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Comparative study of palonosetron and ondansetron in prevention of post operative nausea and vomiting after laparoscopic gynaecological surgeries

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ABSTRACT

Introduction: Post operative nausea and vomiting (PONV) is a common complication after general anaesthesia, specially post laparoscopic surgeries. This study compared efficacy of palonosetron with ondansetron for prevention and management of PONV in patients undergoing laparoscopic gynaecological surgeries.

Materials and Methods : 100 patients, undergoing laparoscopic gynaecological surgery were randomly divided in 2 groups of 50 each. They received either ondansetron(4mg IV) or palonosetron (0.075mg IV) before induction of general anaesthesia. They were monitored post operatively till 72 hours for episodes of nausea, vomiting, overall PONV and adverse effects.

Result: The incidence of overall PONV was significantly less in patients who received palonosetron as compared those who received ondansetron. Also, ondansetron group demonstrated higher use of rescue anti-emetic drug as compared with palonosetron group. No significant difference was found in incidence of adverse effects in both groups.

Conclusion: Palonosetron, having longer duration of action, is more effective in treating long term PONV compared to ondansetron in patients undergoing laparoscopic gynaecological surgeries under general anesthesia.

1. Introduction

Post operative nausea and vomiting is a common distressing symptom occurring after surgery.[1] Occurrence of PONV has decreased significantly from 75%–80% of the "ether" era to about 25%-30% of post surgical patients, where severe and intractable vomiting occurs approximately in 0.18% of this population.[2] The mechanism involves stimulation of receptors located in the chemoreceptor trigger zone, higher cortical centers, vestibular apparatus of the middle ear, and gastro-intestinal tract leading to activation of vomiting center located in Nucleus Tractus Solitarius.[3–6] Various factors contribute towards development of PONV. Patient factors include age, gender, obesity, history of previous PONV or motion sickness, anxiety and co-existing diseases. There is an increased incidence noted in female patients after puberty, especially during menstruation or pregnancy.[7] Inhalation agents and opioids are associated with higher incidence of PONV.[7] Surgeries such as laparoscopy; procedures involving eyes, ears, nose, throat; breast surgeries; intra-abdominal procedures; orchipexy ; and extracorporeal shock wave lithotripsy are also known to have higher incidence of PONV.

Ondansetron is a serotonin (5-HT_3) receptor antagonist commonly used to treat PONV. Another anti-emetic from the same class of drugs is palonosetron which has been approved in March 2008 for prevention of PONV.[8] It is a second generation serotonin receptor antagonist having highest binding affinity to 5-HT_3 receptors (pki-10.45) and longer mean elimination half life (40 hours). These properties of palonosetron are attributed to its allosteric binding and positive cooperativity with 5-HT_3 receptors, leading to effects persisting beyond receptor binding time.[8,9] Our study aims to compare palonosetron with

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ondansetron for prevention and management of PONV, in terms of efficacy, duration of action, adverse effects and overall patient satisfaction.

2. Materials and Methods

This randomized, prospective study conducted in our institute, included 100 patients randomly divided in 2 groups receiving either ondansetron or palonosetron. Inclusion criteria of study was females of age group 20 to 60 years, ASA grade I or II with no recent history of PONV or motion sickness or use of anti-emetic drugs, undergoing laparoscopic gynaecological surgery of duration >45 minutes, under general anaesthesia. Patients who were pregnant, lactating, had systemic diseases or allergic to study drugs were excluded. After pre-anaesthetic assessment and informed consent for the drug to be used, patients were kept NPO for 6 hours. Pre-operatively, monitoring was done according to ASA standards. A peripheral vein was cannulated. IV palonosetron (0.075mg) or ondansetron (4mg) was administered to patients randomly before induction of anaesthesia. IV propofol (1.5-2.5mg/kg) and IV fentanyl (1-2mcg/kg) were used for induction of anaesthesia. Endotracheal intubation was performed after IV succinylcholine (2mg/kg)/ IV atracurium (0.5mg/kg) / IV rocuronium (0.8-1mg/kg). Anaesthesia was maintained with 50% air and 2% sevoflurane / 1.2% isoflurane in oxygen. H eart rate and blood pressure were kept within 20% range of baseline values. Controlled Mechanical Ventilation maintained end tidal CO_2 between 30 to 35 mm of Hg. Post surgery, patients were reversed with IV neostigmine (0.05mg/kg) and IV glycopyrrolate (0.008mg/kg) and extubated after achieving complete reversal of anaesthesia with adequate, spontaneous and regular tidal volume.

Patients were monitored post operatively till 72 hours for occurrence of nausea and vomiting, severity of nausea according to visual analogue scale (VAS=0 - no nausea, VAS=10 -worst nausea) and need of rescue antiemetic drug. Nausea was defined as an unpleasant sensation associated with urge to vomit. Vomiting was defined as forceful expulsion of gastric contents from mouth. Metoclopramide (10mg IV) was used as rescue anti-emetic drug when 2 episodes of PONV occurred or at VAS >5 or if patients requested for treatment. A complete response was defined as absence of PONV and no use of rescue anti-emetics. Side effects of 5-HT_3 antagonists which are headache, dizziness, drowsiness, constipation, myalgia were evaluated.

3. Results

Table 1 depicts that there is significant difference ($p<0.001$) in episodes of nausea during 0-6 hours postoperatively in both groups, with lesser episodes with ondansetron as compared to palonosetron. While for 6-24 and 24-72 hours postoperatively, nausea was significantly less with palonosetron as compared with ondansetron. However, no significant difference was noted in mean number of nausea episodes recorded over 0-72 hours for both the drugs. Also, significant difference was noted in episodes of vomiting during 0-6 hours postoperatively, with no episodes with ondansetron as compared to palonosetron which had few vomiting episodes, as depicted in Table 2. While for 6-24 and 24-72 hours postoperatively, mean episodes of vomiting were found to be significantly less with palonosetron as compared with ondansetron. Also, significant difference was noted in mean number of vomiting episodes recorded over 0-72 hours for both the drugs, revealing lesser mean episodes with palonosetron.

Table 3 depicts non-significant difference in mean number of PONV episodes observed over 0-72 hours for palonosetron and ondansetron. But there is significant difference in PONV episodes during 0-6 hours postoperatively, with lesser episodes with ondansetron. However, for 6-24 hours and 24-72 hours postoperatively, mean episodes of overall PONV were found to be significantly less with palonosetron as compared with ondansetron. Also, as observed in overall 0-72 hours, use of rescue drug with ondansetron was significantly more as compared with palonosetron. No significant difference in incidence of adverse effects occurred with both groups.

4. Discussion

PONV is leading cause of delayed discharge, unanticipated hospital admission after ambulatory surgeries, pulmonary aspiration, wound dehiscence and dehydration. Apfel et al.[10] stated that patients receiving inhaled anaesthesia, females with history of PONV or motion sickness, and post operative use of opioids were important risk factors of PONV and each risk factor increased PONV incidence to 21%, 39%, 61% and 79%.

Rojas C et al.[9] showed, that palonosetron triggers 5-HT3 receptor internalization and induces prolonged inhibition of receptor. Park et al.[11] studied use of ondansetron 8 mg and palonosetron 0.075 mg before anaesthesia induction on patients with two or more risk factors and observed that palonosetron was better in PONV prevention upto 24 hours. Moon et al.[12] compared ondansetron and palonosetron in PONV prevention in high risk patients with three or more risk factors and found palonosetron to be more effective for 2-24 hours. We also found similar results in this study. Kovac AL et al.[13] studied palonosetron in dose of 0.025mg, 0.05mg and 0.075mg IV out of which dose of 0.075mg was superior to placebo during first 24 hours. FDA has also approved 0.075mg as minimum effective dose of palanosetron for PONV prophylaxis.[14] Therefore we decided to use palanosetron 0.075mg IV for this study.

Our results show no significant difference in nausea episodes recorded for 0-72 hours for both drugs. However,

Table 1: Comparison of mean number of post operative episodes of nausea

Time (hours)	Group- P (Mean number of episodes±SD)	Group- O (Mean number of episodes±SD)	p value (t test)
0-2	0.18±0.38	0.04±0.19	**0.00*** **
2-6	0.26±0.44	0.02±0.14	**0.00*** **
6-24	0.20±0.40	0.58±0.49	**0.00*** **
24-72	0.02±0.14	0.50±0.50	**0.00*** **
0-72	0.66±0.65	1.14±0.70	0.68

Table 2: Comparison of mean number of post operative episodes of vomiting

Time (hours)	Group- P (Mean number of episodes±SD)	Group- O (Mean number of episodes±SD)	p value (t test)
0-2	0.04±0.19	0.0±0.0	**0.04***
2-6	0.16±0.37	0.0±0.0	**0.00*** **
6-24	0.20±0.14	0.26±0.44	**0.00*** **
24-72	0.00±0.00	0.26±0.44	**0.00*** **
0-72	0.22±0.41	0.52±0.64	**0.00*** **

Table 3: Comparison of mean episodes of overall PONV

Time (hr)	Group-P (Mean PONV±SD)	Group-O (Mean PONV±SD)	p value (t test)
0-2	0.18±0.38	0.04±0.19	0.00***
2-6	0.30±0.46	0.02±0.14	0.00***
6-24	0.20±0.40	0.60±0.49	0.00***
24-72	0.02±0.14	0.54±0.50	0.00***
0-72	0.70±0.68	1.20±0.72	0.78

a significant difference is noted in mean number of episodes of nausea during 0-2 and 2-6 hours postoperatively in both groups, with lesser number of episodes with ondansetron (0.04±0.19 and 0.02±0.14 respectively) as compared to palonosetron (0.18±0.38 and 0.26±0.44 respectively). While for 6-24 and 24-72 hours postoperatively, nausea was significantly less with palonosetron. This shows that ondansetron has better nausea control during 0-6 hours of post-operative period, but owing to the better anti-nausea effects demonstrated by palonosetron over next 6-72 hours and no significant difference between effects of the two drugs during overall 0-72 hours of post-operative monitored period, we suggest that palonosetron is at par with ondansetron for control of post-operative nausea, with the effect of single dose extending over second and third post-operat ive days. Similar to our study, Park et al.,[11] compared palonosetron and ondansetron in laparoscopi c gynaecological surgery, and found that incidence of nausea was significantly lower in palonosetron group than in ondansetron group during 0-24 hour time interval of post operative period.

Our study reveals that there is a significant difference in mean episodes of vomiting during 0-2 and 2-6 hours postoperatively, with no episodes of vomiting with ondansetron as compared to palonosetron which had 0.04±0.19 and 0.16±0.37 mean number of vomiting episodes respectively. However, for 6-24 and 24-72 hours postoperatively, vomiting was significantly less with palonosetron. Also, significant difference was noted in mean episodes of vomiting recorded for 0-72 hours for both drugs, wherein palonosetron showed lesser episodes. This implies that even though ondansetron has better anti-emetic effect in initial post-operative period ; palonosetron is still emerging as the better anti-emetic drug in overall post-operative period of 0-72 hours, including remarkable results during late post-operative period of 6-72 hours. Our results are similar to the study conducted by Kim YY et al.[15] in 2013 which concluded that incidence of vomiting during the 72 hour postoperative period was lower with palonosetron than that with ondansetron. However, contrary to our study, Candiotti et al.[14] and Park et al.[11] demonstrated that palonosetron has more prominent anti-nausea effect than anti-vomiting effect.

Our observations also depict that there is a non-significant difference in overall PONV episodes observed in 0-72 hours in the two study groups. But there is a significant difference ($p<0.001$) in the number of episodes of PONV during 0-2 and 2-6 hours postoperatively, with a mean value of 0.04±0.19 and 0.02±0.14 episodes, respectively, with ondansetron which is less than mean value of 0.18±0.38 and 0.30±0.46, respectively, with palonosetron. However, for 6-24 and 24-72 hours postoperatively, mean episodes of overall PONV were found to be significantly less ($p<0.001$) with palonosetron. Again, ondansetron has a favourable

result in controlling overall PONV during initial 6 hours of post-operative period. But comparing the two drugs during overall 0-72 hours, palonosetron has emerged as equipotent to ondansetron, with significantly better results in 6-72 hours.

This result is simulating the results of other study conducted by Moon YE et al.,[12] which demonstrated that frequency of PONV during 24 hour postoperative period was lower in palonosetron group than in ondansetron group. Similarly, Bajwa et al.[16] concluded that palonosetron is a better drug than ondansetron for prevention of PONV in patients undergoing day care surgical procedures. However, in contrast to our study, Chun et al.[17] observed that 0.075 mg palonosetron significantly reduced the incidence of PONV during 0-24 hour postoperative period; but it did not reduce PONV during 24-72 hour postoperative period as compared to the placebo group, even though it significantly reduced overall incidence of PONV during the 0-72 hour postoperative period. This observation, where efficacy of palonosetron in post operative period of 24-72 hours was not as overwhelming as expected, was attributed to a generalized lower incidence of PONV in this period in both palonosetron and placebo groups due to decreased use of opioids.

We also found that use of rescue drug with ondansetron was significantly more as compared to palonosetron. Studies conducted by Bajwa et al.[16] and Moon YE et al.[12] have also demonstrated similar results depicting lesser requirement of rescue drug in patients who were given palonosetron as compared to those given ondansetron. However, Laha B et al.[18] reported no significant difference between the two drugs while comparing post-operative need for rescue anti-emetics.

The 5-HT_3 antagonists palonosetron and ondansetron have an enviable safety profile with most side effects being mild and transient. A small frequency of patients in both study groups experienced non serious adverse effects like short duration headache, constipation, dizziness, drowsiness and myalgia. W e observed no significant difference in incidence of adverse effects with both groups. Results of this study are consistent with results demonstrated by Park et al.,[11] Kim YY et al.[15] and Laha B et al.[18] in their respective studies comparing palonosetron and ondansetron. Also, Bajwa SS et al.[16] concluded through a prospective, double blind study that palonosetron has got significantly less incidence of side effects like headache, dizziness, myalgia and constipation as compared to ondansetron.

5. Conclusion

This study shows that a single IV dose of 0.075mg palonosetron le d to effective control of PONV and hence lesser requirement of additional anti-emetics for as long as 72 hours post operatively. Ondansetron, having shorter duration of action, requires repeat doses which may extend from twice to thrice a day, which decreases its cost-effectiveness, as compared to the long duration anti-emetic action of single dose of palonosetron. Therefore, this study provides a valid reason to use palonosetron for management of PONV.

6. Conflicts of interest

None.

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