International Journal of Health Sciences and Research
www.ijhsr.org ISSN: 2249-9571

Original Research Article

A Comparative Study of Combination Therapy of Palonosetron plus Dexamethasone versus Dexamethasone Alone For Prophylaxis of Postoperative Nausea and Vomiting In Elective Surgery under General Anaesthesia

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ABSTRACT

Background: Postoperative nausea and vomiting is an unpleasant and distressing adverse effect after anaesthesia and surgery which may result in wound dehiscence, bleeding, dehydration, electrolyte imbalance, pulmonary aspiration of gastric contents and delayed hospital discharge leading more expenses to the patient. Multiple studies were being conducted to find out an amicable solution to this problem.
Aims and Objectives: The study was to compare the efficacy of preoperative palonosetron plus dexamethasone combination therapy versus dexamethasone monotherapy for the prevention of postoperative nausea and vomiting (PONV) following any elective surgery under general anaesthesia.
Methods: It was a prospective, randomized controlled and double blind study where 100 patients of either sex, ASA I & II, aged 18-65 years were enrolled to receive either10 mg dexamethasone and 0.075 Palonosetron or 10 mg dexamethasone (total volume of 5 ml made with normal saline) slow IV, 10 minutes before induction of anaesthesia.
Results: During the first 24 hours postoperative, the incidence of nausea, retching and vomiting in the palonosetron plus dexamethasone group were 20%, 18% and 16% respectively and lesser as compared to 40%, 30% and 38% in the dexamethasone group alone, with p=0.04, p=0.24 and p=0.02 respectively. Complete response was more in the palonosetron plus dexamethasone group (80% versus 60%) with p=0.04
Conclusion: The study showed that prophylactic administration of intravenous palonosetron plus dexamethasone can effectively control postoperative nausea and vomiting as compared to dexamethasone alone.

Key words: - PONV, Combination, Palonosetron, Dexamethasone

INTRODUCTION

Postoperative nausea and vomiting is an unpleasant and distressing complication after anaesthesia and surgery which may result in wound dehiscence, bleeding, dehydration, electrolyte imbalance, pulmonary aspiration of gastric contents and delayed hospital discharge causing more expenses to the patient. [1] It has got an incidence of 30% to 40% in normal population undergoing general anaesthesia, while the incidence touches a peak of 75% to 80% in certain high risk groups. [2] So, understanding its neurophysiology, sorting out the risk factors and cumulating knowledge about the various antiemetics available are the need of the hour.

Risk factors of postoperative nausea and vomiting (PONV) include younger age, female gender, nonsmoker, better ASA status, [3] previous history of postoperative nausea and vomiting (PONV) and motion sickness, anxiety, gastroparesis, type and duration of surgical procedure, decreased perioperative fluids; use of volatile anaesthetics, nitrous oxide, large dose of neostigmine or intraoperative and postoperative opioids for the pain management. [4] And as a relief to the discomfort caused to the patients by PONV, an array of anti-emetics are available, which include the traditional ones (like scopolamine, promethazine, droperidol, metoclopramide), non-traditional ones (like propofol, dexamethasone) and the newer serotonin receptor antagonists (like palonosetron, granisetron, ondansetron). [5] Currently 5HT3 receptor antagonists are frequently used for the prevention of postoperative nausea and vomiting (PONV) because of their efficacy and fewer side effects. Combination therapy has been shown to be superior to the use of a single agent which may be due to the multifactorial causation of PONV involving multiple pathways and receptors. Choosing agents that act through different mechanisms is the key to the successful use of combination therapy. [6]

Palonosetron, second generation serotonin receptor antagonist, has been shown to be superior to other drug in preventing nausea and vomiting as it has greater receptor binding affinity and longer half life. [2]

Dexamethasone may exert central anti emetic action mainly through the activation of the glucocorticoid receptor in the nucleus of solitary tract, the nucleus of raphe and the area postrema. Additionally dexamethasone can prevent nausea and vomiting associated with intravenous and epidural opioids for postoperative pain control. [2] It has also been demonstrated that combining a 5-HT3 receptor antagonist (ondansetron, palonosetron) with dexamethasone is more effective in preventing postoperative nausea and vomiting (PONV) than ondansetron, palonosetron or dexamethasone alone.

So, keeping in mind the recently concluded fact that a multimodal management and routine antiemetic prophylaxis resulted in an increased level of patients satisfaction than symptomatic treatment in high risk population, which was supported by the numerous studies done on this topic, [7,8] we would compare the antiemetic effect of dexamethasone alone (monotherapy) and palonosetron with dexamethasone (combination therapy) in the management of postoperative nausea and vomiting in our study.

AIMS AND OBJECTIVE

The aim of the study was to find out and compare the efficacy of preoperative palonosetron plus dexamethasone combination therapy versus dexamethasone monotherapy for the prevention of postoperative nausea and vomiting (PONV) following any elective surgery under general anaesthesia.

MATERIALS AND METHODS

The study was a randomized, prospective, double blind one conducted in a tertiary care centre, at Imphal, Manipur during September 2015 to October 2017. After taking approval from the Institutional Ethics Committee and written informed consent from 100 patients of either sex, scheduled for elective surgery under general anaesthesia, aged 18-65 years and ASA I&II were assigned into two groups by computer generated randomization as PD and D groups to receive combination of 0.075 mg palonosetron with 10 mg dexamethasone and 10 mg dexamethasone respectively. Patients with intestinal, liver or renal disease, pregnant or menstruating patients, psychiatric disorder, patients with history of motion sickness and postoperative nausea and vomiting (PONV), on antiemetic drugs within 24 hrs preoperatively, patients who received cancer chemotherapy within the past four weeks and emetogenic radiotherapy within the past 8 weeks were

excluded from the study. Patients hypersensitive to 5 HT3 antagonists and dexamethasone and on chronic steroid therapy or immunocompromised were also not considered for the study.

Sample size was calculated based on a previous study [9] and assuming an alpha value of 5% and power of 80%, with complete response of 67% and 90% ($p<0.05$) in palonosetron with dexamethasone and dexamethasone alone respectively in 2-24 hrs, the size of the study was fixed at 50 with consideration of any drop outs.

A uniform anaesthetic technique was advocated for all the patients. All patients were advised overnight fasting and premedicated with tablet alprazolam 0.5mg and tablet ranitidine 300mg orally the night before surgery.

Injection ranitidine 50 mg and glycopyrrolate 0.2 mg were given by intravenous (IV) route, half an hour before start of the anaesthetic procedure. The study drugs prepared in identical syringes, containing either 10 mg dexamethasone and 0.075 palonosetron or 10 mg dexamethasone (total volume of 5 ml made with normal saline) were then injected. The study drugs were administered slow IV, 10 minutes before induction of anaesthesia.

After preoxygenation, induction was done with i.v. propofol 1.5 mg/kg, followed by i.v. vecuronium bromide 0.08 mg/kg with 100% oxygen to facilitate direct laryngoscopy and intubation with endo-tracheal tube of appropriate size. The anesthesia was maintained with sevoflurane, nitrous oxide in oxygen, followed by intermittent bolus doses of vecuronium bromide (0.01-0.02 mg/kg body weight). Butorphanol 15 microgram/kg was used as an analgesic. At end of the operation, residual neuromuscular blockade was reversed with Inj neostigmine 2.5 mg and glycopyrrolate 0.5 mg.

Intraoperative monitoring of heart rate (HR), non-invasive blood pressure (NIBP), electrocardiography (ECG), oxygen saturation (SpO_2), and end-tidal carbon dioxide ($ETCO_2$) were done.

After the surgery, data was collected upto 24 hours postoperatively. The follow up of the patients during the first 2 hours were undertaken in the post-anaesthesia care unit (PACU) and thereafter (2-24 hrs.) in the ward and patients were evaluated for postoperative nausea vomiting (PONV), rescue antiemetic and adverse effects of drugs for the first 24hrs after anaesthesia. Metoclopramide 10 mg was given as the rescue antiemetic.

The severity of postoperative nausea and vomiting (PONV) was measured on a four-point (0-3) scoring system based on the study reference [10] PONV score 0 = no nausea and no retching, 1 = complaining of sickness and retching, 2 = vomiting one or two time in 30 min and 3 = vomiting more than two times in 30 min

The data collected were analyzed using Statistical Package for Social Sciences (SPSS Inc. Chicago 2, USA) windows based version 21.0 and were presented in a tabulated manner. Comparisons between the groups were performed by using Fisher's Exact test or Chi Square test as appropriate. The results were expressed in mean±SD and number (%.) and $p<0.05$ was considered to be significant.

RESULTS AND OBSERVATIONS

The demographic parameter in the two groups were comparable and are shown in Table 1

Table 1 showing the comparison and distribution of demographic parameter in the two groups.

Sl no	*Parameter*	*Palonosetron plus dexamethasone group(N=50)*	*Dexamethasone group(N=50)*	*p value*
1	Age in year(Mean±SD)	40.29±10.66	40.66±11.01	0.81
2	Sex (Male:Female)	12:38	16:34	0.50
3	Weight in Kgs (Mean±SD)	60.36±14.3	58.32±10.2	0.42
4	Height in Cms (Mean±SD)	156.3±6.6	158.1±7.3	0.20
5	ASA(I:II)	39:11	38:12	1.00
6	H/O smoking (Yes:No)	38:12	33:17	0.38
7	Duration of Anaesthesia (mins)	79.4±26.6	79.8±25.7	0.94
8	Duration of surgery (mins)	69.6±30	68.7±26.5	0.88

p<0.5 is significant

The incidence of nausea, retching and vomiting were more in the dexamethasone group in the first 0-2 hours and was statistically significant except for retching with a p value of 0.15. Maximum number of rescue antiemetic were given in dexamethasone group while complete response were recorded more in the palonosetron plus dexamethasone group (p=0.04). In the next 2-24 hours, more patients with nausea, retching and vomiting were recorded in dexamethasone group even though not significant. There were also more patients with complete response in the palonosetron group with lesser requirement of rescue as shown in table 2. So, the distribution in the overall 0-24 hours was more favourable in the palonosetron group with significant lesser incidence of nausea and vomiting and more complete response.

Table 2 showing the distribution of PONV parameters in the two groups at different time intervals.

Time duration	*Parameters*	*Palonosetron plus dexamethasone group(N=50)*	*Dexamethasone group(N=50)*	*p value*
0-2 hours	*Nausea*	10(20%)	20(40%)	0.04*
	Retching	8(16%)	15(30%)	0.15
	Vomiting	8(16%)	19(38%)	0.02*
	Complete response	40(80%)	30(60%)	0.04*
	Rescue	10(20%)	20(40%)	0.04*
2-24 hours	*Nausea*	3(6%)	6(12%)	0.49
	Retching	2(4%)	3(6%)	1.0
	Vomiting	3(6%)	6(12%)	0.48
	Complete response	47(94%)	44(88%)	0.48
	Rescue	3(6%)	6(12%)	0.48
0-24 hours	*Nausea*	10(20%)	20(40%)	0.04*
	Retching	9(18%)	15(30%)	0.24
	Vomiting	8(16%)	19(38%)	0.02*
	Complete response	40(80%)	30(60%)	0.04*
	Rescue	10(20%)	19(38%)	0.07

p<0.05 is significant

The adverse effects such as headache and dizziness were minimal and comparable in the two groups, as shown in Table 3

Table 3 showing the comparison and distribution of side effects in the two groups

Parameter	*Palonosetron plus dexamethasone group(N=50)*	*Dexamethasone group(N=50)*	*p value*
Headache	1	1	1.00
Dizziness	1	1	1.00

p<0.5 is significant

DISCUSSION

Postoperative nausea and vomiting is an unpleasant and distressing adverse effect after anaesthesia and surgery faced by the patients with an incidence of 30% to 40% in normal population undergoing general anaesthesia, while the incidence touches a peak of 75% to 80% in certain high risk groups. [2]

Palonosetron is a second generation serotonin receptor antagonist which has been shown to be superior to other drug in preventing acute, chronic and chemotherapy induced nausea and vomiting as it has greater receptor binding affinity and longer half life (37hrs) [2] and found to be more effective antiemetic than granisetron [9] and ondansetron. [11] Dexamethasone, an inexpensive, effective and safe anti emetic, exerting its anti emetic action mainly through the activation of the glucocorticoid receptor in the nucleus of solitary tract, the nucleus of raphe and the area postrema is also found to be an effective antiemetic. [2] There were some debates in relation to the dose of palonosetron [12] and dexamethasone [13] as the prophylaxis of PONV during our study. We considered to use the dose of 0.075mg of palonosetron as it was most frequently used in various previous studies. [2,8]

The effectiveness of a combination therapy with 5HT3 inhibitors (e.g. ondansetron, ramosetron and palonosetron) and dexamethasone as prophylaxis of PONV in highly emetogenic surgical procedures like laparoscopic surgeries and chemotherapy were compared in numerous

studies conducted. Similarly, our study has been conducted comparing palonosetron-dexamethasone combination and dexamethasone monotherapy as prophylaxis of PONV in any elective surgery under general surgery.

In our study, patient's age, weight, height, gender, ASA, type of surgery, duration of surgery and duration of anaesthesia in the both the groups were comparable. This has been able to reduce the preoperative risk factors bias among the study groups.

In the present study, the incidence of nausea, retching and vomiting were significantly lesser for the palonosetron plus dexamethasone group (20%, 16% and 16% respectively) in the first 0-2 hrs observation than the dexamethasone group (40%, 30% and 38% respectively). Similar results were reported on the study done by Mansour EE, [8] where the incidence of PONV for palonosetron plus dexamethasone and dexamethasone alone at 0-6 hrs which were 12 % and 36% respectively. Seung-hwaRyoo et al [2] also showed similar results favouring palonosetron plus dexamethasone for the control of PONV.

The incidence of nausea, retching and vomiting in 2-24 hrs postoperative period were 6%, 4% and 6% respectively in palonosetron plus dexamethasone group and 12%, 6% and 12% respectively in the dexamethasone group and the results were almost comparable(P>0.05). However, Seung-hwaRyoo et al [2] found the incidence of nausea and vomiting as 42% and 16% respectively in palonosetron-dexamethasone group versus 59% (p=0.025) and 20% respectively in dexamethasone group during 6-24 hrs and this may be attributed due to the involvement of all female patients and used of intravenous patient controlled opioid analgesic in their study. The study by Mansour EE [8] also found out that the incidence in the palonosetron plus dexamethasone group were found to be gradually decreased when compared to dexamethasone group during 6-12 hrs and 12-24 hrs. The incidence of nausea and vomiting was 12% for palonosetron plus dexamethasone and 36% for dexamethasone during 6-12 hrs (p<0.01) and during 12-24 hrs the incidence of nausea and vomiting were 16% v/s 48% in palonosetron plus dexamethasone and dexamethasone respectively (p<0.01). The higher incidence of PONV in the later part of their study as against our finding may be due the enrollment of laparoscopic patients which itself are high risk for PONV. In the same study, regarding complete response for PONV it was observed to be 84% and 48% in palonosetron plus dexamethasone group and dexamethasone group respectively (p<0.01) over 24 hrs. These results were comparable to our study as the complete response were observed in 80% and 60% in palonosetron plus dexamethasone and dexamethasone group respectively over 24 hrs which was statistically significant.(p=0.049)

The use of antiemetic in our study was significantly reduced in palonosetron plus dexamethasone group than in dexamethasone group during first 2hrs (20% vs40%) (p=0.049) respectively and it was reduced in the palonosetron plus dexamethasone group in the overall 24 hours postoperative. However, Mansour EE [8] also reported that the difference in use of rescue antiemetic in palonosetron plus dexamethasone and dexamethasone group was statistically significant during 6-12 hrs (2% vs 20% respectively) (p<0.01), 12-24 hrs (2% and 28% respectively) (p<0.01) and 0-24 hrs (4% and 30% respectively) (p<0.01).

Likewise, Seung-hwa Ryoo et al [2] found out that the use of rescue antiemetic was significantly reduced in palonosetron plus dexamethasone than in dexamethasone group (13% vs 24% respectively) (p=0.043). However in the next 6-24 hrs the results of both the groups were comparable (11% vs 12% respectively) which may be due to the onset and the duration of the drugs used.

In our present study, the incidence of adverse effects was minimum and not statistically significant. There was only one

episode of headache as well as dizziness in both the groups during 0-24 hrs which was comparable with the study done by Mansoor EE [8] where only one patient in the palonosetron plus dexamethasone group complained of headache. However Seung-hwa Ryoo et al [2] found out that headache occurred more frequently in the palonosetron plus dexamethasone group than the dexamethasone alone group (20% vs 10% respectively) but it was not statistically significant (p=0.067). Headache, which is one of the commonest side effects of 5-HT3 receptor antagonist, occurs more frequently in patients who received palonosetron plus dexamethasone combination therapy, but in our study the results were inconclusive; and this may be due to lower sample size to assess the adverse effects.

Our study was not without any limitations. Use of butorphanol as an analgesic which being an opioid has nausea as its side effect while propofol as the induction agent has some anti emetic effect. The study should have concentrated mainly on emetogenic surgeries like strabismus surgery, bariatric surgery, laparoscopic cholecystectomy rather than including any surgery under general anaesthesia. The study period was only upto 24 hrs after the surgery. Hence if the patient had any complain of nausea and vomiting after that period, the incidence of PONV during 24-48 hrs could not be collected.

CONCLUSION

It can be concluded from the present study that combination therapy of intravenous palonosetron and dexamethasone was more effective than monotherapy of dexamethasone alone in prevention of postoperative nausea and vomiting in patients undergoing any elective surgery following general anaesthesia without any major adverse effects.

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How to cite this article: Devi NA, Devi LE, Bhattacharya A et al. A comparative study of combination therapy of palonosetron plus dexamethasone versus dexamethasone alone for prophylaxis of postoperative nausea and vomiting in elective surgery under general anaesthesia. Int J Health Sci Res. 2018; 8(5):97-103.

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