Original Article

Comparison of palonosetron and dexamethasone with ondansetron and dexamethasone for postoperative nausea and vomiting in postchemotherapy ovarian cancer surgeries requiring opioid-based patient-controlled analgesia: A randomised, double-blind, active controlled study

Address for correspondence:
Dr. Sohan Lal Solanki, Department of Anaesthesiology, Critical Care and Pain, Tata Memorial Hospital, Dr E Borges Road, Parel, Mumbai - 400 012, Maharashtra, India.
E-mail: me_sohans@yahoo.co.in

Amit Kumar, Sohan Lal Solanki, Gauri Raman Gangakhedkar, T S Shylasree[1], Kailash S Sharma

Departments of Anaesthesiology, Critical Care and Pain and [1]Gynaecological Oncology, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, Maharashtra, India

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ABSTRACT

Background and Aims: Patients undergoing ovarian cancer surgery after chemotherapy and requiring opioid-based patient-controlled analgesia (PCA) are at high-risk of postoperative nausea and vomiting (PONV). We aimed to assess the effect of palonosetron and dexamethasone combination for these patients for prevention of PONV. **Methods:** This study included 2 groups and 150 patients. At the time of wound closure, patients in group A received ondansetron 8 mg intravenous (IV) + dexamethasone 4 mg IV and group B received palonosetron 0.075 mg IV + dexamethasone 4 mg IV. Postoperatively for 48 hours, group A patients received ondansetron 4 mg 8 hourly IV, group B patients received normal saline 8 hourly IV in 2 cc syringe. The primary objective was the overall incidence of PONV. Independent *t*-test, Chi-square test, and Fisher's exact test were used and multivariate regression analysis was done. **Results:** Vomiting was significantly higher in group A (37.3%) as compared with group B (21.3%) at 0–48 hours ($P = 0.031$). Significantly more patients in Group A had nausea as compared with group B at 90–120 minutes (30.66% vs 18.66%, $P = 0.043$) and 6–24 hours (32.0% vs 22.66%, $P = 0.029$). PCA opioid usage in microgram was significantly higher in group A at 0–24 hours (690.53 ± 332.57 vs 576.85 ± 250.79, $P = 0.024$) and 0–48 hours (1126.10 ± 512.18 vs 952.13 ± 353.85, $P = 0.030$). **Conclusion:** Palonosetron with dexamethasone is more effective than ondasetron with dexamethasone for prevention of PONV in post-chemotherapy ovarian cancer surgeries receiving opioid-based patient controlled analgesia.

Key words: Ondansetron, ovarian neoplasm, palonosetron, postoperative nausea and vomiting

INTRODUCTION

Postoperative nausea and vomiting (PONV) is one of the few most unpleasant postoperative discomforts to the patients and leads to various, complications such as aspiration pneumonitis, suture dehiscence, oesophageal rupture, or pneumothorax.[1] Risk factors for PONV include patient specific like female gender, non-smoker, and patients with a history of motion sickness or experience of previous PONV; anaesthesia technique specific like use of volatile anaesthetics, the perioperative use of opioids, and nitrous oxide; and

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surgery specific like laparoscopic surgery[2] and long duration of surgery and gynaecological surgeries.

The general incidence of PONV is about 30% and is about 75%–80% in high-risk groups.[3] It is associated with delayed recovery and prolonged hospital stay and is associated with significant morbidity.

The use of opioid-based intravenous patient-controlled analgesia (IV-PCA) for controlling postoperative pain has become widespread. Yet, while IV-PCA is effective in controlling postoperative pain, continuous administration of opioid can cause or aggravate PONV.

The 5-HT_3 receptor antagonists are effective antiemetic drugs with more safety and favourable side effect profile as they lack the sedation, dysphoria, and extrapyramidal side effects of other commonly used antiemetics. The consensus guidelines by the Society of Ambulatory Anaesthesia 2014 recommend 5-HT_3 antagonist as the first line of prophylaxis for PONV under general anaesthesia.[4]

Ondansetron is the first generation 5-HT_3 antagonist, and it was the first 5-HT_3 antagonist to be marketed. It has been frequently used for control of PONV.[5]

Palonosetron is the second generation 5-HT_3 antagonist with unique chemical structure and longer half-life of 40 hours and found to be very effective in chemotherapy-induced nausea and vomiting (CINV) as well as PONV.[4,6]

Dexamethasone with a 5-HT_3 antagonist is an excellent combination therapy,[7] because the 5-HT_3 antagonist is most effective against early vomiting (within 6 hours after surgery),[8] whereas dexamethasone is effective against both early and late nausea and vomiting, and especially so against late vomiting (within 48 hours after surgery).

Women undergoing ovarian cancer surgery who had received chemotherapy earlier and receiving postoperative opioid-based IV-PCA are at high risk of PONV,[4,9] for whom multimodal strategies are most effective.

We hypothesised that palonosetron being a longer acting and more effective drug in CINV would be better in preventing PONV after post-chemotherapy ovarian cancer surgery.

The purpose of this prospective, randomised, active controlled, double-blind study was to compare the efficacy of ondansetron with dexamethasone versus palonosetron with dexamethasone in post-chemotherapy ovarian cancer patients undergoing open surgery and receiving opioid-based patient-controlled analgesia.

METHODS

This prospective, randomised, active controlled, double-blind interventional study was started after approval from Institutional Ethics Committee and was prospectively registered with Clinical Trials Registry-India (CTRI/2015/09/006223). The study was conducted as per the Indian Council of Medical Research guidelines for biomedical research in human subjects.

Sample size calculation was based on previous study[10] which showed 4% incidence of vomiting in palonosetron group as compared with 18% incidence in ondansetron group in patients receiving IV-PCA after gynaecological laparoscopic surgery. Assuming the same (14%) difference in PONV in our study, with a power of 80% ($\beta = 0.2$) and significant level of 5% ($\alpha = 0.05$), our sample size was 150 patients with 75 patients in each group.

In this study, American Society of Anesthesiologist grade I and II, females in the age group 18 to 70 years, who were diagnosed as ovarian cancer [International Federation of Gynecology and Obstetrics (FIGO) staging I to III] and who had received last dose of chemotherapy (platinum and taxols) at least 3 weeks earlier and planned to undergo open ovarian cancer surgery under general anaesthesia and requiring opioid-based IV-PCA for postoperative pain management were included. Patients having a midline incision limited to 1–2 cm above umbilicus were included. A well-informed consent (in English, Hindi, or Marathi language) regarding participation in this study was obtained from all the patients a day prior to surgery.

Exclusion criteria were smokers or patients with past history of smoking, cognitive impairment or an active psychiatric condition, patients with known liver and kidney diseases, history of palonosetron/ondansetron/dexamethasone or fentanyl allergy, use of corticosteroids, psychoactive drugs, or any other medication with known emetic or antiemetic effect within 24 hours prior to surgery and history of opioid abuse. Patients who were shifted

on endotracheal tube for postoperative mechanical ventilation were also excluded from the study.

One hundred and fifty patients were selected by computer-generated randomisation sheet generated in institutional clinical research secretariat. Allocation concealment was done by a sequentially numbered opaque envelope technique after induction of anaesthesia in the operating room. Group randomisation (two groups with 75 patients in each group) was done by a member of study team who was not involved in patient's management and data collection.

All patients underwent a thorough preanaesthetic examination and all routine laboratory test including haemogram, coagulogram, biochemical indices, x-ray chest, ECG, and other investigation, if needed, for the surgical procedure and treatment of disease.

On the day of surgery, on the operating table, standard monitoring (electrocardiogram, pulse oximeter, noninvasive blood pressure, capnography) was established and intravenous access was secured. Anaesthesia was induced with fentanyl 2 mcg/kg and propofol 2 mg/kg IV. Tracheal intubation was facilitated by rocuronium 1.0 mg/kg or vecuronium 0.1 mg/kg IV. Anaesthesia was maintained with isoflurane in oxygen and nitrous oxide (40:60). Muscle relaxation was maintained by intermittent bolus doses of rocuronium or vecuronium. Intraoperative analgesia was maintained by intermittent IV boluses of fentanyl as per attending anaesthesiologists' discretion. Ventilation was controlled and rest of the anaesthetic management was as per institutional protocol. Lactated ringer solution was given as maintenance fluid.

At the time of closure of the abdominal wound, patients in group A received IV ondansetron 8 mg with dexamethasone 4 mg, whereas patients in group B received IV palonosetron 0.075 mg with dexamethasone 4 mg.

In addition, patients in group A received IV ondansetron 4 mg (2 ml solution) three times a day (eight hourly) in postoperative period, whereas patients in group B received IV normal saline (2 ml solution) three times a day (eight hourly) for 48 hours postoperatively. Study drugs were prepared by an anaesthetist who was not a part of team for postoperative monitoring and data collection in postanaesthesia care unit (PACU) and ward. These drugs were filled in 5 ml syringes and these syringes were labelled as study drug. The resident anaesthetist or nurses who were responsible for administration of drug to the patients were also unaware of the group allocation of the patient. All patients received injection IV diclofenac 75 mg and local anaesthetic infiltration to the abdominal wound toward end of surgery. Nausea, vomiting, and retching were observed for 48 hours. In the recovery room, as soon as patient was shifted, IV-PCA was attached to the patient with a dedicated IV line for PCA. Intravenous metoclopramide 10 mg was given as rescue antiemetic and IV diclofenac 50 mg as rescue analgesic.

The primary end point of this study was the overall incidence of PONV between the groups. The incidences of PONV were assessed in PACU every half an hour for 2 hours and at intervals of 2–6, 6–24, 24–48 hours postoperatively. Nausea was defined as subjective unpleasant sensation with concomitant awareness of the urge to vomit. Vomiting was defined as forceful expulsion of stomach contents through the mouth. Retching, the laboured spasmodic rhythmic contractions of the respiratory muscles without the expulsion of the gastric contents, was also regarded as vomiting.

Secondary endpoints were to compare the intensities of nausea (verbal rating scale, 0 = no nausea, 10 = worst nausea imaginable)[11] and pain (verbal rating scale, 0 = no pain, 10 = worst pain imaginable). Nausea was rated according to mild, moderate, and severe when VAS was 1–3, 4–6, and 7–10, respectively. Additionally, cumulative volume of IV-PCA opioid administered during each observation period, rescue analgesics and antiemetic requirements, discontinuation of IV-PCA opioid ahead of time, and adverse events (dizziness, drowsiness, headache, constipation, urinary retention, and pruritus) were noted. Patient's satisfaction score was recorded from 0 to 10 (0 = highly dissatisfied, 10 = highly satisfied).

For statistical analysis of data, SPSS 22.0 (SPSS, IBM, USA) was used. Continuous variables (age, height, weight, BMI, duration of anaesthesia) were analysed using independent *t*-test. Nominal data (incidence of nausea, vomiting) were analysed using Chi-square test and Fisher's exact test as applicable. Multivariate regression analysis was done for factors found to be significant on univariate analysis. *P* value <0.05 was considered significant.

RESULTS

In total, 216 female patients were screened. One hundred and ninety-one patients were found eligible. Forty-one patients were excluded from the study due to logistic issues like nonavailability of PCA cassette in dispensary or nonavailability of IV-PCA pump, because we have limited numbers of IV-PCA pumps. Six patients denied consent. One hundred and fifty patients were included with 75 patients randomised in each group [Figure 1].

ASA status, BMI, number of chemotherapy cycles received and duration of anaesthesia were comparable in both the groups. Patients in group A were significantly younger as compared with group B (47.83 ± 10.67 years' vs 51.25 ± 9.75 years, $P = 0.04$) despite randomisation [Table 1]. On multivariate regression analysis, age is not found to be an independent predictor of vomiting at 0–24 h (95% confidence interval [CI] 0.961–1.035, $P = 0.887$) and 0–48 h (95% CI 0.950–1.018, $P = 0.341$).

Overall incidence of vomiting in 0- to 48-hour postoperative period was 29.3%. This was significantly higher in group A as compared with group B (37.3% vs. 21.3%, *P*–value = 0.031) [Table 2].

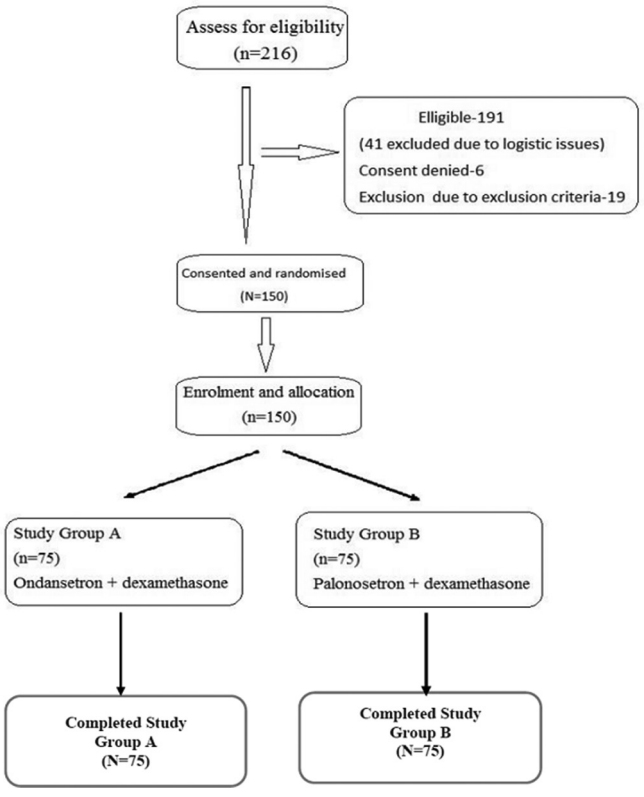

Figure 1: Consort diagram showing randomisation and the treatment allocation

In group A, the percentage of nausea was 62.7% compared with group B, where it was found to be 49.3%. This difference in nausea episodes was not statistically significant ($P = 0.241$). The overall nausea incidence was found to be 56% [Table 2].

Significantly more patients in Group A had nausea as compared with group B at 90-120 minutes (30.66% vs 18.66%, $P = 0.043$) and 6-24 hours (32.0% vs 22.66%, $P = 0.029$) and was comparable for all other time intervals postoperatively.

Pain (VAS) scores (means ± SD) at rest were similar in group A and group B at 0-24 hours' period (2.58 ± 0.88 vs 2.54 ± 0.85, $P = 0.788$) as well as at 0-48 hours' period (2.48 ± 0.79 vs 2.43 ± 0.76, $P = 0.772$) postoperatively. Pain (VAS) scores (means ± SD) at movement were also similar in group A and group B at 0-24 hours' period (3.71 ± 0.90 vs 3.78 ± 0.92, $P = 0.835$) as well as at 0-48 hours' period (3.63 ± 0.80 vs 3.66 ± 0.83, $P = 0.916$) postoperatively. Pain scores were also similar in both groups at all other study intervals postoperatively.

PCA fentanyl used in microgram was significantly higher in group A at 0–24 hours (690.53 ± 332.57 vs 576.85 ± 250.79, $P = 0.024$) and 0–48 hours (1126.10 ± 512.18 vs 952.13 ± 353.85, $P = 0.030$) postoperatively.

On multivariate regression analysis, IV-PCA uses were not found to be an independent factor for vomiting at 0–24 h (95% CI 0.999–1.001, $P = 0.989$) and 0–48 h (95% CI 0.999–1.001, $P = 0.0841$).

Table 1: Demographic profile

Parameters/Groups	Group A (*n*=75)	Group B (*n*=75)	*P*
Age (years), mean±SD	47.83±10.67	51.25±9.75	0.04*
BMI (kg/m^2), mean±SD	24.27±4.94	23.72±4.22	0.52
ASA 1:2	43:32	38:37	0.413
Chemotherapy cycles, median	4	4	1.000
Duration of anaesthesia (min), mean±SD	216.4±53.66	215.93±64.94	0.717

BMI – Body mass index; ASA – American Society of Anesthesiologists. *Statistically significant

Table 2: Vomiting and nausea during 0-48 h periods

Parameters/groups	Group A (*n*=75)	Group B (*n*=75)	*P*
Vomiting (0-48 h), *n* (%)	28 (37.3)	16 (21.3)	0.031*
Nausea (0-48 h), *n* (%)	47 (62.7)	37 (49.3)	0.241
Mild nausea, (VAS 1-3)	45	36	
Moderate nausea (VAS 4-6)	2	1	

VAS – Visual analogue scale. *Statistically significant

The total rescue antiemetic ($P = 0.168$) as well as rescue analgesic ($P = 0.779$) were comparable in both study groups.

Patient's satisfaction scores were comparable in both the groups. One patient had abdominal distension in 24- to 48-hour period that resolved without further intervention; one patient had low urine output in 6- to 24-hour period and that resolved without any intervention. No patient experienced any dizziness, drowsiness, headache, or pruritus.

DISCUSSION

The present study was restricted to female non-smokers undergoing open ovarian cancer surgery after at least 3 weeks of chemotherapy who used opioid-based IV-PCA postoperatively. These patients were high-risk candidates for PONV as at least three risk factors out of four were present (female gender, previous history of PONV or motion sickness, nonsmoking status, and postoperative use of opioids) as listed by Apfel *et al*.[12] Therefore, these were expected to have a high incidence of PONV.[12,13]

We found that the palonosetron with dexamethasone group showed overall decreased vomiting compared with ondansetron with dexamethasone group (37.3% vs. 21.3%, $P = 0.031$). Overall nausea was comparable in both groups, but VAS scores for nausea were significantly higher in group A for study interval 90–120 min and for 6–24 hours

Use of IV-PCA is associated with better patient satisfaction compared with other modes of opioid administration.[14] Opioid-based IV-PCA are one of the major and effective modalities of postoperative pain relief, which are often suboptimally used due to their attribution to PONV. Causes of PONV can be central or peripheral. Central sensory stimuli are transmitted by the chemoreceptor trigger zone (CTZ), area postrema, and nucleus of the solitary tract to the vomiting center, three nerves and seven neurotransmitters for activation of vomiting centre, which makes the prophylaxis and treatment complex. The antiemetic premedication can reduce the rate of PONV.[15] The CTZ contains receptors for dopamine, serotonin, opioids, acetylcholine, and the neurotransmitter substance P. When stimulated, each of these receptors gives rise to pathways leading to vomiting and nausea. Present in high concentrations in the vomiting centre, substance P seems to be involved in the final common pathways that give rise to vomiting. Stimuli are relayed from the gut to the vomiting center via the vagus nerve that is a peripheral cause.

Different drug combinations and regimens have been tried from time to time and many guidelines are formulated by societies, but these are applied in clinical practice with variable success rate. However, satisfying therapeutic benefit has not been achieved by the current range of agents including older 5-HT_3 antagonists, which do not offer long protection.

This study used equipotent doses of palonosetron and ondansetron (single dose of palonosetron and 8 hourly doses of ondansetron) and evaluated the efficacy of palonosetron (which has already been proven effective in prevention of CINV and PONV) with dexamethasone, against ondansetron with dexamethasone. Dual antiemetic regimen was used in concordance with recent guidelines by Society of Ambulatory Anaesthesia.[4]

Our study is in agreement with a study by Kim *et al*.[10] They have observed a 4% incidence of vomiting with palonosetron when compared with 18% with ondansetron. The incidence of vomiting has been much lower than that observed in our study. This could be attributed to the continuous infusion of 16 mg ondansetron by PCA pump in both groups.

Our study also correlates well with a systemic review and meta-analysis by Xiong *et al*.[16] for comparison of palonosetron and ondansetron for prevention of PONV within 24 hours after surgery. Their primary outcomes were postoperative nausea, postoperative vomiting, or both in early (0–6 hours) or late (0–24 hours) postoperative period. Nine randomised controlled trials comprised of 741 participants were included. They found that palonosetron provides more effective prophylaxis against early postoperative nausea (RR = −0.51), late postoperative nausea (RR = −0.41), and late postoperative vomiting (RR = −0.77) compared with ondansetron.

Singh *et al*.[17] compared palonosetron to placebo, ramosetron, granisetron, and ondansetron in a meta-analysis involving adult undergoing elective surgery under general anaesthesia and concluded that palonosetron is as safe as and more effective than placebo, ramosetron, granisetron, and ondansetron in preventing delayed PONV. For early PONV, it has higher efficacy over placebo, granisetron, and ondansetron.

Our study also correlates with results of studies by Kim *et al.*[10] and Singh *et al.*[17] with palonosetron and dexamethasone group being more effective against late (6–24 hours) nausea and vomiting from 0 to 48 hours.

In an another meta-analysis by Ying *et al.*[18] including 10 RCTs comparing palonosetron with first-generation 5-HT_3 receptor antagonist or placebo to prevent PONV, significant statistical difference in favour of palonosetron in prevention of PONV (acute and delayed) was found, while side effects were comparable between palonosetron and control groups.

When compared as rescue medication by Keith *et al.*[19] in a randomised multicentric trial, palonosetron and ondansetron in patients already received first-generation 5-HT_3 antagonist ondansetron as prophylaxis, there was no difference between primary efficacy endpoints between groups, while palonosetron group showed less emesis in 0–72 h interval.

Kovac *et al.*[20] in a multicenter, randomised, double-blind study compared three doses of palonosetron with placebo on incidence of PONV in patients for 72 hours after surgery. They concluded that a single dose of 0.075 mg IV palonosetron effectively reduced the severity of nausea and delayed the time to emesis and treatment failure in the inpatient surgical setting. They also found that lower doses were not effective.

Although nitrous oxide is attributed to PONV,[4,21] it is recommended to minimize concentration of volatile anaesthetic to reduce incidence of PONV. We preferred to use nitrous oxide instead of avoiding it so that the concentration of volatile anaesthetic agent used did not exceed the minimal alveolar concentration value.[4]

Our study has few limitations. First, patients in ondansetron with dexamethasone group were younger as compared with group A ($P = 0.04$), and younger age is itself a risk factor for PONV. Second, the opioid consumption in IV-PCA was more in the group A for 0–24 hours ($P = 0.024$) and 0–48 hours ($P = 0.040$) periods, which is also a risk factor for PONV. Although both of these were found to be not independent factors for predicting vomiting on multivariate analysis, we also did not look into duration of use of nasogastric tube in postoperative period, as it may also cause nausea and vomiting.

CONCLUSION

Single dose of palonosetron with dexamethasone combination is more effective than equipotent doses of ondansetron with dexamethasone given toward end of surgery along with ondansetron given 8 hourly for prevention of PONV up to 48 hours in post chemotherapy ovarian cancer surgeries receiving opioid-based patient controlled analgesia.

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Conflicts of interest

There are no conflicts of interest.

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