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Original Article

Comparison between Palonosetron and Ondansetron in Prevention of Chemotherapy Induced Nausea Vomiting

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Abstract:

Background: Chemotherapy induced nausea and vomiting (CINV) is the commonest and the most incapacitating experience of thepatient undergoing cancer chemotherapy. Poorly controlled CINV sometimes make patients to refuse further treatment. This study aimed to compare the efficacy and safety of Palonosetron and Ondansetron in preventing CINV during cancer chemotherapy.

Methods: This randomized controlled trial was conducted in the Department of Pharmacology and Therapeutics of Sylhet MAG Osmani Medical College from January 2021 to December 2021. There were 190patients enrolled initially; 14 patients from both groups withdraw themselves. Finally, 91 patients of Palonosetron and 85 patients of Ondansetron treated were recruited. The Palonosetron group were treated with Palonosetron at 0.25 mg and the Ondansetron group were treated with Ondansetron 8.0 mg intravenously, 30min before chemotherapy. After that Palonosetron 0.5 mg single time and Ondansetron 8.0 mg orally three times a day were given and total follow-up period was seven days. Episode of nausea and vomiting graded according to the guideline "Common Terminology Criteria for Adverse Events (CTCAE)", version 4.0, which was published by the US Department of Health and Human Services (National Institute of Health and National Cancer Institute).

Result: The groups were matched for the age ($p = 0.263$), gender ($p = 0.630$), body weight ($p = 0.846$),site of malignancy ($p = 0.375$), and drugsused for chemotherapeutic ($p = 0.301$) in both study groups. Palonosetron treated patients experienced significant lower episode of nausea in day-1 ($p = <0.001$) and day-2 ($p = 0.025$), and in case vomiting in day-1 ($p = 0.026$) compared to Ondansetron. Significantly higher number of patients of Palonosetron compared to Ondansetron treated group showed complete response in both acute phase ($p = 0.026$), delayed phase ($p = 0.036$) and finally in overall phase ($p = 0.014$). Only four patients experienced with treatment failure in Ondansetron treated group. Observed adverse effects were in low intensity and not caused to stop the treatment procedure.

Conclusion: Palonosetron was found to be more efficacious and well tolerated in preventing acute, delayed and overall phase of chemotherapy induced nausea and vomiting in this study.

Key words: CINV, Palonosetron, Ondansetron, Efficacy, Safety.

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Introduction:

Chemotherapy induced nausea and vomiting (CINV) are the commonest side effects of the cytotoxic chemotherapy that are used in cancer treatment[1] and is frequently responsible for deterioration in quality of life.[2]

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Even CINV sometimes produce life threatening complications including dehydration, electrolyte imbalance, physical damage to the esophagus (Mallory-Weiss tears)[3] and also responsible for malnutrition, wound dehiscence, aspiration pneumonia in cancer patients.[4] Based on the Emetogenic property, the anti-cancer drugs are classified into four groups. Highly emetogenic drugs e.g., Cisplatin, Cyclophosphamide, Dacarbazine and Streptozocin produce CINV in >90% of patients. Moderate emetogenic drugs

e.g.,Carboplatin, Cyclophosphamide (<1.5 g/m^2), Cytarabine (>1 g/m^2), Doxorubicine, Epirubicinetc. produce CINV in 31–90% patients. Whereas Low emetogenic drugs include Bortezomib, Etoposide, Fluorouracil, Methotrexate etc. produce CINV in 10–30% patients. Minimal emetogenic drugs are Busulfan, Vinblastine, Vincristine etc. produce CINV in less than 10% patients.[3,5]

There are two phases of CINV - acute phase and delayed phase. Acute phase CINV starts from few minutes of drug treatment and persists up to 24 hours and delayed phase starts after 24 hours of drug treatment. CINV develops within 7 days of chemotherapy treatment even after using of anti-emetic agents and requires rescue medicine is called breakthrough emesis. Anticipatory emesis may develop prior to administration of subsequent chemotherapy, usually observed in patients had history of CINV in previous treatment cycle. When breakthrough emesis happened in subsequent chemotherapy cycles is called refractory emesis.[2,3]

CINV is multifactorial; patient's factors and chemotherapy related factors. Patient's factors include female gender, younger age, anxiety, depression, history of motion sickness, pregnancy induced nausea and vomiting, CINV in previous cycle. Chemotherapy related factors include dose and emetogenicity of the drug is using.[2-5]

Exact pathophysiology of CINV is not fully understood yet. Multiple organs and neurotransmitters are thought to be responsible for developing CINV. CINV induced by stimulating certain neurotransmitter in gastro-intestinal tract and the chemoreceptor trigger zone.[2,4] It is thought that the serotonin receptors located in vagal afferent nerves plays major role in CINV. Chemotherapy stimulates serotonin secretion from enterochromaffin cells of small intestine, which binds with serotonin receptors thus leads emesis.[6]

Ondansetron is a first-generation competitive serotonin receptor antagonist, which is commonly used to prevent emesis. It is a potent, highly selective, and acts on both central and peripheral nervous system. Its short plasma half-life (2–4 hours) causing its short duration of action and thus required multiple doses per day.[7] With the emergence of second-generation serotonin receptor antagonist like Palonosetron showed better receptor specificity and longer elimination half-life (40 hours). Thus,Palonosetron prevent effectively both acute and delayed phase response of CINV.[8-10]

The 5-HT3 receptor antagonists inhibit the effect of serotonin peripherally on vagal afferent nerves in the gastrointestinal tract and centrally in the central nervous system (CNS), specially at the chemoreceptor trigger zone (CTZ) resulting in their antiemetic effect.[11] Ondansetron acts as a competitive antagonist on 5-HT3 receptor and can easily displaced by high concentrations of serotonin.[12] Whereas, Palonosetron is highly selective, competitive, high-affinity 5-HT3 receptor antagonist, which has very little or no affinity for other receptors, including dopaminergic, muscarinic, adrenergic, and opioid receptors. Its binding affinity to specific receptor is 30-times greater than another5-HT3 receptor antagonist.[13]

5-HT3 receptor antagonists are generally well tolerated. However, the most frequently reported adverse effects are headache, constipation, dizziness, tiredness, fatigue, sedation, and gastrointestinal disturbances such as abdominal pain or diarrhea. They are usually mild to moderate intensity and transient, and rarely requiring drug discontinuation. Insignificant ECG change also observed, which returned to baseline usually within 24 hours. Intravenous administration may produce Bezold-Jarisch reflex, a decompressor reflex, which resulting sudden decrease in blood pressure and may lead to apnea.[14-15]

Several studies from abroad showed that Palonosetron effectively control CINV in both acute and delayed phase. So far, there is a lack of published data form Bangladesh. In this context, this study was intended to see the effectiveness and safety of Palonosetron over ondansetron in controlling CINV.

Methods and Materials:

This study double-blind randomized clinical trial conducted in the Department of Pharmacology & Therapeutics in collaboration with Department of Radiotherapy of Sylhet M. A. G. Osmani Medical College Hospital, Sylhet, from January 2021 to December 2021. This study included previously diagnosed cancer patients suffering from breast carcinoma, lung carcinoma, rectal carcinoma and carcinoma of cervix and undergone chemotherapy with emetogenic drugs (e.g., Cyclophosphamide, Carboplatin, 5-Fluorouracil, Etoposide and Doxorubicin). Extreme aged patients and those were known hypersensitive to any drugs of selective serotonin (5-HT3) receptor blocker.

After taking informed written consent, patients were enrolled into two study groups by lottery method. After a brief history taking, physical examination and investigation, the patients were treated with Palonosetron 0.25 mg and Ondansetron 8.0 mg intravenously 30 minutes before the chemotherapy. After initial intravenous dose, they were further treated with Palonosetron at a dose of 0.5 mg tablet single time daily and Ondansetron at a dose of 8 mg tablet 8 hourly for following 7 days. The patients were followed for 7 days. During the follow-up, all patients were being hospitalized for 7 days in order to close monitoring of the patients. During hospitalization, acute phase response such as, the number and frequency of emetic episodes, severity of nausea, and use of rescue medicine (if used) were recorded. Episode of nausea and vomiting graded according to the guideline "Common Terminology Criteria for Adverse Events (CTCAE)", version 4.0, which was published in 2010 by the U.S. Department of Health and Human Services (National Institute of Health and National Cancer Institute). Delayed phase response monitored closely in the same way. Drugs related adverse effect were noted accordingly.

The primary outcome parameters of drug response were complete response (when there was no episode of vomiting and no more than Grade-1 nausea and no use of rescue medicine during the study period), partial response (when there were 1 to 2 episodes of vomiting, Grade 2 nausea and no use of rescue medicine during the study period), and treatment failure (when there were several episodes of vomiting or more than Grade-2 nausea that need to use rescue medicine).[16] Secondary outcome parameters were development of drug observed adverse effect, such as headache, constipation, diarrhea, abdominal pain and dry mouth.

All data were compiled and analyzed by using window-based computer software device with Statistical Package for Social Science (SPSS), version 25. Quantitative data were expressed as mean and standard deviation and comparison was done between the groups by unpaired 't' test. ANOVA used to compare more than two mean values, Post-hoc Tukey test further for analyses. Qualitative data were expressed in frequency and percentage and comparison was done by using Chi-Square (χ^2) test or Fisher's Exact test. A probability value of less than 0.05 was considered as statistically significant. The study protocol was approved by the Sylhet M.A.G. Osmani Medical College Ethical Committee (SOMC/2021/40). Before taking the consent, purpose and methods of the study, risk and benefits of the study, confidentiality of the data and their right to withdraw themselves at any stage of the study were explained.

Result

This randomized controlled trial conducted on the selected cancer patients who underwent for chemotherapy. There was a total of 190 patients initially enrolled in this study; 14 patients withdraw their consent as they not interested to stay in hospital for 7 days. So, final analyses were made from 91 Palonosetron and 85 Ondansetron treated patient's group. Both the treated drug groups were matched for their mean age ($t = 1.123$, $p = 0.263$), age distribution ($\chi^2 = 3.308$, $p = 0.345$), gender ($\chi^2 = 0.0231$, $p = 0.630$), site of malignancy ($\chi^2 = 3.101$, $p = 0.375$), chemotherapeutic drugs used to treat them ($\chi^2 = 3.657$, $p = 0.301$), chemotherapy cycle ($\chi^2 = 1.650$, $p = 0.895$), and body weight ($t = 0.195$, $p = 0.846$) (Table-1).

Table 1: Comparison between the Palonosetron and Ondansetron treated group.

Age	Palonosetron treated n (%)	Ondansetron treated n (%)	p-value
Age distribution			
25 – 35	4 (4.4%)	5 (5.9%)	*0.347
36 – 45	34 (37.4%)	21 (24.7%)	
46 – 55	42 (46.2%)	47 (55.3%)	
56 – 65	11 (12.1%)	12 (14.1%)	
Mean age ± SD	47.05±7.40	48.29±7.22	**0.263
Gender			
Male	29 (31.9%)	30 (35.3%)	*0.630
Female	63 (68.1%)	55 (48.3%)	
Body weight	70.98±6.38	70.80±5.69	*0.846
Site of malignancy			
Breast	30 (33.0%)	20 (23.5%)	*0.375
Cervix	27 (29.7%)	25 (29.4%)	
Lung	17 (18.7%)	24 (28.2%)	
Rectum	17 (18.7%)	16 (18.8%)	
Chemotherapeutics			
CPL+5FU	33 (36.3%)	33 (38.8%)	*0.301
CPL+5FU+DXR	27 (29.7%)	20 (23.5%)	
5FU+Folinix	21 (23.1%)	15 (17.6%)	
ETO+CP	10 (11.0%)	17 (20.0%)	
Chemotherapeutic cycle			
First cycle	13 (14.3%)	12 (14.1%)	*0.895
Second cycle	29 (31.9%)	26 (30.6%)	
Third cycle	25 (27.5%)	28 (32.9%)	
Fourth cycle	14 (15.4%)	9 (10.6%)	
Fifth cycle	9 (9.9%)	8 (9.8%)	
Sixth cycle	1 (1.1%)	2 (2.4%)	

CPL: Cyclophosphamide, 5FU: Fluorouracil, DXR: Doxorubicin, ETO: Etoposide, CP: Carboplatin

Significant more favorable reduction of nausea observed in Palonosetron treated patients compared to the Ondansetron treated patients in follow-up day-1 (χ^2 = 15.591, p = <0.001) and day-2 (p = 0.025). There was no significant difference observed in day-3, day-4 and day-5. Feeling of nausea became abolished in day-6 and day-7 (Table-2). In case of vomiting, more significant improvement observed in Palonosetron treated patients on day-1 compared to Ondansetron treated patients (p = 0.026). The differences of grades of vomiting were not significant from day-2 to day-4, and vomiting became absent from day-5 to day-7 (Table-3).

Table 2: Effect of drug treatment on nausea grade between the study groups

Day	Palonosetron treated n (%)	Ondansetron treated n (%)	p-value
Day-1			*<0.001
Grade-0	73 (80.2%)	46 (54.1%)	
Grade-1	13 (14.3%)	20 (23.5%)	
Grade-2	5 (5.3%)	19 (22.4%)	
Day-2			**0.025
Grade-0	54 (59.3%)	37 (43.5%)	
Grade-1	37 (40.7%)	45 (52.9%)	
Grade-2	0	3 (3.5%)	
Day-3			*0.598
Grade-0	71 (78.0%)	63 (74.1%)	
Grade-1	20 (22.0%)	22 (25.9%)	
Day-4			*0.297
Grade-0	85 (93.4%)	75 (88.2%)	
Grade-1	6 (6.6%)	10 (11.8%)	
Day-5			**0.111
Grade-0	91 (100%)	82 (96.5%)	
Grade-1	0	3 (3.5%)	

*Chi-Square test, **Fisher's exact test

Table 3:Effect of drug treatment on vomiting grade between the study groups.

Day	Palonosetron treated n (%)	Ondansetron treated n (%)	p-value
Day-1			*0.026
Grade-0	75 (82.4%)	59 (69.4%)	
Grade-1	16 (17.6%)	22 (25.9%)	
Grade-2	0	4 (4.7%)	
Day-2			**0.05
Grade-0	69 (75.8%)	52 (61.2%)	
Grade-1	22 (24.2%)	33 (38.8%)	
Day-3			**0.468
Grade-0	83 (91.2%)	74 (87.1%)	
Grade-1	8 (8.8%)	11 (12.9%)	
Day-4			**0.265
Grade-0	91 (100.0%)	80 (94.1%)	
Grade-1	0	5 (5.9%)	
Day-5			*0.232
Grade-0	91 (100%)	83 (97.6%)	
Grade-1	0	2 (2.4%)	

*Fisher's exact test, **Chi-Square test

Mean number of vomiting initially reduced on day-1, then raised on day-2, and then gradually reduced on subsequent days in both drugs treated groups (Figure-1). Significantly lower mean vomiting episodes observed in day-1 (t = 4.439, p = <0.001), day-2 (t = 5.274, p = <0.001), day-3 (t = 9.417, p = <0.001) and day-4 (t = 19.739, p = <0.001). Vomiting episode became completely absent on day-4 onward in Palonosetron treated patients and on day-6 onward in Ondansetron treated patients. Day-to-day variations in mean vomiting episode also found statistically significant in both Palonosetron (F = 33.916, p = <0.001) and Ondansetron (F = 51.343, p = <0.001) treated patient's groups. Based on the criteria of clinical response, significant favorable response observed in Palonosetron treated patients in the Acute CINV (p = 0.026), Delayed CINV (χ^2 = 4.389, p = 0.036) and Overall response (p = 0.014). Based on the definition, treatment failure observed in 4 (4.7%) of the Ondansetron treated patients (Figure 2).

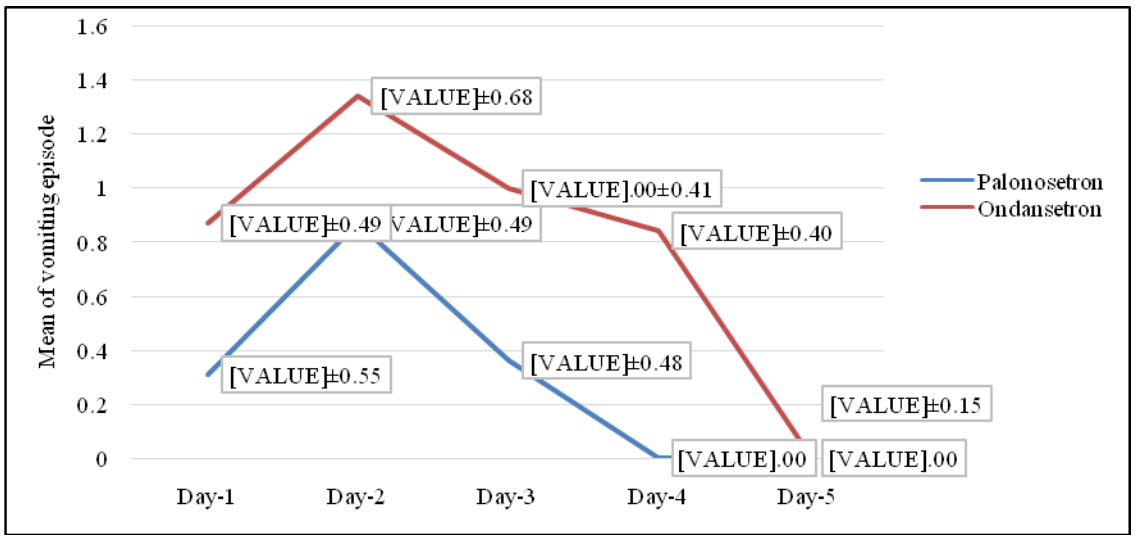

Figure1: Mean change of vomiting episode between the study groups.

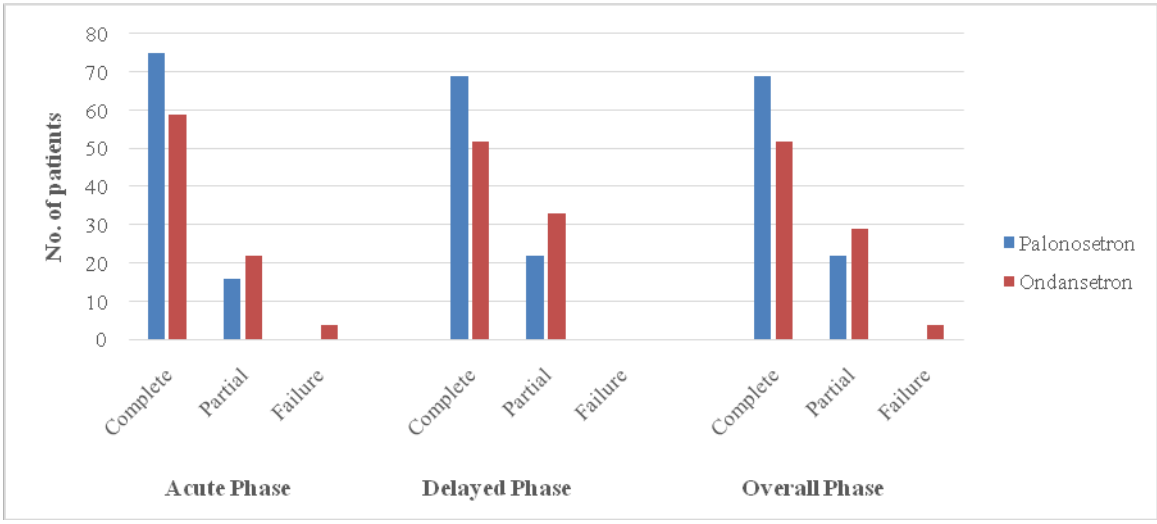

Figure2: Clinical response of anti-emetic drug therapy in preventing CINV.

Among the Palonosetron treated patients, frequently observed adverse effects were headache (13.3%),dizziness (10.9%) and abdominal cramp (6.6%) patients. On the other side, headache, dizziness, abdominal cramp, dry mouth and diarrhea complained by 17.6%, 12.9%, 9.4%, 4.7% and 3.5% patients respectively by the Ondansetron treated patients. However, the differences were not found statistically significant between the groups, p-values were 0.413, 0.689, 0.488, 0.052 and 0.111 respective adverse effects.

Discussion

Chemotherapy is a common modality for treatment of cancer. Regardless of the fact that chemotherapy improves survival; it has its own toxicity and side-effects. CINV if inadequately controlled by antiemetic treatment, will limit a patient's ability and desire to eat and drink, significantly reduce quality of life, threaten the success of therapy and may result in increased mortality, morbidity and importantly, health care costs. Prevention of nausea and vomiting is critical in the management of patients with cancer. Before the introduction of 5HT3 receptor antagonists, patients were often unable to complete chemotherapy regimens due to profound nausea or vomiting.

There was a total of 190 patients with malignancy enrolled in this study. Due to discontinuation of follow-up period by the patients, final comparison was done on 91 Palonosetron treated patients and 85 Ondansetron treated patients. The studied groups were matched for mean age (p = 0.263) and age distribution (p = 0.347), gender (p = 0.630),body weight (p = 0.846),site of malignancy (p = 0.375), chemotherapeutic drugs used (p = 0.301) and chemotherapeutic cycle of observation (p = 0.895). There was female predominance observed due to the Breast carcinoma and Cervical carcinoma, which comprised 57.9% of total study population (102 of 176 patients).

The drugs used for the chemotherapy were Cyclophosphamide, Fluorouracil, Doxorubicin, Etoposide and Carboplatin in this study. The drugs Carboplatin and Doxorubicin were moderate emetogenic. Etoposide and Fluorouracil belongs to low emetogenic drug. Cyclophosphamide belong to highly emetogenic drug groups.[17] So, it can be said that all types of chemotherapeutic agents based on emetogenicity were being used in this study.

Palonosetron found to response significantly (p = 0.026) during acute phase CINV in this study; 82.4% in Palonosetron versus 69.4% in Ondansetron treated patients. Parathoduvil et al.[16] reported more than (80%) complete response in both groups (89.6% in Palonosetron and 80.2% in Ondansetron treated patients). Anusha and Saravanan[18] also found higher complete response in acute phase in their study; 84% among the Palonosetron and 73% among the Ondansetron treated patients. However, both of their study did not show significant difference between the study groups.

Palonosetron also responded significantly (p = 0.036) in delayed phase CINV in this study; 75.8% in Palonosetron versus 61.2% in Ondansetron treated patients. Significantly higher response in delayed phase CINV also reported by Parathoduvil et al.[16] and by Anusha and Saravanan[18]. Parathoduvil et al.[16] reported comparatively higher rate of compete response in both Palonosetron (86.6%) and Ondansetron (70.8%) than this study (75.8% versus 61.2% respectively). In contrast, Anusha and Saravana[18] reported comparatively lower rate of complete response in both Palonosetron (55%) and Ondansetron (28%) compared to this study.

In Overall, complete response to antiemetic drug treatment achieved by 75.8% patients treated with Palonosetron and 61.2% patients treated with Ondansetron and the response was significant (p = 0.014). Similar significant (p = 0.008) higher complete response also observed by Parathoduvil et al.[16], where they found 82.1% complete response in Palonosetron treated patients and 65.1% in Ondansetron treated patients. Anusha and Saravanan[18] also reported significantly higher (p = 0.004) complete response in Palonosetron treated patients, but the response rates were relatively smaller than this study (51% for Palonosetron and 25% for Ondansetron). Similar higher complete response rate to this study, but insignificant, reported by Jain et al.[8]

Gralla et al.[19] compared single time use of two different dosages of Palonosetron (0.25 mg and 0.75 mg) with Ondansetron in their study. According to their research report, Palonosetron

at the dose of 0.25 mg showed far better efficacy than Palonosetron 0.75 mg and Ondansetron. Complete response by Palonosetron (0.25 mg) was 81.0% versus 68.6% (p = 0.0085) in acute phase, 74.1% versus 55.1% (p = <0.001) in delayed phase, and 69.3% versus 50.3% (p = <0.001) in case of overall response compared to the Ondansetron. There is a similarity of complete response found between this study and study by Gralla et al.[19] in acute and delayed phase CINV.

Failure to response to drug therapy for CINV only observed in Ondansetron treated patients. However, those patients were required to use rescue medication. Treatment failure observed in both treating drug groups by Jain et al.,[8]Parathoduvil et al.,[16]Grala et al.,[19] Gupta et al.,[20] Patil et al.,[21] and Todi[22]. The frequencies were found relatively higher (but insignificant) in Ondansetron treated group than Palonosetron treated group in every previous studies.

There was no adverse event with severe intensity happened in this study that require to stop the drug. Headache, dizziness and abdominal cramp found in Palonosetron group, whereas Ondansetron group developed additional two adverse effect (dry mouth and diarrhea). However, the number of patients experienced adverse effects were limited and the differences between the drug groups were insignificant. Parathoduvil et al.[16] also reported similar adverse effects except dizziness. Their study did not find significant difference. Commonly observed adverse effects in previous studies were headache, dizziness and constipation.[8,16,18-21] However, patients in this study did not complaint about constipation.

Conclusion:

Palonosetron was found to be more efficacious and well tolerated in preventing acute, delayed and overall phase of chemotherapy induced nausea and vomiting. Palonosetron more preferable to use in the prevention of chemotherapy induced nausea and vomiting than Ondansetron due to its more efficacy, better tolerability and single time use. However, further comparative study is hereby recommended including patients of single malignancy and using of specific one chemotherapeutic agent.

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