

To Compare Antiemetic Efficacy of Palonosetron Alone Versus Palonosetron Combined with Dexamethasone as a Prophylactic Regimen for the Prevention of Postoperative Nausea and Vomiting in Patients Undergoing Laparoscopic Surgery Under General Anesthesia

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ABSTRACT

Introduction: Postoperative nausea and vomiting (PONV) is often the most common complication following anesthesia and surgery particularly laparoscopic. Thus, this most common complication should be prevented. This study was done to determine whether a combination of Palonosetron and dexamethasone would be more effective than Palonosetron alone in prevention of PONV in female patients undergoing laparoscopic abdominal surgeries

Material and Methods: 106 female patients of ASA physical status I,II, aged 18-60 years admitted for elective laparoscopic surgical procedures were included in this prospective double blind observational study. Postoperatively nausea, vomiting, retching and use of rescue antiemetic and side-effects like headache, dizziness and drowsiness were noted at 6 hr, 12 hr, 24 hr and 48 hr by an investigator from the patient's monitoring records and then data was analyzed.

Results: Nausea, retching, vomiting episodes at 6 hr were significantly decreased ($p < 0.05$) in palonosetron and dexamethasone group. At 12 hr vomiting episodes were significantly decreased in palonosetron dexamethasone group and no significant difference was observed for nausea, retching at 12 hr. No significant difference in both groups observed at 24 hr and 48 hr, however complete response was significantly higher in palonosetron dexamethasone group.

Conclusion: Both palonosetron and palonosetron combined with dexamethasone are effective in treatment of postoperative nausea and vomiting in females undergoing laparoscopic surgeries under general anesthesia, however complete response is seen with later.

Keywords: PONV, Palonosetron, Dexamethasone.

antihistamines, and dopamine receptor antagonists) have been tried in PONV prophylaxis. No single antiemetic drug has been proved to be a universal solution to PONV. In general, multimodal combination therapy has superior efficacy for PONV prophylaxis compared to monotherapy.^{1,2}

Palonosetron is the latest, potent and selective second generation 5-HT₃ receptor antagonist. Its interaction pattern with the 5-HT₃ receptor is different from earlier 5-HT₃ receptor antagonists, enabling a higher binding affinity and longer half-life. The mean terminal elimination half-life, following single intravenous (IV) dose, is approximately 40 hours and therefore the duration of action exceeds 24 hrs, and may extend to 48 hours.

Dexamethasone causes better control of late PONV probably by inhibiting prostaglandin synthesis, decreasing 5HT levels in the nervous system, and anti-inflammatory action. A meta analysis concluded that the best prophylaxis of PONV is by combining dexamethasone with selective 5 HT3 receptor antagonists. The purpose of the study was to find out whether a combination of Palonosetron and dexamethasone or Palonosetron alone would be more effective in prevention of PONV in female patients undergoing laparoscopic abdominal surgeries.

MATERIAL AND METHODS

After the Institutional Ethics Committee's approval, written informed consent of 106 female patients was obtained. The patients included in this prospective double blind observational study were of ASA physical status I-II, aged 18-60 years and admitted for elective laparoscopic surgical procedures. They had no history of drug allergy, emesis and were not given opioid for postoperative analgesia. Patient who refused for consent and having history of peptic ulcer disease, adrenal insufficiency, diabetes mellitus, heart disease, renal disease, having received cancer chemotherapy or emetogenic radiotherapy were excluded from the study. All the patients were randomly divided into two groups using computer generated random number table.

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INTRODUCTION

Postoperative nausea and vomiting (PONV) is often the most common complication following anesthesia and surgery particularly laparoscopic surgery. Although PONV is not life-threatening in most cases, it can cause hematomas and increased wound pain as a result of unfortunate movements; it may provoke surgical suture dehiscence and therefore jeopardizes the success of the surgery performed. It also applies to all situations in which an increase in intracavitary pressures (e.g. intraocular, intracranial) should be avoided. PONV also leads to delayed recovery, patient dissatisfaction, unexpected hospital admission, delayed return to work and greater demands on the time resources of the postoperative care staff. These indirect costs usually far exceed the direct cost of antiemetics. Thus, this most common complication should be prevented.

Several pharmacological therapies (butyrophenones,

Pre anesthetic check up included general examination, systemic examination and airway assessment. Investigations were done as required. All selected patients were given tablet alprazolam 0.25mg at night prior to the surgery and were kept nil per orally for 8 hrs. Group 1 included patients in which IV palonosetron 0.075mg was given whereas Group 2 included patients in which IV palonosetron 0.075mg and dexamethasone 8mg combination was given.

In the operation room an IV line was secured. The anesthetic technique was standardized for all the patients. Standard monitors were attached namely; 5-leads electrocardiography (ECG), pulse oximetry (SpO₂), and non-invasive blood pressure monitor (NIBP). After obtaining baseline vital signs, the prophylactic antiemetic was given in a double blind manner. Both drugs were mixed with normal saline to prepare equal volume (5 ml) in a syringe and labeled '1' for palonosetron and '2' for palonosetron + dexamethasone combination. This was to make sure that the patient and designated anesthesiologist could not identify the antiemetic drug. Premedication was done with midazolam 0.05mg/kg IV and then preoxygenation with 100% O₂ for 3 minutes. Anesthesia induction was done with fentanyl 2µg/kg IV and Propofol 2–3 mg/ kg IV. Endotracheal intubation was facilitated by the use of vecuronium at a dose of 0.1 mg/ kg IV. After smooth intubation, bilateral air entry was checked and the endotracheal tube was fixed. Then, the patient was put on mechanical ventilator. General anesthesia was maintained with isoflurane 1-2%, oxygen and air mixture (FiO₂= 0.5). Injection tramadol 50mg IV and paracetamol 1gm IV were given. Intra operative intra abdominal pressure ranges were noted. Immediately before the end of surgery, isoflurane was discontinued. For the post operative analgesia, all patients received port site infiltration with bupivacaine (0.25%, 15ml). 1 gram paracetamol by IV drip and 50mg tramadol IV was given eight hourly. At the time of emergence, residual neuromuscular block was reversed by 0.05 mg/ kg of neostigmine IV and IV glycopyrrolate (0.1mg for each 0.5mg of neostigmine). Extubation was done after suction of the oropharynx and adequate recovery from GA. Anesthesia time (from the start of induction to discontinuation of isoflurane), the time of surgery (from the surgical incision to the placement of surgical dressings), and recovery time (from discontinuation of isoflurane until the patient could lift head for 5 seconds on command) were recorded. Patients were shifted to post anesthesia care unit (PACU) and oxygen was administered at 3 l/min.

Only those patients were included who had surgery time duration of two or less than two hours and intra operative intra abdominal pressures in the range of 8 to 12 mm Hg. None of the patients excluded from the study. Patients' post operative monitoring was done at 6 hr, 12 hr, 24 hr and 48 hr by an investigator for nausea, vomiting, retching, side-effects (headache, dizziness and drowsiness) and use of rescue antiemetic (rescue drug

injection metoclopramide-10 mg was given if more than two episodes of vomiting occur within a period of half hour).

Nausea is defined as the subjectively unpleasant sensation associated with awareness of the urge to vomit. Retching is defined as the labored, spastic, rhythmic contraction of the respiratory muscles without the expulsion of the gastric contents. Vomiting is defined as the forceful expulsion of gastric contents from the mouth. Complete response is defined as no nausea, vomiting or retching and no need of rescue anti-emetic medicines within postoperative 48 hrs. The number of complete responders was recorded.

STATISTICAL ANALYSIS

Statistical analysis was done using SPSS windows version 20.0 (trial version) software. Chi square test, one way ANOVA and unpaired t-test were applied. Results were expressed in mean ± SD and p value <0.05 which is considered statistically significant.

RESULTS

The patient characteristics are given in Table1. All the patients were demographically comparable with respect to age, BMI, ASA grading. The mean duration of surgery was 94.6 ± 6.9 minutes and 92.7 ± 7.8 in palonosetron group and palonosetron dexamethasone group respectively (p value = 0.207) which was also demographically comparable. Distributions of antiemetic characteristics are given in Table 2.

Adverse effects that may be noticed in patients receiving 5HT3 receptor antagonist include abdominal distention, chest discomfort, constipation, cough, dizziness, dryness of mouth, sinus bradycardia, and throat irritation. However the incidence of adverse effects in both groups was nil. The incidence of complete response among both groups after 48 hours was higher in (palonosetron and dexamethasone) group 2 (48 patients-90.6%) than (palonosetron) group1 (33 patients-62.3%) with statistical significant difference (chi sq=11.778, p=0.001) as shown in figure 1.

DISCUSSION

In our study, we compared the antiemetic efficacy of palonosetron monotherapy with palonosetron-dexamethasone combination therapy in 106 female patients undergoing abdominal laparoscopic surgery for prevention of PONV.

The etiology of PONV following laparoscopic surgery remains unclear, but is probably associated with the effect of intraperitoneal CO₂ insufflation leading to stretching and irritation of peritoneum. The abdominal insufflation during laparoscopy increases the abdominal pressure with subsequent dilatation of intestinal loops which could influence the secretion of 5HT. The mucosal enterochromaffin cells of the intestinal tract contain approximately 90% of 5HT present in

	Palonosetron	Palonosetron+dexamethasone	P value
Age(years)	43.03±11.8	42.35±10.34	0.754
BMI(kg/m ²)	22.34±2.59	22.03±3.70	0.612
ASA grade I	60.40%	62.30%	0.842
ASA grade II	39.60%	37.70%	
Duration of Surgery(min)	94.6226±6.92328	92.7925±7.89440	0.207

Table-1: Distribution of patients demographic

	Palonosetron	Palonosetron + dexamethasone	Chi square test	P value
Nausea				
0-6 hrs	20.8%	3.8%	7.102	0.008
6-12 hrs	11.3%	5.7%	1.093	0.269
12-24 hrs	3.8%	0.0%	2.038	0.153
24-48 hrs	0.0%	0.0%	-	-
Retching				
0-6 hrs	11.3%	0.0%	6.360	0.012
6-12 hrs	7.5%	1.9%	1.889	0.169
12-24 hrs	1.9%	0.0%	1.010	0.315
24-48 hrs	0.0%	0.0%	-	-
Vomiting				
0-6 hrs	9.4	0.0	5.248	0.022
6-12 hrs	13.2	1.9	4.867	0.027
12-24 hrs	3.8	0.0	2.038	0.153
24-48 hrs	0.0	0.0	-	-
Rescue antiemetic	11.3%	1.9%	3.824	0.051

Table-2: Distribution of antiemetic characteristics

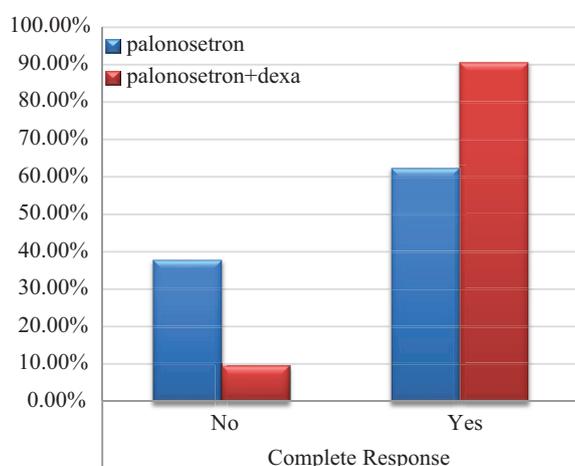


Figure-1: Distribution of Complete Response between both the groups

the body. PONV is influenced by many factors including age, gender, smoking habit, history of PONV or motion sickness, preoperative anxiety, type and duration of surgery, volatile anesthetics, nitrous oxide and postoperative opioid analgesics. Palonosetron exhibits far higher receptor affinity (almost 30 fold)¹ and more potent binding with 5-HT3 receptors than other 5-HT3 antagonists.² In addition, it also triggers functional effects that persist beyond its binding to the 5-HT3 receptor at the cell surface leading to prolonged duration of action and longer half life (40 h).³ Dose of Palonosetron (75mcg is the more effective dose for the prevention of PONV after major gynecological and laparoscopic surgery than 25mcg or 50 mcg).⁴ Furthermore, Palonosetron also exhibits anti-nauseatic property which is in contrast to other 5-HT3 blockers. Kovac et al.⁵ reported complete response rates of 56% and 70% between 0-24 h and 24-72 h respectively in palonosetron pre-treated patients after gynecological surgeries. Candiotti et al⁶ also reported complete response rate of 43% between 0-24 h and 49% during 24-72 h postoperatively in patients receiving palonosetron 0.075 mg. Bala et al.⁷ reported complete response rate of 57% and 95% in palonosetron group during 0-24 h and 24-48 h after laparoscopic cholecystectomy surgeries. In the present study of palonosetron monotherapy group, during post operative period of 0-6hr, 6-12hr, and 12- 24hr, the incidence of nausea was 20.8%, 11.3%, and 3.8%; the incidence of retching was 11.3%, 7.5%, 1.9%; and

the incidence of vomiting was 9.4%,13.2%,3.8% respectively. None of the patients experienced nausea, retching and vomiting during 24-48 hr period. The complete response rate in this group was 62.3% during 48hrs period post operatively.

Dexamethasone is a long acting antiemetic with minimal side effects. Prophylactic use of dexamethasone has been found to be effective in reducing the incidence of PONV during 24 h after laparoscopic cholecystectomy.⁸⁻¹⁰ It can potentiate the effect of other antiemetics by various mechanisms like, prostaglandin antagonism, release of endorphins and bradykinin reduction. The combination of dexamethasone and 5-HT3 antagonists appears to be more effective than single-drug prophylaxis in patients at high risk for PONV.¹¹⁻¹³

In the present study of palonosetron-dexamethasone combination group, the incidence of nausea was 3.8% and 5.7% during 0- 6hr, 6-12hr post operatively. The incidence of both retching and vomiting was 1.9% during 6-12 hr period. None of the patients experienced nausea, vomiting and retching during 12-48 hr period. The complete response rate during 48hrs was 90.6%.

Addition of dexamethasone to palonosetron also reduced the requirement of rescue antiemetic medication and was associated with greater patient satisfaction. However Park et al¹⁴ comparing palonosetron with palonosetron and dexamethasone 4 mg combination in gynecological laparoscopic procedures reported no significant difference in PONV among groups. The incidence of PONV was 9.8% and 14% in palonosetron and combination group respectively. Blitz et al¹⁵ compared 0.075 mg palonosetron and 8 mg dexamethasone combination therapy with palonosetron monotherapy in patients undergoing outpatient laparoscopic surgeries and reported low incidence of PONV in both the groups (Palonosetron+Dexamethasone, 1.7%; Pal, 6.8%).

Our patients were at high risk for PONV due to non-smoking habits, female gender and laparoscopic surgery. Though, all these factors were well balanced among the groups. Our high incidence of PONV in early postoperative period was most likely due to the use of volatile anesthetics and use of opioid both intraoperatively. Apfel et al¹⁶ reported that the use of inhalational anesthetics with nitrous oxide should be considered as a leading cause of early PONV while the use of postoperative

opioid was associated with late PONV in high risk patients. Kovac et al.⁵ and Candiotti et al.⁶ also used volatile anesthetics with nitrous oxide and reported high incidence of PONV in their studies. Dexamethasone also alleviates pain but mechanism of action is not known and we have not observed this in our patients. It is possible that reduction in prostaglandin synthesis mediated by dexamethasone contributes to analgesia.¹⁷ Fujii and Itakura¹¹ also reported that prophylactic therapy with dexamethasone 8 mg was effective in reducing PONV as well as analgesic requirement after laparoscopic cholecystectomy. In a recent study, Murphy *et al*¹⁸ reported that the use of preoperative dexamethasone enhanced post discharge quality of recovery after laparoscopic cholecystectomy and reduced nausea, pain, and fatigue in the early postoperative period. There were no severe adverse effects in any group of patients in our study. In particular, there were no wound infections or delay in healing in patients receiving dexamethasone.

We used palonosetron in the dose of 0.075 mg which has been found to be the minimum effective dose in various studies.^{3,4} Dexamethasone 8 mg is the most commonly used dose for the prophylaxis of PONV in various studies.^{9,10} The timing of prophylactic antiemetic administration is also important. Dexamethasone is found to be more effective when given at the induction of anesthesia.

CONCLUSION

The combination of palonosetron with dexamethasone is not more effective than palonosetron alone in the treatment of postoperative nausea and vomiting in females undergoing laparoscopic surgeries under general anesthesia. However, statistically significant better complete response is seen with the former.

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