Original Article

Comparison of efficacy of palonosetron-dexamethasone combination with palonosetron or dexamethasone alone for prophylaxis against post-operative nausea and vomiting in patients undergoing laparoscopic cholecystectomy

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ABSTRACT

Background and Aims: Post-operative nausea and vomiting (PONV) is highly distressing and unpleasant symptom. Dexamethasone and palonosetron are effective antiemetics with minimal side effect profile. This study compares the efficacy of palonosetron or dexamethasone alone and their combination (palonosetron plus dexamethasone) for prevention of PONV after laparoscopic cholecystectomy. **Methods:** This prospective, randomised, double-blind trial was done on 187 adults, American Society of Anesthesiologists Grade I and II patients, aged 18–75 years undergoing laparoscopic cholecystectomy. They were allocated to three groups which were to receive either of the three treatment regimens: dexamethasone 8 mg (Group D, $n = 57$), palonosetron 0.075 mg (Group P, $n = 66$) or dexamethasone 8 mg plus palonosetron 0.075 mg (Group PD, $n = 64$). The primary outcome was incidence of PONV in 24 h and the secondary outcome was a number of rescue antiemetic required. One-way ANOVA test was used to compare the means amongst three groups. To compare the proportions in the groups, Chi-square test/Fisher's exact test/Two proportions Z-test was applied as appropriate. **Results:** Overall incidences of PONV in the study 24 h postoperatively were 23.4% in PD, 27.2% in P group and 56.14% in D group ($P < 0.001$). Requirement of rescue antiemetic was more in dexamethasone group than other two groups (PD = 1 time, P = 1.38 times and D = 1.5 times). **Conclusion:** Palonosetron alone and palonosetron-dexamethasone combination were equally effective in the prevention of PONV. Dexamethasone alone was least effective amongst the three groups. There is no difference between palonosetron and palonosetron-dexamethasone for PONV prevention.

Key words: Cholecystectomy, dexamethasone, laparoscopic, palonosetron, post-operative nausea vomiting

INTRODUCTION

Post-operative nausea and vomiting (PONV) is the second common complaint in post-operative period after pain.[1] It is a highly distressing and unpleasant symptom that significantly interferes with smooth emergence from anaesthesia and markedly increases patient discomfort.

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PONV is generally short lasting, repeated nausea, vomiting or retching can lead to more serious and undesirable consequences such as dehydration, electrolyte imbalance, heightened perception of pain, aspiration of gastric contents, suture dehiscence and oesophageal rupture had also been reported.[2,3] Although such serious complications are rare, experiencing PONV leads to dysphoria, dissatisfaction and an overall poor experience about surgery and anaesthesia. Although nausea and vomiting in post-operative period was reported to occur in 20%–30% of all surgical patients, laparoscopic surgery and especially laparoscopic cholecystectomy significantly increase the incidence of PONV to as high as 50%.[4,5] According to Apfel's simplified risk score female gender, non-smoker, history of motion sickness and use of post-operative intravenous (IV) opioid additively contribute 20% each to incidence of PONV. Hence, PONV incidence can be as high as 80%, when all four risk factors are present.[6]

Palonosetron is a second-generation 5-HT3 receptor antagonist having greater receptor binding affinity with a half-life of 40 h and is more effective than granisetron 1 mg and ondansetron 4 mg in preventing PONV. Dexamethasone reported to be effective and safe for prevention of PONV following different surgeries including breast surgery and laparoscopic cholecystectomy.[6-8]

A multimodal approach to PONV has been advocated in recent guidelines and literature.[6] Literature also suggests that the benefit associated with combined interventions can be estimated by multiplying the benefit associated with each intervention. Although most of the literature and a recent guideline favours the use of dexamethasone and palonosetron, some studies differ in opinion. In this context, we hypothesised that the combination of palonosetron and dexamethasone will be better antiemetic for PONV prophylaxis than the individual medication and this study was planned to accept or reject that hypothesis.

METHODS

After obtaining approval from the Institutional Ethics Committee, a randomised, double-blinded control trial was planned, and the trial registration was done with the Clinical Trial Registry India (CTRI/2013/05/003630). One hundred and eighty-seven adults who fulfilled the inclusion criteria (age: 18–75 years, American Society of Anesthesiologists (ASA) physical status I and II, undergoing laparoscopic cholecystectomy under general anaesthesia) were enrolled in the study from May 2013 to May 2015 after getting informed consent. Patients who had any of the exclusion criteria (history of motion sickness, were pregnant or menstruating, having coexisting gastrointestinal pathology, known smokers, on chronic antiemetic medications, previously on opiates within 48 h before surgery and any history of allergy to palonosetron or dexamethasone) were excluded from the study [Consort diagram Figure 2].

One independent investigator randomised the patients into three groups (as per computer-generated random numbers) which were to receive either of three treatment regimens: dexamethasone 8 mg (Group D), palonosetron 0.075 mg (Group P) or dexamethasone 8 mg plus palonosetron 0.075 mg (Group PD). An independent OT technician, not involved in the study, prepared the study drugs based on randomisation as per sealed envelope. All the three drugs were drawn in identical 5 ml syringes and diluted up to 5 ml with normal saline and labelled as 'antiemetic'. The study drugs were injected slowly over 30 s just before the induction of anaesthesia. Patients, anaesthesiologist involved in intra-operative care and investigator collecting data in post-operative ward were unaware of the group allocation.

A standardised balanced anaesthesia technique was followed in all patients. Patients received tablet ranitidine 150 mg and tablet alprazolam 0.5 mg at night before surgery and repeated 2 h before surgery in the morning with a sip of water. Induction of anaesthesia was with injection midazolam 0.03 mg/kg, fentanyl 2–2.5 mcg/kg and thiopentone 2–5 mg/kg. Endotracheal intubation was facilitated by injection vecuronium 0.08–0.12 mg/kg. Controlled mechanical ventilation and anaesthetic gases (sevoflurane in 50% O_2 and air) were provided using Drager Fabius GS Premium anaesthesia machine. Intra-operative monitoring was done with 5-lead electrocardiogram, SpO_2, $EtCO_2$, non-invasive blood pressure and nasopharyngeal temperature. Ryle's tube was inserted through a suitable naris in all patients to deflate the stomach for better laparoscopic visualisation. At the end of surgery, anaesthesia was terminated and extubation done after reversing any residual muscle paralysis by injection neostigmine 0.05 mg/kg plus injection glycopyrrolate 10 mcg/kg. All appropriate steps of extubation protocol were followed (Ryle's tube removal after gastric content suctioning, nasopharyngeal suctioning and ETT cuff

deflation) and patients shifted to post-anaesthesia care unit (PACU). Multimodal post-operative analgesia was provided by injecting 15 ml of 0.25% bupivacaine infiltrated at trocar entry sites aided by 1 g paracetamol IV every 6 h (first dose given near the end of surgery) and injection diclofenac 1 mg/kg every 8 h first dose given near the end of surgery.

All patients were monitored and given O_2 in the PACU. Primary outcome was incidence of nausea and vomiting in 24 h. Secondary outcome was the number of rescue antiemetic required. Injection metoclopramide 10 mg IV was used as rescue antiemetic. Nausea was defined as the unpleasant sensation associated with awareness of the urge to vomit; vomiting was defined as the forceful expulsion of gastric contents from the mouth. Failure of PONV prophylaxis was defined as any episode of nausea, vomiting, retching and/or use of rescue antiemetic. Incidence of any PONV, a number of rescue antiemetic required was measured at 0, 1, 2, 6, 12 and 24 h postoperatively. We measured PONV, as PONV 1 = no nausea and vomiting; 2 = nausea but no vomiting; 3 = nausea and vomiting.

Sample size was calculated assuming 30% difference in the PONV incidence rate between the groups (where Group 1 or Group 2 and Group 3 incidence rate was assumed to be 25% and 55%, respectively). At minimum 80% power of the study and 95% confidence interval, calculated sample size of each of the group came out to be 40. Finally, in this study, we have targeted to take at least fifty patients in each of the three groups.

For continuous variables, data were considered normal when standard deviation <1/2 mean value. One-way ANOVA was used to compare the means among three groups. As p value of one way ANOVA, was non significant, multiple comparison tests were not performed. To compare the proportions in the groups, Chi-square test/Fisher's exact test was applied as appropriate. Two proportions *Z*-test was used to compare the proportions between two independent groups [when sample size multiply by proportion ($n*p$) was ≥ 5]. $P < 0.05$ was considered as statistically significant. Statistical package for social sciences, version 22 (SPSS-22, IBM, Chicago, USA) was used for data analysis.

RESULTS

There were no statistically significant differences between the groups in age, sex, ASA physical status and duration of anaesthesia [Table 1]. Immediately after shifting the patient to post-operative area, incidence of PONV was measured as 7.8%, 10.6% and 38.6% in PD, P and D group, respectively ($P < 0.001$). After 1 h postoperatively, 15.6% in PD group, 15.2% in P group and 26.3% in D group reported PONV ($P = 0.210$). At 2 h postoperatively, nobody in PD group complained of PONV, whereas 4.5% in P group and 12.3% in D group reported PONV ($P = 0.007$). No patient in PD group and 7.6% in P group and 7% in D group reported PONV at 6th h ($P = 0.047$) [Table 2]. No patient reported any incidence of nausea and vomiting after 6th h till 24th h postoperatively in our study [Figure 1].

Overall incidences of PONV in our study (primary outcome) were 23.4% in PD, 27.2% in P and 56.14% in D group in 24 h postoperatively ($P < 0.001$). We found that compared to male patients, PONV incidence was quite high (27.9% [PD], 33.3% [P] and 69.04% [D]) in female patients. For males, there was

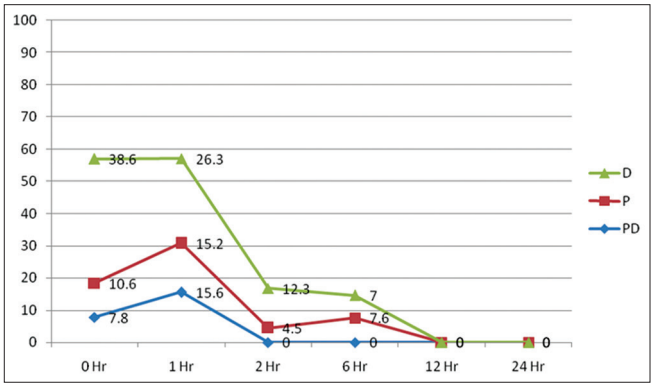

Figure 1: Incidence of post-operative nausea and vomiting versus time in the study groups

Table 1: Demographic profile in three study groups

Groups	PD (*n*=64)	P (*n*=66)	D (*n*=57)	*P*
Age (mean±SD)	42.41±14.26	42.45±13.56	43.57±11.74	0.864*
Sex ratio (male/female)	21/43	21/45	15/42	0.709**
ASA physical status (I/II) (%)	46 (71.9)	50 (75.8)	41 (71.9)	0.850**
	18 (28.1)	16 (24.2)	16 (28.1)	
Duration of anaesthesia (mean ±SD)	56.01±17.16	55.68±13.35	58.16±17.49	0.657*

*One-way ANOVA, **Chi-square test. *P*<0.05 considered as significant. SD – Standard deviation; ASA – American Society of Anesthesiologists

Table 2: Incidence of postoperative nausea and vomiting in postoperative period in three study groups

PONV score	PD group (%)	P group (%)	D group (%)	*P*
Immediately after shifting in PACU				
1	59	59	35	
2	2	3	10	
3	3	4	12	
PONV yes	5 (7.8)	7 (10.6)	22 (38.6)	<0.001
PONV no	59 (92.2)	59 (89.4)	35 (61.4)	
PONV at 1 h				
1	54	56	42	
2	8	3	5	
3	2	7	10	
PONV yes	10 (15.6)	10 (15.2)	15 (26.3)	0.210
PONV no	54 (84.4)	56 (84.8)	42 (73.7)	
PONV at 2 h				
1	64	63	50	
2	0	3	3	
3	0	0	4	
PONV yes	0 (0)	3 (4.5)	7 (12.3)	0.007
PONV no	64 (100)	63 (95.5)	50 (87.7)	
PONV at 6 h				
1	64	61	53	
2	0	1	2	
3	0	5	2	
PONV yes	0 (0)	5 (7.6)	4 (7)	0.047
PONV no	64 (100)	61 (92.4)	53 (93)	
Patient developing PONV in 24 h (yes)	15 (23.4)	18 (27.2)	32 (56.14)	<0.001
Sex-wise PONV incidence	Male 3/21 (14.2)	Male 3/21 (14.2)	Male 3/15 (20)	0.814
	Female 12/43 (27.9)	Female 15/45 (33.3)	Female 29/42 (69.04)	0.002
Age-wise PONV incidence (years)				
Age <50	12/45 (26.6)	14/46 (30.4)	27/44 (61.3)	0.001
Age ≥50	3/19 (15.7)	4/20 (20)	5/15 (33.3)	0.453
Use of rescue antiemetic=*n* (number of antiemetic multiple required in that group in 24 h)	15 (1.0 times)	25 (1.38 times)	48 (1.5 times)	

PONV – Post-operative nausea and vomiting Chi-square test/Fisher exact test (when expected frequency <5) used to compare the proportions, *P*<0.05 significant

no statistically significant difference in the incidence rate among three groups ($P = 0.814$) while for the female, it was significant ($P = 0.002$) [Table 2]. PONV was seen more commonly in younger (<50 years) age group than older (≥50 years) age group in all three study groups (26.6%, 30.4% and 61.3%, respectively, in PD, P and D groups). For <50 age group, there was statistically significant difference in the incidence rate among three groups ($P = 0.001$) while for the ≥50 year age group, it was not significance ($P = 0.453$) [Table 2].

Rescue antiemetic was required for 15 patients in PD group (1.0 times; times here means the average number of rescue antiemetic required per person in that group in 24 h) whereas for 18 patients in P group (1.38 times) and for 32 patients in D group (1.5 times) who developed PONV. Hence, the requirement was significantly more in D > P > PD groups [Table 2]. Proportion of occurrence of postoperative nausea and vomiting in the three groups in 24 h postoperatively had been shown in Table 3.

DISCUSSION

Overall incidences of PONV in our study (primary outcome) were 23.4% in PD, 27.2% in P and 56.14% in D group in 24 h postoperatively. Palonosetron is a highly effective 5-HT3 antagonists and has favourable side effect profile in comparison to others drugs used in the past for prevention and treatment of PONV.[9-12] Dexamethasone is reported to be an effective antiemetic having central antiemetic action through an activation of the glucocorticoid receptors in the bilateral nuclei *tractus solitarii* in the medulla.[13-15] Dexamethasone 8 mg is effective and safe for the prevention of PONV following different medical and surgical conditions.[15-19] Multimodal approach to PONV has been advocated in recent guidelines and medical literature[11-13] With a better understanding of

pathophysiology of PONV involving different sets of receptors, combination therapy with antiemetics acting through different pathways appear to be the logical choice. A fair number of trials had shown the efficacy of dexamethasone as an antiemetic.[20-22] However, in our study, dexamethasone was least effective as a single medication and addition of it to palonosetron did not increase the efficacy of combined medications. The cause of these findings is not clear and further study needs to be done. There are few studies that questioned the efficacy of dexamethasone as mono or combination therapy as antiemetic,[12,23] and our study also put a question mark on it.

Overall incidence of PONV in first 24 h was highest in D group whereas PD and P groups had a significantly lesser incidence of PONV. There is no statistically significant difference in incidence between P and PD group. It suggests that addition of dexamethasone with palonosetron did not increase the efficacy of combination regimen in the prevention of PONV.

Table 3: Proportion of occurrence of postoperative nausea and vomiting in three groups in 24 h

Groups comparison	*Z*	*P*	Inference
PD versus P	0.5	0.610	Group PD and P are equal, no significant difference
PD versus D	3.7	0.0002	Significant
P versus D	3.3	0.001	Significant

Two proportions *Z*-test was used to compare between two groups

Palonosetron and palonosetron-dexamethasone combination - both are effective and the combination is not better than palonosetron alone.

Injection metoclopramide (10 mg) was used as rescue antiemetic for patients who complained of PONV. Although pharmacologically metoclopramide is a weak antiemetic in comparison to 5-HT3 blocker, we chose it, because it is widely available and used as an antiemetic drug in our institute with reasonably acceptable side effects profile. Its mechanism of action (D2 receptor blockade) is also different from the studied drugs. Requirement of rescue antiemetic was more in dexamethasone group than other two groups (PD = 1 times, *P* = 1.38 times, *D* = 1.5 times; times here means the average number of rescue antiemetics required per person) [Table 2]. From this, we imply that patients who developed PONV, the number of times rescue antiemetic required was highest in dexamethasone group and least in palonosetron-dexamethasone group.

We also studied the trend of incidence of PONV overtime for first 24 h and we found that no patient complained of PONV in three study groups after 6 h. This result is different from other studies, which showed a variable incidence of PONV continuing in the first 24 h and beyond. Probable explanation for this may be the possible emetic effect of different anaesthetic agents

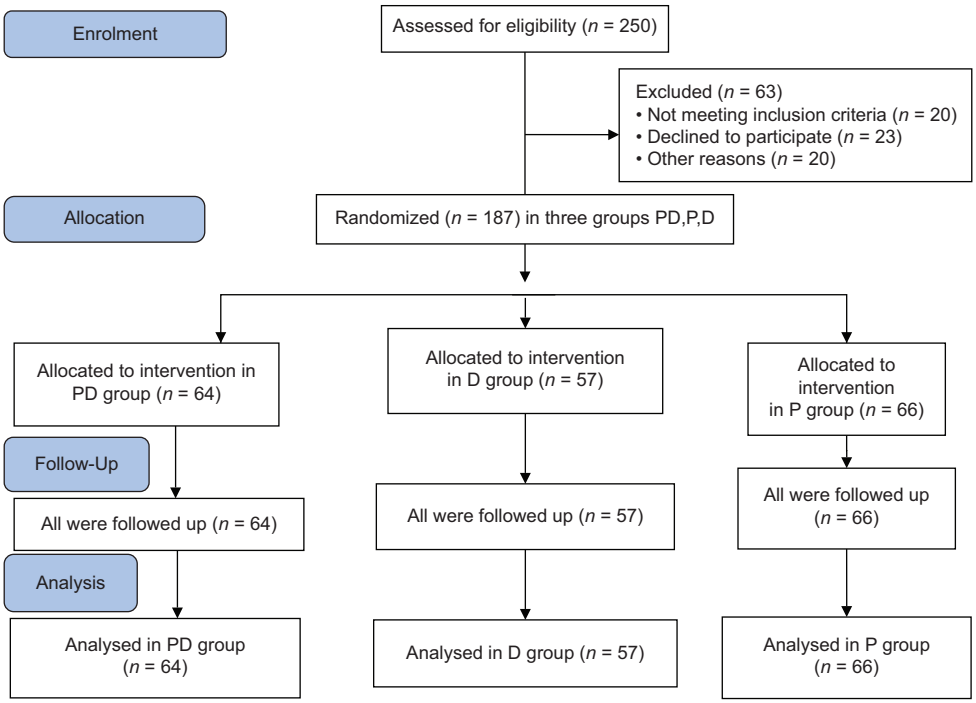

Figure 2: Consort flow diagram

used intraoperatively. Opioids such as fentanyl, sevoflurane as well as the laparoscopic surgery itself are known to have emetic properties. Elimination half-life of fentanyl is 2–4 h.[5] Residual effect of these emetic intraoperative anaesthetics can be implicated as the cause of PONV in first 6 h, by which time, most of these drugs' plasma concentrations would have been reduced by metabolism and elimination. Female sex is a known independent risk factor, and our study reciprocated the same. In addition, the highest incidence (69.04%) of PONV was found in females receiving dexamethasone. We studied the relationship of PONV with age. Incidence of PONV in younger age group (<50 years) was higher (26.6%, 30.4% and 61.3%) than older (≥50 years) (15.7%, 20% and 33.3% in PD, P and D groups, respectively) [Table 2]. This is in accordance with other studies.[4-6]

There are few limitations in our study. Pre-operative medications for chronic co-morbidity (diabetes and hypertension etc.,) could not be controlled. Post-operative nil per oral status and diet were not identical in all patients. Incidence of PONV and antiemetic effects of study drugs beyond 24 h could not be studied because of our study design. Our study population was limited to ASA physical Status I and II. We could not include ASA physical status III (and beyond) patients in view of ethical issue as well as limitations arising due to fixed intraoperative anaesthetic technique.

CONCLUSION

Palonosetron and palonosetron-dexamethasone combination were better than dexamethasone alone for preventing PONV in laparoscopic cholecystectomy patients. Statistically insignificant difference was found ($P > 0.05$) in efficacy between palonosetron alone and palonosetron-dexamethasone combination which suggests they are equally effective in the prevention of PONV.

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Conflicts of interest
There are no conflicts of interest.

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