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Olanzapine as prophylactic antiemetic in breast cancer patients - A prospective comparative study in a tertiary care Centre

[1]Dr. Sukainnya Buragohain, Jorhat Medical College and Hospital, Jorhat, Assam – 785001 India.

[2]Prof. Dr. Indrani Bhagawati, Nalbari Medical College and Hospital, Nalbari, Assam – 781351 India.

[3]Prof. Dr. Neelakshi Mahanta, State Cancer Institute, Guwahati- 781032, Assam India.

[4]Prof. Dr.Diptimayee Devi, Gauhati Medical College and Hospital, Guwahati – 781032, AssamIndia.

Corresponding Author: Dr. Sukainnya Buragohain, Jorhat Medical College and Hospital, Jorhat, Assam – 785001 India.

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Abstract

Context: The prevention of chemotherapy induced nausea and vomiting (CINV) by olanzapine can improve patients adherence to treatment.

Aims and objectives: To study the efficacy of olanzapine as prophylactic antiemetic in parenteral highly emetogenic chemotherapy (HEC) regimen of breast cancer and to compare its side effects with aprepitant.

Settings and Design: Prospective, comparative, open-label, non-randomized study was conducted on 146 eligible breast cancer patients, equally distributed into aprepitant and olanzapine groups.

Methods and Material: The Multinational Association of Supportive Care in Cancer (MASCC) Tool (MAT) and Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 was used for evaluation.

Statistical analysis used: Chi-square test and unpaired t test was applied to test for statistical significance using ©2021 GraphPad Prism. P value ≤ 0.05 was considered significant. Data were represented using frequency distribution table and bar diagrams.

Results: Patients achieving Complete Response (CR, no emesis and no rescue medication) was significantly higher in olanzapine treated group. Nausea was significantly controlled but vomiting wasn't significantly controlled with olanzapine when compared with aprepitant.

Assessment of side effects showed significantly increased sedation on day 2 on those receiving olanzapine in comparison to aprepitant.

Conclusions: Olanzapine has significant results in controlling CINV caused by parenteral HEC regimens

when compared with aprepitant in acute, delayed and overall period with minimal increase in sedation.

Keywords: Antiemetic, Aprepitant, Breast Cancer, Chemotherapy induced nausea and vomiting, Olanzapine

Introduction

Breast cancer accounts for highest incidence (1 in 4 cancer cases) of cancer related mortality (1 in 6 cancer deaths) among women in many countries including India. [1] Although, use of cytotoxic chemotherapy in breast cancer have made progress, nausea and vomiting remain serious side effects causing negative impact on patients' quality of life and their compliance with cancer chemotherapy. [2] Therefore, the search for an ideal anti-emetic is ongoing.

Olanzapine is an FDA approved atypical anti-psychotic, suggested to be effective for CINV because of its simultaneous inhibitory action on multiple receptors that includes the dopamine receptors D1, D2, D3 and D4, the serotonin receptors 5HT2A, 5HT2C, 5HT3 and 5HT6, the alpha-1 adrenergic receptor, the histamine receptor H1 and multiple muscarinic receptors. So, this study was undertaken with following objectives

Primary objective

To determine the efficacy of olanzapine compared to aprepitant as a prophylactic antiemetic in parenteral HEC regimen of breast cancer.

Secondary objective

To evaluate any side effects of olanzapine in comparison to aprepitant.

Materials and Methods

A prospective, comparative, open-label, non-randomized study over one year period from May 2020 to April 2021 was conducted on breast cancer patients undergoing chemotherapy. 146 patients at the day-care Centre who met the inclusion criteria were part of the study after their written informed consent was obtained.

Inclusion criteria

1. Chemotherapy naive breast cancer patients ≥18 years of age, scheduled to receive parenteral highly emetogenic chemotherapy (HEC) regimen.

Additional eligibility criteria were

- Serum creatinine ≤ 2.0 mg/dl.
- Aspartate aminotransferase (AST) and/or alanine amino trans ferase (ALT) level not more than 3 times the upper limit of the normal range.
- Absolute neutrophil count of at least 1500/mm^3
- Haemoglobin at least 8 g/dl.
- Platelet count at least 1 x 10^5/µl.
- Total leucocytes count at least 4000 /mm^3.
- Electrolytes within normal range.
- Left ventricular ejection fraction ≥50%.

Exclusion criteria

1. Nausea or vomiting in the 24 hours before enrollment.
2. Patients receiving multi-day HEC regimen.
3. Severe cognitive compromise and known history of central nervous system disease (e.g., brain metastases or seizure disorder).
4. Treatment with another anti-psychotic agents, concurrent opioid therapy, sedating or central nervous system -depressing agents.
5. Known hypersensitivity to olanzapine.
6. Known cardiac arrhythmia, uncontrolled congestive heart failure, or acute myocardial infarction within the previous 6 months.
7. Patients with history of uncontrolled diabetes mellitus.
8. Pregnant and lactating women, severely debilitated patients.
9. Those who refuse to give consent.

Study tool

Pre-tested, peer reviewed questionnaire was used to collect the data from the participants. The Multinational Association of Supportive Care in Cancer (MASCC) Antiemesis Tool (MAT) was used to assess CINV.

Study population

Chemotherapy naive breast cancer patients scheduled to receive parenteral HEC regimen such as Adriamycin and Cyclophosphamide (AC), Taxotere, Adriamycin and Cyclophosphamide (TAC) and Taxotere, Carboplatin and Herceptin (TCH) were included and followed for five days immediately post-chemotherapy.

The two groups were

1. **Aprepitant group**

- Day 1: Capsule aprepitant 125 mg per os (PO) stat, inj. ondansetron 8mg intravenous (I.V.) bolus slowly, inj. dexamethasone 8 mg I.V. stat, 1 hour before chemotherapy.
- Post-chemotherapy Day 2, 3: Capsule aprepitant 80 mg PO once daily (OD) morning (AM).
- Post-chemotherapy Day 2, 3, 4: Tablet dexamethasone 8 mg PO OD AM.
- Combi-pack kit of aprepitant capsules 125/80 mg available in hospital supply was used in this group.

2. **Olanzapine Group**

- Day 1: Tablet olanzapine 10 mg PO stat, inj. OndanseTron 8mg I.V. bolus slowly, inj. dexamethasone 8 mg I.V. stat, 1 hour before chemotherapy.
- Post-chemotherapy Day 2, 3, 4: Tablet olanzapine 10 mg PO OD at bedtime (HS).
- Post-chemotherapy Day 2, 3, 4: Tablet dexamethasone 8 mg PO OD AM.

Olanzapine mouth dissolving tablets 10 mg physicians sample was used in this group.

Sample size and sampling

Using two-tailed z-test of proportions between two groups, a sample size of 146 is calculated from previous study. [3] Purposive sampling method was used.

Data collection procedure

All demographic details and required parameters were noted. Data was collected using questionnaire which included The Multinational Association of Supportive Care in Cancer (MASCC) Antiemesis Tool (MAT). [4] It includes questions on the occurrence and frequency of nausea and vomiting and also the intensity of nausea is assessed on a 100 mm visual analog scale to measure severity on a scale of 0-10.

In the study, severity scores were graded as mild (scores 1-4), moderate (scores 5-7) and severe (scores 8-10) and were assessed by Common Terminology Criteria for Adverse Events (CTCAE) version5.0. [5] The patients were assessed for only one chemotherapy cycle and rescue therapy was permitted for nausea and vomiting depending on the clinical circumstances.

They were followed till five days from the day of receiving parenteral HEC regimen. Telephonic contact was made from the study site to confirm that patients were taking study medications appropriately and were maintaining accurate records of dosing times, treatment response and any adverse events. The diary was reviewed with the patient at the next visit. Treatment tolerability was monitored, as well as by adverse events.

Baseline safety assessments were obtained at the pre-study visit, and vital signs and electrocardiograms were monitored on the day of treatment. Before each first cycle of chemotherapy, baseline blood work was done to appropriately dose chemotherapeutic agents.

Study Outcome

The primary objectives were assessed as such: The primary endpoint of the efficacy analysis was the proportion of patients who achieved complete response (CR) defined as no nausea and vomiting episodes and no rescue therapy on Day 0-1 (acute period), on Days 2-5 (delayed period) and on Days 0-5 (overall study period). In addition, secondary endpoints of efficacy were assessed as the proportions of patients who achieved a response to treatment in the following categories: 1) no nausea 2) no vomiting, in all the three assessment periods (acute, delayed and overall).The secondary objective was assessed by evaluating any side-effects of olanzapine where patients were asked to record daily levels of increased sedation using a visual-analogue scale ranging from 0 (none) to 10 ("as bad as it can be") for 5 days following chemotherapy.

Results and analysis

Chi-square test and unpaired t test was applied to test for statistical significance using ©2021 GraphPad Prism. P ≤ 0.05 was considered significant. Data were represented using frequency distribution table and bar diagrams.

Ethical Considerations

Ethical approval and clearance were obtained from:

1. Institutional Ethics Committee of Gauhati Medical College and Hospital, Guwahati with the ethical approval letter no. MC/190/2007/Pt-11/Dec-2019/29.
2. Institutional Ethics Committee of State Cancer Institute, Gauhati Medical College, Guwahati with the ethical approval letter no. SCI/ECR/2020/06.

Informed written consent was taken from the patients who met the inclusion criteria and concern was taken to protect confidentiality and not to disclose patients' identity.

Results

Of the 146 eligible patients, 72 patients were equally distributed into aprepitant group and olanzapine group (figure 1). However, 2 patients were lost to follow-up. Their baseline demographic characteristics were compared (table 1).

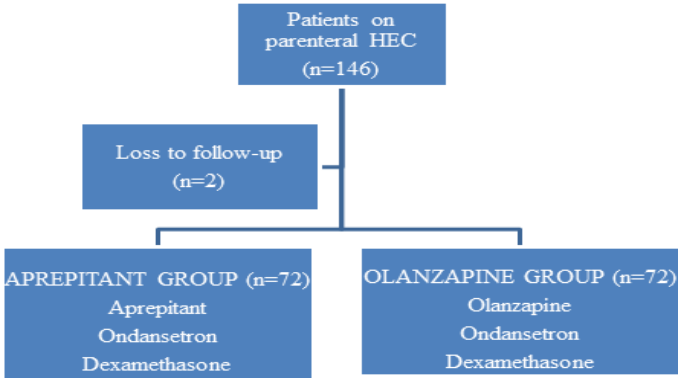


Figure 1: Distribution of study patients.

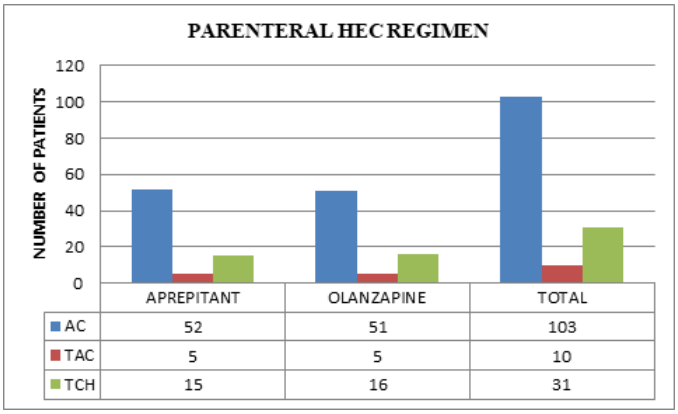
Table 1: Baseline demographic characteristics

Character	**A prepitant (n=73)**	**Olanzapine (n=73)**	**Total (n=146)**
AGE (in years)	45 ± 8.2	45 ± 8.5	45 ± 8.3
BSA (in m^2)	1.48 ± 0.1	1.57 ± 0.1	1.49 ± 0.1
Sex			
Females	73 (100)	73 (100)	146 (100)
Males	0 (0)	0 (0)	0 (0)
Menstrual status			
Premenopausal	39 (53.4)	38 (52)	77 (52.7)
Postmenopausal	34 (46.6)	35 (48)	69 (47.3)
Co-morbidities			

Absent	51 (69.9)	51 (69.9)	102 (70)
Htn	12 (16.4)	11 (15)	23 (16)
Dm	2 (2.7)	2 (2.7)	4 (3)
Htn+dm	6 (8.2)	7 (9.6)	13 (9)
Others	2 (2.7)	2 (2.7)	4 (3)
Dietary habit			
Alcohol intake	5 (6.8)	4 (5.4)	9 (6.2)
Ajcc clinical prognostic staging			
IA	9 (12.3)	6 (8.2)	15 (10.3)
IB	6 (8.2)	4 (5.5)	10 (6.8)
IIA	9 (12.3)	15 (20.5)	24 (16.4)
IIB	2 (2.7)	2 (2.7)	4 (2.7)
IIIA	10 (13.7)	11 (15.1)	21 (14.4)
IIIB	11 (15.1)	14 (19.2)	25 (17.1)
IIIC	5 (6.8)	6 (8.2)	11 (7.5)
IV	21 (28.8)	15 (20.5)	36 (24.7)

Age and BSA are expressed in mean ± standard deviation. Sex, menstrual status, co-morbidities, dietary habits, AJCC Clinical prognostic staging are expressed as number (*n*) and percentage in parenthesis.AC (71%), TAC (7%) and TCH (22%) were the parenteral HEC received by the patients (figure 2).

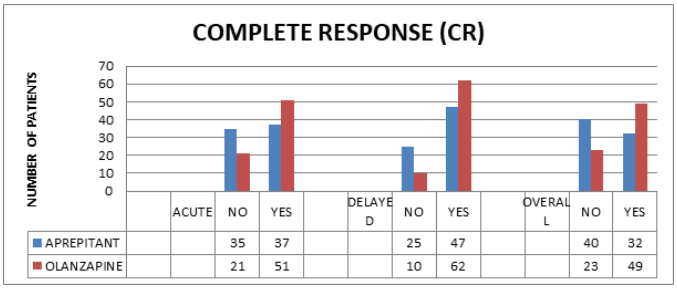
Figure 2: Status of parenteral HEC Regimen (AC, TAC, TCH)



The primary and secondary efficacy endpoints were assessed by using Chi-Square test in ©2021 GraphPad Prism where $P \leq 0.05$ was considered as statistically significant.

Primary efficacy endpoint, CR, was evaluated in all the three assessment periods; overall (68% vs. 44%), delayed (86% vs. 65%) and acute (71% vs. 51%) which was significantly higher in the olanzapine group than in the a prepitant group (figure 3). Thus, the primary endpoint of efficacy was analyzed.

Figure 3: Status of CR on acute, delayed and overall study period.



In the acute period, the proportion of patients having no nausea was significantly higher in the olanzapine group compared to aprepitant group (83% vs. 63%), although those having no vomiting with olanzapine weren't significantly different when compared with aprepitant (88% vs. 89%) (figure 4). Similarly, in the delayed and

overall study period, the proportion of patients having no nausea was significantly higher in the olanzapine group but there was no significant difference in the incidence of vomiting in either group (figure 5, 6).

Figure 4: Evaluation of acute CINV

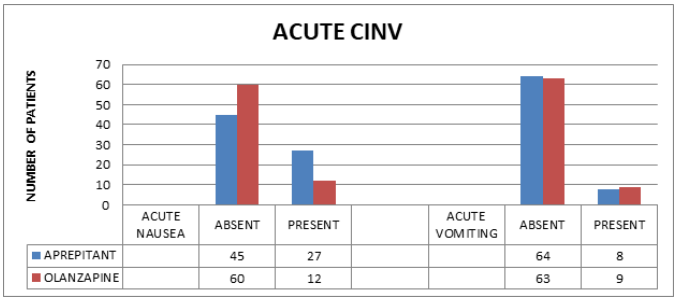


Figure 5: Evaluation of delayed CINV

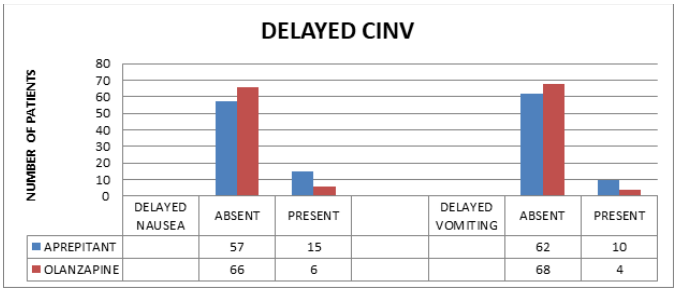
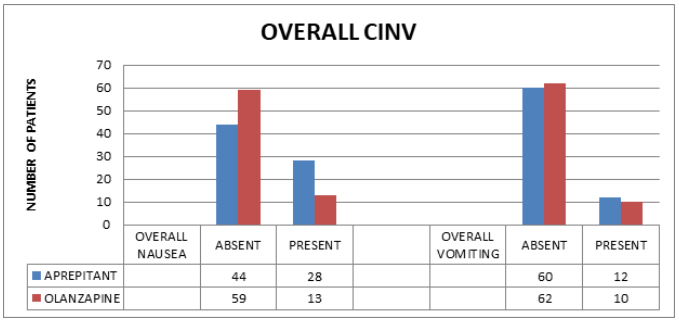


Figure 6: Evaluation of overall CINV



In standard group, out of 28 (39%) patients; 14 (50%), 12 (43%) and 2 (7%) had grade 1, grade 2 and grade 3 nausea respectively. In treatment group, of the 13 (18%) patients; 8 (62%) and 5 (38%) had grade 1 and grade 2 nausea respectively (figure 7). In standard group, out of 12 (17%) patients; 8 (67%) and 4 (33%) had grade 1 and grade 2 vomiting respectively. Similarly, in the treatment group, out of 10 (14%) patients; 8 (80%) and 2 (20%) had grade 1 and grade 2 vomiting respectively (figure 8).

Figure 7: Grading of nausea according to CTCAE V5.0

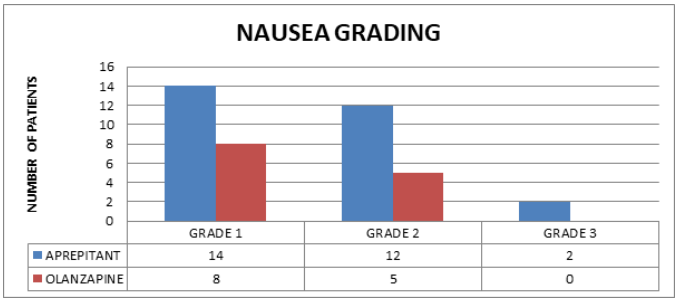
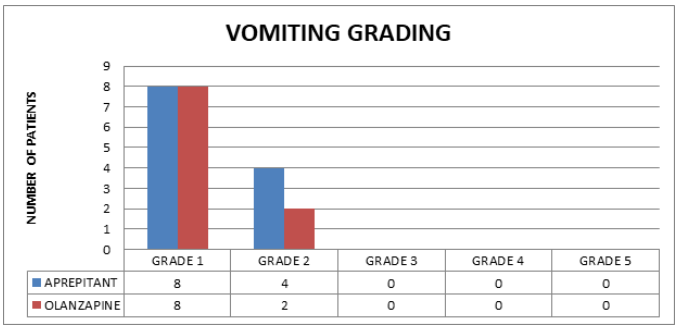
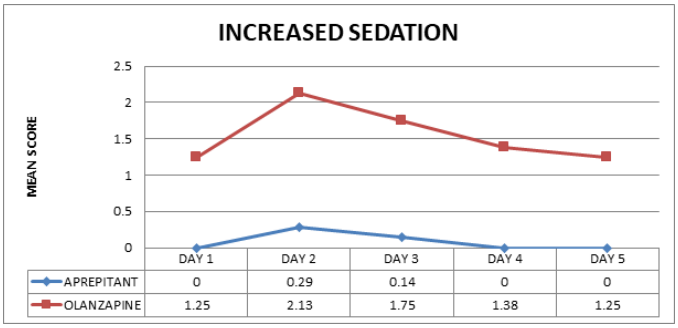


Figure 8: Grading of vomiting according to CTCAE V5.0



Assessment of adverse effects has shown that patients receiving olanzapine had significantly increased sedation on day 2 in comparison to aprepitant (figure 9). The sedation slowly resolved on days 3, 4, and 5, even though patients continued olanzapine on days 2, 3 and 4 post-chemotherapy. No patient dropped out of the study because of increased sedation.

Figure 9: Side-effects of olanzapine



Discussion

In this study, all eligible 146 patients were females, which is consistent with other studies suggesting that breast cancer in men is an extremely rare disease. [6, 7]

The average age of the studied patients was 45 years. In various population-based studies done in different parts of the country, more than 80% of Indian patients are younger than 60 years of age. The average age of breast cancer patients has been reported to be around 50–53 years. [8]

The average body surface area (BSA) was found to be 1.49 m^2. BSA, despite limitations, is used for calculating the dose of cytotoxic drugs in chemotherapy regimens frequently. [9, 10]

In the present study, 53% and 47% of females were of premenopausal and postmenopausal status respectively which can be comparable with Aich RK et al. study which states that the odds of developing breast cancer in premenopausal women was higher than postmenopausal women. [11]

About 70% of patients in both the groups had no co-morbidities associated. Overall, 16% had hypertension (HTN), 9% had HTN with diabetes mellitus (DM) and 3% had DM and other co-morbidities. All of the above-mentioned co-morbidities were, to a degree, associated with the lifestyle behavior. [12]

Overall, 6% of the patients had dietary habits such as occasional alcohol intake. This observed lower rate of risk factor might be due to the general minor pattern of risky habits prevalence in Indian females. Prevalence of alcohol consumption is <1% in Indian women as studies have shown. [13]

Similar to Amer MH et al study, most patients had unilateral primary breast cancer. [14] Earlier studies have reported right-sided lateralization for different organ cancers except for breast cancer. [15] In the present study, breast cancer was noted to be predominantly on the left side (50%) than on the right side (49%) and bilateral (1%).

The majority of the patients in our study were American Joint Committee on Cancer (AJCC) TNM Clinical Prognostic stage IV in both the groups because women often don't present for early medical care due reasons such as illiteracy, lack of awareness and financial constraints. [16, 17]

According to National Comprehensive Cancer Network (NCCN) guidelines, HEC regimen are those that cause chemotherapy induced nausea and vomiting (CINV) in >90% of patients in the absence of effective antiemetic prophylaxis. In this study, three parenteral HEC regimens were included; AC, TCH and TAC.

In the present study, the proportion of patients with primary endpoint of efficacy, CR was significantly higher in the olanzapine group than in the aprepitant group in all the three assessment periods which is comparable with the study findings done by W. Yeo et al.[18]

Nausea was significantly controlled in olanzapine group when compared with aprepitant group in all the three assessment periods; acute (83% vs. 63%), delayed (92% vs. 79%) and overall (82% vs. 61%) which is similar to the study findings done by W. Yeo et al.[18] Grading of nausea was done according to CTCAE V5.0 where in olanzapine group, 62% had mild (Grade 1) and 38% had moderate (Grade 2) nausea. While, in aprepitant group, 50% had mild (Grade 1), 43% had moderate (Grade 2) and 7% had severe (Grade 3) nausea. Thus, nausea was better controlled with olanzapine. In a study done by Shiva Prakash, et al., in the olanzapine treated group, majority had nausea of moderate severity (67%) and 33% had a severe grade, while in the aprepitant group, 36% of the patients had severe grade nausea and 64% with mild to moderate grade nausea.[20]

Vomiting wasn't significantly controlled in olanzapine group when compared with aprepitant group in all the three assessment periods; acute (89% vs. 88%), delayed (94% vs. 86%) and overall (86% vs. 83%). Grade 1 (80% vs 67%) and Grade 2 (20% vs. 33%) vomiting was found in both olanzapine vs. aprepitant group. Two other studies done by Navari RM et al.and Babu et al.have compared the combination of olanzapine, ondansetron and dexamethasone with aprepitant, ondansetron and dexamethasone in which both reported similar antiemetic efficacies between the two arms so that Babu et al.concluded that olanzapine could be a cost-effective alternative for the prevention of CINV in patients who need to receive parenteral HEC. [19, 21]

The patients receiving olanzapine, as compared with those receiving aprepitant, had significantly increased sedation on day 2. The sedation gradually resolved on days 3, 4, and 5, even though patients continuously received olanzapine on days 2, 3 and 4 post – chemo thera pies. No incidence of patient drop out from the study was reported. These findings were similar to a study done by Navari RM et al. [3]

For this reason, unless olanzapine is administered as a premedication before chemotherapy, bedtime administration is usually recommended. This commonly frequent side-effect of increased sedation could also effectively relieve insomnia and agitation caused by dexamethasone as suggested by the study done by Tan L et al.[22]

Other common side effects with olanzapine include postural hypotension, anticholinergic side effects and fatigue. [23] However, these were not reported in our study.

Study Limitations

Randomization and blinding wasn't done. We evaluated only one dose level of olanzapine (10 mg) but lower or higher doses may have an effect on efficacy and, or adverse effects. The study did not address the efficacy of olanzapine in multi-day HEC regimen.

Conclusion

Our study showed that olanzapine when compared with standard antiemetic aprepitant prevents acute, delayed and overall CINV caused by parenteral HEC regimens. Also, olanzapine significantly controls nausea in all the three assessment periods immediately post-chemotherapy with minimal increase in sedation.

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