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PONV prophylaxis after laparoscopic procedures - Comparison between Palonosetron 0.075mg, Palonosetron 0.15mg and a Palonosetron-Dexamethasone combination : a randomised controlled trial

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Abstract : *Background :* Postoperative nausea and vomiting (PONV) is one of the common complications after surgery. This randomized double-blind study was planned to compare the effectiveness of different antiemetic regimens for PONV prophylaxis in moderately high-risk patients.

Methods : One hundred and sixty adult ASA grade I-II female patients undergoing day care gynecological laparoscopic procedures were randomly allocated into four groups. Group 1 patients (Control group) received 4 mg ondansetron, group 2 (P75 group) patients received 0.075 mg palonosetron, group 3 (P150 group) patients received 0.150 mg palonosetron, and group 4 (PD group) patients received 0.075 mg palonosetron and 8 mg dexamethasone after induction of anesthesia. Anesthesia was induced with propofol and fentanyl, and maintained with N2O-isoflurane in oxygen. The number of complete responders, frequency of nausea and vomiting episodes and the requirement of rescue antiemetic during 0-6 h, 6-24 h and 24-72 h after surgery were recorded.

Results : Patients receiving dexamethasone and palonosetron combination had significantly less vomiting ($p = 0.03$) and required less rescue antiemetic as compared to Control group ($p = 0.014$). The incidence of nausea was low in all palonosetron groups as compared to the ondansetron group. The complete response rate was significantly high in the PD group as compared to other groups ($p = 0.012$). There was no significant difference in nausea and vomiting in patients receiving palonosetron 0.075 mg or 0.15 mg.

Conclusions : We conclude that a dexamethasone-palonosetron combination is more effective than ondansetron and palonosetron alone for the prevention of PONV, while palonosetron 0.150 mg has no significant benefit over 0.075 mg for PONV prophylaxis in moderately high-risk patients.

Introduction

Postoperative nausea and vomiting (PONV) remains a most distracting side effect after general anesthesia. The incidence of PONV following laparoscopic surgery is unacceptably high and ranges between 50 and 70% without active intervention (1, 2). Postoperative emesis not only predisposes patients to wound dehiscence and psychological distress (3), but frequently delays their discharge from the hospital after planned ambulatory surgery (4). The ondansetron and palonosetron as first and second generation of 5-hydroxytryptamine-3 (5-HT3) receptor antagonists are commonly used for the prevention of PONV in moderate to high-risk patients because of better efficacy and favorable side effects as compared to other antiemetics (5, 6). Compared with ondansetron, palonosetron has greater affinity for 5-HT3 receptors (7), although a recent meta-analysis has shown that palonosetron was not more efficacious than ondansetron in the prevention of early PONV after laparoscopic surgery (8). However, a dose-response trend was observed with increasing doses of palonosetron in the prevention of PONV during the first 24 hours after surgery (9). Palonosetron has also been recommended in quite high doses (0.25-0.75 mg) for the prophylaxis of chemotherapy-induced nausea and vomiting (10), although higher doses of palonosetron are not used frequently for the prophylaxis of PONV.

Dexamethasone has recently emerged as a potentially useful antiemetic for the prophylaxis of PONV with minimal side effects after a single dose administration. The efficacy of dexamethasone has been reported to be equivalent to 5-HT3 antagonists when used alone (11-14). Few studies have shown the synergistic action of dexamethasone with

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5-HT3 antagonists and found that the combination of drugs was more effective at reducing PONV as compared to each drug alone (15-16). Therefore, this randomized double-blind study has been designed to compare the efficacy of palonosetron 0.075 mg, palonosetron 0.150 mg and a palonosetron-dexamethasone combination with conventional antiemetic ondansetron for the prevention of PONV in patients undergoing day care gynecological laparoscopic procedures. The primary aim of the study was to compare the number of complete responders among groups.

Materials and methods

This randomized parallel group trial was conducted at a tertiary care hospital after Ethical Committee approval and written informed consent from the patients. A total 160 female patients of ASA physical status I-II between 19 and 60 years of age scheduled to undergo day care laparoscopic gynecological procedures were included in the study. Patients with gastrointestinal diseases, smoking habits, body mass index higher than 40 Kg m-2, past history of motion sickness or excessive PONV were excluded. The patients were randomly allocated to four groups: Group 1 patients received 4 mg ondansetron (control group), group 2 patients received 0.075 mg palonosetron (P75 group), group 3 patients received 0.150 mg palonosetron (P150 group), and group 4 patients received 0.075 mg palonosetron and 8 mg dexamethasone intravenously before induction of anesthesia (PD group). The random allocation of patients was done using a computer-generated random number chart, with the numbers kept sequentially in opaque sealed envelopes, which were opened just before shifting the patient inside the operation room. The study drugs were prepared by a person not involved in patient management or data collection. The anesthesiologist who collected postoperative data, surgeon and the patients were blinded to the group allocation. Ethics approval for this randomized double-blind trial was obtained from the "Institute Ethics Committee" of the institute (ref. no.MS/23142). The study was registered into a clinical trial registry (CTRI/2014/11/005214).

The patients were kept fasting for 8 hours for solid food and received oral alprazolam and ranitidine at night and 2 hours before surgery. Anesthesia was induced with propofol (2-3 mg Kg-1) and fentanyl (2 µg Kg-1). Vecuronium was used to facilitate endotracheal intubation. Anesthesia was maintained with isoflurane and 60% N_2O in oxygen. Routine monitoring of the electrocardiographam (ECG), non-invasive blood pressure (NIBP), and pulse oximetry (SpO_2) was used during the intra-operative period. After induction, a nasogastric tube was inserted and suction was applied to empty the stomach of air and other contents. The intra-abdominal pressure was maintained between 10 to 15 mmHg during laparoscopy. All patients received intramuscular diclofenac sodium 75 mg, approximately 20 to 30 minutes before the end of the procedure. After completion of surgery, the residual neuromuscular blockade was reversed with the intravenous administration of glycopyrrolate 10 µg Kg-1 and neostigmine 50 µg Kg^{-1}. The duration of CO_2 insufflation and the total volume of fluid administered during surgery were recorded.

The patients were assessed during 6 hours after surgery in the post anesthesia care unit for the incidence and severity of nausea and vomiting by a blinded observer. The severity of nausea was assessed by using a visual analogue scale (VAS; 0-10; 0 = no nausea and 10 = worst possible nausea). A score of 5 or more was considered as severe nausea. Rescue antiemetic metoclopramide 10 mg IV was given on complaining of severe nausea or having any vomiting episode. Postoperative pain was assessed using a visual analogue scale (VAS; 0-10; 0 = no pain, 10 = worst imaginable pain) and injection diclofenac 1.5 mg Kg-1 was given on demand or when VAS was found 4 or more. Any drug-related adverse effects like headache, dizziness, and abdominal disturbances (constipation/diarrhea) were recorded. The patients were discharged home 6 hours after surgery if they were fully awake, pain free, having no nausea or vomiting, and were instructed to take metoclopramide 10 mg orally if having severe nausea or vomiting. They were contacted by telephone on the next day and then after two days to determine the incidence of PONV, antiemetic requirement and adverse effects during the period ranging between the 6th to 24th hour and the 24th to 72d hour after surgery. Complete response rate (no emesis and no rescue antiemetic) (primary outcome), during acute (0-6 h), early (0-24 h) and late (24-72 h) postoperative period was calculated.

Statistical analysis

The statistical analysis was performed using IBM SPSS software version 22.0. The normally distributed data were compared using one-way ANOVA. For intergroup comparisons, independent student t-test was used. A Bonferroni's correction was

applied for multiple comparisons. The categorical variables like incidence of PONV and complete response rate were compared using Chi-square tests or Man Whitney U tests. All statistical tests were performed at a significance level of $\alpha = 0.05$. Sample size was calculated presuming 50% incidence of PONV in patients undergoing laparoscopy. Power analysis assuming at least 30% reduction in the incidence of PONV after antiemetic prophylaxis, with 80% power showed that a minimum of 37 patients was required in each group. To minimize the effect of data loss, a total 160 patients was enrolled.

Results

In total, 160 patients were recruited from February 2015 to October 2018. Two patients of PD group were lost at follow up (Fig. 1). The demographic data of the patients and the type of surgical procedures performed were comparable between groups (Table 1). The duration of surgery was around 30 to 80 minutes in all groups. Propofol and fentanyl consumptions were comparable between groups. The duration of anesthesia and CO_2 insufflation, and amount of intraoperative intravenous fluid administration was also comparable between groups (Table 2).

The incidence of vomiting was less than 25% in all groups. Patients receiving palonosetron and dexamethasone had significantly less PONV at 0-24 h and 0-72 h as compared to the Control group. The complete response rate was 97.5%, 92.5% and 95% during 0-24 h, 0-72 h, and 24-72 h, respectively, in the PD group as compared to 72.5%, 57.5% and 80% in the Control group (Table 3).

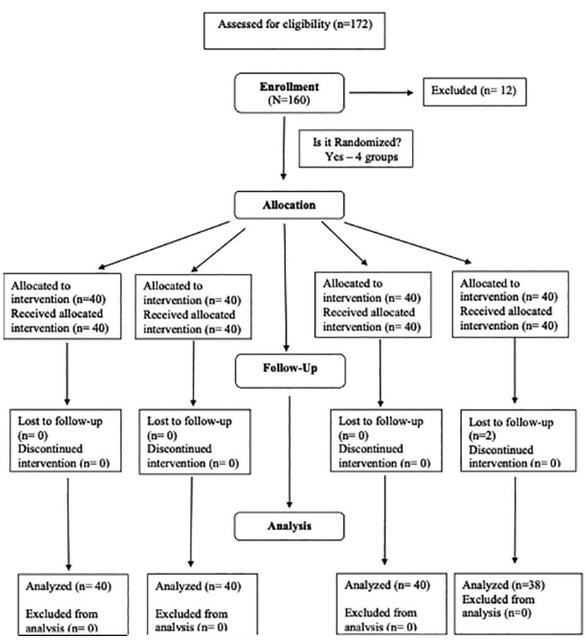

Fig. 1. — Flowchart.

Although the incidence of nausea was low in all palonosetron groups as compared to the ondansetron group (Control group), it was not statistically significant (Table 4). Patients receiving the dexamethasone and palonosetron combination required significantly less rescue antiemetic medications as compared to the Control group ($p = 0.014$). There was no significant difference in nausea and vomiting in patients receiving palonosetron 0.075 mg or 0.15 mg (Table 4).

The intraoperative heart rate and blood pressure were within normal limits and comparable between groups. The postoperative pain scores and rescue analgesic requirements were also comparable between groups. No episode of diarrhea or dizziness was recorded. Two patients in the P75 group and one in the P150 group complained of headache. One patient required hospital admission due to high grade fever during the postoperative period.

Discussion

The incidence of PONV following day care surgery is equally high and may range from 30 to 70% (17-18). Several risk factors have been identified such as female gender, non-smoking status, certain drugs used during the perioperative period (volatile anesthetics, nitrous oxide, opioids, neostigmine, …), and intra-abdominal and laparoscopic surgeries (19). Various receptor antagonists and drug combinations have been suggested for PONV prophylaxis and treatment in moderate to high risk patients. The present study was conducted to compare the most recommended drugs for high risk PONV patients in a single platform. In the present study, we found that the patients receiving the dexamethasone and palonosetron combination had a very low incidence of PONV as compared to the other groups. The complete response rate during 0-72 h after surgery was 57.5% in the ondansetron group (Control group) and 75-77.5% in patients receiving palonosetron alone, while it was 92.5% in the PD group. The incidence and severity of nausea was low (7.5%) in all groups receiving palonosetron as compared to the Control group. There was no significant difference in nausea, vomiting and complete response rate between the P75 and P150 groups.

The selective 5-HT3 antagonists, palonosetron, has been proven a particularly valuable addition to the armamentarium against PONV. Though, the use of palonosetron has reduced the risk of PONV, it has

Table 1
Demographic data

Variables	Control group (n=40)	P75 group (n=40)	P150 group (n=40)	PD group (n=38)
Age (Yr)	29.30±5.0	30.82±5.4	29.21±6.28	28.51±5.6
Weight (Kg)	59.00±11.9	58.55±9.7	57.00±10.76	58.52±9.32
ASA (I:II)	32:8	33:7	32:8	27:10
Diagnosis				
Infertility	25	28	29	24
Adenexal mass	1	3	3	4
Ovarian cyst	9	4	6	6
Endometrial cyst	3	5	1	3
Polycystic ovarian disease	2	0	1	1
Surgery				
Diagnostic hysterolaparoscopy	25	28	29	24
Lap. Cystectomy	12	9	7	9
Salpingo-ophrectomy	1	3	3	4
Ovarian drilling	2	0	1	1

Data presented as mean ± SD or number of patients.

Table 2
Intraoperative data

	Control group (n=40)	P75 group (n=40)	P150 group (n=40)	PD group (n=38)	P value (CI)
Duration of CO_2 insufflation (min)	54.28±24.16 (38.26, 62.18)	44.81±21.38 (34.42, 61.72)	45.26±28.47 (35.41, 58.62)	51.70±26.61 (36.71,54.32)	0.162 (.062, .236)
Duration of surgery (min)	66.68±34.08 (56.39,78.30)	54.51±20.73 (54.68,74.38)	54.62±32.47 (44.24,65.00)	63.90±30.75 (48.31,62.21)	0.093 (.023, .297)
Duration of Anesthesia (min)	86.24±38.85 (74.39,99.40)	69.02±24.16 (69.24,89.51)	68.70±32.95 (58.16,79.23)	78.90±31.45 (61.48,77.72)	0.149 (.050, .338)
IV fluid (ml)	1000±474 (848.5,1151. 5)	1334±384 (1211.5,1457.5)	1325±461 (1177.5,1472.5)	1653±821 (1390.9,1916.6)	0.081 (.012, .261)

Data presented as mean± SD (CI).

Table 3
Complete response rate

	Control group (n=40)	P75 group (n=40)	P150 group (n=40)	PD group (n=38)	P value (CI)
(0-72 h)	23 (57.5%). (37.8, 72.4)	30 (75%) (62.5, 92.4)	31 (77.5%) (65.1, 87.5)	37 (92.5%)* (82.6, 100.0)	0.012 (.013,.466)
(0-6 h)	37 (92.5%) (77.6, 100.0)	38 (95%) (87.6, 100)	37 (92.5%) (77.6, 100.0)	39 (97.5%) (92.5, 100.0)	0.78 (.068,.246)
(6-24 h)	32 (80%) (65.1, 92.4)	33 (82.5%) (58.0, 94.8)	35 (87.5%) (77.5, 95.0)	39 (97.5%) (90.1, 100.0)	0.09 (.099,.328)
(0-24 h)	29 (72.5%) (55.1, 90.0)	31 (77.5%) (65.1, 87.5)	33 (82.5%) (70.0, 99.9)	39 (97.5%)* (92.5, 100.0)	0.034 .024,.319)
(24-72 h)	34 (85%) (72.5, 97.4)	38 (95%) (87.6, 100.0)	39 (97.5%) (92.5, 100.0)	38 (95%) (82.6, 100.0)	0.12 (.027,.349)

Data presented as number of patients (%). *Alpha value calculated for between groups comparison was found to be 0.00625. It was found significant between group 1 and 4

not been completely eliminated (8). Palonosetron was found to be well tolerated and safe, and has been used in doses up to 0.75 mg in elderly patients (with high frequency of co-morbidities) receiving moderately emetogenic chemotherapy (14). A dose-response trend in the complete response rate has been observed with increasing doses of palonosetron during 0-72 hours after surgery. In a multicenter double-blind study comparing three doses of palonosetron (0.025, 0.050 and 0.075 mg), Kovac et al. (20) found that palonosetron 0.075 mg was associated with less intense nausea during the 0–72 h period ($p < 0.001$) and significantly delayed median time to emesis ($p = 0.002$) as compared to placebo. The complete

Table 4
Postoperative Nausea-vomiting

	Control group (n=40)	P75 group (n=40)	P150 group (n=40)	PD group (n=38)	P value (CI)
Nausea					
(0-72 h)	8 (20%) (3.9,26.9)	3 (7.5%) (0,17.1)	3 (7.5%) (0,15.3)	3 (7.5%) (0,15.3)	0.25 (.052,.355)
(0-6 h)	1(2.5%) (.0,5.8)	1 (2.5%) (.0,9.9)	-	-	1.00
(6-24h)	4 (10%) (.1,22.4)	2 (5%) (.0,12.5)	2 (5%) (.0,12.4)	1 (2.5%) (.0,9.9)	0.63 (.045,.290)
(0-24 h)	5(12.5%) (.1,22.4)	2 (5%) (.0,12.5)	2 (5%) (.0,12.5) -	1 (2.5%) (.0,9.7)	0.43 (.039,.324)
(24-72 h)	3 (7.5%) (.1 ,14.6)	1 (2.5%) (.0,7.3)		2 (5%) (.0,12.7)	0.51 (.037,.362)
Vomiting					
(0-72 h)	9 (22.5%) (7.6, 37.3)	8 (20%) (10, 37.4)	6 (15%) (1, 24.9)	1 (2.5%)* (.0, 7.5)	0.03 (.136,.316)
(0-6 h)	1 (2.5%) (.0, 9.9)	2(5%) (.0, 17.5)	2 (5%) (.0, 14.8)	1 (2.5%) (.0, 9.9)	1.00 (.045,.271)
(6-24 h)	5 (12.5%) (2.6, 27.2)	5 (12.5%) (.2, 22.4)	3 (7.5%) (.1, 22.3)	-	0.09 (.013,.338)
(0-24 h)	6 (15%) (.1, 24.9)	6 (15%) (1, 24.9)	5 (12.5%) (2.6, 27.2)	1 (2.5%) (.0, 7.59)	0.06 (.083,.351)
(24-72 h)	3 (7.5%) (1.9, 15.3)	1 (2.5%) (.0, 9.9)	1 (2.5%) (.0, 7.6)	-	0.40 (.087,.285)
Antiemetic	17(42.5%) (25.1, 54.9)	8(20%) (10,37.4)	6(15%) (1, 24.9)	2*(5%) (.0, 17.5)	0.014 (.0128,.597)

Data presented as number of patients (%) and (CI). *Alpha value calculated for between 4 groups comparison was found to be 0.00625. It was found significant between group 1 and 4.

response rates for placebo and palonosetron 0.075 mg were 36% and 56% for the 0–24 h period (p = 0.001), and 52% and 70% for the 24–72 h period (p = 0.002), respectively, while complete response rate for 0.025 mg and 0.050 mg palonosetron were not found superior to placebo. Basu et al (21) reported that a single dose of 0.25 mg palonosetron was superior to granisetron (3.0 mg) or ondansetron (8.0 mg) in completely preventing postoperative nausea and vomiting for the first 24 h after middle ear surgery. The incidence of emesis-free patients was 100% during the 0-6 h and 96% during the 6-24 h postoperative period in the palonosetron groups. In the present study, the complete response rate was higher in both palonosetron groups as compared to the ondansetron group during the 0-72 h period, though there was no significant difference observed in the complete response rate between the P75 and P150 groups. In contrast to other 5-HT3 blockers, palonosetron also exhibits anti-nauseous effect even at lower doses (0.025 mg). In the present study, the incidence and severity of nausea was very low in all patients receiving palonosetron (P75, P150, and PD group) and none of the patient required rescue antiemetic medications.

Dexamethasone acts through the antagonism of prostaglandins, serotonin inhibition in the gut, and by releasing endorphins. It has been reported as effective as 5-HT_3 blockers for the prevention of PONV in laparoscopic cholycystectomy patients (15). However, the combination of dexamethasone and 5-HT3 blockers was found to be more effective in PONV prophylaxis than each drug alone (22-24). A recent meta-analysis comparing different categories of drugs used to reduce the incidence of PONV following laparoscopic cholecystectomy has shown that dexamethasone and 5-HT3 blockers combination should be preferred in the high-risk category of patients (14), although the different doses of anti-emetics were not compared in this meta-analysis. In the present study, we also found a very low incidence of nausea and vomiting in patients receiving palonosetron and dexamethasone. No significant adverse effects were reported in any group, except for headache, which was managed using simple analgesics like paracetamol. The main limitation of our study was that we did not include a placebo group due to the high incidence of PONV after laparoscopic surgery. The differences in the average time taken for nausea and vomiting to appear

could not be analyzed, as most of the patients were discharged 6-8 h after surgery and many patients who had nausea or vomiting after discharge could not record the exact time. All our patients were females undergoing gynecological surgery, therefore our results cannot be generalized to another population. Further, large multicentric trials are needed to evaluate the efficacy and safety of high dose palonosetron for PONV prophylaxis in high risk patients.

We conclude that a dexamethasone and palonosetron combination is superior to ondansetron and palonosetron alone, while palonosetron 0.150 mg shows no significant benefit over palonosetron 0.075 mg for the prevention of PONV after gynecological laparoscopic day care surgery.

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