

A Randomized Double-blind Control Study Comparing the Efficacy of Palonosetron Versus a Combination of Dexamethasone with Palonosetron in Preventing Post-operative Nausea and Vomiting in Patients Undergoing Laparoscopic Cholecystectomy

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Abstract

Introduction: Post-operative nausea and vomiting (PONV) is distressing symptoms occurring after anesthesia and surgery with incidence of about 20–30% during the first 24 post-operative hours. In patient undergoing laparoscopic cholecystectomy (LC), the incidence is as high as 63–72%.

Objective: The objective of this study was to compare the efficacy of “palonosetron” versus a combination of “dexamethasone and palonosetron” in preventing PONV in patients undergoing LC.

Materials and Methods: A total of 84 patients were randomized into two groups. Group I received palonosetron (0.075 mg) and Group II received a combination of palonosetron (0.075 mg) and dexamethasone (8 mg). Incidence of PONV was measured using visual analog score from the time of arrival to recovery until discharge at specified intervals. The absence of nausea and vomiting was considered as complete response (CR). Requirement of rescue antiemetic (metoclopramide) in each group was noted.

Results: At 0–2 h, CR of 85.7% in Group II and 66.7% in Group I was observed ($P = 0.040$). During 2–24 h, CR in Group II in comparison to Group I (88.1% vs. 69%, $P = 0.033$) was more. During 0–24 h, CR of 85.7% of patients in Group II and 66.7% of patients in Group I ($P = 0.040$) was observed. Between 24 h till discharge, 100% in Group II and 97.6% in Group I showed CR ($P = 0.314$). Requirement for rescue antiemetic was higher in Group I ($P = 0.026$).

Conclusion: A combination of palonosetron and dexamethasone significantly reduced the incidence of PONV during the first 24 h. After 24 h, both groups showed similar efficacy.

Key words: Complete response, Dexamethasone, Palonosetron, Post-operative nausea and Vomiting

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INTRODUCTION

Post-operative nausea and vomiting (PONV) is the most common distressing symptoms with incidence around 20–30% occurring in the first 24 post-operative hours.^[1,2] The incidence can be as high as 70–80% in high-risk patients.^[3] The incidence of PONV after general anesthesia

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is also determined by various other factors such as patient sex, habits such as smoking, presence of motion sickness, or previous PONV and also surgical factors such as type of surgery (laparoscopic surgeries, strabismus, middle ear surgeries, stomach, duodenum, and gallbladder surgeries^[1,4,5] are at high risk of PONV), duration of surgery (high incidence if duration is more than 3 h), and use of opioids and nitrous oxide.^[1,4] A simplified scoring system was developed by Apfel *et al.* [Figure 1] to predict the incidence of PONV in undergoing surgery under general anesthesia. The incidence of PONV may vary from 10% when no risk factors are present to as high as 80% when all four risk factors are present.

Emetic episodes can predispose to aspiration of gastric contents, wound dehiscence, bleeding, rise in intracranial pressure, fluid and electrolyte imbalance, and psychological distress.^[6,7] PONV may also delay discharge from post-anesthesia care unit (PACU) and is the leading cause of unexpected hospital admissions after planned ambulatory surgery.^[1] After planned ambulatory surgery. The incidence of PONV in patient undergoing laparoscopic cholecystectomy (LC) is around 63–72%.^[8,9] The use of prophylactic antiemetic in these patients is justified.

Vomiting center, which is located in the lateral reticular formation of the medulla oblongata in close proximity to the nucleus of the solitary tract in the brain stem, has access to the motor pathways that are responsible for the visceral and somatic output involved in vomiting. Main sensors of somatic stimuli are located in the gut and chemoreceptor trigger zone in the area postrema. Other stimuli are those from oropharynx, mediastinum, peritoneum, and genitalia as well as afferents from the central nervous system.^[10,11] Five neurotransmitter systems appear to play important roles in mediating the emetic response [Figure 2].

Five neurotransmitter systems appear to play important roles in mediating the emetic response. Various pharmacological agents used in preventions and treatment of PONV such as antihistamines, butyrophenones and dopamine receptor antagonists. Of these 5-hydroxytryptamine-3 receptor antagonist have been chosen as first line of therapy because of their fewer side effect profile.^[12]

Palonosetron is a second generation 5-HT₃ antagonist that has recently been approved for prophylaxis against PONV. It has a higher receptor affinity due to its binding to receptor in an allosteric positively cooperative manner and so has a much longer half-life (36–40 h) than other 5-HT₃ antagonists.^[13] Palonosetron has been evaluated for prophylaxis against PONV in two placebo-controlled trials.^[14,15] Based on these trials, the minimum effective dose of palonosetron in the setting of PONV is 0.075 mg.

Dexamethasone is a corticosteroid whose prophylactic antiemetic effect has been documented in laparoscopic surgery, and its efficacy reported to be equal as 5-HT₃ antagonists.^[16,17] When combined with dexamethasone, the efficacy of palonosetron was much improved for both early and delayed chemotherapy-induced nausea and vomiting (CINV).^[18]

On the basis of promising results shown in combination therapy of palonosetron with dexamethasone in CINV, combination of palonosetron and dexamethasone may studied as a choice for prophylaxis in patients at high risk for PONV. Therefore, the present study was designed to compare palonosetron versus palonosetron and dexamethasone combination for the prevention of PONV in patients undergoing LC.

MATERIALS AND METHODS

The present study was a randomized control trial conducted between July 2013 and July 2014 at Apollo Hospital, Chennai, after getting informed consent from the patient and also ethical committee approval. 84 patients of American Society of Anesthesiologists (ASA) physical status I and II and aged between 25 and 60 years were included in the study and randomly divided into two Groups I and II based on computer randomization.

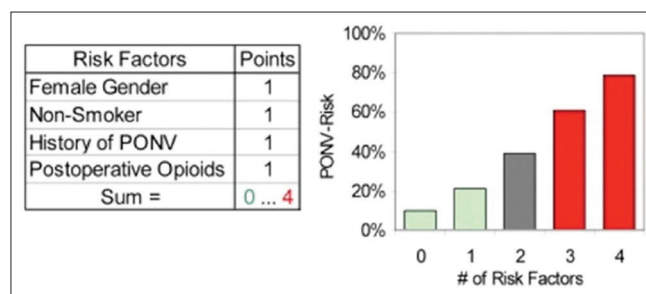


Figure 1: Apfel score

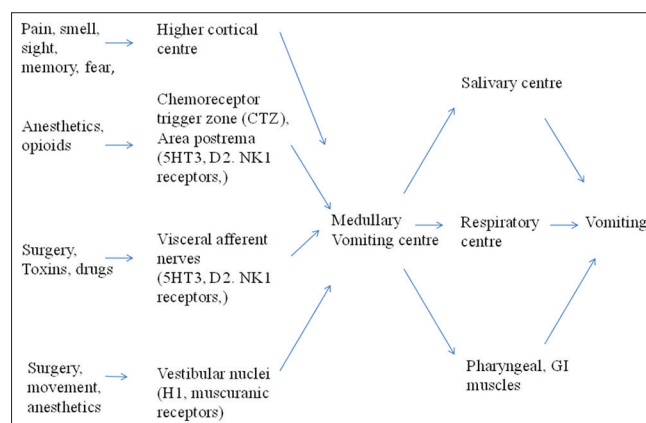


Figure 2: Pathophysiology of vomiting

Patients who are allergic to study drug, prolonged surgery more than 3 h, patient who received antiemetic 24 h before surgery, history of motion sickness or PONV, history of bronchial asthma, pregnant patient, and conversion from laparoscopy to laparotomy were excluded from the study. Before day of surgery, all patients were explained about visual analog scale for nausea and pain. All patients were premedicated with tablet pantoprazole 40 mg on the night before surgery and 8 h fasting before surgery was observed.

The study drug palonosetron is available as palonosetron hydrochloride 0.075 mg in 1.5 ml ampoule. Group I - patient received 0.075 mg of palonosetron i.v diluted to 4 ml with 0.9% sodium chloride solution. Group II - patient received 0.075 mg of palonosetron and dexamethasone 8 mg i.v diluted to 4 ml with 0.9% sodium chloride solution. Drug solution was prepared in identical syringes by a person not involved in the study.

After performing a thorough machine check and attaching all ASA standard monitors, patients were pretreated with the study drugs. Anesthesia was induced by injection propofol 2 mg/kg i.v, injection fentanyl 2 mcg/kg i.v, and vecuronium 0.1 mg/kg i.v. After endotracheal intubation, anesthesia was maintained by desflurane 6% with air in oxygen (FiO_2 0.4). After induction, nasogastric tube was inserted and suction was applied to empty the stomach of air and other contents. Ventilation was mechanically controlled and adjusted to maintain end-tidal CO_2 (end-tidal carbon dioxide [ETCO_2]) at 35–40 mmHg throughout the surgery as measured by anesthesia gas analyzer. Intraoperatively, heart rate (HR), non-invasive blood pressure (NIBP), saturation using pulse oximeter (SPO_2), and ETCO_2 were noted every 10 min until the end of surgery. The total duration of surgery (from incision to application of bandage) and anesthesia (from induction to discontinuation of the inhaled anesthetic agent) was noted. Total duration of CO_2 insufflations was also noted.

Before tracheal extubation, the nasogastric tube was suctioned again and then removed. At the end of anesthesia, glycopyrrolate 10 mcg/kg i.v and neostigmine 50 mcg/kg i.v were administered for reversal of residual neuromuscular blockade and trachea extubated once the patient satisfied the extubation criteria. Before skin closure, the surgeon was asked to inject 0.25% bupivacaine (5 ml) at the fascial level of each surgical portal. In addition, all patients received injection diclofenac 75 mg by infusion for post-operative analgesia 30 min before end of the procedure. Postoperatively, all patients were observed for PONV from time of arrival to recovery room till 36 h or until discharge, whichever is longer. All episodes of PONV during the post-operative period were recorded by a blinded observer at the time intervals of 0–2 h, 2–24 h,

and from 24–36 h or until discharge. Nausea was assessed using VAS scale. A score of >5 was considered severe, 5 = moderate and <5 minimal, and 0 = nil. Rescue antiemetic metoclopramide 10 mg i.v was given for moderate and severe nausea, vomiting episode, or at patients request and repeated if necessary. Complete response (CR) was defined as no nausea and vomiting with no administration of rescue antiemetic medication during the 24 h observation period and will be the primary efficacy end point.

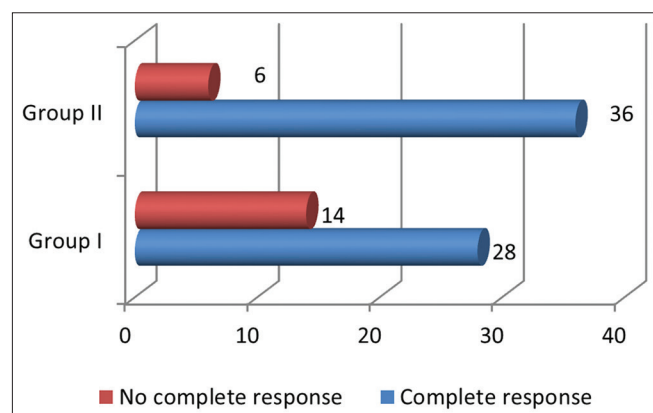
RESULTS

The statistical analysis was carried out using Statistical Package for the Social Sciences V11.0. All the continuous variables were assessed for the normality using Shapiro–Wilk's test. All normally distributed variables are expressed as mean \pm standard deviation. Median (interquartile range) comparisons of all the normally distributed continuous variables were done by independent sample *t*-test or ANOVA based on number of groups. Comparison of all the non-normally distributed continuous variables was done by Mann–Whitney *U*-test or Kruskal–Wallis test based on number of groups. All categorical variables were expressed as either percentage or proportions. Comparisons of categorical variables were done by Chi-square test or Fischer's exact test based on number of observation. $P < 0.05$ was considered as statistically significant. Data entry and validation were done on MS Excel spreadsheet. The sample size has been calculated on the basis of a previous study, which shows the incidence of PONV in patients undergoing LC who have not received any antiemetic prophylaxis as 70%.^[8,9] Presuming that after palonosetron prophylaxis, there would be 30% reduction in incidence,^[15] power analysis with $\alpha = 0.05$ and $\beta = 0.90$ showed that we need to enroll 38 patients in each group. To minimize the effect of data loss, 42 patients were recruited in each group.

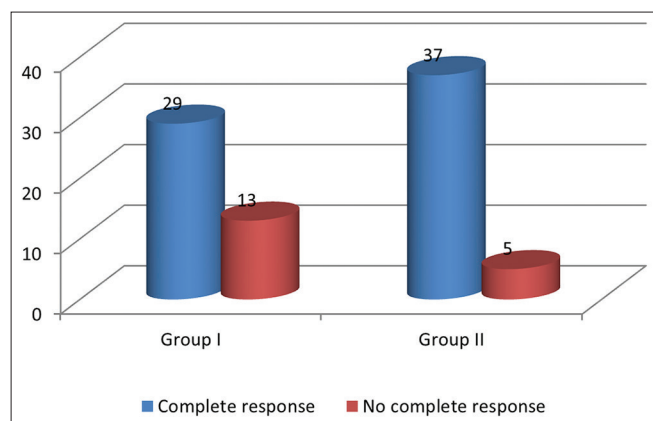
The mean age of patients in Group I was 42.43 ± 7.96 years and in Group II was 43.29 ± 7.09 years. The mean weight of patients in Group I and II was 71.12 ± 6.60 kg and 70.36 ± 2.48 kg. The mean height of patient was 163.34 ± 6.50 cm in Group I and 163.29 ± 5.47 cm in Group II. Group I consisted of 27 females and 15 males and Group II consisted of 30 females and 12 males. Distribution of ASA I:II patients was 27:15 in Group I and 31:11 in Group II. Both the groups were well matched with respect to age, weight, height, sex ratio, and ASA grades ($P > 0.05$) [Table 1]. The mean baseline HR of Group I was 76.84 ± 4.43 and in Group II was 75.34 ± 4.15 , the mean systolic blood pressure in Group I was 130.29 ± 9.51 and in Group II was 129 ± 8.86 , the mean diastolic blood pressure (DBP) in Group I was 78.67 ± 4.80 and in Group II was 78.74 ± 4.45 , and the mean oxygen saturation (SPO_2) in Group I was 99.88

± 0.33 and in Group II was 99.88 ± 0.33 . Both the groups were well matched with respect to mean HR, BSP, DBP, and SPO_2 . The mean duration of surgery in Group I was 59.05 ± 6.91 and in Group II was 60.02 ± 6.99 , the mean duration of anesthesia in Group I was 80.40 ± 7.15 and in Group II was 79.43 ± 7.50 , and mean duration of CO_2 insufflations in Group I was 47.52 ± 6.66 and Group II was 47.86 ± 6.29 . Both the groups were comparable with regard to mean duration of CO_2 insufflations, surgery, and anesthesia. Both the groups were comparable with regard to intraoperative vital parameters such as HR, blood pressure, and saturation over time interval ($P > 0.05$).

All the patients were observed for 2 h (0–2 h) in the PACU. During their stay in PACU, HR, NIBP, and pain scale were monitored every 30 min and SPO_2 was monitored continuously. All episodes of PONV were also assessed at 30 min interval. We used the total incidence of nausea and vomiting to present PONV. After 2 h, patients were shifted to the ward and from 2 h until discharge episodes of PONV were recorded at 2, 4, 8, 12, 24 h, and until discharge.



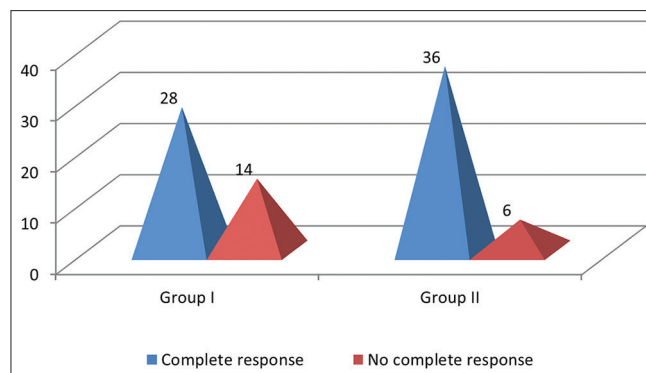
Graph 1: Incidence of complete response, nausea, vomiting, and post-operative nausea and vomiting during 0–2 h: Values are expressed as n (%)



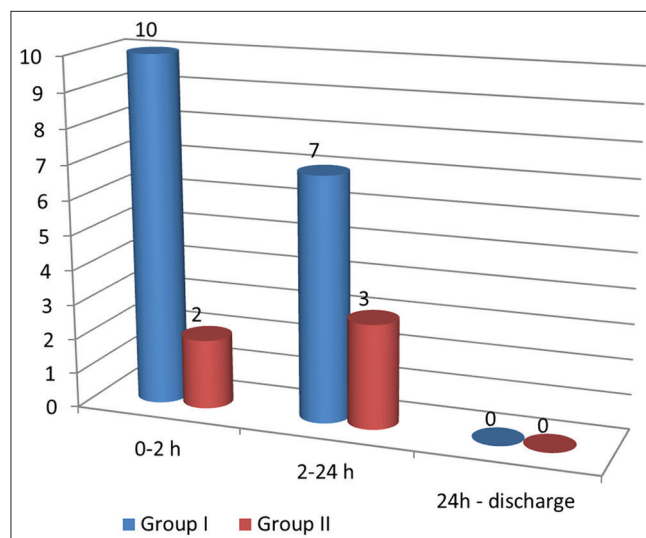
Graph 2: Incidence of complete response, nausea, vomiting, and post-operative nausea and vomiting during 2–24 h: Values expressed as n (%)

During the first 2 h postoperatively, 36 patients (85.7%) in Group II did not complain of nausea compared to 28 patients (66.7%) in Group I (p value 0.228) [Table 2] and 37 patients (88.1%) in Group I and 40 patients (95.2%) in Group II did not experience vomiting ($P = 0.433$), and the difference was not statistically significant. However, CR was observed in 85.7% of patients in Group II as compared to 66.7% of patients in Group I, and the difference was statistically significant ($P = 0.040$) [Graph 1 and Table 5].

During 2–24 post-operative hours, 88.1% of patients in Group II were nausea free, whereas 69% of patients did not experience nausea in Group I ($P = 0.205$) [Table 3] and 39 patients (92.9%) in Group II did not experience vomiting compared with 37 (88.1%) patients in Group I ($P = 0.713$). The results were not statistically significant. During 2–24 h time period, significantly more patients showed CR in Group II in comparison to Group I (88.1% vs. 69% $P = 0.033$) [Graph 2].



Graph 3: Incidence of complete response, nausea, vomiting, and post-operative nausea and vomiting during 0–24 h: Values expressed as n (%)



Graph 4: Requirement of rescue antiemetic. Values expressed as n (%)

Table 1: Demographic data (mean±SD) unless specified

Data	Group I (n=42)	Group II (n=42)	P value (between groups)
Age (years)	42.43±7.96	43.29±7.09	0.604
Weight (kg)	71.12±6.60	70.36±2.48	0.486
Height (cm)	163.34±6.50	163.29±5.47	0.971
M: F	15:27	12:30	0.641 (Fischer's exact test)
ASA I: II	27: 15	31:11:00	0.479 (Fischer's exact test)

SD: Standard deviation, ASA: American Society of Anesthesiologists

Table 2: Incidence of CR, nausea, vomiting, and PONV during 0–<2 h: Values are expressed as n (%)

Data	Group I n=42 (%)	Group II n=42 (%)	P value (between groups)
CR	28 (66.7)	36 (85.7)	0.040 (Fischer's exact test)
No CR	14 (33.3)	6 (14.3)	

PONV: Post-operative nausea and vomiting, $P < 0.05$ statistically significant difference between the groups, CR: Complete response

Table 3: Incidence of CR, nausea, vomiting, and PONV during 2–24 h: Values expressed as n (%)

Data	Group I n=42 (%)	Group II n=42 (%)	P value (between groups)
CR	29 (69)	37 (88.1)	0.033 (Fischer's exact test)
CR	29 (69)	37 (88.1)	
No CR	13 (31)	5 (11.9)	

PONV: Post-operative nausea and vomiting, $P < 0.05$ statistically significant difference between the groups, CR: Complete response

During 0–24 h, CR was observed in 85.7% of patients in Group II and 66.7% of patients in Group I, and the difference was statistically significant ($P = 0.040$) [Graph 3 and Table 4]. During the time period of 24 h post-surgery and until discharge of patient, CR was observed in all the patients (100%) in Group II, whereas 41 patients (97.6%) showed CR in Group I with no significant difference between the groups. During the entire post-operative hours until discharge of patient, 36 patients (85.7%) showed CR in Group II as compared to 28 patients (66.7%) in Group I, and the difference was statistically significant ($P = 0.040$).

Rescue antiemetic in the form of metoclopramide 10 mg was administered intravenously to patients who experienced moderate or severe nausea or vomiting or at patient request. During 0–2 h, 10 patients in Group I and two patients in Group II required rescue antiemetic therapy and the difference was significant ($P = 0.026$). Between 2 and 24 h, higher numbers of patients in Group I (7) required rescue antiemetic than in Group II (3), and the difference was statistically insignificant [Graph 4]. Between 24 and 48 h, no patient required rescue antiemetic in either of the groups [Table 6].

DISCUSSION

PONV is a common sequel of general anesthesia. Although PONV is almost always self-limiting and non-fatal, it can cause significant morbidity, including dehydration, electrolyte imbalance, suture tension and dehiscence, venous hypertension and bleeding, esophageal rupture, and life-threatening airway compromise. Each vomiting episode delays discharge from the recovery room by about 20 min.

Patients undergoing LC are at a particularly high risk for the development of PONV, and an incidence of 63–72% is reported when no prophylactic antiemetic is provided. The 5-HT₃ receptor antagonists are considered the first-line therapy because of their efficacy and safety. However, their absolute efficacy is disappointing and they have relatively short elimination half-life of < 12 h. Dexamethasone a corticosteroid has emerged as potentially useful prophylaxis for PONV when used as a single agent. Addition of dexamethasone as a part of multimodal approach to 5-HT₃ antagonists has been shown to decrease PONV symptoms compared with the use of 5-HT₃ antagonists alone after LC. Palonosetron, a second generation 5-HT₃ receptor antagonist, is an established antiemetic drug for CINV, and combination therapy using palonosetron and dexamethasone has been found to be safe and more effective than palonosetron alone.

In view of the promising results for combination of dexamethasone with palonosetron in CINV, in the present study, we have compared the efficacy of palonosetron with palonosetron and dexamethasone combination for the prevention of PONV in patients undergoing LC. 84 ASA I and II patients scheduled for LC were randomly divided into two groups. Group I patients received 0.075 mg palonosetron only and Group II patients received 0.075 mg palonosetron and dexamethasone 8 mg. In the present study, both the groups were well matched with respect to demographic data, baseline parameters, duration of anesthesia, surgery and CO₂ insufflations, and intraoperative hemodynamics.

Significantly more number of patients had CR in palonosetron-dexamethasone combination group (Group II) compared to only palonosetron group (Group I) between 0 and 24 h. Between 0 and 24 h, 85.7% of patients showed CR in Group II as compared to 66.7% in Group I ($P = 0.040$). CR was observed in 97.6% of patients in Group I and 100% of patients in Group II between 24 h and discharge, with no significant difference between the groups. Significantly more number of patients required rescue antiemetic in Group I than Group II between 0 and 2 h period.

In the present study, 14 (33.3%) patients treated with 0.075 mg palonosetron (Group I) experienced nausea

Table 4: Incidence of CR, nausea, vomiting, and PONV during 0–24 h: Values expressed as n (%)

Data	Group I n=42 (%)	Group II n=42 (%)	P value (between groups)
CR	28 (66.7)	36 (85.7)	0.040
Number CR	14 (33.3)	6 (14.3)	

PONV: Post-operative nausea and vomiting, $P < 0.05$ no statistically significant difference between the groups, CR: Complete response

Table 5: Incidence of CR, nausea, vomiting, and PONV during 0 h–discharge: Values expressed as n (%)

Data	Group I n=42 (%)	Group II n=42 (%)	P value (between groups)
CR	28 (66.7)	36 (85.7)	0.040
Nausea	14 (33.3)	6 (14.3)	

PONV: Post-operative nausea and vomiting, $P < 0.05$ statistically significant difference between the groups, CR: Complete response

Table 6: Requirement of rescue antiemetic. Values expressed as n (%)

Time interval	Group I n=42 (%)	Group II n=42 (%)	P value (between groups)
0–2 h	10 (23.8)	2 (4.8)	0.026 (Fischer's exact test)
2–24 h	7 (16.7)	3 (7.1)	0.178
24 h–discharge	0	0	0

$P < 0.05$ statistically significant difference between groups in 0–2 h

during 0–24 h time interval. Kovac *et al.*^[14] have also reported nausea in 50%. Of patients who had two or more risk factors for PONV and were pretreated with palonosetron 0.075 mg. In that study, 70% of patients in the placebo group experienced nausea between 0 and 24 h.

In the present study, 23.81% of patients in Group I experienced vomiting during 0–24 h and 0–48 h which is similar to that reported by Kovac *et al.*^[14] between 0–24 h (40%) and 0–72 h (44%) and Candiotti *et al.*^[15] (0–24 h - 33% and 0–72 h - 36%). None of the patients in the present study vomited between 24 h and till discharge, whereas Kovac *et al.*^[14] and Candiotti *et al.*^[15] reported emetic episodes in 4% and 9% of patients, respectively, between 24 and 72 h. The difference in the emetic episodes after 24 h between our studies and these two previous studies could be because of the use of opioids for post-operative analgesia in these studies. In our study, the patients did not receive post-operative opioids for analgesia.

In the present study between 0 and 24 h post-operative time interval, CR rate was 66.7% in patients who received palonosetron 0.075 mg. In the previous studies by Kovac *et al.*^[14] and Candiotti *et al.*^[15] the CR rate was 56% and 43% at 0–24 h time interval. For the 24–till discharge interval after surgery, the CR rate in our study was 97.6% which is similar to that reported by Bhattacharjee *et al.*^[19] (90%) but higher than

that reported by Kovac *et al.*^[14] (70%) and Candiotti *et al.*^[15] (49%). The lower CR rates in these studies could be because of the patient population chosen that had two or more risk factors for PONV, use of opioids for post-operative pain and including day care patients by Candiotti *et al.*^[15]

During the secondary time interval of 0–2 h, 2–24 h, and 0–till discharge, the CR rate in our study was 66.7%, 69%, and 66.7% in Group I which is consistent with that reported by Kovac *et al.*^[14] between 0 and 6 h (61%), 6 and 72 h (56%), and 0 and 72 h (52%) but higher than that reported by Candiotti *et al.*^[15] (0–6 h = 49%, 6–72 h = 45%, and 0–72 h = 39%). To the best of our knowledge, no previous study has been carried out to compare the efficacy of palonosetron versus a combination of dexamethasone and palonosetron for the prevention of PONV. However, combination of palonosetron-dexamethasone has been found to be better than palonosetron alone for CINV. Palonosetron 0.25 mg and dexamethasone 8 mg produced high early CR rates (84%) falling to 59% for late CINV.^[18]

The incidence of vomiting was lower in Group II as compared to Group I between 0 and 2 h and 2 and 24 h, but results were not statistically significant. No patient in either of the groups vomited between 24 h and discharge. A CR rate was significantly higher in Group 2 at all-time intervals except during 24 h–till discharge when the CR rate was statistically insignificant.

In the present study, only 1 patient (2.4%) in Group I experienced mild nausea between 24 h and till discharge. During 24 h–till discharge, the incidence of CR was high in both groups (97.6% in Group I and 100% in Group 2). The higher CR rate in both the groups after 24 h in our study may be because of the longer acting drugs used. Palonosetron itself has a half-life of 36–40 h and dexamethasone is also found to be better for late PONV. Moreover, we avoided opioids for post-operative analgesia.

In the present study, significantly higher number of patients required rescue antiemetic in Group I as compared to Group II between 0 and 2 h. Between 2 and 24 h, the number of patients requiring rescue antiemetic was high in Group I when compared with Group II, but results were not statistically significant to conclude that Group II had less requirement of antiemetic. No patient required rescue antiemetic between 24 h and till discharge in both the groups. It is probable that the action of dexamethasone has not started by the time surgery was completed. Perhaps that may be the reason that requirement of rescue antiemetic was comparable between the groups during 0–2 h.

In the present study, all these factors were well balanced among the groups. Fentanyl was used in the dose of 2 µg/kg for all the patients. Patients with a history of

motion sickness or previous PONV and menstruating females were excluded from the study because they are considered high risk for PONV. Therefore, the difference in the rates of patients experiencing PONV among the groups can be attributed exclusively to the study drugs.

In the present study, palonosetron was used in the dose of 0.075 mg which has been found to be the minimum effective dose in various studies.^[14,15] A wide dose range of dexamethasone has been used in the prophylaxis of PONV after various types of surgeries. The dose most often used is 8–10 mgs.^[20-22] Therefore, dexamethasone 8 mg was administered for the prevention of PONV in our study.

The timing of prophylactic antiemetic administration is important. We administered the drugs at the beginning of the procedure. It is recommended that palonosetron should be administered 30 min before prophylaxis for CINV and immediately before induction of anesthesia for the prevention of PONV.^[23] It has been confirmed recently that dexamethasone is more effective when given at the induction of anesthesia.^[24] Therefore, we administered palonosetron and palonosetron dexamethasone combination before induction of anesthesia.

CONCLUSION

The use of a combination therapy of palonosetron and dexamethasone than palonosetron alone for LC procedures has distinct advantage in the first 24 h. Hence, it is recommended to use a combination of palonosetron and dexamethasone. Whenever palonosetron is used it is necessary to follow-up the patient for a period of at least 36 h for side effect. The ideal time to use palonosetron to prevent PONV is at the time of induction. The use of palonosetron intraoperative reduces the need for rescue antiemetics in succeeding 24 h period, thereby providing a cost benefit to patients.

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