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Efficacy of Palonosetron and Dexamethasone for Prevention of Post-operative Nausea and Vomiting in Female Patients Undergoing Laparoscopic Cholecystectomy: A Prospective Randomised Double-Blind Trial

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Abstract

Objective: Post-operative nausea and vomiting is a frequent complication following anaesthesia. We compared the efficacy and safety of intravenous palonosetron and intravenous dexamethasone as prophylactic antiemetic in patients undergoing laparoscopic cholecystectomy.

Methods: After obtaining institutional ethical committee approval, 100 adult female patients undergoing laparoscopic cholecystectomy were randomised to receive 4 mg dexamethasone (group I, n = 50) or 0.075 mg palonosetron (group II, n = 50) intravenously (IV) over 2-5 minutes prior to induction of anaesthesia. Standard anaesthetic technique was followed, and the residual neuromuscular block was antagonised at the end of the procedure. A single anaesthesiologist assessed all the cases for post-operative nausea and vomiting (PONV) for 24 hours. The complete response rate and the overall patient satisfaction were noted. If patient experienced PONV, injection metoclopramide 10 mg was given as rescue antiemetic IV.

Results: A total of six patients had vomiting within 6 hours (four patients in groups I and two patients in group II), whereas none had vomiting after 6 hours ($P = .39$). Complete response rate was 88 and 90% in both group I and group II. Three patients in both group I and group II required rescue antiemetics. Ninety-two percent patients were completely satisfied in group I, while 96% patients were fully satisfied in group II.

Conclusion: Intravenous administration of palonosetron (0.075 mg) is as effective as dexamethasone (4 mg) as prophylactic antiemetic without any untoward side effects for female patients undergoing laparoscopic cholecystectomy.

Keywords: Post-operative nausea vomiting, palonosetron, dexamethasone, laparoscopy, patient satisfaction, anaesthesia

Introduction

Post-operative nausea and vomiting (PONV) is a frequent complication following anaesthesia and despite recent advances in its prophylaxis, may occur in up to 80% patients depending on the existence of risk factors.[1]

Though PONV is rarely associated with catastrophic sequelae, it is a disagreeable experience associated with patient discomfort and dissatisfaction, delayed recovery room discharge, prolonged hospital stay and increased health care costs.[2-4] It is estimated that an episode of vomiting prolongs post-anaesthetic care unit (PACU) stay by about 25 minutes.[5] Prevention of PONV especially in high risk patients significantly improves post-operative ratings of well-being and satisfaction.[6] Morbidity associated with PONV includes wound dehiscence, dehydration, electrolyte disturbance, interference with nutrition and, very rarely, oesophageal rupture (Boerhaave syndrome) or aspiration pneumonitis.[7]

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Table 1. Demographic, incidence of PONV and patient satisfaction in the two groups

Parameter	Group I (n = 50)	Group II (n = 50)	*P*
Age (years)	30.2 (6.6)	30.48 (6.9)	.97
Weight (kg)	50.4 (5.16)	52.6 (4.9)	.82
ASA grade (I/II)	40/10	42/8	.60
Duration anaesthesia (minute)	62.5 (6.2)	58.3 (5.8)	.49
Duration surgery (minute)	55.6 (6.5)	50.6 (5.1)	.08
Vomiting (n)			
First 6 hours	4	2	.39
6-24 hours	0	0	0
Nausea (n)			
First 6 hours	3	2	.64
6-24 hours	2	2	1
Emesis score			
First 6 hours (1/2/3)	44/2/4	45/3/2	.64
6-24 hours (1/2/3)	50/0/0	50/0/0	1
Complete response rate n (%)	44 (88)	45 (90)	.75
Patient satisfaction (%)	92	96	.23

Recent interest has focussed on the adoption of a multimodal approach to tackle this problem and novel therapy of PONV management. Various drugs have been used in times for preventing PONV including anticholinergics, phenothiazine, antihistamines, butyrophenones and steroids but most of these have short-lasting action or are associated with side-effects. Dexamethasone is widely used in all types of surgery to reduce PONV. Its precise mechanism of action is unknown but has been proposed to be due to activation of glucocorticoid receptors in the medulla, inhibition of central production of prostaglandins or by blocking the release of endogenous opioids.[8,9] The newer antiemetic group of drugs, 5-hydroxy trypamine receptor antagonist (5-HT3-RA) receptor antagonists, eg, ondansetron, granisetron and tropisetron are considered very safe and effective. Palonosetron, a newly introduced second generation 5-HT3 receptor antagonist, is said to be more selective and potent in this regard.[10] It has the highest binding affinity and longer half-life of approximately 40 hours as compared to other agents of this class, which confers it a prolonged duration of action. Though previous studies evaluating the use of palonosetron for PONV prevention have yielded encouraging results, its role in PONV prevention is still unclear and far from routine.[11] Moreover, relative efficacy of palonosetron as compared to dexamethasone has not been established.

Main Points

- Postoperative nausea vomiting is a common problem following general anaesthesia in female patients undergoing laparoscopic surgeries.
- Palonosetron is a new second generation 5-HT3 receptor antagonist but its relative efficacy with respect to dexamethasone is not established.
- We compared palonosetron with dexamethasone prophylaxis and found it to be safe and as effective an antiemetic as dexamethasone.

This prospective randomised, double blinded study was conducted to compare the efficacy of prophylactic intravenous palonosetron and intravenous dexamethasone in patients undergoing laparoscopic cholecystectomy surgery with the primary aim of comparing the incidence of PONV.

Methods

After obtaining ethical committee approval from Mata Gujri Memorial Medical College and Lions Seva Kendra Hospital [MGM/PRI-85(A); 3.10.2017], this prospective, randomised, double-blinded clinical study was done in 100 adult female patients (18-50 years) of American Society of Anaesthesiology (ASA) physical status I and II undergoing laparoscopic cholecystectomy. After written informed consent, the patients were assigned to one of the two prophylactic treatment groups according to random number table as follows:

Group-I—receiving intravenous dexamethasone (4 mg) (n = 50);

Group-II—receiving intravenous palonosetron (0.075 mg) (n = 50).

Patients with history of allergy or contraindication to any of the study drugs, pregnant and lactating mother, patients having uncontrolled systemic diseases (eg, cardiovascular,

renal, hepatic, pulmonary, haematological, endocrinal and metabolic disorders), history of previous PONV and motion sickness, females in the premenstrual period (25th day of menstrual cycle till first 4 days of the cycle) and patients with body weight more than 75 kg were excluded from the study.

All patients received tablet alprazolam (0.5 mg) and ranitidine (1.0 mg kg^{-1}) orally night before and on morning of surgery. Injection ranitidine was continued at 8 hourly intervals for the first 24 hours. All patients were fasted for solids till 6 hours prior to surgery and for clear fluids till 2 hours prior to surgery.

In the preoperative room, a large bore (16 or 18G) intravenous cannula was secured, and all the patients received Ringer's lactate solution as per requirement.

On arrival to the operating room, routine monitoring devices were attached, and baseline blood pressure, pulse rate, oxygen saturation (SpO_2), electrocardiogram and core temperature (by placing temperature probe in nasopharynx) were recorded at baseline (time 0) and then measured at 15 minute interval till the end of anaesthesia.

The patients were randomly allocated into two groups of 50 each using a computer-generated randomisation table, to receive a single dose of either inj. dexamethasone (4 mg) or inj. palonosetron (0.075 mg) intravenously (IV) over 2-5 minutes prior to induction of anaesthesia. The masking of group allocation was maintained using sealed opaque envelops, which were opened once a patient was laid on the operating table. An independent anaesthesiologist who was not involved in the study opened the envelopes and prepared the medications (both palonosetron 0.075 mg and dexamethasone 4 mg) in an isolated area as injectable solutions in normal saline to a total volume of 5 mL in identical syringes and handed over the syringe to the person conducting the anaesthetic. Hence, the patient, the anaesthesiologist who cared for the patient intraoperatively and the PACU personnel were unaware of the group allocation.

Before IV induction of anaesthesia, all the patients were preoxygenated with 100% oxygen by facemask for a period of 3 minutes. Anaesthesia was induced with inj. thiopentone sodium (4-5 mg kg^{-1}) and inj. tramadol (2 mg kg^{-1}) IV. Tracheal intubation was facilitated with inj. succinylcholine (1.5 mg kg^{-1}) IV, and thereafter anaesthesia was maintained with isoflurane in 60% nitrous-oxygen and intermittent boluses of vecuronium bromide. Ventilation was adjusted to maintain end tidal carbon dioxide between 35 and 45 mmHg.

At the end of the operative procedure, the residual neuromuscular block was antagonised by injection neostigmine methyl sulphate (0.05 mg kg^{-1}) and injection glycopyrrolate (0.4 mg), and the trachea was extubated. Post-operative pain relief was provided with injection diclofenac 75 mg and injection acetaminophen 1 gm at the end of procedure followed by regular 8 hourly doses and infiltration of bupivacaine hydrochloride (0.25%) around the laparoscopic port sites. All patients breathed 100% oxygen with a fresh gas flow of 6 L min^{-1} until awakening. In PACU, all patients were supplemented with oxygen at the flow rate of 5 L min^{-1} by facemask for 2-3 hours. Our primary outcome was post-operative nausea or vomiting occurring within 24 hours. A single anaesthesiologist assessed all the cases for PONV (by direct questioning or spontaneous patient reporting) at 30 minutes interval up-to first 3 hours, then hourly till 6 hours and then 6 hourly intervals in the ward for 24 hours. Early PONV was defined as any episode of PONV during first 6 hours and late PONV as episodes occurring from 6 to 24 hours. The PONV was assessed using emesis score (1: no nausea and vomiting, 2: nausea or retching but no vomiting and 3: vomiting). Patient's recovery was assessed using a recovery score (defined as 0: unarousable, 1: arousable by loud sound, 2: drowsy and 3: fully awake).

The complete response rate was assessed for the study medications. It was defined as number of patients where there was complete absence of episodes of either nausea or vomiting and was recorded at 24 hours. Injection metoclopramide 10 mg was given as rescue antiemetic IV as required. When the patients were fully able to take oral fluids, intravenous drip was omitted and oral liquids were allowed. The overall patient satisfaction was assessed at 24 hours post-operatively by questioning the patient regarding her satisfaction of the post-operative experience with reference to PONV, and it was rated as "Yes" when she was completely satisfied and "No" for incompletely satisfied or totally unsatisfied response and the result was reported as percentage of people who were completely satisfied.

Statistical Analysis

For statistical analysis, data were entered into a Microsoft Excel spreadsheet and then analysed by using the IBM Statistical Package for the Social Sciences (SPSS) version 20 (IBM SPSS Corp.; Armonk, NY, USA).

A previous study had reported the incidence proportion of vomiting with dexamethasone as 56%, expecting 50% reduction in incidence proportion of vomiting using palonosetron with 80% power and 5% level of significance. A sample of 48 subjects per group was found to be sufficient for this study (total 96 subjects). We recruited 100 patients (50 subjects in each group) to account for the dropouts.[12] Data have been summarised as mean and standard deviation for numerical variables and count and percentages for categorical variables. The median and the interquartile range have been stated for numerical variables that are not normally distributed. Student's independent sample's t-test was applied to compare normally distributed numerical variables between groups; unpaired proportions were compared by Chi-square

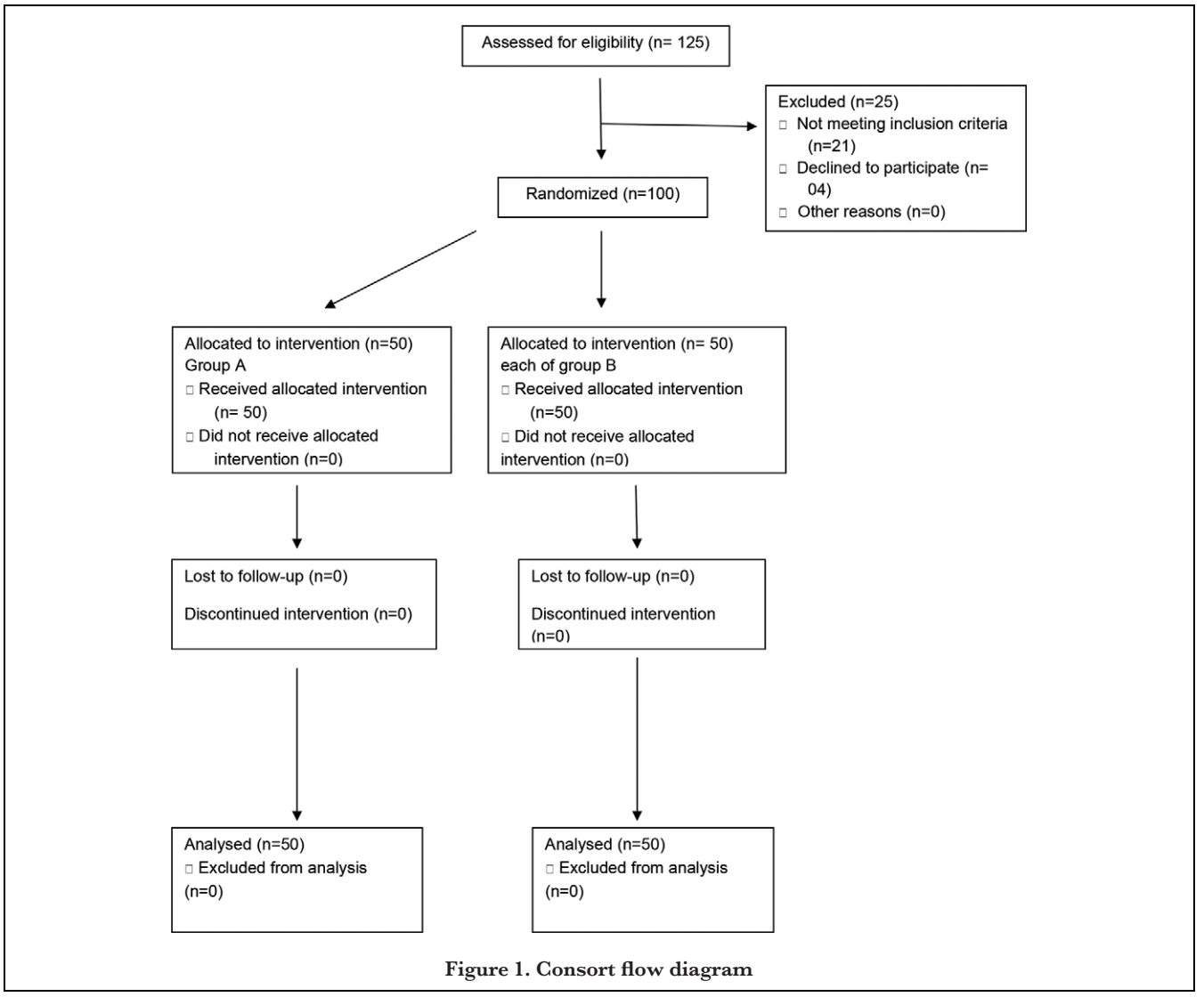

Figure 1. Consort flow diagram

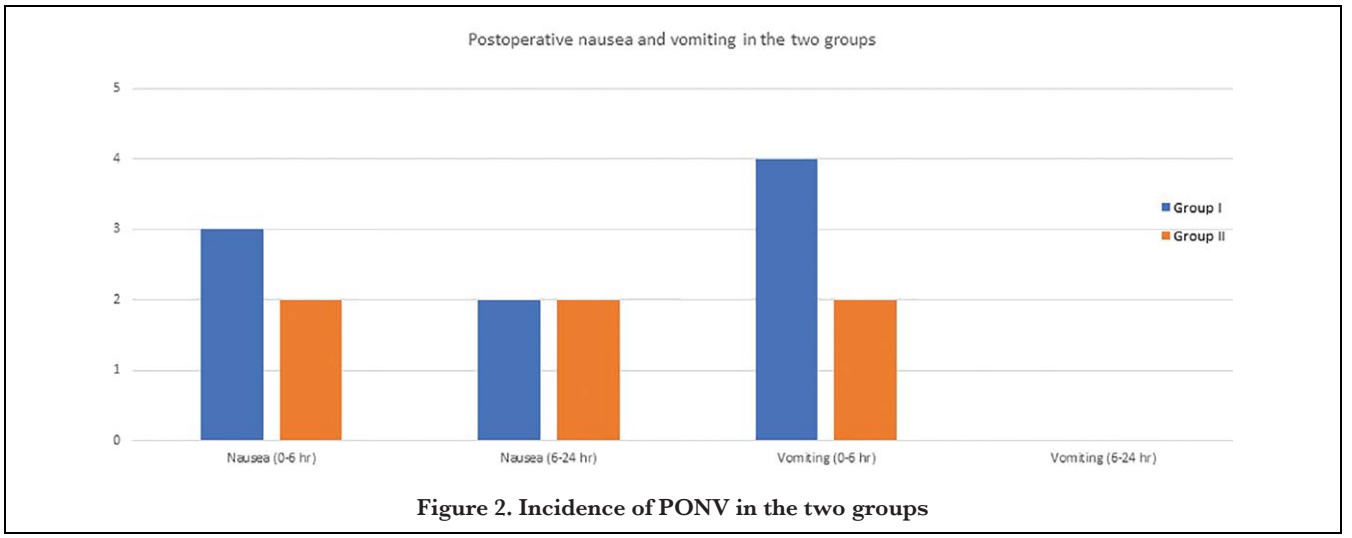

Figure 2. Incidence of PONV in the two groups

test or Fischer's exact test, as appropriate. $P \leq .05$ was considered for statistically significant.

Results

In the present study, a total of 125 patients undergoing laparoscopic cholecystectomy were screened for eligibility and 100 patients satisfying the inclusion criteria were included (Figure 1). Patient demographics and type/duration of surgery were similar in the two groups (Table 1). A total of six patients had vomiting within 6 hours (four patients in group I and two patients in group II), whereas none had vomiting after 6 hours (Table 1) ($P = .39$) (Figure 2). The incidence of nausea was also similar in the two groups (first 6 hours, three in group I and two in group II; 6-24 hours, two in each group) ($P = .64$) (Figure 2). Complete response rate was 88% in group I and 90% in group II ($P = .75$). Three patients in both group I and group II required rescue antiemetics. The hemodynamic parameters were similar in the two groups at different time points. All patients were fully awake in the post-operative period. Ninety-two percent patients were completely satisfied with their perioperative experience about PONV in group I, while 96% patients were fully satisfied in group II.

Discussion

PONV is one of the most dreaded side effects after surgery performed under general anaesthesia. In our study, a single dose of palonosetron was found to be of comparable efficacy in preventing PONV as compared to dexamethasone in adult female patients undergoing laparoscopic abdominal surgeries.

The risk factors for PONV include female gender, history motion sickness or PONV, nonsmoker and the use of perioperative opioids. The incidence of PONV is reported to be 10, 20, 39, 61 and 79%; if none, 1, 2, 3 or 4 of these risk factors are present, respectively.[1] In addition, duration of surgery more than 30 minutes and certain surgical procedures like gynaecologic or general abdominal procedures, head and neck surgery, eye surgery and laparoscopic procedures increase the risk of PONV.[13] In our study, patients were nonsmoker females aged <50 years undergoing abdominal laparoscopic procedures of around 1 hour duration, and opioids were used intraoperatively. As per Apfel classification, the preoperative risk of PONV is approximately 40%, whereas the overall incidence of PONV in our study was 11%. This can be attributed to the effectiveness of PONV prophylaxis provided by our study drugs.

Dexamethasone is a corticosteroid with strong anti-inflammatory and prolonged antiemetic effect. It has been shown to be an effective antiemetic in a variety of clinical settings (patients undergoing adenotonsillectomy, thyroidectomy, cholecystectomy and abdominal hysterectomy).[14,15] Dexamethasone was reported as equivalent or superior to 5HT-3 receptor antagonist such as granisetron for prevention of PONV during cancer chemotherapy.[16]

Palonosetron injection is a new, potent and long acting 5-HT3 receptor antagonist. Palonosetron has also been reported to be superior to other 5-HT3 antagonist like ondansetron, and granisetron in previous studies comparing them for PONV prophylaxis.[17]

Emad E. Mansour et al.[18] showed that dexamethasone in combination with palonosetron significantly reduced the incidence of PONV at 12-24 hours post-operatively as compared to dexamethasone alone. In a study done on Korean women, the combination of palonosetron and dexamethasone was more effective in reducing PONV than was dexamethasone monotherapy. However, the combination did not show additional benefits compared with palonosetron alone in preventing PONV after thyroidectomy.[19]

In previous studies, palonosetron monotherapy was found to be similarly effective to its combination with dexamethasone in outpatient laparoscopy.[20,21] This suggests that palonosetron is sufficiently effective alone and does not require combination in low to moderate risk patients. In our study population, monotherapy with palonosetron or dexamethasone alone proved to have similar efficacy with a complete response rate of 90 and 88%, respectively.

The previous studies involving palonosetron and dexamethasone have compared combination therapy with monotherapy, and there is no head-to-head comparison. The results of addition of dexamethasone to palonosetron on PONV have been inconsistent. The variability in the results can be due to different patient populations, anaesthesia techniques, assessment methods, risk factors for PONV, use of opioid infusion, geographical location and ethnic influences. In our study, the overall incidence of PONV was low probably because our patients did not receive post-operative opioids, all patients received scheduled doses of H2-receptor antagonist (ranitidine), and we had excluded females with history of motion sickness or PONV.

Dexamethasone is known to cause side effect such as increased incidence and severity of infection, adrenal suppression and delayed healing in surgical patients.[21] In the present study, dexamethasone and palonosetron both the drugs were not associated with any significant adverse effects in intraoperative and post-operative period, and the side effects observed were comparable in the two groups.[22]

There are a few limitations of the present study. The first is the absence of a placebo group. However, as previously discussed, PONV is a very distressing symptoms and the patient population consisted of those standing at higher

risk of PONV; and hence, including a placebo group would have meant depriving a group of patients of standard of care, which poses ethical concerns. Second, this was a single centre trial. If the study was conducted multicentrically, the generalisability would have increased as the study drugs could have been tested in geographically distinct populations. Use of monotherapy was another limitation as a combination therapy would be expected to be more effective.

Conclusion

In conclusion, intravenous administration of palonosetron (0.075 mg) is as effective as dexamethasone (4 mg) as a prophylactic antiemetic agent without any untoward side effects for female patients undergoing laparoscopic cholecystectomy surgery.

Ethics Committee Approval: Ethical committee approval was received from the Mata Gujri Memorial Medical College and Lions Seva Kendra Hospital, Kishanganj, [MGM/PRI-85(A); dated 3.10.2017].

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

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