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# Palonosetron versus Ondansetron as Prophylaxis against Postoperative Nausea and Vomiting (PONV) after Laparoscopic Sleeve Gastrectomy: A Randomized Controlled Trial

**Ayman A. Elrashidy[1], Mohamed Elsherif[2*], Wahiba Elhag[2], Omar Abdelaziem[3], Sherif Abdelaziem[4,5], Reda Sobhi Abdel-Rahman[1]**

[1]Anesthesia Department, Faculty of Medicine, Tanta University, Tanta, Egypt
[2]Bariatric and Metabolic Surgery Department, Hamad Medical Corporation, Doha, Qatar
[3]Faculty of Medicine, Qatar University, Doha, Qatar
[4]Surgery Department, Faculty of Medicine, Tanta University, Tanta, Egypt
[5]Surgery Department, Hamad Medical Corporation, Doha, Qatar

Email: Elrashidy66@hotmail.com, *drmlll.endocrine@gmail.com, Hibahamid@hotmail.com, Omoustafa@hamad.qa, Saziem@hotmail.com

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## Abstract

**Introduction:** Postoperative nausea and vomiting (PONV) are prevalent symptoms after laparoscopic surgeries with an incidence rate of (54% - 79%) in bariatric procedures. Despite its popularity, limited studies assessed the effect of antiemetics for PONV prophylaxis after laparoscopic sleeve gastrectomy (LSG). The aim of this trail is to compare the effectiveness of a single pre-induction intravenous dose of Palonosetron versus Ondansetron for prophylaxis of PONV, 24 hours after LSG. **Subjects and Methods:** This prospective randomized controlled double-blind parallel-group study was conducted from May till December 2019. Recruited patients were consented and randomized using a closed envelop method into two groups with fifty patients each. The total number of nausea and vomiting attacks in the 24 hours postoperatively was considered as a primary end point. The secondary end points were the frequency of nausea, retching and vomiting attacks in the 24 hours post-surgery. The severity of nausea was evaluated using a 10 cm visual analogue scale (VAS). **Results:** This RCT included 100 patients divided into 2 groups of 50 patients each. Patients received either 75 mcg Palonosetron (Group I) or Ondansetron 4 mg (group II). Group I had statistically significant fewer episodes of nausea, retching and vomiting in the first 4 hours (P = 0.022) and from 4 to 12 hours (P = 0.024) but not after 12 hours post LSG. Total episodes of nausea, retching and vomiting in 24 hours postoperative

were significantly less in group I (P = 0.021). **Conclusion:** A single dose of intravenous 75 mcg Palonosetron is superior to Ondansetron 4 mg in preventing PONV for patients after LSG.

## Keywords

Palonosetron, Ondansetron, Postoperative Nausea and Vomiting, PONV, Retching Laparoscopic Sleeve Gastrectomy, LSG, Bariatric Surgery

## 1. Introduction

Nausea and vomiting represented one of the most prevalent symptoms occurring after laparoscopic surgery especially among morbidly obese patients undergoing bariatric surgery with an incidence rate of (54% - 79%) [1] [2]. It is a major concern in the recovery period as it can result in many complications such as electrolyte abnormalities, dehydration, and aspiration of gastric content which may all lead to prolonging the hospital length of stay and delaying discharge. Several factors may contribute to higher incidence and intensity of postoperative nausea and vomiting (PONV) including younger age, female patients, the use of volatile anesthetics, postoperative use of opioids, a history of PONV or motion sickness and smoking [2]. In attempts to minimize the incidence of PONV, various antiemetic drugs can be used with variable response and efficacy [3]. One of these anti-emetics is the selective, five hydroxyl heptamine 3 receptor antagonists ($5HT_3$) which act both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the brain stem to prevent vomiting [4] [5]. Among them, Palonosetron is the second-generation ($5HT_3$) receptor antagonist that possesses a higher binding affinity and longer half-life compared to older generations of ($5HT_3$) Ondansetron (40 hours vs, 3.5 - 5.5 hours) respectively [6] [7]. Therefore, studies had shown that it may be more effective than ondansetron against nausea and vomiting in patients using chemotherapy [8].

Studies assessed the effect of antiemetic medications for prophylaxis of nausea and vomiting after bariatric surgery are limited [2]. Moreover few studies compared antiemetic medication for prophylaxis of PONV after laparoscopic sleeve gastrectomy (LSG), despite the popularity of LSG procedures and lack of standardized protocolto effectively manage PONV [9]. To the best of our knowledge, there areno randomized controlled trials (RCT) compared the effects of Ondansetron with the second generation Palonosetron.

Type of surgery, patient characteristics, anesthesia technique and postoperative care are all factors that can contribute to the occurrence and intensity of postoperative nausea and vomiting [10].

Palonosetron has an average duration of action between 24 to 48 hours after a single intravenous dose administration. This could be explained by its relatively long half-life of about 40 hours [11].

Laparoscopic sleeve gastrectomy (LSG) has been described as a first-stage operation before more complex procedures. Postoperative nausea and vomiting (PONV) are relevant complications after bariatric surgery, appearing more frequently after sleeve gastrectomy, secondary to a drastic reduction in the gastric volume. However, other causes can be identified including anesthetic drugs used, incorrect protocols for prophylaxis of nausea and vomiting, or even several surgical details [11].

Therefore, the aim of the current RCT is to compare the effectiveness of a single pre-induction intravenous dose of Palonosetron versus a single pre-induction of intravenous Ondansetron for prophylaxis of PONV during the first 24 hours after laparoscopic Sleeve gastrectomy.

## 2. Subjects and Methods

### 2.1. Trial Design

This is a prospective randomized controlled double-blind parallel-group study. This trail was conducted in Tanta University Hospital, Tanta, Egyptin the period from May 2019 till December 2019. Ethical approval for the current study was obtained from Tanta University Hospital committee and patients were consented for participation in the study. Recruited patients were consented and randomized into two groupsusing a closed envelop method for randomization with fifty patients in each group.

### 2.2. Participants

Patient ages ranged from 22 to 50 years old with ASA (American Society of Anesthesiologists) physical status of I or II undergoing laparoscopic sleeve gastrectomy (LSG) under general anesthesia were included in the current trial.

All patients received information about the study during the preoperative evaluation session and were able to contact the investigators if they had any questions. Written consent was then given when the patients arrived at the hospital.

Patients were excluded from the study if they use any other type of anti-emetic medication, Corticosteroids, or psychoactive drugs in the last 24 hours prior to the surgery date, had vomiting or retching in the last 24 hours before surgery, diagnosed with any gastrointestinal tract (GIT) disease associated with vomiting, had hypersensitivity to the study medications and had alcohol or substance abuse.

### 2.3. Pre-Anesthesia and Anesthetic Management

The preoperative assessment was done one to three days prior to surgery including general and systemic clinical examination; patients were informed about the anesthesia technique.

Patients were put on NPO (Nil Per Oss) for 8 hours prior to surgery time.

The pre-anesthesia regimen, anesthesia procedure, and LSG technique were standardized for all patients.

In the operative room, basal heart rate (HR), mean arterial pressure (MAP), peripheral capillary oxygen saturation ($SPO_2$), electrocardiogram (ECG), capnography ($PCO_2$) were recorded.

A cannula of suitable size was inserted for anesthesia and fluid administration. Just before anesthesia induction, patients received either Palonosetron 75 mcg intravenous or Ondansetron 4 mg intravenous as per the randomization process.

Patients received intravenous fluids at a volume of 10 - 15 mL/kg total body weight (TBW). Oxygenation using a face mask for 3 minutes was used prior to the induction of anesthesia. Anesthesia was induced using midazolam (0.05 - 0.15 mg/kg TBW). All patients received Fentanil (1 - 2 μg/kg lean body weight (LBW), and propofol (1.5 - 2 mg/kg ideal body weight was given plus rocuronium (1.2 mg/kg IBW) to facilitate endotracheal intubation.

Anesthesia was then maintained using sevoflurane inhalation (1% - 2%) and continuous infusion of remifentanil (0.1 - 0.4 μg/kg/min LBW).

Ventilation was controlled and adjusted to keep endtidal partial pressure of $CO_2$ between 35 - 40 mm/Hg.

All patients were extubated using sugammadex 2 mg/kg IBW. All patients received Tramadol 100 mg intramuscular 15 minutes before the end of surgery and postoperative analgesia using patient-controlled fentanyl 2 mcg/kg intravenous.

Patients were transferred fully awake to PACU (Post Anesthesia Care Unit) where the following symptoms were monitored for episodes of nausea, retching (involuntary attempt to vomit without expulsion of gastric content), and Vomiting (actual expulsion of gastric content).

## 2.4. Surgical Technique

$CO_2$ pneumoperitoneum 18 mmHg was created by open technique througha supraumbilical incision. Additional dilating trocars were introduced under vision.

Inspection of the abdominal cavity to explore any gross pathology. The gastro-splenic ligament was divided along the greater curvature 4 cm from the pylorus up to left diaphragmatic crus with ultrasonic shears. Left crus and angle of His were freed from attachments. The stomach was divided along the lesser curvature from antrum up to the angle of His with buttressed (SeamGuard) linear stapler 60 mm (COV-Black-Purple-Tun//ECH-Black-Green-Gold-Blue) over the bougie/calibration tube (38, 40Fr) introduced into the stomach.

Fat pad staple line reinforcement at the angle of His with PDS 3.0. Bougie was removed, antrum was cross clamped and leak test was performed with methylene blue through the oro-gastric tube to confirm that no leak noticed. Methylene blue was aspirated and the oro-gastric tube was removed. Hemostasis was secured. Operative site lavage was done. Resected stomach was removed. Ports greater than 10 mm were closed with Vicryl 0. Ports were removed under vision, the abdomen was desufflated. Wounds were closed with subcuticular Monocryl 4.0. Dressings were then applied. Counts were correct. The patient woke up in the OR and was transferred to the recovery room/PACO.

## 2.5. Primary and Secondary end Points

The total number of nausea and vomiting attacks in the 24 hours postoperatively was considered as a primary end point of the current study. The secondary end points were frequency of nausea, retching and vomiting attacks individually in the 24 hours post-surgery.

## 2.6. PONV Assessment

The severity of nausea was evaluated using a 10 cm visual analogue scale (VAS) [8] at three-time intervals along the postoperative 24 hours, from 0 - 4 hours, 4 - 12 hours and 12 - 24 hours after surgical procedure.

The VAS scale for nausea consisted of a 10 cm horizontal line starting with "no nausea" at the left end and "worst nausea" at the right end of the scale. The patient indicated the intensity of nausea experienced by moving a pointer on the scale. The distance between the left scale end and the point determined by the patient represented the severity of his nausea. This distance is measured in centimeters [12] (**Figure 1**).

During the preoperative visit, patients were familiarized with a 10 cm VAS scale which usually used for pain assessment.

Intravenous Metoclopramide was used as a rescue medication in a dose of 10 mg given if (VAS) scale is 5 cm or more.

## 2.7. Statistical Analysis

Calculation of sample size was done based on the estimation of 50 subjects would be required per each group in order to detect two-thirds reduction in the frequency of postoperative nausea and vomiting from the control treatment from 40% to 15% with 80% power and 5% probability of type I error. Data were captured on structured case report forms. Normally distributed numerical variables of both groups were compared using Student's t-test, or by Mann-Whitney U test, if otherwise. Fisher's exact test was used for intergroup comparison of categorical variables. Missing data were not imputed. All analyses were two-tailed. Statistically, significance implied if $p < 0.05$. The raw data were entered using Microsoft Excel Sheet and analyzed using SPSS software for windows, version 19.00.

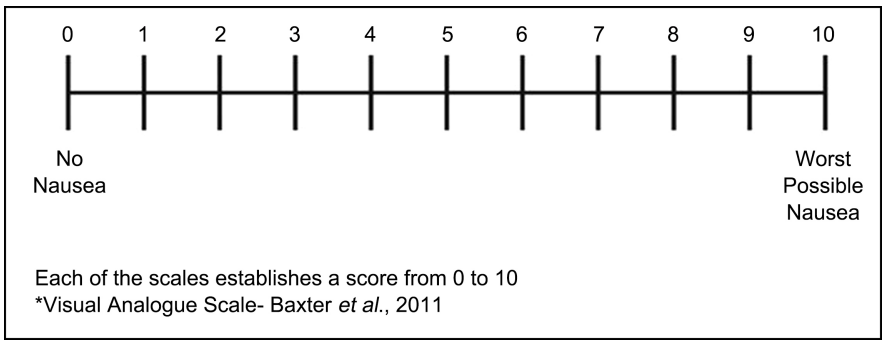


**Figure 1.** Visual Analogue Scale (VAS).

## 3. Results

This randomized controlled study included a total of 100 patients divided into 2 comparable groups of 50 patients each. Patients were randomly assigned to receive either 75 mcg Palonosetron (Group I) or Ondansetron 4 mg (group II) as prophylaxis against postoperative nausea and vomiting (PONV). None of the recruited patients was excluded from the study.

Demographic data and surgery related characteristics were shown in Table 1. No statistically significant differences were found between both groups regarding age, gender, weight, body mass index, duration of surgery, duration of anesthesia and duration of insufflation.

Applying the VAS scale of nausea on the two groups showed that group I had statistically significant lower episodes of nausea, retching and vomiting in the first 4 hours and in the period from 4 to 12 hours post-surgical procedure compared to group II. No statistically significant difference was found after 12 hours of surgery. Total episodes of nausea, retching and vomiting in 24 hours postoperative were found to be significantly less in group I as shown in Figure 2.

Nausea attacks occurred in two patients (4%) from the Palonosetron group in the first 4 hours after laparoscopic sleeve gastrectomy, compared to nine patients (18%) in Ondansetron group. This difference was statistically significant with, P = 0.022. Two patients (4%) experienced nausea episodes in group I compared to eight patients (16%) in group II in the period from 4 to 12 hours postoperatively with a statistically significant difference, P = 0.024.

Table 2 showed that none of Palonosetron patients (group I) developed nausea from 12 to 24 hours after surgery, while only one patient (2%) in group II had nausea attacks in the same period of time, which is a statistically non-significant difference. P = 0.88. Total nausea episodes in 24 hours were significantly lower in group I compared to group II with 8% and 36% respectively, P = 0.021.

**Table 1.** Demographic data and surgery related parameters.

| | Group I<br>Mean (range) | Group II<br>Mean (range) | P value |
|---|---|---|---|
| Age (years) | 42 (22 - 50) | 44 (22 - 50) | 0.64 |
| Gender | | | 0.93 |
| Male | 14 (28%) | 11 (22%) | |
| Female | 36 (72%) | 39 (78%) | |
| Weight (Kg) | 92 (79 - 157) | 98 (84 - 164) | 0.51 |
| BMI ($Kg/m^2$) | 46 (35.4 - 55.6) | 41 (36 - 56.8) | 0.79 |
| Duration of anesthesia (min) | 77 (65 - 90) | 73 (60 - 94) | 0.12 |
| Duration of Surgery (min) | 44 (38 - 71) | 47 (38 - 76) | 0.82 |
| Duration of insufflation (min) | 30 (24 - 64) | 31 (22 - 56) | 0.88 |

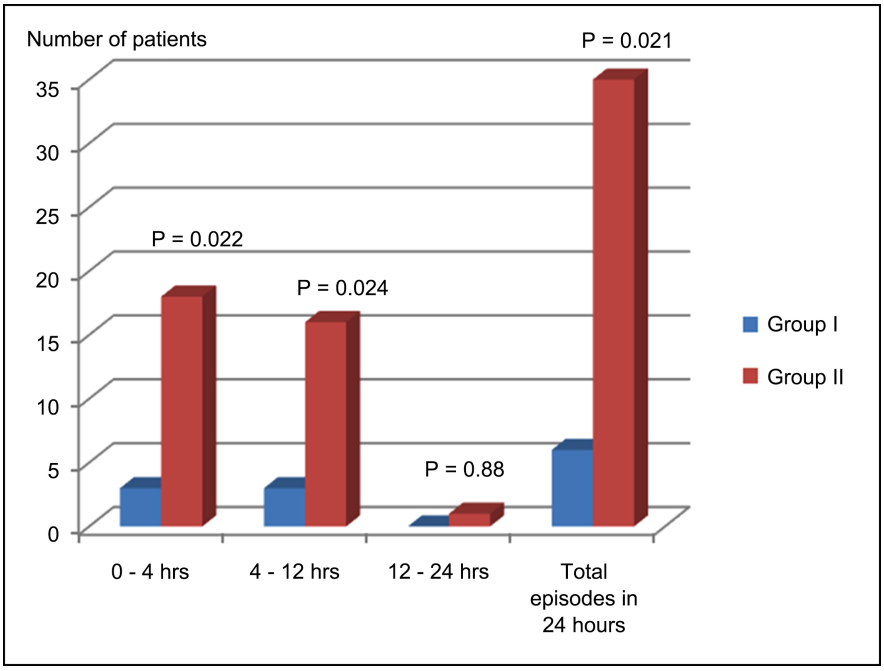


**Figure 2.** Incidence of nausea, retching, and vomiting in both groups.

**Table 2.** Incidence of nausea in both groups.

| Time in hours | Group I | Group II | P value |
|---|---|---|---|
| 0 - 4 | 2 (4%) | 9 (18%) | 0.022* |
| 4 - 12 | 2 (4%) | 8 (16%) | 0.024* |
| 12 - 24 | 0 (0%) | 1 (2%) | 0.88 |
| Total episodes in 24 hours | 4 (8%) | 18 (36%) | 0.021* |

The P value is from intergroup comparison by Man Whitney U test; *Indicates a significant P value.

None of Palonosetron patients (group I) developed retching episodes in the first 4 hours after LSG, compared to two patients (4%) in the Ondansetron group (group II). This difference was statistically significant with, P = 0.032. Only one patient (2%) experienced retching episodes in group I compared to five patients (10%) in group II in the period from 4 to 12 hours postoperatively with a statistically significant difference, P = 0.026. in the first 24 hours after surgery, only one patient (2%) experienced retching attacks in the Palonosetron group, compared to seven patients (14%) in the Ondansetron group with a statistically significant difference, P = 0.019. as shown in Table 3.

Vomiting episodes were significantly higher in group II compared to group I in the first four hours after surgery, P = 0.018 as well as from 4 - 12 hours postoperatively with P = 0.026 as shown in Table 4. Total episodes of vomiting in 24 hours after surgery were significantly higher in the Ondansetron group compared to the Palonosetron group, p = 0.012. However, from 12 - 24 hours after surgery none of the patients developed vomiting in both groups.

**Table 3.** Incidence of retching in both groups.

| Time in hours | Group I | Group II | P value |
|---|---|---|---|
| 0 - 4 | 0 (0%) | 2 (4%) | 0.032* |
| 4 - 12 | 1 (2%) | 5 (10%) | 0.026* |
| 12 - 24 | 0 (0%) | 0 (0%) | 0.94 |
| Total episodes in 24 hours | 1 (2%) | 7 (14%) | 0.019* |

The P value is from intergroup comparison by Man Whitney U test; *Indicates a significant P value.

**Table 4.** Incidence of vomiting in both groups.

| Time in hours | Group I | Group II | P value |
|---|---|---|---|
| 0 - 4 | 1 (2%) | 7 (14%) | 0.018* |
| 4 - 12 | 0 (0%) | 3 (6%) | 0.026* |
| 12 - 24 | 0 (0%) | 0 (0%) | 0.95 |
| Total episodes in 24 hours | 1 (2%) | 10 (20%) | 0.012* |

The P value is from intergroup comparison by Man Whitney U test; *Indicates a significant P value.

## 4. Discussion

Several factors can affect the incidence of postoperative nausea and vomiting including type and duration of surgical procedure, type and dose of anesthetic medication used, and analgesia used for postoperative pain control [13].

Vomiting reflex originated mainly from the central stimulation of $5HT_3$ receptors (located in the medullary chemoreceptor trigger zone) triggered by anesthetic medication. Moreover, releasing serotonin from enterochromaffin cells of the small intestine and vagal $5HT_3$ receptor stimulation will augment the vomiting reflex [14].

High incidence of PONV after laparoscopic procedures is attributed to a variety of factors including age, stage of obesity, history of previous PONV, smoking, surgical procedure, anesthesia technique, and degree of postoperative pain [15].

PONV are relevant complications after bariatric surgery, appearing more frequently after restrictive procedures, such as sleeve gastrectomy, secondary to a drastic reduction in the gastric volume [16].

In the current study, we standardized demographic data, type and duration of surgical procedure, anesthesia regimen, antibiotics used, and analgesic medication in the postoperative period. Thus, we proposed that any postoperative difference in nausea and vomiting episodes are attributed to the studied antiemetic medication used.

Ondansetron is considered the standard treatment to control PONV. Its mechanism of action is through competitive inhibition of $5HT_3$ receptors located centrally in the chemoreceptor trigger zone with its projections to the vomiting

center located in the lateral reticular formation in the medulla oblongata and peripherally in the vagus nerve terminals of the gut. This competitive inhibitory action of ondansetron can prevent emetogenic stimuli from triggering the vomiting reflex [17] [18].

Palonosetron is a novel $5HT_3$ receptor antagonist, initially approved for preventingnausea and vomiting induced by chemotherapy in cancer patients.

Rojas C *et al.*, had demonstrated a higher binding affinity and longer biological half-life of Palonosetron when compared to older generations of $5HT_3$ receptor antagonists. The primary mechanism of action of Palonosetron in the prevention of PONV is probably similar to ondansetron and the difference between them could originate from different pharmacokinetics and pharmacodynamics as well as receptor binding property of the drug [19].

In our study, we used Ondansetron and Palonosetron for PONV prophylaxis as a single intravenous dose given prior to induction of anesthesia. Ondansetron dose used was 4 mg which lies within its known effective dose range [20], while for Palonosetron, the authors had decided to use 75 mcg based on the previous experience reported by Kovac and coolings, who recommended the dose of 75 mcg Palonosetron as more effective than 25 and 50 mcg in preventing nausea and vomiting in gynecological and laparoscopic surgeries [21].

The authors were unable to include a placebo control group in this study as it is unethical to let the patients untreated and suffer the distressing symptoms of PONV when a proven effective medication is available [22].

In the current study, the incidence of PONV was found to be significantly higher in the Ondansetron group when compared to Palonosetron in the first 12 hours postoperatively (0.12% versus 68% respectively). While after 12 hours of operation, both groups showed no significant difference in terms of PONV incidence. This could demonstrate the higher efficacy of palonosetron over ondansetron in preventing the early postoperative nausea and vomiting.

Ondansetron and Palonosetron were equally effective between 12 and 24 hours postoperatively as none of the patients in both groups had developed either retching or vomiting.

These results came in agreement with Fogie *et al.* who reported a higher frequency of PONV on ondansetron patients in the first 6 hours after surgery [23]. Similar findings were demonstrated by Lopez Rolanto *et al.*, supporting the higher efficacy of Palonosetron over traditional ondansetron in controlling early PONV [24].

On the other hand, Baisakhi Laha *et al.* suggested that the anti-emetic efficacy of Palonosetron is comparable to that of Ondansetron for preventing PONV in the first 24 hours after laparoscopic cholecystectomy, and he concluded that the difference in half-lives (Ondansetron 3.5 - 5.5 hours versus Palonosetron 40 hrs) and binding affinities to $5HT_3$ receptors of Palonosetron explained the superiority of its anti-emetic effect over ondansetron [25]. Such diversity could be explained by the variance of Ondansetron doses used, as Baisakhiused 8 mg On-

dansetron which is double the dose we used in the current study.

Other published articles studied Palonosetron in PONV prophylaxis supported our findings, where Van den Bosch JE, found superior efficacy of Palonosetron over ondansetron for patients after thyroidectomy in the 2 - 12 hours period following surgery [22]. These various results could be explained by the diversity of patient characteristics; duration of surgery performed as well as the type of anesthesia medication used.

## 5. Conclusion

Palonosetron in a single dose of 75 mcg intravenous is superior to Ondansetron 4 mg in preventing PONV for patients after laparoscopic sleeve gastrectomy.

## Recommendation

Using Palonosetron in a single dose of 75 mcg intravenous is recommended for the prevention of PONV in laparoscopic sleeve gastrectomy. Further studies are advised to be conducted for different types of surgeries and patient characteristics.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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