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To Compare the Anti-emetic Efficacy, Duration of Action, and Side Effects of Palonosetron, Ondansetron, and Granisetron for Anti-emetic Prophylaxis of Post-operative Nausea and Vomiting in Patients Undergoing Laparoscopic Abdominal Surgeries

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Abstract

Aims and Objectives: The aim of the study was to compare the anti-emetic efficacy, duration of action, and side effects of Palonosetron, Ondansetron, and Granisetron for anti-emetic prophylaxis of post-operative nausea and vomiting. *Methodology:* We conducted a prospective, randomized, double blind study on patients undergoing laparoscopic abdominal surgeries. The total 120 patients were divided into three groups of 40 patients. Patients of group A were given injection palonosetron (0.075 mg), group B were given injection ondansetron (4 mg), and group C were given injection granisetron (1 mg), intravenously along with premedication, fifteen minutes prior to induction of general anaesthesia. We analyzed the anti-emetic efficacy, duration of action, and side effects of palonosetron, ondansetron, and granisetron. *Results:* Total incidence of nausea and vomiting was maximum in ondansetron group with total of 74 compared to 36 in granisetron and 12 in palonosetron group, considering overalapping data in all time intervals and this difference was found to be statistically major. In ondansetron group 18 patients had complete response, while complete response was higher in granisetron group (24) and highest with 28 patients in palonosetron group and this difference was statistically substantial. ($p < 0.05$). Headache and sedation was found in ondansetron group in 2 and 4 patients respectively while only 1 patient had headache in palonosetron group, 7 patients complained of headache in granisetron group. *Conclusion:* We conclude that palonosetron is more effective in comparison to granisetron and ondansetron in the prevention of PONV in patients undergoing elective abdominal laproscopic surgeries.

Keywords: Ondansetron; Granisetron and palonosetron' anti-emetic prophylaxis.

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Introduction

The incidence of PONV is 30–40% in a normal population with a topmost of 75–80 in some high-risk groups.[1] With the advent and usage of lesser emetogenic anaesthesia techniques and discovery of newer anti-emetogenic drugs for the post-operative nausea and vomiting prophylaxis, the

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prevalence of PONV has reduced significantly by about 50%.

Post-operative nausea and vomiting is by definition termed as nausea and vomiting which occurs within *24 hours* after surgery. Patient's clinical status, the form of surgical procedure, length of anaesthesia and surgery are few of the vital risk factors in determining of PONV. It involves three nerves and seven neurotransmitters for activation of vomiting centre, which makes the prophylaxis and treatment a tedious and complex process. Premedicating the patient with anti-emetics can reduce the rate of post-operative nausea and vomiting significantly. Various pharmacological agents, regimens, and practises were developed over a period of time, but they have restricted efficiency due to numerous side effects.[2]

Five-hydroxytryptamine subtype 3 (5-HT3) receptor antagonist are considered as one of the utmost effective anti-emetogenic agents with better safety and lesser side effects as they deprived of potential side effects of commonly used anti-emetogenic agents such as sedation, dysphoria and extra-pyramidal adverse effects.

The present study was a randomized double-blind, prospective study to compare the anti-emetic efficacy, duration of action, and side effects of intravenous palonosetron, ondansetron, and granisetron for anti-emetic prophylaxis of post-operative nausea and vomiting in patients undergoing elective laparoscopic abdominal surgeries under general anaesthesia.

Aims and Objectives

To compare the anti-emetic efficacy, duration of action, and side effects of intravenous-palonosetron, ondansetron, and granisetron for anti-emetic prophylaxis of post-operative nausea and vomiting in patients undergoing elective laparoscopic abdominal surgeries under general anaesthesia.

Materials and Methods

After approval by the Institutional Ethical Committee and taking written informed consent from the patient, 120 adult patients of American Society of Anesthesiologist physical status I and II, aged between *18* and *58 years* of either gender, posted for elective laparoscopic abdominal surgery under general anaesthesia from *Jan 2017* to *June 2018* in a tertiary care hospital were enrolled for current study. All the patients were undergo pre-anaesthetic assessment before enrollment.

The total 120 patients were correspondingly divided into three groups of 40 patients each according to a computer-generated random table. The study drug preparation was done by an assistant who was uninformed of our study protocol and it was done in identical 2.5 *ml* volume with normal saline to ensure blinding of the anaesthesiologist. The same was administered IV before induction of anaesthesia. The randomized process was blinded from the patients, the anaesthesiologist, and the investigators, who collected post-operative data. Patients of either sex *aged 18–55 years*, ASA I–II and posted for elective abdominal laparoscopic surgeries were included in the study. Patients with prior history of post-operative nausea and vomiting, complains of motion sickness in the past or at present. History of gastroeseophageal reflux disease, systemic hypertension, endocrine or metabolic disorders, hepatic or renal disease, cardio-pulmonary dysfunction, gastrointestinal disorders, psychiatric diseases, taken any anti-emetic *24 hours* former to the surgery and morbidly obese patients and pregnant females were excluded.

Thorough investigations include haemoglobin, complete blood count, bleeding time, clotting time, fasting blood sugar level, chest *x*-ray, urine routine and microscopic examination, serum creatinine, liver function tests.

Patients were randomly divided into three groups as described below:

Group 1	Patients receiving IV Ondansetron (4 mg)
Group 2	Patients receiving IV Granisetron (1 mg)
Group 3	Patients receiving IV Palonosetron (0.075 mg)

Informed consent of the patients were taken. All the patients were asked to fast overnight. All patients were given an anti-anxiety medication in the form of tab alprazolam 0.25 *mg* and an antacid in the form of tab ranitidine 150 *mg*, the night prior to surgery and were kept fasting for *six* to *eight hours* before the surgery. On arrival to operation-theatre, routine monitoring of heart rate, systemic arterial blood pressure, pulse oximetry (SpO_2), electrocardiogram (ECG) was initiated. After securing intravenous line, an infusion of Ringer lactate fluid was started. Patients were given premedication with intravenous midazolam (1 *mg*), fentanyl (2 µg kg^{-1}), and glycopyrrolate (0.2 *mg*) trailed by study medication according to our group allocation, fifteen minutes prior to induction of general anaesthesia.

After pre-oxygenation, induction was done with propofol (2 *mg* kg^{-1}), and tracheal intubation

was enabled with vecuronium bromide 0.08 $mgkg^{-1}$. Anaesthesia was maintained with isoflurane, N_2O (60%) in oxygen. All patients were ventilated mechanically to maintain an $EtCO_2$ between *35* and *40 mmHg*. Supplementary analgesia during the surgery was attained with fentanyl (25 µg). At the conclusion of surgery, the residual neuromuscular blockade was antagonized with suitable doses of neostigmine (0.05 $mgkg^{-1}$) and glycopyrrolate (0.01 $mgkg^{-1}$). Extubation was accomplished when the respiration was adequate and patient was able to obey simple commands.

The reference line systemic arterial blood pressure, pulse rate, and SpO_2 were recorded as a baseline parameter following premedication, after induction and then at *five min* intervals till one hour and then at every *15 min* till the end of surgery. They were watched for any hypotension, hypertension, arrhythmias, hypoxemia, and bronchial spasm. Hemodynamic variations occurring during study period were managed with volume expansion, vasopressor or atropine, if required.

Post-operatively, nausea or emetic episodes were documented by the resident doctors without the information of which group of anti-emetic drug was given to which of the patients. The side effects like headache, dizziness, and drowsiness were also noted. Post-operatively, patients were given intravenous injection of paracetamol (1 *gm*) for analgesia purpose.

Patients were asked about nausea and vomiting at *2, 4, 6,* and *12 hours* by direct questioning of the anaesthesiologist, blinded to which treatment the patient has received. Complete response was defined as no nausea, retching or vomiting and no need of rescue medication within *12 hours* in the post-operative period. At the end of each interval, an anaesthesiologist registered whether vomiting had occurred and asked the patients accordingly. Rescue medication in our study was metoclopramide 10 *mg* which was given intravenous if required.

Statistical Analysis

All the collected data was entered in Microsoft Excel sheet and then transferred to SPSS software ver. 17 for analysis. Qualitative data was presented as frequency and percentages and analyzed using chi-square test. Quantitative data was presented as mean and SD and comparison of variables in more than 2 groups was done by ANOVA test. p - value < 0.05 was taken as level of significance.

Results

All the three groups were comparable as far as age, weight and NPO (nil per oral) status was concerned. The three groups were also comparable for duration of anaesthesia and surgery, pre-operative pulse rate, systolic BP and diastolic BP were concerned ($p > 0.05$) (shown as in **Table 1**).

In ondansetron group 16 patients complained of nausea, 8 patients complained of nausea in granisetron group and 5 patients of palonosetron group in *0–4 hours*. 14 patients grieved from nausea in ondansetron and 6 patients in granisetron group suffered with nausea within same time frame and 2 patients in palonosetron group suffered nausea during *4–8 hour*. 11 patients suffered from nausea in ondansetron and 5 patients in granisetron group suffered with nausea within same time frame and 0 patients in palonosetron group suffered nausea during *8–12 hour*. There was statistically substantial difference in all three groups (shown as in **Table 2**).

In ondansetron group, a total of 13 patients complained of vomiting while 7 patients complained of vomiting in granisetron group and 4 patients of palonosetron group in *0–4 hours*. 11 patients grieved from vomiting in ondansetron

Table 1: General characteristics among the three groups

General characteristics	Ondansetron	Granisetron	Palonosetron	p - value
Age	33.88 + 13.1	32.16 + 9.1	31.13 + 8.8	0.499
Weight	51.7 + 5.1	51.10 + 4.2	50.2 + 3.7	0.307
NPO	11.2 + 0.7	10.9 + 0.5	11.1 + 0.7	0.107
Duration of surgery	59.17 + 16.7	58.6 + 16.1	57.2 + 15.5	0.85
Duration of anaesthesia	93.5 + 20.2	92.6 + 19.9	91.5 + 18.8	0.92
Pulse Rate (*min*)	86.1 + 3.1	85.1 + 3.2	84.8 + 3.3	0.16
Systolic BP (*mmHg*)	114 + 5.6	113 + 5.4	112 + 5.1	0.25
Diastolic BP (*mmHg*)	82.3 + 5.1	82.1 + 4.9	80.6 + 4.3	0.22

and 6 patients in granisetron group suffered with vomiting within same time frame and 1 patients in palonosetron group suffered vomiting during *4–8 hour*. 9 patients suffered from vomiting in ondansetron and 4 patients in granisetron group suffered with vomiting within same time frame and 0 patients in palonosetron group suffered vomiting during *8–12 hour*. There was statistically noteworthy variance in all three groups (shown in **Table 2**).

Total incidence of nausea and vomiting was maximum in ondansetron group with total of 29 compared to 15 in granisetron and 9 in palonosetron group and this difference was found to be statistically momentous during *0–4 hour*, total incidence of nausea and vomiting was maximum in ondansetron group with total of 25 compared to 12 in granisetron and 3 in palonosetron group and this difference was found to be statistically noteworthy during *4–8 hour*, total incidence of nausea and vomiting was maximum in ondansetron group with total of 20 compared to 9 in granisetron and 0 in palonosetron group and this variance was found to be statistically substantial during *8–12 hour* **(**shown as in **Table 3)**.

In ondansetron group, total 18 patients had complete response, while complete response was higher in granisetron group which were 24 and highest with 28 patients in palonosetron group and this difference was statistically noteworthy (p - 0.04) **(**shown in **Table 4)**, also (shown in **Fig. 1**).

Headache and sedation was found in ondansetron group in 2 and 4 patients respectively. While only 1 patient had headache in palonosetron group, 7 patients complained of headache in granisetron group (shown in **Fig. 2)**.

There was very less alteration in number of patients who needed rescue medication in all the three groups. Among three groups 7, 5 and 2 patients required rescue medication in ondansetron, granisetron and palonosetron group respectively.

Table 2: Number of patients with post-operative nausea (PON) and post-operative vomiting in different groups in study population.

	Time	Ondansetron	Granisetron	Palonosetron	p - value
Post-perative nausea	*0–4 hour*	16 (25%)	8 (20%)	5 (12.5%)	0.04
	4–8 hour	14 (15%)	6 (10%)	2 (10%)	0.002
	8–12 hour	11 (12.5%)	5 (5%)	0 (7.5%)	0.001
	Total	40 (100%)	40 (100%)	40 (100%)	
Post-operative vomiting	*0–4 hour*	13 (25%)	7 (20%)	4 (12.5%)	0.03
	4–8 hour	11 (15%)	6 (10%)	1 (10%)	0.007
	8–12 hour	9 (12.5%)	4 (5%)	0 (7.5%)	0.005
	Total	40 (100%)	40 (100%)	40 (100%)	

Table 3: Number of patients with total post-operative nausea and vomiting (TPNV) in different groups in study population.

Time	Ondansetron	Granisetron	Palonosetron	p - value
0–4 hour	29 (25%)	15 (20%)	9 (12.5%)	0.001
4–8 hour	25 (15%)	12 (10%)	3 (10%)	0.001
8–12 hour	20 (12.5%)	9 (5%)	0 (7.5%)	0.001
Total	40 (100%)	40 (100%)	40 (100%)	

Table 4: Number of patients with complete response (CR) *i.e.*, free from both nausea and vomiting throughout intra-operative and post-operative period.

Groups	TNV	CR	Total
Ondansetron	22 (55%)	18 (45%)	40 (100%)
Granisetron	16 (41%)	24 (59%)	40 (100%)
Palonosetron	12 (31%)	28 (69%)	40 (100%)

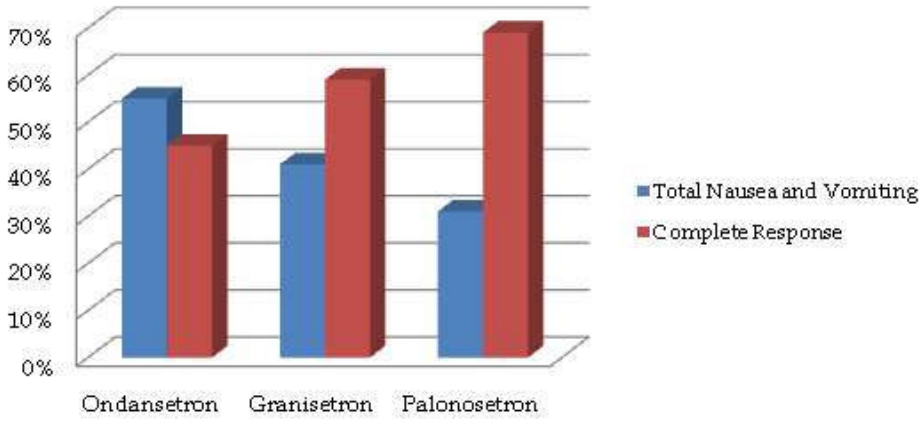

Fig. 1: Number of patients with complete response (CR) *i.e.*, free from both nausea and vomiting throughout intra-operative and post-operative period.

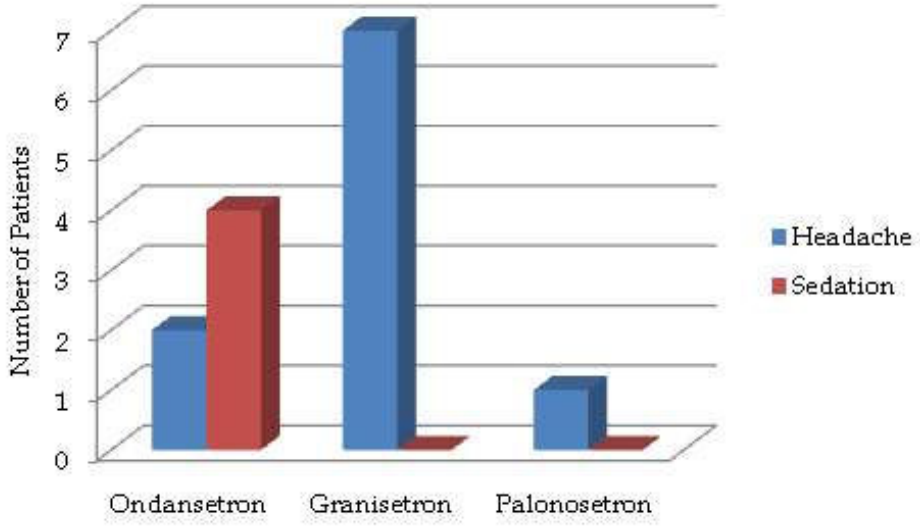

Fig. 2: Side effects experienced by number of patients in different groups

Discussion

The aetiology of the PONV is intricate and multifactorial. Pre-operative anxiety, positive pressure ventilation, inhalational anaesthetic agents, and nitrous oxide increase the jeopardy of PONV. Anaesthetic agents initiate the vomiting reflex by stimulating the central 5-HT3 receptors on the chemoreceptor trigger zone (CTZ). PONV is more common in younger age group and in obese patients.[3,4] Apfel *et al.*, 2004 considered laparoscopic surgery, female gender, non-smokers, a history of PONV, motion sickness, and post-operative opioid therapy as important independent causal factors for PONV.[5]

Anti-emetic drugs incline to have more noticeable action at one or two receptors while 5-HT3 receptor antagonists are highly specific and selective for its action against nausea and vomiting by binding to the serotonin 5-HT3 receptor in the chemoreceptor trigger zone (CTZ) and at vagal efferent in the gastrointestinal tracts.[6,7]

In the current study, as per the demographic data obtained the mean age of study population in ondansetron group was 33.88 + 13.1, granisetron group was 32.16 + 9.1 and in palonosetron group was 31.13 + 8.8 and there was no noteworthy variance between all groups. Obesity is usually seen to be associated with increased incidence of PONV. In our study the mean weight was 53.7 + 5.1 *kg*, 51.10 + 4.2 *kg*, 49.2 + 3.7 *kg* in ondansetron, granisetron and in palonosetron group and the episodes of PONV was non-pointedly higher in ondansetron, granisetron as compared to palonosetron.

The occurrence of PONV may be linked with many features including: Age and gender (female gender and younger age than adulthood increase the risk of PONV); previous history of motion sickness or PONV; smoking status (smoking decreases the risk of PONV); post-operative opioid use; nature and length of surgery; anaesthesia and ambulation.[8–10] In the current study, the mean duration of anesthesia and surgery were almost comparable with no substantial statistical variance in all three groups. In the study, directed by Sukhminderjit Singh Bajwa *et al.,* 2011, the mean duration of surgery in ondansetron group was 27.86 ± 4.68 and in palonosetron group was 29.24 ± 3.88 and the mean duration of anaesthesia in ondansetron group was 36.42 ± 2.58 and in palonosetron group was 38.26 ± 2.96.[7] In the current study, pre-operatively the mean pulse rate, SBP, DBP in all the groups showed no substantial alteration. This findings is in arrangement with the study directed by Neha Sharma *et al.,* there was no substantial changes in systolic and diastolic pressure among the groups of studied patients.[11]

In the current study, in ondansetron group, a total of 16 patients grieved of nausea, 8 patients complained of nausea in granisetron group and 5 patients of palonosetron group in *0–4 hours*. 14 patients grieved from nausea in ondansetron and 6 patients in granisetron group agonised with nausea within same time frame and 2 patients in palonosetron group agonized nausea during *4–8 hour*. 11 patients grieved from nausea in ondansetron and 5 patients in granisetron group agonized with nausea within same time frame and 0 patients in palonosetron group suffered nausea during *8–12 hour*. There was statistically noteworthy difference in all three groups. This findings is in contract with the study shown by Neha Sharma *et al.,* nausea was observed in 18 patients, 10 patients, 3 patients of ondansetron, granisetron and palonosetron group respectively and this difference was statistically momentous.[11]

Similarly in the study conducted by Kumkum Gupta *et al.,* 2014, 30% patients grieved from nausea in ondansetron group, 5% patients in palonosetron group within *0–4 hrs*. There was statistically substantial modification in all two groups.[12]

In the current study, in ondansetron group, a total of 13 patients complained of vomiting, 7 patients complained of vomiting in granisetron group and 4 patients of palonosetron group in *0–4 hours*. 11 patients grieved from vomiting in ondansetron and 6 patients in granisetron group grieved with vomiting within same time frame and 1 patients in palonosetron group agonized vomiting during *4–8 hour*. 9 patients suffered from vomiting in ondansetron and 4 patients in granisetron group agonized with vomiting within same time frame and 0 patients in palonosetron group grieved vomiting during *8–12 hour*. There was statistically noteworthy variance in all three groups. This findings is in arrangement with the study shown by Neha Sharma *et al.,* nausea was detected in 18 patients, 10 patients, 3 patients of ondansetron, granisetron and palonosetron group respectively and this difference was statistically substantial.[11] Similarly in the study, directed by Kumkum Gupta *et al.,* 2014, 25% patients agonized from vomiting in ondansetron group, 5% patients in palonosetron group within *0–4 hrs*. There was statistically momentous variance in all two groups.[12] Comparable findings were observed in the study led by Park *et al.,* 2011 in which palonosetron was superior to ondansetron for control of post-operative nausea and vomiting.[13]

In the current study, total occurrence of nausea and vomiting was maximum in ondansetron group with total of 29 compared to 15 in granisetron and 9 in palonosetron group and this difference was found to be statistically noteworthy during *0–2 hour*, total occurrence of nausea and vomiting was extreme in ondansetron group with total of 25 compared to 12 in granisetron and 3 in palonosetron group and this variance was found to be statistically momentous during *4–8 hour*. Total occurrence of nausea and vomiting was all-out in ondansetron group with total of 20 compared to 9 in granisetron and 0 in palonosetron group and this transformation was found to be statistically important during *8–12 hour*.

In the current study, in ondansetron group 18 patients had complete response, while complete response was higher in granisetron group (24) and highest with 28 patients in palonosetron group and this difference was statistically significant. ($p < 0.05$). This findings is in arrangement with the study directed by Neha Sharma *et al.,* palonosetron was linked with greater patients gratification than granisetron and ondansetron 69%, 59% and 45% of patients, respectively ($p = 0.032$) and this modification was found to be statistically unimportant.[11] Palonosteron was further more effective at dropping PONV rates than granisetron and ondansetron. This could reflect the high receptor affinity of palonosetron for 5-HT3, with a low affinity established for other receptors including 5-HT1A, 5-HT1D, 5-HT2A and 5-HT2C, and the longer duration of action.[14,15] Palonosetron was superior to ondansetron in reducing overall PONV.[16]

In the current study, headache and sedation was observed in ondansetron group in 2 and 4 patients respectively. While only 1 patient had headache in palonosetron group, 7 patients complained of headache in granisetron group. Likewise in the study directed by Park *et al.*, 2011 in which headache was observed in 8.9% and 6.7% while dizziness was present in 11.1% and 11.1% of ondansetron and palonosetron group correspondingly (though statistically not noteworthy).[13]

In the current study, there was very less variance in number of patients who required rescue medication in all the three groups. Metoclopramide was used as our rescue medication. It is a "prokinetic drug" that stimulates the muscles of GIT counting muscles of lower esophageal sphincter, stomach, and small intestine by networking with receptors for acetylcholine and dopamine on gastrointestinal muscles and nerves. It reduced the reflux of gastric acid by strengthening the muscles of lower esophageal sphincter. Amongst three groups 7, 5 and 2 patients needed rescue medication in ondansetron,granisetron and palonosetron group individually. This findings is in covenant with the study shown by Neha Sharma *et al.*, in which need for additional rescue anti-emetic medication was required in 13.3% of patients with palonosetron, 30.0% with granisetron and 46.7% with ondansetron (p = 0.02) in this study.[11] Likewise in the study shown by Park *et al.*, in which rescue medication in was used in 15.6% and 17.8% of palonosetron and ondensetron group correspondingly though statistically not important.[13]

Both palonosetron and granisetron are 5-HT3 antagonists; however, palonosetron has a superior binding affinity and a lengthier biological half-life when matched to older 5-HT3 antagonists such as granisetron and interrelates with 5-HT3 receptors in an allosteric, positively co-operative manner at other sites, leading to long-lasting effects on receptor ligand binding and functional responses.[17,18] This could be the reason for the improved control of late onset PONV (nausea 2–48 h, p = 0.037) in the palonosetron group compared to the granisetron group even though the findings of the two drugs were almost analogous in early onset PONV.

Conclusion

Palonosetron is more effective in comparison to granisetron and ondansetron in the prevention of post-operative nausea and vomiting in patients undergoing elective abdominal laproscopic surgeries. Ondansetron, granisetron and palonosetron were comparable in the prevention of early PONV, but palonosetron was much more operational in the prevention of delayed PONV according to our study.

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