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Palonosetron-dexamethasone versus ondansetron-dexamethasone to prevent postoperative nausea and vomiting undergoing laparoscopic sleeve gastrectomy: a preliminary, randomized, double blinded study

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Abstract

Introduction: Post-operative nausea and vomiting (PONV) is associated with wound dehiscence, pulmonary aspiration, electrolyte disturbances, delayed recovery and patient dis-satisfaction. The present study was aimed to compare antiemetic efficacy of intravenous palonosetron with dexamethasone versus ondansetron with dexamethasone to prevent PONV in patient undergoing laparoscopic sleeve gastrectomy (LSG).

Materials and Method: Prospective, double blind randomized study of 24 morbidly obese patients planned for LSG. Preoperative gastric emptying scintigraphy (GES) done to know about gastric emptying. All patients premedicated with tablet ranitidine 150 mg a night before and 2 hours before surgery. Patients randomized into two groups PD (n=12) and OD (n=12) according to antiemetic agents used 30 min prior induction. Perioperative hemodynamic parameter were measured every 10 min interval during intraoperative and incidence of PONV along with hemodynamic parameters were assessed at arrival 0, 6, 12, 24, 48 and 72 hours postoperative period.

Observation and Results: Demographic data, perioperative hemodynamic parameters were well matched. The overall incidence of nausea/vomiting was 54.6%/18.2% and 63.6%/18.2% in group PD and group OD; respectively during 72 hours follow-up. The total dose of rescue antiemetic was 10 mg in group PD and 11.67 in group OD (p=3.14). GES done in 8 patients (PD; 3 and OD; 5) indicated normal gastric emptying and only one patient had PONV in this subset.

Conclusions: In this preliminary study, palonosetron and ondansetron in combination with dexamethasone had comparable antiemetic efficacy after LSG. Further studies can be conducted to find-out the role of preoperative GES as a tool to predict PONV.

Keywords: Laparoscopic sleeve gastrectomy, wound dehiscence, pulmonary aspiration, gastric emptying scintigraphy

Introduction

Morbidly obese patients undergoing laparoscopic bariatric surgery i.e. laparoscopic sleeve gastrectomy (LSG) pose considerable challenges to the anesthesiologist because of co-morbidities like hypertension, diabetes mellitus, stroke and obstructive sleep apnea.[1] Besides these, post-operative nausea and vomiting (PONV) is one of the most distressing experiences associated with laparoscopic abdominal surgeries (incidence; 54-92% if no prophylactic measure are taken).[2,3] Over the last few years, several studies have laid an emphasis on the efficacy of a balanced antiemetic approach, involving drugs acting at different sites and receptors.[4-6] Previously, benefits of combination antiemetic therapy with ondensetron and dexamethasone have been highlighted in laparoscopic gastroplasties.[6] However, the antiemetic efficacy of a combination of palonosetron hydrochloride and dexamethasone in laparoscopic sleeve gastrectomies has not been previously evaluated. We hypothesized that palonosetron with dexamethasone provide better control of PONV as longer duration of antiemetic action than ondansetron with dexamethasone combination in morbidly obese patients undergoing laparoscopic sleeve gastrectomy using a desflurane based anesthetic and stroke volume variation (SVV) guided fluid management.

Materials and Method

The prospective, double blind randomized study was conducted from July 2011 to December 2012 on 24 morbidly obese patients admitted in endocrinology ward, at tertiary level hospital. The study was approved by institutional ethical committee under NK/965/MD. Participants were morbid obese adults (BMI > 32.5), either gender, 20-60 years, ASA physical status II or III planned for laparoscopic sleeve gastrectomy under general anaesthesia after appropriate evaluation. Risk-estimation for PONV was estimated by using Apfel-scoring in all the patients.[7] Gastric Emptying Scintigraphy (GES) was also done to rule out gastroperesis. GES is analyzed by calculating the percent retention of gastric contents at the end of 2 hours and at the end of 4 hours. Normal values are <50% retention at 2 hours and <10% retention at 4 hours. Patients were instructed to nil per oral for 8 hours before surgery. Tablet ranitidine 150 mg orally was given to all the patients a night before surgery and two hours prior to surgery.

The patients were divided in a double blinded randomized manner into two groups using a computer generated randomization chart and sealed opaque

envelope technique. Patients received either palonosetron 1µg/kg lean body weight (LBW) (max 0.075 mg) and dexamethasone 0.1 mg/kg LBW (max 8 mg) (group PD) or ondansetron 0.1 mg/kg LBW (max 8 mg) with dexamethasone 0.1 mg/kg LBW (max 8mg) (group OD) intravenously 30 min before induction.

Induction of anaesthesia was done with fentanyl 2µg/kg LBW and propofol 2-2.5 mg/kg LBW and succinylcholine 2 mg/kg was administered to facilitate endotracheal intubation. Muscle relaxation was maintained with intermittent bolus of vecuronium. Anaesthesia was maintained with a mixture of nitrous oxide (N_2O) with oxygen (50:50) and 4-6% desflurane by Datex-Ohmeda Aestiva/ 5 machine. A 20 gauge arterial cannula was inserted in the radial artery for invasive blood pressure monitoring and a double lumen central venous catheter was inserted in right internal jugular vein under guidance of ultrasound (5-10 MHz linear probe of Sonosite) using all aseptic precaution. Carbon dioxide (CO_2) was insufflated into the peritoneal cavity until the intra-abdominal pressure was 10-12 mm of Hg which was maintained throughout the surgery. Temperature was kept within normal limits by using appropriate warming devices.

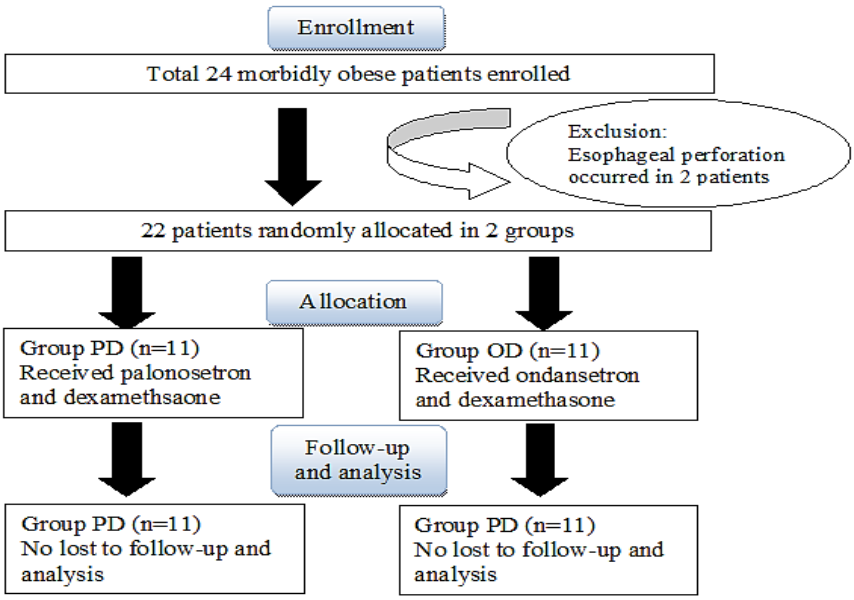
Intraoperative HR, SBP, DBP, MBP, SPO_2 and SVV were continuously monitored intra operatively till the end of surgery and HR, SBP, DBP, MBP at interval of 0, 1, 6, 12, 24, 48, 72 hours in the postoperative period. All the patients received Inj. Diclofenac 1-1.5 mg/kg at the end of the surgery. After reversal of neuromuscular blockade with Inj. neostigmine and glycopyrrolate patients were extubated on meeting the extubation criteria and shifted to PACU.

Postoperatively, all patients were followed up for episodes of PONV (nausea, retching and vomiting) for 72 hours after reversal of anaesthesia at interval of 0, 0-6, 6-12, 12- 24, 24- 48 and 48-72 hours. Inj. Metoclopramide 10 mg was used as rescue antiemetic for nausea VAS score >4 and vomiting episode. Inj. paracetamol 1 gm was used for postoperative pain when pain VAS score was >4. The total dose of rescue antiemetic and analgesic was recorded. Side effect of the study drugs were observed for 72 hours.

Statistical Analysis: The data was entered and statistically analyzed with M S Excel Spread Sheet and Statistical Package for Social Sciences (SPSS version 14. Reg). Mean & medians were calculated for all quantitative variables and for measures of dispersion (standard deviation and standard error). Normality of data was checked by measures of Kolmogorov Smirnov tests. For normally distributed data means were compared using unpaired t-test. For skewed data & scores, Mann –Whitney test was applied .To see difference between time related variables, Repeated Measure ANOVA Test was applied. Qualitative or categorical variables were described as frequencies and proportions. Proportions were compared by using Chi square or Fisher's exact test whichever was applicable. All statistical tests were two-sided and were performed at a significance level of α=.05.

Obeservations and Results

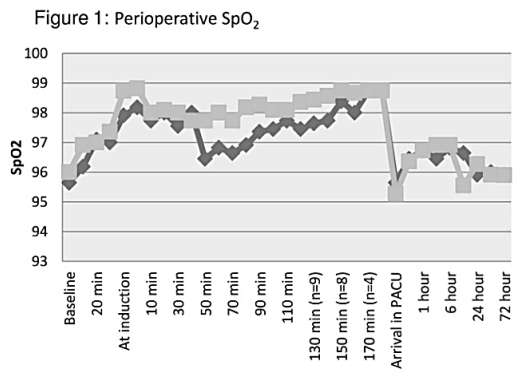
Twenty four ASA II & III patients were scheduled for LSG under GA met the inclusion criteria. Intraoperative surgical complication (esophageal perforation) occurred in two patients and this modified the subsequent management of these patients. So these two patients were excluded from the study. Therefore, data of 22 patients (11 in each) was statistically analysed.

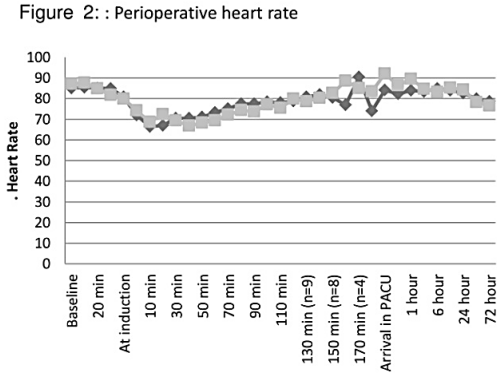


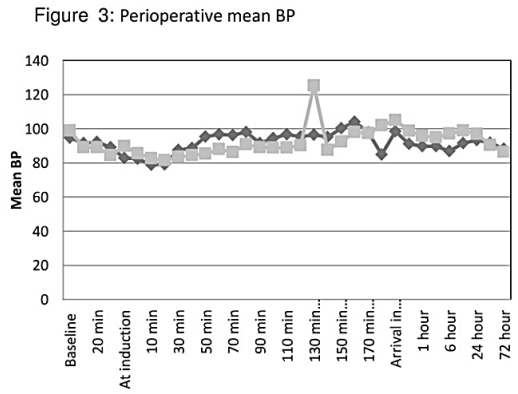
Consort chart: Enrollment, allocation, follow-up and analysis of 24 patients. Esophageal perforation occurred in 2 patients that lead to change in further management, so excluded.

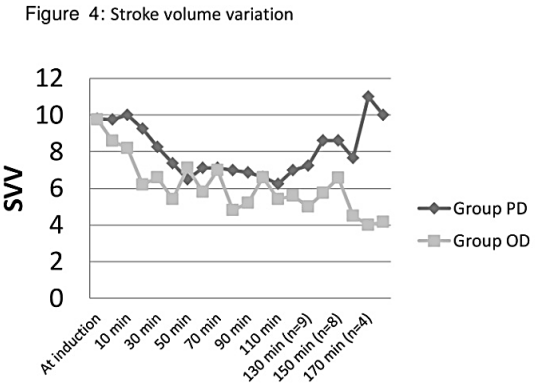
Demographic data were well matched (p>0.05) in both the groups. Both the groups did not differ with respect to duration of anaesthesia, surgery, CO_2 insufflation, total intravenous fluid used and intraoperative blood loss (p> 0.05; Table 1). Perioperative haemodynamic parameters i.e. arterial oxygen saturation, heart rate, blood pressure and SVV were not statistically different between the both groups (Fig. 1-4).

Image 1: Comparison of hemodynamic parameters between group PD (lighter block) and group OD (darker blocks) where Fig. 1 showed SpO_2, Fig. 2 showed heart rate, Fig. 3 showed mean BP and SVV in Fig. 4 were compared between both groups. Values expressed as mean ± SD. P value was >0.05, not considered as statistically significant different









The incidence of nausea was 18.2%, 9%, 27.3, 0%, and 54.6% in group PD between 0-6 h, 6-12 h, 12-24 h, 24-72 h and 0-72 h respectively. The incidence of nausea at the same intervals in group OD was 18.2%, 18.2%, 18.2%, 9.1%, and 63.6% respectively. The incidence of nausea was comparable between both the groups (P>0.05; Fig. 5). The incidence of vomiting was comparable in both the groups (p>0.05). At 0-6 h, 6-12 h, 12-24 h, 24-72 h and 0-72 h in group PD 9.1%, 9.1%, 0%, 0%, and 18.2% and in group OD 0% 0%, 9.1%, 9.1%, and 18.2% patients experienced vomiting (Fig. 6). No significant differences seen in complete response (CR) in group PD and OD (p>0.05). In time interval 0-6 h, 6-12 h, 12-24 h, 24-72 h and 0-72 h group PD, CR was 81.8%, 90.9%, 72.7%, 100% and 45.5% and in group OD 81.8%, 81.8%, 81.8%, 90.9% and 36.4% respectively (Fig. 7). The total dose of rescue antiemetic used was also not significant between both the groups. In 0-72 h, the mean dose of metoclopramide used was in group PD 10.00 mg and 11.67 mg in group OD (Fig. 8). The mean GES in 3 patients of Group PD was 80.54 min and 79.22 min in 5 patients of Group OD which was in normal range and comparable between both groups (p=0.952). Out of them, only one episode of vomiting in group PD and 2 patients in both the groups had nausea despite normal GES. The total dose of PCM (mean) administered was 2.63 gms in group PD as compared to group OD 2.45 (p = 0.576) and these values did not differ statistically. No significant adverse event related to study drugs were noted in any patient enrolled for the study.

Image 2: Incidence of nausea, vomiting and complete response was comparable among both the group (p>0.05) that showed in Fig. 5, 6, 7 respectively. Complete response indicates total control over PONV/ suppression of PONV. The total dose of rescue antiemetics were also comparable between both group (p>0.05) showed in Fig. 8.

Figure 5: Incidence of nausea

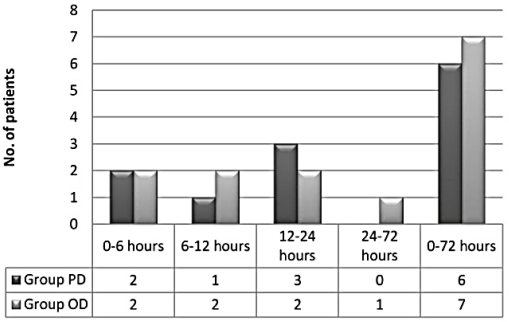


Figure 6 : Incidence of vomiting

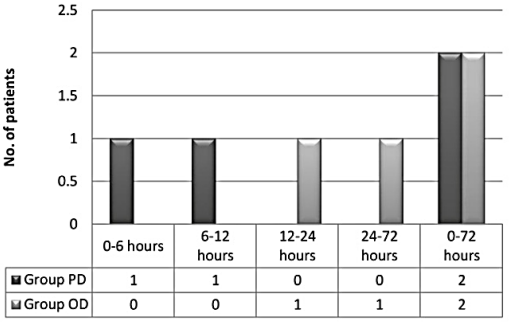


Figure 7 : Complete response

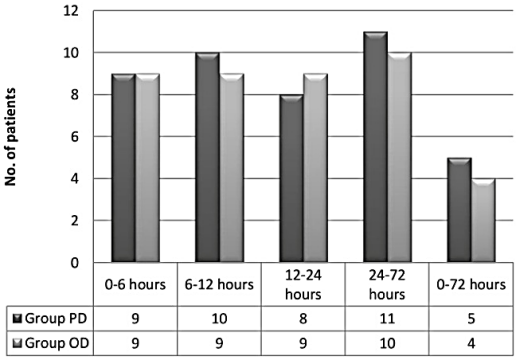


Figure 8: Rescue antiemetics

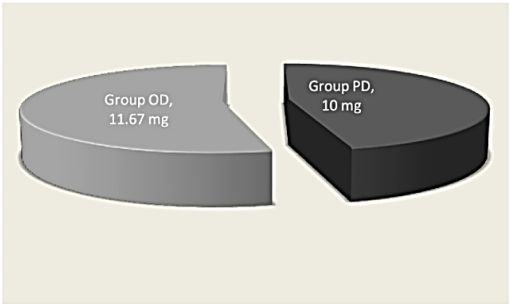


Table 1: Values expressed as mean± SD. P< 0.05 considered statistically significant. * = GES was done to rule-out gastroparesis in 3 patients of group PD and 5 patients of Group OD, GES time >240 minutes considered as gastroparesis. £= median (interquantile range), $= ratio, §= range, ¥= number (percentage)

	Group PD (n=11)	Group OD (n=11)	P value
Age (years)	45.27 ± 10.59	35.55 ± 12.62	0.064
Weight (kgs)	105.36 ± 26.07	117.18 ± 24.26	0.284
Height (cm)	153.74± 8.91	159.54 ± 8.01	0.124
BMI (kg/m^2)	44.61 ± 10.92	45.83 ± 7.98	0.769
LBW (kgs)[£]	52.53 (41.43-70.19)	59.54 (43.3-76)	0.139
Gender (M:F)[$]	1: 10	3:8	0.586
ASA status(II:III)[$]	9:2	11:0	0.476
Preop Gastric emptying scintigraphy (GES; min)*	80.54 ± 38.70	79.22 ± 22.61	0.952
Apfel-score[§]	1-3	1-3	1.000
Co-morbidities[¥]			
Diabetes mellitus	5 (45.5%)	4 (36.4%)	1.000
Hypertension	8 (72.7%)	5 (45.5%)	0.387
Hypothyroidism	5 (45.5%)	6 (54.6%)	1.000
Duration of anaesthesia (hours)	3.39 ± 0.330	3.36 ± 0.446	0.216
Duration of Surgery (hours)	2.16 ± 0.150	2.40 ± 0.49	0.144
CO_2 insufflation (hours)	1.65 ± 0.332	1.75 ± 0.42	0.524
Total I.V fluid (ml)	2245.45 ± 358.78	2072.73 ± 314.34	0.243
Blood loss (ml)	325.45 ± 107.36	299.09 ± 131.94	0.613

Discussion

In this study, 18.2% patients treated with 8 mg ondansetron (0.1mg/kg) and 8 mg dexamethasone (0.1mg/kg) experienced PONV during 0-6 hour time interval. In laparoscopic gastroplasties, Mendes et al[6] have also reported similar incidence of PONV (18.8%) in patients pre-treated with ondansetron (0.1mg/kg, max 8 mg) and dexamethasone (0.1mg/kg, max 10 mg) following 6 hours follow-up. In another study in laparoscopic bariatric surgery, Mausa et al[7] compared the incidence of PONV in patients treated with either granisetron 1 mg, granisetron plus droperidol 1.25mg and granisetron 1 mg plus dexamethasone 8 mg and placebo for 0-24 hour interval. Authors observed that only 20% patients treated with granisetron plus dexamethasone had PONV in 24 hour follow up period. The incidence of PONV was 54.5% in group PD and 63.6% in group OD (p=1.00) during 72 hour follow up in present study. This difference is probably because most of the patients enrolled in present study were females with high emetogenic potential and longer follow-up time.

The nausea intensity and vomiting episode was evaluated in 3 groups: group HDO (haloperidol 2mg, dexamethasone 8 mg, ondansetron 8 mg), group OD (ondansetron 8mg, dexamethasone 8 mg) and group O (ondansetron 8 mg) in 90 patients (30 each group) underwent laparoscopic sleeve gastrectomy during 36 hours follow- up. The authors reported lower nausea intensity in group HDO compare with group O and similar episode of vomiting among groups.[22] In another study, PONV episodes were evaluated in 117 patients underwent laparoscopic sleeve gastrectomy with propofol and remifentanyl based anaesthesia. The authors observed similar PONV episode in 45 patients (34-60%) received either ondansetron 4 mg with dexamethasone 4 mg and 54 patients (41-67%) did not received antiemetic prophylaxis during 24 hours follow-up.[23]

The 5-HT_3 antagonists are popular prophylactic drugs for PONV and are considered to be the first line agents in high risk patients. Complex antagonism with 5-HT_3 receptor at these sites can block the interaction of vomiting reflex caused by emetogenic stimuli.[24] Ondansetron was the first 5-HT_3 antagonist to become commercially available for PONV and has been followed by many others including granisetron, dolasetron, tropisetron, ramosetron, azasetron and palonosetron. The optimal effective dose of ondansetron was found to be 8 mg orally administered 1 to 2 hours before anaesthesia or 4mg intravenously at the end of anaesthesia. It has a relatively short half-life of 3-5 hours and under goes extensive metabolism in liver. Five percent is excreted unchanged in urine.[24,25] Palonosetron, a second generation 5-HT_3 receptor antagonist is an established antiemetic drug for chemotherapy induced emesis.[9] It has also been used successfully to prevent PONV. It is effective for prophylaxis against both acute and delayed emesis. FDA approved its use for prevention of PONV in 2008.[10] Far higher receptor affinity and a much longer half-life (40h) than other 5-HT_3 antagonists confer a prolonged duration of action.[26]

Dexamethasone, a corticosteroid has emerged as potentially useful prophylaxis for PONV even as a sole agent.[2,7] It has strong anti-inflammatory actions and may significantly reduce tissue inflammation around surgical sites and thus reduce the ascending parasympathetic impulses (e.g. vagus) to the vomiting center and reduce PONV. Addition of dexamethasone to 5-HT_3 antagonists as a part of multimodal approach has been shown to decrease PONV symptoms when compared with the use of 5-HT_3 antagonists alone after laparoscopic bariatric surgeries.[6,8]

A variety of factors including age, female gender, previous history of PONV, smoking, high doses of neostigmine for the reversal of neuromuscular blockade, duration and type of surgery e.g. laparoscopic surgery, anaesthetic technique and postoperative pain are considered to affect the incidence of PONV. The use of opioids for intraoperative pain is also associated with an increased incidence of PONV.[3,11-13] In the present study, all these factors were well balanced among the groups. All the patients of both groups received fentanyl 2 µg/kg LBW intravenously for analgesia. In the present study, palonosetron was used in the dose of 1µg/kg LBW, max 0.075 mg which has been found to be the minimum effective dose evaluated in previous 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 mg.[2,16] We choose dexamethasone 8 mg to be administered for prevention of PONV in our study.

Patients with delayed gastric emptying secondary to an underlying disease like diabetes mellitus, gastrointestinal obstruction, hypothyroidism, uraemia, neuromuscular disorders, increased intra-abdominal pressure and pregnancy may be at increased risk for emesis after surgery. Premedication with for example, opioids and barbiturates, given to allay preoperative anxiety may also delay gastric emptying thereby predisposing to PONV.[13,17] GES was done using nuclear scan technology. The gastric emptying was measured after eating food containing radioactive substance for a period of 4 hours. GES assessed in 3 patients of Group PD and in 5 patients of Group OD was normal and well matched between both groups.

In this study, intraoperative fluid administration was given according to guidance of stroke volume variation (SVV) that was measured by Flowtrac that was attached to arterial line. The trigger for fluid administration in the study was SVV more than 10% and a bolus of 100 ml was given. In a previous study, the effect of intra-operative fluid replacement on PONV in patient undergoing laparoscopic gastric bypass

surgery was observed and the authors found that there was a significantly higher incidence of PONV in patients who received smaller volume of intravenous fluid intraoperatively.[27]

However in patients undergoing laparoscopic surgeries various anaesthesia and surgery related complications has been reported following the use of new generation $5HT_3$ antagonist include anaphylaxis, migraine type headache, seizure and CO_2 embolism.[18-21] None of these complication were observed in any of our participant. However, esophageal perforation occurred in 2 patients who required surgical repair and subsequent management in ICU.

Enumerating limitations of our study, the number of patient analysed were only 22 (11 in each) and 2 patients were excluded due to esophageal perforation. We did not include a placebo group as patients undergoing laparoscopic gastroplasties are considered a high risk patient population for PONV[6,8] and it is unethical to withhold prophylactic antiemetic therapy in these patients.

Conclusion

A complete relief from PONV was not obtained with either of study drugs. Though the difference was not statistically significant, palonosetron-dexamethasone group provided better control of PONV during 72 postoperative hours follow-up after laparoscopic sleeve gastrectomy under general anaesthesia.

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