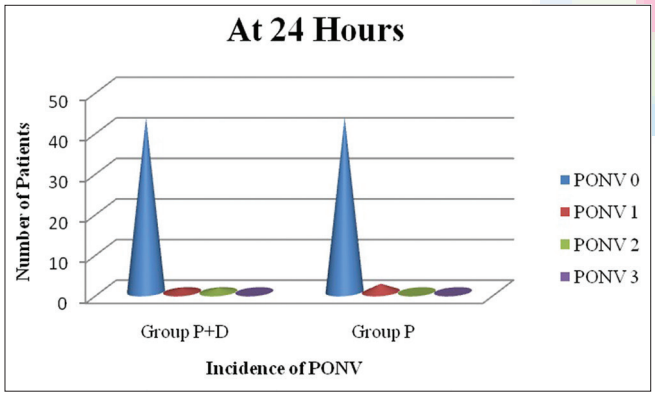

Figure 5: Incidence of postoperative nausea and vomiting at 6–24 h

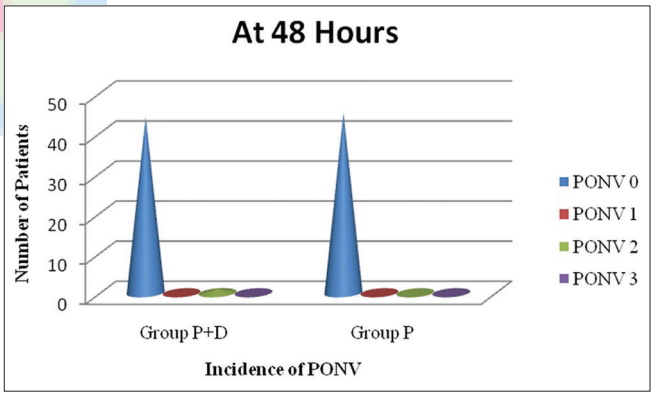

Figure 6: Incidence of postoperative nausea and vomiting at 24–48 h

Table 4: Incidence of postoperative nausea and vomiting (2 h, 6 h, 24 h, and 48 h)

Group	At 2 Hours				At 6 Hours				At 24 Hours				At 48 Hours			
	1		2		1		2		1		2		1		2	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
0	35	77.8	35	77.8	43	95.6	41	91.1	43	95.6	43	95.6	44	97.8	45	100
1	8	17.8	6	13.3	1	2.2	0	0.0	1	2.2	2	4.4	0	0.0	0	0.0
2	2	4.4	3	6.7	0	0.0	2	4.4	1	2.2	0	0.0	1	2.2	0	0.0
3	0	0.0	1	2.2	1	2.2	2	4.4	0	0.0	0	0.0	0	0.0	0	0.0
Total	45	100	45	100	45	100	45	100	4.5	100	45	100	45	100	45	100

For 2 hours: x^2=1.486; Df=3; *P*=0.686 (Non Significant). For 6 hours : x^2=3.381; Df=3; *P*=0.337 (Non Significant). For 24 hours : x^2=1.333; Df=2; *P*=0.513 (Non Significant). For 48 hours : x^2=1.011; Df=1; *P*=0.315 (Non Significant)

Table 5: Incidence of post operative nausea and vomiting in both the groups

Nausea and vomiting	Group P+D (*n*=45) *n* (%)	Group P (*n*=45) *n* (%)
Yes (PONV score 1,2,3)	11 (24.4%)	10 (22.2%)
NO (Complete responders - PONV score 0)	34 (75.5%)	35 (75.7%)
Total	45 (100%)	45 (100%)

x^2:0.062, df: 1, *P*=0.083

Table 6: Need for rescue antiemetic in both the groups

Need for rescue antiemetic	Group P+D (*n*=45) *n*(%)	Group P (*n*=45) *n*(%)
No (PONV score 0,1)	42 (93.3%)	41 (91.1%)
Yes (Score>=2)	3 (6.7%)	4 (8.9%)
Total	45 (100%)	45 (100%)

x^2:0.155, df: 1, *P*=0.694

Discussion

PONV is a common occurrence after laparoscopic surgeries. Nowadays, 5-HT3 receptor antagonists are routinely used to prevent PONV in the patients undergoing surgeries under general anesthesia. Food and Drug Administration has approved the use of palonosetron for prophylaxis of PONV in 2008 and is now available in India. Its unique properties have led to it being called second-generation 5HT3 antagonists. Higher receptor affinity and much longer half-life than other 5HT3 antagonists (e.g., ondansetron) confer a prolonged duration of action.[9] Palonosetron at any dose has not been found to prolong the QTc interval in contrast to the older drugs of the same group.[10] This dose has been used by Stoltz *et al*. for evaluating the pharmacokinetic and safety profile of palonosetron.[11]

Similarly, the use of dexamethasone in the prophylaxis of PONV was recommended by Bisgaard *et al*. in 2003 who showed that the preoperative use of dexamethasone (8 mg) reduced pain, fatigue, nausea and vomiting, and duration of convalescence in patients undergoing noncomplicated laparoscopic cholecystectomy and was recommended for routine use.[12] Our study was designed in a way so as to control all the factors that can interfere with the interpretation of the result of the study with a standardized anesthetic regimen.

Adverse effects were most frequently reported for the association of dexamethasone with a 5-HT3 receptor antagonist. Adverse effects that have been reported are headache, dizziness, drowsiness and sedation, constipation, muscle pain, and transient elevation of liver enzymes.[3] Therefore, the side effects of this combination were also studied in this study. In our study, five patients in Group P + D and eight patients in Group P had an incidence of headache and dizziness overall. The incidence of side effects was comparable in both the groups and was not much significant clinically.

Blitz *et al*. in 2012 evaluated the efficacy of palonosetron with dexamethasone versus palonosetron alone for the prevention of postoperative and postdischarge nausea and vomiting (PNDV) in subjects undergoing laparoscopic surgeries with high emetogenic risk, and they found that the combination therapy of palonosetron and dexamethasone did not reduce the incidence of PONV or PDNV when compared with palonosetron alone.[13]

A similar study was done by Ghosh *et al*. in 2011. It was found that the palonosetron and dexamethasone combination was not more effective than palonosetron alone in the prevention of PONV in patients undergoing laparoscopic cholecystectomy under general anesthesia. They recommended not adding dexamethasone to palonosetron as it will further increase the cost and expose the patient to the risk of added side effects, without any extra benefits.[5]

The results of the above two studies were in accordance with our study where addition of dexamethasone to palonosetron did not offer an added advantage over the use of palonosetron alone for the prevention of PONV. However, one study was published recently in 2014 by Bala *et al*., where they found that in patients undergoing laparoscopic surgeries, the palonosetron–dexamethasone combination was more effective as compared to only palonosetron for reducing PONV after laparoscopic cholecystectomy.[14] The methodology used by them was different from our study. This could be the reason for the possible differences in the study The possible limitations that this study could have is the limited sample size and the fact that it is practically impossible to exclude all the risk factors which lead to PONV.

We conclude that the addition of 8 mg of dexamethasone does not significantly reduce the incidence of PONV when given along with 75 micrograms of palonosetron. This combination also does not have any increased incidence of side effects.

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Conflict of interest

There are no conflicts of interest.

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