Efficacy of 5mg Versus 10mg Olanzapine for Prevention of Highly Emetogenic Chemotherapy Induced Nausea & Vomiting: A Randomized Phase II Study from Nepal

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ABSTRACT

Introduction: The most common side effects of chemotherapy are nausea and vomiting. Olanzapine is one of the important drug used as a prophylaxis for the prevention of chemotherapy-induced nausea and vomiting. It is important to know the efficacy and toxicity of low-dose (OLD) compared to standard-dose (OSD) olanzapine for the prevention of chemotherapy-induced nausea and vomiting caused by highly emetogenic chemotherapy.

Methods: A randomized study was conducted for this study where patients were randomly assigned to receive either OSD or OLD orally. Both groups received dexamethasone and granisetron intravenously before chemotherapy. Patients were asked to record daily episodes of nausea and vomiting/retching, the intensity of symptoms, and the need for rescue therapy. Data were analyzed using an independent t-test to compare the mean proportions between two doses of olanzapine. The frequency was analyzed using descriptive statistics.

Results: In this study, each group contained 48 patients. There was an absence of nausea (95.83% vs. 87.50%; p= 0.33), acute vomiting (93.75% vs. 95.83%; p= 0.64), and delayed vomiting (91.66% vs. 93.75%; p= 0.69) between OLD and OSD. Complete response was (89.58% vs 89.58% ; p=1.00) and total control was (87.50% vs 79.16% ; p= 0.27) between OLD and OSD respectively. Rescue therapy was required in 8.33% of patients in each group. No significant differences in toxicities were noted between treatment arms.

Conclusion: OLD had comparable efficacy and toxicity compared to OSD in the management of CINV, Hence, OLD could be effective and cheap prophylaxis for CINV against HEC in low-resource countries.

Keywords: Cancer; Nausea; Nepal; Vomiting.

INTRODUCTION

Cancer is one of the most serious and dreadful disease prevalent today and is also one of the leading cause of death worldwide.[1] Chemotherapy plays a pivotal role in cancer management, despite having the most common and serious adverse effects of CINV. Guidelines for the prevention of CINV suggests that the combination of dexamethasone, olanzapine, and serotonin (5HT3) receptor antagonist (5HT3RA) is one of the standard management protocols for Highly Emetogenic Chemotherapy (HEC). They have given a fixed dose of others but not of olanzapine. They have suggested 10mg as a standard dose for most of the patients and a low dose (5mg), especially for older and over-sedated patients.[2] This study aims to assess and compare the frequency of nausea and vomiting in patients premedicated with standard versus low-dose olanzapine. Another aim is to assess and compare different adverse effects (somnolence, fatigue, extrapyramidal, etc.) between standard and low-dose olanzapine group.

METHODS

A randomized comparative analytical study was carried out among 96 cancer patients at the Clinical Oncology department of Bir Hospital and the Medical Oncology Department of Bhaktapur Cancer Hospital. Patients diagnosed with any type of cancer of any stage receiving HEC defined as cisplatin of any dose or Carboplatin AUC ≥4 or cyclophosphamide ≥ 1500 mg/

m2 or doxorubicin ≥ 60 mg/m2 or its combination for the standard number of allocated cycles and Eastern Cooperation Oncology Group (ECOG) performance status of 0 to 2 were included whereas patient allergic reaction to any of the given drugs and patient giving the previous history of extrapyramidal symptoms or intolerance to drugs were excluded. All the eligible patients fulfilling the inclusion criteria, and presenting to Oncology Out Patient Department or Emergency Department during the study period were enrolled in the study. Eligible patients were subjected to two arms. An equal number of envelopes were marked either arm A or arm B.

Patients were allowed to choose any envelope randomly and were assigned to the same group as chosen by the draw. All patients received dexamethasone 12mg, 1mg of granisetron both as intravenous bolus 30 to 60 minutes before chemotherapy on day 0. Patients in arm A (OSD) received 10mg oral Olanzapine 30 to 60 minutes before chemotherapy on day 1 followed by oral olanzapine once a day before sleep from day 1 to 3. Patients in arm B (OLD) received 5mg of olanzapine on day 0 and the following 3 days. Use of oral lorazepam 0.5 to 2 mg every 6 hours as needed was allowed as a breakthrough antiemetic for CINV refractory to the assigned treatment arm. The protocol was continued with each chemotherapy cycle. From the day of the start of the chemotherapy, until day 5, patients were asked to record daily episodes of nausea and vomiting/retching, the intensity of symptoms, and the need for rescue therapy in a diary.

The patients were contacted to remind them about the recording events in a self-administered patient form which was provided to patients. Toxicities of especially olanzapine were recorded like somnolence, fatigue, akathisia, dystonia, constipation and weight gain. All toxicities were graded using Common Terminology Criteria Adverse Events (CTC AE) version 4.0. Complete Response (CR) rates (no emesis, no rescue) were analyzed at overall period (0–120 hours). The total control (TC) rate (no nausea, vomiting, and no rescue) was also calculated. The use of breakthrough vomiting was also noted. For monitoring of safety, blood sugars, lipid profile, Liver function test, and Electrocardiogram (ECG) were done if clinically indicated.

The procedure was repeated for a minimum of four subsequent chemotherapy cycles and was compared between two groups. Demographic data of patients were collected and recorded in standard proforma. All the Data collection was done on a standardized data collection sheet. Patient demographics and clinical characteristics age, sex, and ECOG performance status, were obtained along with the date of enrollment, chemotherapy cycle and treatment regimen in the Performa. Data analysis was performed upon completion of the study. The data were entered using SPSS version 20

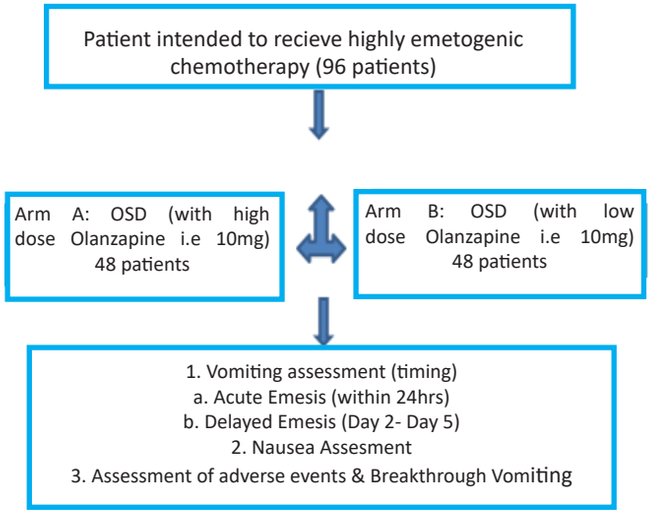

Figure 1. Distribution & Randomization of study patients

software. Statistical analysis was done using an independent t-test to compare the mean proportions between two doses of olanzapine. The frequency of the acute period, delayed period and overall period was analyzed for descriptive statistics. A 95% confidence interval was considered statistically significant. Results obtained from the study were discussed concerning currently available kinds of literature and a conclusion was drawn based on these results and any recommendations regarding current practices were made.

Approval from the Institutional Review Board (IRB) of NAMS was taken and written informed consent was obtained from all patients (96) included in this study. Patients were assured of full confidentiality during and after the study period. The consent was taken only after a better understanding of the advantages, disadvantages and complications of the procedures.

RESULTS

A total of 96 patients were enrolled in the study, 48 in group OLD and 48 in group OSD. The majority of the patients (57.29%) were female and lung cancer (37.50%) was the most common cancer among them. In regards to acute vomiting, 93.75% and 95.83% of study sample had no vomiting in OLD and OSD respectively. Furthermore, in delayed vomiting 91.66% and 93.75% had no vomiting in OLD and OSD respectively. In both groups there were no significant difference as shown in table 2. Nausea was also well controlled in both groups with 95.83% in low dose group whereas it was 87.50% in standard dose group. Similar to vomiting, there was no significant difference of nausea, between both groups as shown in table 3. TC i.e. no CINV as well as no need of

Table 1: Socio- demographic and clinical distribution in both groups

Characteristics	OLD (n=48)	OSD (n=48)	Total
Age	58.65 ±13.477	49.65 ±14.856	54.15 ±14.816
Sex			
Female	24 (25%)	31 (32.29%)	55 (57.29%)
Male	24 (25%)	17 (17.70%)	41 (42.70%)
Type of cancer			
Lung	26	10	36 (37.50%)
Breast	5	18	23 (23.95%)
Hepatobiliary	1	5	6 (6.25%)
Genitourinary	3	3	6 (6.25%)
Gastrointestinal	4	1	5 (5.20%)
Gynecological	3	1	4 (4.17%)
Others	6	10	16 (16.68%)

OLD; olanzapine low dose, OSD; olanzapine standard dose

rescue therapy was slightly better, with no significant difference, in low dose group 87.50% versus 79.16% in standard dose group. Furthermore, CR i.e. no vomiting no rescue was equal in both of the groups with 89.58% each. Fatigue was the most common adverse effect seen in the study with 4.16% of patients in low dose group and 8.32% in standard dose group with no significant difference. Overall, 6.24% of the patients developed fatigue in the study. Similarly, 3.12% of the patients developed somnolence, all of them from standard dose group without any significant difference in both groups.

Table 2: Incidence of acute and delayed vomiting in both groups

Vomiting	OLD (n=48)	OSD (n=48)	Total (n=96)	P-value
Acute				
Absent	45 (93.75%)	46 (95.83%)	91 (94.79%)	**0.646**
Present	3 (6.25%)	2 (4.16%)	5 (5.20%)	
Delayed				
Absent	44 (91.66%)	45 (93.75%)	89 (92.70%)	**0.695**
Present	4 (8.33%)	3 (6.25%)	7 (7.29%)	

Table 3: Incidence of nausea in both groups

Nausea		OLD (n=48)	OSD (n=48)	Total (n=96)	P-value
Absent		46 (95.83%)	42 (87.50%)	88 (91.66%)	
Present	**Grade I**	1 (2.08%)	3 (6.25%)	4 (4.16%)	0.336
	Grade II	1 (2.08%)	3 (6.25%)	4 (4.16%)	

Table 4 : Incidence of total control and complete response in both groups

Total Control	OLD (n=48)	OSD (n=48)	Total (n=96)	P value
Present	42 (87.50%)	38 (79.16%)	80 (83.33%)	0.273
Absent	6 (12.50%)	10 (20.83%)	16 (16.66%)	
Complete Response				1.00
Present	43 (89.58%)	43 (89.58%)	86 (89.58%)	
Absent	5 (10.41%)	5 (10.41%)	10 (10.41%)	

Table 5: Incidence of adverse effects in both groups

Fatigue		OLD (n=48)	OSD (n=48)	Total (n=96)	P value
Absent		46 (95.83%)	44 (91.66%)	90 (93.75%)	
Present	Grade I	2 (4.16%)	2 (4.16%)	4 (4.16%)	**0.399**
	Grade II	0 (0%)	2 (4.16%)	2 (2.08%)	
Somnolence					
Absent		48 (100%)	45 (93.75%)	93 (96.87%)	**0.213**
Present	Grade I	0	2 (4.16%)	2 (2.08%)	
	Grade II	0	1 (2.08%)	1 (1.04%)	
Constipation		2 (4.16%)	0	2 (2.08%)	
Hyperglycemia		1 (2.08%)	0	1 (1.04%)	
Extrapyramidal symptoms		0	0	0	

DISSCUSSION

Olanzapine has been one of the cornerstones of the management of CINV since its introduction. Olanzapine combined with other agents has shown to be an effective and cheap regimen, especially for developing countries like Nepal. Its dose, either standard or low has proven to

be an effective component of the triplet regimen. Standard dose olanzapine has significantly improved both CR and nausea prevention compared to placebo in patients receiving HEC.[3] Hashimoto et al.[4] showed that a low dose of olanzapine significantly improved CR when compared to placebo.

Our study used dexamethasone, a 5HT3 inhibitor, and olanzapine as a triplet regimen. This combination has shown to be quite efficacious showing a 50% of CR rate from the study of Tienchaianan P et al.[5] in HEC. But they used ondansetron and olanzapine standard dose along with dexamethasone and analyzed very few patients of breast cancer using only doxorubicin and cyclophosphamide. Our study has also shown an overall CR of 89.58% using a standard dose of olanzapine. Despite of different methodology, our results enhance the earlier evidence showing this triplet regimen is effective in prevention of CINV. Our study also compared the efficacy of both doses in the setting of HEC-induced CINV. TC in our study was 87.50% in the low-dose group versus 79.16% in the standard olanzapine group. It was 62.3% in the low dose group and 59.2% in the standard dose group in a study by Yanai T et al.[6] While using the same regimen of dexamethasone, 5HT3 inhibitor and olanzapine in both low and standard doses, the CR was 77.3% and 76.2% in low and standard doses of olanzapine respectively in the study by Mukhopadhyay S et al.[7] Collectively, we can infer that low dose olanzapine is efficacious than the standard dose which our study also demonstrated.

Nausea was also well controlled in our study in both groups. Overall, nausea was absent in 95.83% of patients in the low-dose group and 87.50% in the standard-dose group. This was comparably low in the study by Sukauichai S et al.[8] with 42.9% in the low dose group and 45.7% in the standard dose group. The contrasting result could be due to the variability of the chemotherapy regimen between the studies. But the result concludes no significant differences in nausea between both doses in both of the studies. Overall, low dose olanzapine was equally efficacious to standard dose in our study. This result was similar to Ithimakin S et al.[9] who reported 5 mg olanzapine to yield similar CR rates relative to 10 mg olanzapine. This statement was also supported in a meta-analysis by Chow R et al.[10] where, study suggested that a low dose olanzapine prophylactic regimen may be as efficacious as a standard dose. Taken together, the low dose olanzapine can be used as standard of care rather than standard dose olanzapine.With effective treatment come some adverse effects. Olanzapine has few common side effects of somnolence, fatigue, constipation, hyperglycemia etc. In our study, fatigue was the most common adverse effect seen in our study. Only 3.12% of the patients had somnolence and was also found to be non-significant between the two groups. All the adverse effects were within grade 2 and managable. The result of Sukauichai et al.[8] was different as somnolence was the most common side effect. It was seen in 63% of the patients. The vast difference in result could be due to different factors like age of the patient recruited in the study, development of tolerance to olanzapine due to factors like alcohol etc. Moreover, comparing both the groups there was no statistical difference in both studies. This enhance that using either low dose or standard-dose olanzapine for prophylaxis of CINV, adverse effects are comparable.

CONCLUSION

Low-dose olanzapine has shown to be equally efficacious as a standard dose with fewer side effects. Hence, low dose olanzapine could be given as a prophylaxis for CINV against HEC. This strategy would be effective, cheap and with minimal toxicities.

REFERENCES

1. Griffin AM, Butow PN, Coates AS, Childs AM, Ellis PM, Dunn SM, et al. Original article On the receiving end V : Patient perceptions of the side effects of cancer chemotherapy in 1993. Ann Oncol. 1996;7(2):189–95. [FullText] [PubMed] [DOI]

2. Dow-hillgartner E, Pharmd Σ. Antiemesis. Natl Compr Cancer Network NCCN Clin Pract Guidel Oncol. 2023. [Full Text]

3. Navari RM, Qin R, Ruddy KJ, Liu H, Powell SF, Bajaj M, et al. Olanzapine for the Prevention of Chemotherapy-Induced Nausea and Vomiting. N Engl J Med;2016;375:134-42.[Full Text] [PubMed] [DOI]

4. Hashimoto H, Abe M, Tokuyama O, Mizutani H, Uchitomi Y, Yamaguchi T, et al. Olanzapine 5 mg plus standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting (J-FORCE): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2020;21(2):242–9. [FullText] [PubMed] [DOI]

5. Tienchaiananda P, Nipondhkit W, Maneenil K, Sa-nguansai S, Payapwattanawong S, Laohavinij S, et al. A randomized , double-blind , placebo-controlled study evaluating the efficacy of combination olanzapine , ondansetron and dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving doxorubicin plus cyclophosphamide. Ann Palliat Med 2019;8(4):372–80. [FullText] [PubMed] [DOI]

6. Yanai T, Iwasa S, Hashimoto H, Ohyanagi F, Takiguchi T, Takeda K, et al. A double-blind randomized phase II dose-finding study of olanzapine 10 mg or 5 mg for the prophylaxis of emesis induced by highly emetogenic cisplatin-based chemotherapy. Int J Clin Oncol. 2018;23(2):382–8. [FullText] [PubMed] [DOI]

7. Sandip Mukhopadhyay, Premnath Dutta, Sanatan Banerjee, Biswamit Bhattacharya, Supreeti Biswas RMN. Low-dose olanzapine, sedation and chemotherapy- induced nausea and vomiting: a prospective randomized controlled study. Futur Oncol. 17(16):2041–56. [FullText] [PubMed] [DOI]

8. Sukauichai S, Ketkaew C, Othaganont N, Promsuwan P. Efficacy of Olanzapine 5 mg versus 10 mg for the Prophylaxis of Chemotherapy-Induced Nausea and Vomiting in Patients Receiving High Emetic Risk Chemotherapy without Neurokinin-1 Receptor Antagonist. Asian Pac J Cancer Prev. 2022;23:2137–43. [FullText] [PubMed] [DOI]

9. Ithimakin S, Theeratrakul P, Laocharoenkiat A, Nimmannit A. Randomized, double blind, placebo controlled study of aprepitant versus two dosages of olanzapine with ondansetron plus dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving high-emetogenic chemotherapy. Support Care Cancer.2020. [FullText] [PubMed] [DOI]

10. Chow R, Navari RM, Terry B, Deangelis C, Horn E. Olanzapine 5 mg vs 10 mg for the prophylaxis of chemotherapy - induced nausea and vomiting : a network meta - analysis. Support Care Cancer. 2022;1015–8. [Full Text] [PubMed] [DOI]