

## A PROSPECTIVE OBSERVATIONAL STUDY TO COMPARE THE ANTIEMETIC EFFICACY AND SAFETY PROFILE OF TWO COMBINATIONS NAMELY ONDANSETRON-DEXAMETHASONE VERSUS PALONOSETRON-DEXAMETHASONE IN PROPHYLAXIS OF CISPLATIN INDUCED EMESIS

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### ABSTRACT

#### BACKGROUND

Chemotherapy Induced Nausea and Vomiting (CINV) are among the most distressing symptoms for cancer patients and preventing this can lead to a better treatment outcome. Serotonin (5-HT<sub>3</sub>) receptor antagonists in combination with Dexamethasone remains the mainstay of treatment in chemotherapy-induced emesis. The purpose of this study is to compare the antiemetic efficacy and safety profile of Ondansetron, a first generation 5-HT<sub>3</sub> receptor antagonist versus Palonosetron, a second generation 5-HT<sub>3</sub> receptor antagonist, both in combination with Dexamethasone, in Cisplatin-induced emesis. This prospective observational study done over a period of 1 year included 120 adult patients scheduled for their first cycle of Cisplatin based chemotherapy regimen in a tertiary care centre of Kerala. These patients were divided into two groups of 60 patients each; group 1 received Ondansetron (8 mg) with Dexamethasone (8 mg) and group 2 received Palonosetron (0.25 mg) with Dexamethasone (8 mg) combinations both intravenously 30 minutes prior to Cisplatin administration. Efficacy of two regimens were compared in terms of complete response rate [CR rate: no emesis and no significant nausea (nausea <3 in nausea scale)] between two groups, in acute (0-24 hours) and delayed (>24-120 hours) phases of 1<sup>st</sup> and 2<sup>nd</sup> cycles of Cisplatin chemotherapy. Other parameters that were assessed include number of emetic episodes, frequency of nausea and treatment related adverse effects in both the groups. Nausea and vomiting was assessed using Multinational association of supportive care in cancer Antiemetic Tool (MAT). Results were analysed using Chi-square test. Analysis showed that Palonosetron-Dexamethasone combination was found to be more effective in preventing CINV in terms of CR rate and significantly higher responses were seen in delayed phases of both 1<sup>st</sup> (73.3% vs 50%, P value=0.009) and 2<sup>nd</sup> (78.3% vs 55%, P value=0.007) cycles of Cisplatin chemotherapy. When individual parameters were analysed, it was seen that percentage of patients with severe emesis (>2 emetic episodes) and those with severe nausea (>7 in nausea scale) were lower in Palonosetron group in all phases and significant difference were seen in delayed phases of both cycles. The incidence of treatment related adverse effects were mild and there was no significant difference between two groups.

#### KEYWORDS

Palonosetron, Ondansetron, Dexamethasone, CINV, Cisplatin Induced Emesis.

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#### INTRODUCTION

Chemotherapy-Induced Nausea and Vomiting (CINV) are two of the major factors which contribute to fear, anxiety and apprehension in patients with cancer.<sup>1,2</sup> In addition to various medical complications like dehydration, electrolyte imbalance and Mallory-Weiss tears of the oesophagus.<sup>1,3</sup> It also has considerable economic implications which include costs of antiemetic drugs, additional patient care, extended hospitalization and reduced productivity at work or workdays lost.<sup>1,3,4</sup> Preventing CINV from the start of chemotherapy is important, because successful control in acute phase (0-24 hours after chemotherapy) is associated with reduced incidence of CINV in delayed phase (2-5 days after chemotherapy) and control of emesis in 1<sup>st</sup> cycle is associated with reduced incidence in subsequent cycles.<sup>4,5</sup>

Moreover patients who experience CINV in previous cycle may develop anticipatory nausea and vomiting in later cycles.<sup>1,6,7</sup> Introduction of serotonin (5-HT<sub>3</sub>) receptor antagonists in 1990's revolutionized the control of emesis and have now become the cornerstone of therapy for prevention of CINV.<sup>8,9,10</sup> First-generation 5-HT<sub>3</sub> receptor antagonists, Ondansetron, Granisetron, Dolasetron and Tropisetron in combination with corticosteroids significantly improved the control of acute chemotherapy-induced nausea and vomiting.<sup>8,11</sup> But delayed nausea and vomiting remains a clinical problem.<sup>11,12</sup>

The second-generation 5-HT<sub>3</sub> receptor antagonist, Palonosetron with high receptor binding affinity and long elimination half-life of 40 hours is found to be effective in delayed CINV also.<sup>13,14,15</sup> Palonosetron also inhibits substance P responses in a serotonin-independent manner.<sup>13,16,17</sup> Cisplatin provides a model for antiemetic testing, as it is highly emetogenic and found to cause emesis in 99% of patients without antiemetics.<sup>18,19</sup>

Hence, a comparative study on the antiemetic efficacy and safety profile of two antiemetic regimens, Ondansetron-Dexamethasone combination versus Palonosetron-Dexamethasone combination in Cisplatin-induced emesis was conducted in our tertiary care hospital.

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The maxim for managing chemotherapy-induced emesis is that, prevention is far more effective than treatment of established nausea and vomiting.<sup>20</sup> It also improves the patient compliance to chemotherapy and patients can tolerate dose intensified chemotherapy regimens.<sup>21</sup> With these objectives in mind, we embark upon this study.

**METHODOLOGY**

This was a prospective observational study conducted in the Department of Radiotherapy, Govt. Medical College, Calicut, Kerala, during the 1-year period from September 2009 to September 2010. The Institutional Human Ethics Committee approved the study. Based on the data from previous studies, minimum sample size required for our study was calculated to be 53 patients in each group.<sup>22</sup> Expecting noncompliance to the cytotoxic chemotherapy, 60 patients were included in each group and thus a total of 120 patients were included in the study. Written informed consent was obtained from all patients before the study procedure.

**Inclusion Criteria**

- Patients of both sexes, between the age groups 20 to 70 years.
- Patients scheduled to receive first course of Cisplatin chemotherapy (70-100 mg/m<sup>2</sup> BSA) in combination with 5FU or Paclitaxel or Etoposide.

**Exclusion Criteria**

- Presence of nausea and vomiting and the use of other antiemetic agents during the 24 hours prior to administration of chemotherapy.
- Severely debilitated and patients with known brain, hepatic and renal metastasis.
- Presence of other causes of vomiting such as gastrointestinal obstruction.
- Patients in whom the administration of Dexamethasone was contraindicated.

Age and sex matched patients receiving either Ondansetron with Dexamethasone or Palonosetron with Dexamethasone as antiemetic prophylaxis were selected and grouped. Group 1 patients received first dose of Ondansetron (8 mg) with Dexamethasone (8 mg) injections, 30 minutes prior to Cisplatin administration and was repeated two more times at an interval of 6 hours on the same day. These patients were given oral Ondansetron (8 mg) and Dexamethasone (8 mg) tablets twice daily on 2<sup>nd</sup> to 5<sup>th</sup> days. Group 2 patients received only a single injection of Palonosetron (0.25 mg) with Dexamethasone (8 mg), which was given on the first day, 30 minutes prior to Cisplatin administration and it suffice 5 days post-chemotherapy period. These patients were given MAT (Multinational association of supportive care in cancer antiemetic tool),<sup>23</sup> questionnaire and were advised to mark,

1. Presence or absence of vomiting.
2. Number of emetic episodes.
3. Presence or absence of nausea.
4. Grade of nausea.

During the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup> and 5<sup>th</sup> days of post-chemotherapy period, grade of nausea was marked in a visual analogue scale of 0 to 10. (0 to 3 taken as no significant nausea, 3 to 6 as moderate nausea and 7 to 10 as severe nausea) in the MAT format.

Adverse effects in both the groups, due to antiemetic drugs were also noted during these periods. The same parameters were again assessed in the same patients when they come for 2<sup>nd</sup> cycle of chemotherapy after 21 days.

Nausea and vomiting in two groups were assessed between two groups in terms of complete response rate [CR rate: no emesis and no significant nausea (nausea <3 in nausea scale)]. Other parameters that were assessed are number of emetic episodes, frequency of nausea and treatment related adverse effects between two groups in acute (0-24 hours) and delayed (>24-120 hours) phases of 1<sup>st</sup> and 2<sup>nd</sup> cycles of Cisplatin chemotherapy.

Statistical analysis was done using Statistical Package for Social Service (SPSS) software version 16. Chi-square test and Unpaired 't' test were done for the analysis of data. Results were tabulated and significance was expressed according to the P value, which was kept at a significant level of <0.05. Drop out cases were excluded.

**RESULTS**

120 patients, 60 patients each in Ondansetron with Dexamethasone (Group I) and Palonosetron with Dexamethasone (Group II) were included in the study. Comparison of demographic characters of patients showed no significant difference between two groups (Figures 1, 2 and 3).

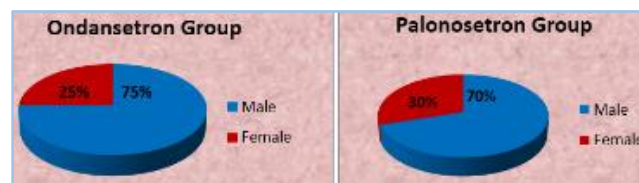


Fig. 1: Comparison of Gender

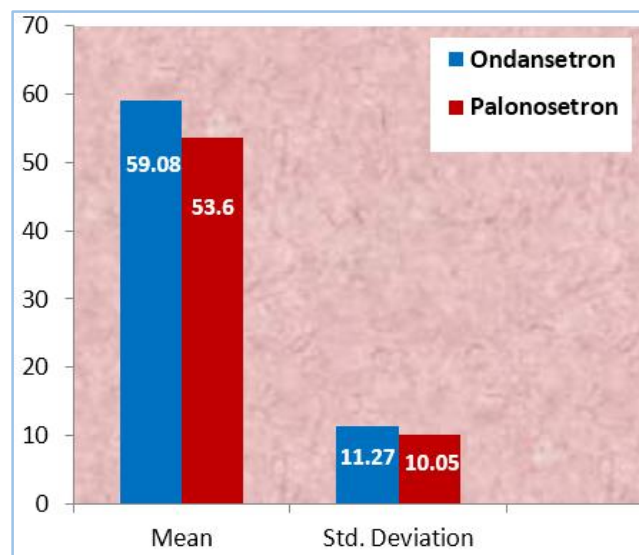


Fig. 2: Comparison of Age

In group I 25% of patients were males and the mean age was 59.08, whereas in group II 30% of patients were males and the mean age was 53.6. P value=0.540 (>0.05). Gender distribution between two groups compared using independent 't' test. (P value=0.733 and t value=2.813). There was no significant difference between two groups.

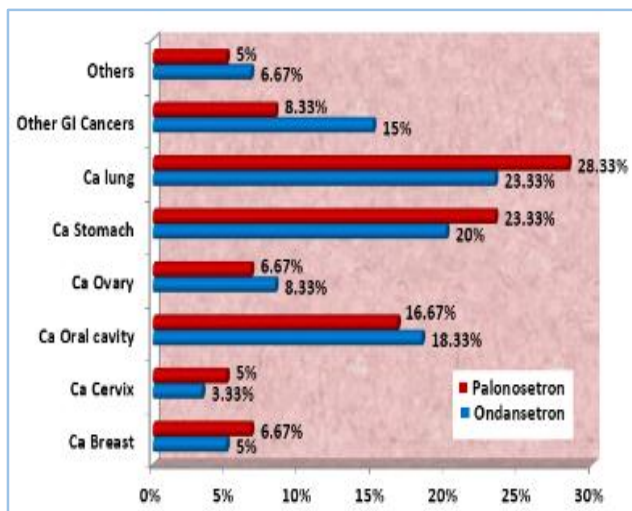


Fig. 3. Comparison of Type of Malignancies

Comparison of type of malignancies between two groups showed no significant difference between two groups (P value=0.943). Carcinoma lung was the most common type of malignancy seen followed by carcinoma stomach and carcinoma oral cavity (Figure 3). Two groups were then compared in terms of achieving complete response rate [CR rate: no emesis and no significant nausea (nausea <3 in nausea scale)] in acute and delayed phases of 1<sup>st</sup> and 2<sup>nd</sup> cycles of chemotherapy.

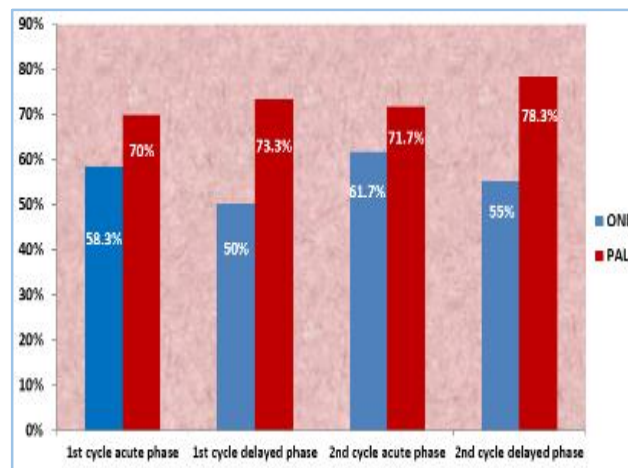


Fig. 4: Complete Response Rate in 1<sup>st</sup> and 2<sup>nd</sup> Cycles of Chemotherapy

CR rate was significantly higher in Palonosetron group than in Ondansetron group in delayed phases of both 1<sup>st</sup> (73.3% vs. 50%, P=0.009) and 2<sup>nd</sup> (78.3% vs. 55%, P=0.007) cycles of chemotherapy. In acute phases even though better responses were seen in Palonosetron group in both the cycles (70% vs. 58.3%, P=0.183 and 71.7% vs. 61.7%, P=0.245), the difference was not statistically significant (Figure 4). Among the patients with nausea and vomiting, the severity of emesis in terms of number of emetic episodes and frequency of nausea were also compared between two groups in acute and delayed phases of 1<sup>st</sup> and 2<sup>nd</sup> cycles (Figures 5, 6 and Tables 1, 2).

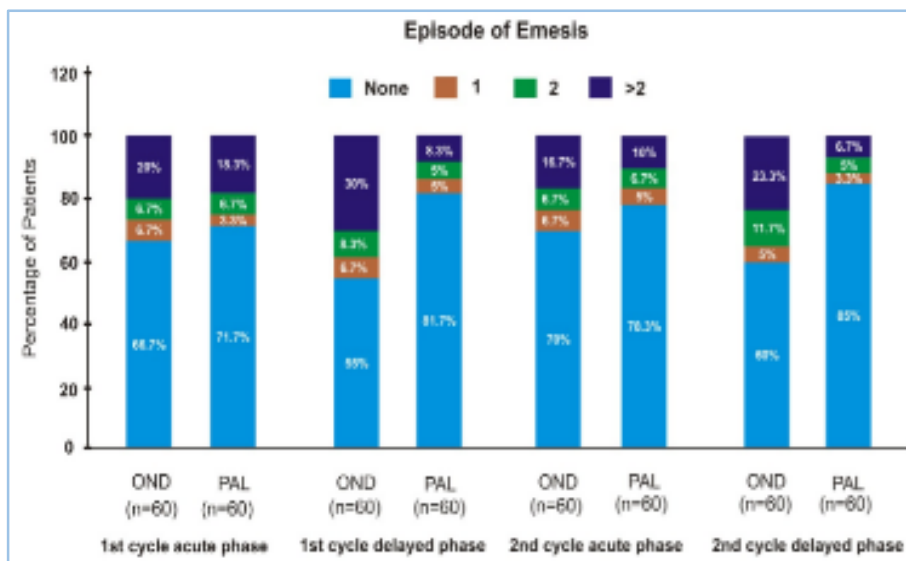


Fig. 5: Episodes of Emesis

Cycle	Phase	Drugs	Number of Emetic Episodes			
			0	1	2	>2
1 <sup>st</sup> Cycle	Acute	Ondansetron	40 (66.7%)	4 (6.7%)	4 (6.7%)	12 (20%)
		Palonosetron	43 (71.71%)	2 (3.3%)	4 (6.7%)	11 (18.31%)
	Delayed	Ondansetron	33 (55%)	4 (6.7%)	5 (8.31%)	18 (30%)
		Palonosetron	49 (81.7%)	3 (5%)	3 (5%)	5 (8.3%)
2 <sup>nd</sup> Cycle	Acute	Ondansetron	42 (70%)	4 (6.7%)	4 (6.7%)	10 (16.7%)
		Palonosetron	47 (78.3%)	3 (5%)	4 (6.7%)	6 (10%)
	Delayed	Ondansetron	36 (60%)	3 (5%)	7 (11.7%)	14 (23.3%)
		Palonosetron	51 (85%)	2 (3.3%)	3 (5%)	4 (6.7%)

Table 1: Comparison of Emetic Episodes in 1<sup>st</sup> and 2<sup>nd</sup> Cycles of Chemotherapy

Emetic episodes were assessed between two groups by calculating percentage of patients with no emesis, 1 episode, 2 episodes and >2 episodes of emesis.

Compared to Ondansetron group, percentage of patients with no emesis were much higher in Palonosetron group in all phases and was significantly higher in delayed phases of Palonosetron group in both 1st (81.7% vs. 55%, P=0.002) and

2nd (85% vs. 60%, P=0.002) cycles of chemotherapy. Among the patients with emesis, percentage of patients with severe emesis (with >2 emetic episodes) were much lower in Palonosetron group in all phases and significant difference were seen in delayed phases of both the cycles (8.3% vs. 30%, P=0.003 and 6.7% vs. 23.3%, P=0.011).

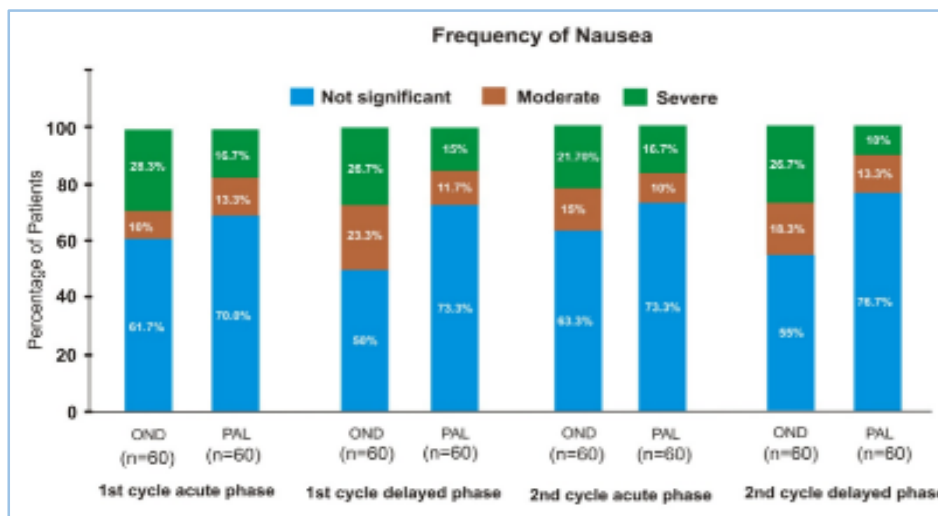


Fig. 6: Frequency of Nausea

Cycle	Phase	Drugs	Frequency of Nausea		
			No Significant Nausea	Moderate	Severe
1 <sup>st</sup> Cycle	Acute	Ondansetron	37 (61.7%)	6 (10%)	17 (28.3%)
		Palonosetron	42 (70%)	8 (13.3%)	10 (16.7%)
	Delayed	Ondansetron	30 (50%)	14 (23.3%)	16 (26.7%)
		Palonosetron	44 (73.3%)	7 (11.7%)	9 (15%)
2 <sup>nd</sup> Cycle	Acute	Ondansetron	38 (63.3%)	9 (15%)	13 (21.7%)
		Palonosetron	44 (73.3%)	6 (10%)	10 (16.7%)
	Delayed	Ondansetron	33 (55%)	11 (18.3%)	16 (26.7%)
		Palonosetron	46 (76.7%)	8 (13.3%)	6 (10%)

Table 2: Comparison of Frequency of Nausea in 1<sup>st</sup> and 2<sup>nd</sup> Cycles of Chemotherapy

Frequency of Nausea was also assessed between two groups. Percentage of patients with no significant nausea (<3 in nausea scale) were much higher in Palonosetron group in all phases and significant differences were seen in delayed phases of both 1<sup>st</sup> (73.3% vs. 50%, P=0.009) and 2<sup>nd</sup> (76.7%

vs. 55%, P=0.012) cycles of chemotherapy. Among the patients with nausea, percentage of patients with severe nausea (>7 in nausea scale) were much lower in Palonosetron group and was significantly lower in delayed phase of 2<sup>nd</sup> cycle (10% vs. 26.7%, P=0.028) (Figure 6 and Table 2).

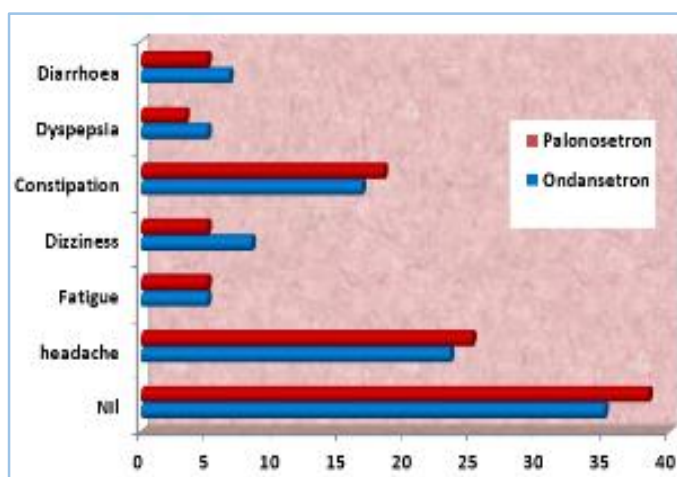
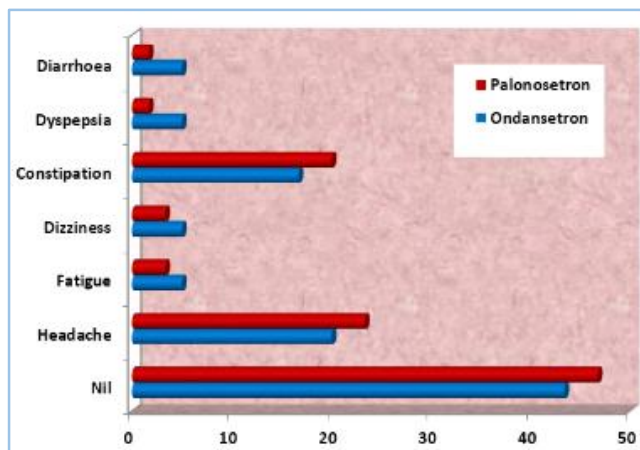


Fig. 7: Comparison of Adverse Effects in 1<sup>st</sup> Cycle





**Fig. 8: Comparison of Adverse Effects in 2<sup>nd</sup> Cycle**

Treatment related adverse effects in both the groups were mild and there was no significant difference between two groups (Figures 7 and 8). More commonly reported side effects were headache and constipation.

## DISCUSSION

In this prospective observational study, we have selected the lowest effective dose of Ondansetron (8 mg) and Palonosetron (0.25 mg), both in combination with Dexamethasone (8 mg) to determine the most effective and safe, prophylactic antiemetic regimen for Cisplatin-induced emesis in patients attending our tertiary care hospital. Effect of drugs were compared in acute (0-24 hours) and delayed (>24-120 hours) phases of 1<sup>st</sup> and 2<sup>nd</sup> cycles of Cisplatin chemotherapy.

Comparison of demographic characteristics of both the groups showed no significant difference between two groups. Palonosetron-Dexamethasone combination provided superior prophylaxis for CINV than Ondansetron-Dexamethasone combination in all phases of chemotherapy. Complete Response rate [CR rate: no emesis and no significant nausea (nausea <3 on nausea scale)] of Palonosetron group was significantly higher in delayed phases of both 1<sup>st</sup> (73.3% vs. 50%,  $P=0.009$ ) and 2<sup>nd</sup> (78.35 vs. 55%,  $P=0.007$ ) cycles and in acute phases, even though better responses were seen in Palonosetron group in both the cycles (70% vs. 58.3%,  $P=0.183$  and 71.7% vs. 61.7%,  $P=0.245$ ), the difference was not statistically significant.

Our study results were consistent with previous study done by Aapro et al, which reported that Palonosetron-Dexamethasone combination provided significantly higher CR rate in delayed emesis (42% vs. 28.3%).<sup>24</sup> In a similar study done by Gralla and Colleagues, Palonosetron achieved higher CR rate in acute (81% vs. 68.6%,  $P<0.01$ ), delayed (74.1% vs. 55.1%,  $P=0.001$ ) and overall phases (69.3% vs. 50.3%,  $P<0.001$ ) of CINV after moderately emetogenic chemotherapy.<sup>25</sup>

Analysis of patients with nausea and vomiting showed that number of emetic episodes and frequency of nausea were much lower in Palonosetron group compared to Ondansetron group. Number of patients with >2 emetic episodes were found to be significantly lower in delayed phases of Palonosetron group in both the cycles (8.3% vs. 30%,  $P=0.003$  and 6.7% vs. 23.3%,  $P=0.011$ ). Though we observed lesser control of nausea than vomiting in all cycles for both the groups, compared to Ondansetron-

Dexamethasone combination, Palonosetron-Dexamethasone combination provided better results. Number of patients with severe nausea were much lower in Palonosetron group in all phases and was significantly lower in the delayed phase of 2<sup>nd</sup> cycle of chemotherapy (10% vs. 26.7%,  $P=0.018$ ).

When both the groups were compared between 1<sup>st</sup> and 2<sup>nd</sup> cycles for persistence of their antiemetic efficacy, it was seen that there was decreased incidence of vomiting in 2<sup>nd</sup> cycle compared to 1<sup>st</sup> cycle. This emphasizes the fact that protection obtained in previous cycles of chemotherapy is one of the most important prognostic factors for CINV and steps to prevent this can definitely improve the quality of life of patients.<sup>5,26</sup> The incidence of treatment related adverse effects were mild and there was no significant difference between two groups. The more common adverse effects seen were headache and constipation.

Moreover, Palonosetron had the advantage of taking a single dose, which suffice 5 days post-chemotherapy period, whereas Ondansetron had to be administered two to three times daily. The introduction of sustained release tablets of Ondansetron has overcome this drawback to a certain extent, which can provide sustained plasma level of the drug by a single daily dose. It also has the advantage of minimal side effects as rapid and high peak blood levels are not attained.<sup>27</sup> Main limitation of Palonosetron is its cost, whereas Ondansetron injections and tablets are much cheaper.

## CONCLUSION

This prospective observational study comparing the prophylactic antiemetic efficacy and safety of Palonosetron-Dexamethasone combination with Ondansetron-Dexamethasone combination demonstrates that Palonosetron provided superior prophylaxis of CINV and significantly higher responses were seen in delayed phase of chemotherapy. The number of emetic episodes and frequency of nausea were also significantly lower for Palonosetron and it has a safety profile similar to that of Ondansetron. Palonosetron thus provides an effective option for delayed onset CINV, which was difficult to manage previously due to limited efficacy of older 5HT<sub>3</sub> receptor antagonists like Ondansetron and also had the advantage of taking a single dose, which greatly improves the patient compliance. This study also revealed reduced incidence of CINV in 2<sup>nd</sup> cycle, compared to 1<sup>st</sup> cycle of chemotherapy, emphasizing the fact that protection obtained in previous cycles is an important factor to prevent emesis in subsequent cycles.

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