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A Comparative Study of the Efficacy and Safety of Olanzapine and Aprepitant Regimens in Highly Emetogenic Chemotherapy

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Abstract

Aim: To compare the efficacy and safety of Olanzapine and aprepitant regimens in highly emetogenic Chemotherapy (HEC).

Materials and methods: A randomized, prospective study was conducted in tertiary care hospital, Bangalore. 84 participants were randomized into two groups. Group A (OPD) received on Day 1 (30 mins prior to chemotherapy): Tab Olanzapine 10 mg p/o, Inj Palonosetron 0.25 mg i.v. and Inj Dexamethasone 20 mg i.v. and on Day 2-Day 4: Tab Olanzapine 10 mg p/o once daily. Group B (APD) received on Day 1 (30 mins prior to chemotherapy): Tab Aprepitant 125 mg p/o, Inj Palonosetron 0.25 mg iv and Inj. Dexamethasone 12 mg i.v. on Day 2-Day 3: Tab Aprepitant 80 mg p/o once daily and Tab Dexamethasone 8 mg p/o once daily, on Day 4: Tab Dexamethasone 8 mg p/o once daily.

Results: In OPD group CR was seen in 88%, 86% and 78% in acute (0-24 hrs), delayed (24-120 hrs) and overall period (0-120 hrs) respectively. In APD group CR was seen in 86%, 83% and 70% in acute, delayed and overall period respectively. Adverse drug reactions (ADR's) were seen in total of 12 participants, 6 in each group, there were no significant grade 3 or 4 toxicities. In OPD group Average FLIE scores on day 1 and day 6 were 30.34 and 32.47 respectively while in APD group it was 32.47 and 39.18 respectively.

Conclusion: Both APD and OPD regimens were comparable in controlling CINV in acute and delayed period. OPD regimen was better in overall period and had less impact on QOL compared to APD regimen.

Keywords: 5-HT3RA; NK1-receptor antagonist; Highly emetogenic chemotherapy

Introduction

Chemotherapy Induced Nausea and Vomiting (CINV) is one of the major and distressing adverse effect of cancer chemotherapy [1]. In the absence of antiemetic therapy, CINV occurs in more than 90% of patients receiving HEC (Highly Emetogenic Chemotherapy), and 30% to 90% receiving MEC (Moderate Emetogenic Chemotherapy) respectively. National Comprehensive Cancer Network (NCCN) guidelines categorized anti-neoplastic agents into 4 groups based on their ability to induce nausea and vomiting. These are HEC, MEC, low emetogenic chemotherapy, and minimal emetogenic chemotherapy. Based on the onset, CINV is classified into acute (immediate onset to 24 hrs), delayed (24 hrs to 7 days post chemotherapy), breakthrough (despite prophylaxis) and refractory [1,2].

Presently, regimens with three categories of drugs are used with highest therapeutic index for CINV [3]. These are 5-hydroxyTryptamine (5HT3) receptor antagonists (Palonosetron), Neurokinin 1 (NK1) receptor antagonists aprepitant (APR) and glucocorticoids (Dexamethasone). Previous studies have opined that despite prophylaxis 61% patients on HEC and MEC still experience CINV. CINV is associated with a significant deterioration in Quality of Life (QOL) [4]. If not treated early, it can result in increased healthcare cost, and poor compliance to subsequent chemotherapy cycles [5]. 90% of patients who experienced either acute or delayed CINV reported an impact on their daily activities [6].

As per the recent NCCN guidelines, there is a third regimen with Olanzapine (OLN) for HEC and MEC [7]. It is recommended for acute and delayed emesis prevention. OLN is an atypical antipsychotic. The antiemetic action is thought to be due to the blockade of Dopamine 2 (D2), and 5HT3 receptors [8]. It is a relatively in expensive drug compared to APR and has been found to be equally effective. Also, it shortens the duration of glucocorticoid requirement and thus can reduce the concern of potential toxicity of the multiple day therapy with Dexamethasone. Previous studies have demonstrated the efficacy, safety, and cost effectiveness of OLN versus APR regimens in CINV. But they mentioned about the need for further studies with larger sample size to address efficacy, safety, and tolerability of the regimen [9]. Our literature search revealed only one published article from India comparing OLN and APR regimens in HEC [10].

With this background, the present study is undertaken to demonstrate the efficacy and safety of OLN and APR regimen in the treatment of HEC induced CINV.

Materials and Methods

This was a randomized, prospective, open label, and comparative study conducted in medical oncology department at Vydehi Institute of Medical Sciences and Research Centre. The duration of the study was one year from January 2017 to December 2017.

Sample size was calculated to be 32 in each group. The study included participants of either gender aged between 18 yrs to 60 yrs,

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receiving chemotherapy with HEC (Cisplatin, Cyclophophamide, Carmustine, Doxorubicin, Ifosfamide, Epirubicin, Dacarbazine) and who were willing to provide a written informed consent.

The study excluded uncooperative patients, those allergic to study medications, on radiotherapy. patients with brain or gastrointestinal metastasis, patients with uremia, GI obstruction, patients with neurological disorders e.g. Parkinson's disease, myotonic dystrophy, patients with uncontrolled diabetes. Pregnant and lactating mothers were also not included in this study.

Participants who met inclusion criteria and consented to the study were randomized based on computer generated table into the following 2 groups:

Group A (OPD regimen)

Day 1 (30 mins prior to chemotherapy):

- Tab Olanzapine 10 mg p/o stat
- Inj Palonosetron 0.25 mg i.v. stat
- Inj Dexamethasone 20 mg i.v. stat

Day 2- Day 4:

- Tab Olanzapine 10 mg p/o once daily

Group B (APD regimen)

Day 1 (30 mins prior to chemotherapy):

- Tab Aprepitant 125 mg p/o stat
- Inj. Palonosetron 0.25 mg i.v. stat
- Inj. Dexamethasone 12 mg i.v. stat

Day 2- Day 3:

- Tab Aprepitant 80 mg p/o once daily
- Tab Dexamethasone 8 mg p/o once daily

Day 4:

- Tab Dexamethasone 8 mg p/o once daily

Patients were followed up at 24 hrs, 72 hrs and on 6th day post chemotherapy. They were given a diary to note down the number of episodes of nausea and vomiting, any adverse eactions, and rescue medication used from the day of chemotherapy to day 6 post therapy. Efficacy assessed based on complete response rates (no vomiting, no rescue) at 24 hrs (acute period), 72 hrs and 6th day post chemotherapy (delayed period).

Rescue medication of Inj. Ondansetron 4 mg i.v. given to all patients who did not respond to above regimen. Quality of life was assessed based on FLIE scale [11]. It is a validated self-report questionnaire consisting of 18 questions, with 9 nausea specific and 9 vomiting specific questions. Each question has response categories which range from one to seven on a modified linear analogue scale. The total score would be in the range of 18 to 126, with higher scores representing less impact of CINV on daily life. FLIE was administered at 24 hrs and 6 days post therapy.

Statistical analysis

SPSS (Statistical Package for the Social Sciences) version 21.0 was used for data analysis and Microsoft word and Excel was used to generate graphs, tables etc. Descriptive statistics such as mean and standard deviation (SD) for continuous variables and percentage for categorical variables was determined.

Mean differences in FLIE scores between the two groups were compared using Mann Whitney U test. Unpaired student`s t test was used to compare age distribution and Chi square test for gender distribution. For all the tests, a p-value of 0.05 or less was considered for statistical significance.

Results

The study was conducted for a period of one year from January 2017 to December 2017. Patients who met the inclusion criteria and who were willing to participate in the study were included in the study.

Initially 64 participants were recruited for the study as per the protocol. Considering drop outs in the study, the sample was increased to 84. Out of 84 participants 80 completed the study. 42 participants who were randomized to Group A received OPD regimen. Remaining 42 participants in group B received APD regimen. 2 participants in each group were lost due to follow up. 40 participants in each group completed the study (Figure 1).

Demographic details

Age distribution: Age distribution between two groups is as shown in Table 1 and Figure 2.

Gender distribution: Gender distribution between two groups is as shown in Table 2.

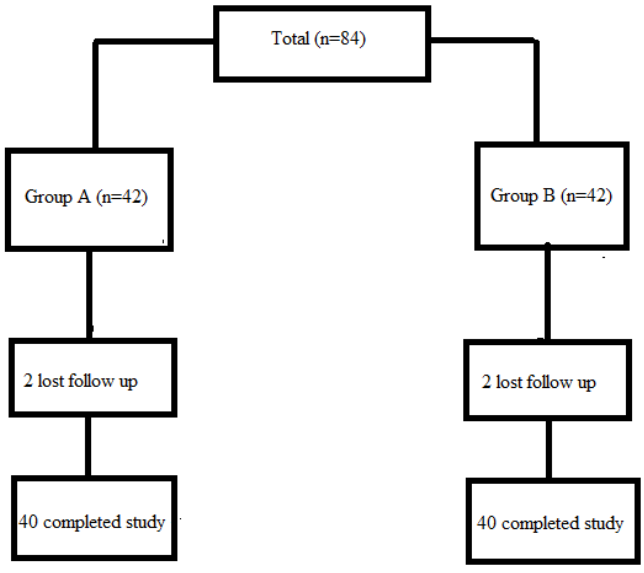

Figure 1: Flowchart of patients enrolled in study

Age (years)	Group A (OPD)	Group B (APD)
20-30	03 (7.5%)	02 (5%)
30-40	13 (32.5%)	06 (15%)
40-50	11 (27.5%)	15 (37.5%)
50-60	13 (32.5%)	17 (42.5%)
n=40 in each group. Using student's t test p=0.12. There was no statistical significance between two groups		

Table 1: Age distribution of participants in study groups.

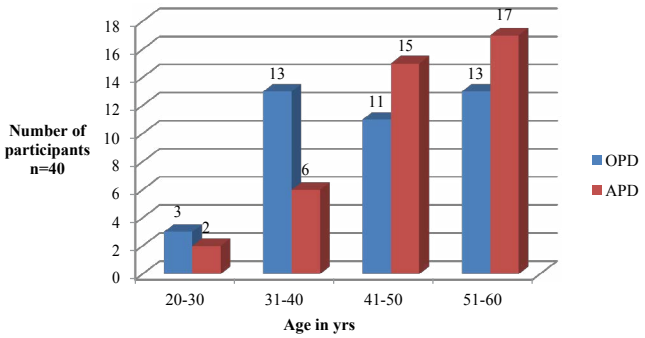

Figure 2: Age distribution of participants in study groups.

n=40 in each group. Using student's t test p=0.12 There was no statistical significance between two groups

SEX	Group A (OPD)	Group B (APD)
Males	0	0
Females	40	40

Table 2: Gender distribution of participants in study groups.

Types of cancers included in this study: Results are as shown in Table 3 and Figure 3.

Chemotherapy cycle: Distribution of participants based on cycle of chemotherapy is shown in Table 4.

Complete Response (CR) rates: CR rates in acute, delayed and overall period shown in Table 5 and Figure 4.

Rescue medication requirement in the study groups: Requirement of rescue medication in two groups is as shown in Table 6.

Incidence of ADR's in study groups is as shown in Table 7 and Figure 5.

Diagnosis	Group A (OPD)	Group B (APD)
Ca Right breast	23	18
Ca Left breast	17	22
n=40 in each group		
Using Chi square test p=0.26		
There was no statistical significance between two groups		

Table 3: Diagnosis based distribution of participants in study group.

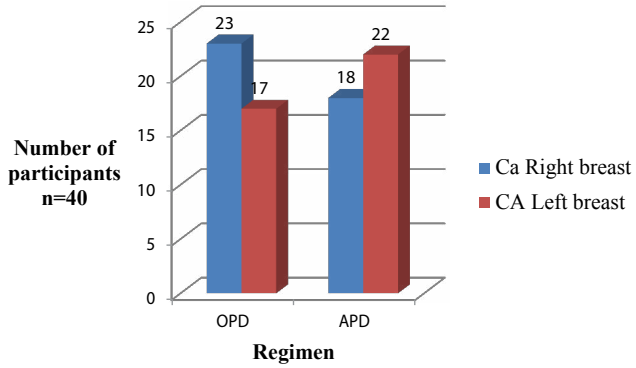

Figure 3: Diagnosis based distribution of participants in study group.

n=40 in each group. Using Chi square test p=0.26. There was no statistical significance between two groups

Chemotherapy cycle	Group A (OPD)	Group B (APD)
AC #1	18	15
AC #2	9	12
AC #3	8	3
AC #4	5	10
AC: Inj Adriamycin, Inj Cyclophosphamide		
n=40 in each group Using unpaired student's t test p=0.003 There was no statistical significance between two group		

Table 4: Chemotherapy cycle based distribution of participants in study groups.

Period	Group A (OPD)	Group B (APD)	P value
Acute	35 (88%)	34 (86%)	0.12
Delayed	34 (86%)	33 (83%)	0.06
Overall	31 (78%)	28 (70%)	0.04*
n=40 in each group.			
Intergroup comparison in each period done using Chi square test			
*(p=0.04) statistically significant			

Table 5: Complete Response rates in study groups.

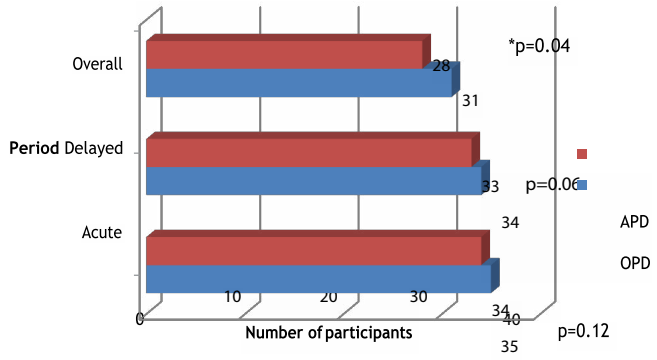

Figure 4: Complete Response rates in study groups.

n=40 in each group. Intergroup comparison in each period done using Chi square test

Rescue medication	Group A(OPD)	Group B(APD)
Yes	02 (5%)	03 (7.5%)
No	38 (95%)	37 (93%)
n=40 in each group		
Using Chi square test p=0.43		
There was no statistical significance between two groups		

Table 6: Requirement of rescue medication in study groups.

ADR	Group A (OPD)	Group B (APD)
Pain abdomen	03 (7.5%)	04 (10%)
Headache	02 (5%)	0
Giddiness	01 (2.5%)	0
Constipation	0	02 (5%)
Total	06 (15%)	06 (15%)
n=40 in each group.		
Using Chi square test p=0.67		
There was no statistical significance between both groups		

Table 7: Incidence of ADR's in study groups.

Average FLIE scores on Day 1 and Day 6 in the study groups: Average FLIE scores on Day 1 and Day 6 were compared between groups. Results are shown in Table 8.

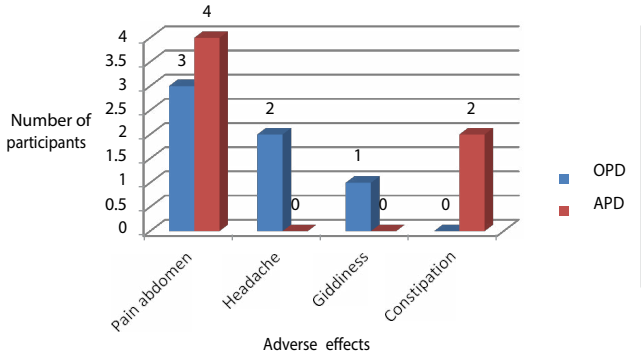

Figure 5: Incidence of ADR's in study groups.

n=40 in each group. Using Chi square test p=0.67. There was no statistical significance between both groups

Average FLIE scores	OPD	APD	p value
Day 1	30.34	32.47	0.56
Day 6	36.28	39.18	0.045*
Average FLIE scores were compared using Mann-Whitney U test. * (p=0.045) statistically significant			

Table 8: Average FLIE scores in the study groups.

Discussion

In this study age mean age ± SD was 45.2 ± 9.32 in Group A and 47.68 ± 7.63 in Group B. (p=0.042). A study was done by Babu et al. [10] to evaluate the efficacy, safety, and cost benefit of OLN when compared to APR in the prevention of CINV in patients receiving HEC. The mean age in this study was 44.78 years and 43.30 years in the APD and OPD arms, respectively (p>0.05). This was comparable to present study. In the study done by Navari [9] to compare the effectiveness of OLN and APR in HEC median age 63 yrs in OPD group, median age 61 yrs in APD group.

All patients included in this study were females and were treated for Ca Breast. Male patients who were treated for solid tumours and on HEC were also on concurrent RT. Hence they were excluded from this study. In the study done by Babu et al. [10] females were the majority in both the groups (70%). 52% of patients in OPD group and 50% patients in APD group were treated for breast cancer. In the study done by Navari [9] 67% were females in OPD group and 69% were females in APD group.50% of patients in OPD group and 55% patients in APD group were treated for breast cancer.

Complete Response rates (CR-no vomiting, no rescue) at 24 hrs (acute period), 72 hrs and 6th day post chemotherapy (delayed period) and overall period (0-120 hrs). In OPD group CR was seen in 88%, 86% and 78% in acute, delayed and overall period respectively. In APD group CR was seen in 86%, 83% and 70% in acute, delayed and overall period respectively. CR rates were significant in overall period. In the study done by Babu et al. [10] CR was 84% for the acute period, 88% for the delayed period, and 78% for the overall period in OPD group. CR was 86% for the acute period, 86% for the delayed period and 80% for the overall period in APD group. OPD was comparable to APD in the control of CINV. The study concluded that there was no significant difference between OLN and APR in preventing CINV with HEC. The efficacy parameters were similar to the present study. In the study done by Navari CR [9] was 97% for the acute period, 77% for the delayed period, and 77% for the overall period in OPD group. CR was 87% for the acute period, 73% for the delayed period and 73% for the overall period in APD group. CR rates were not significantly different in both groups.

In this study ADR's were seen in total of 12 participants. 6 out of 40 participants in each group had ADR. In OPD group 3 complained of pain abdomen, 2 had headache, 1 complained of giddiness. In the APD group 4 complained of pain abdomen, 2 had constipation. There was no significant grade 3 or 4 toxicities. In the study done by Babu et al. [10] the most common ADR's with OLN were drowsiness, sedation and dizziness. Both were grade 1 or 2 and were seen only in 4 patients. Drowsiness lasted for duration of 18-36 hrs in these 4 patients. In the APD arm constipation and dizziness were seen in 2 cases. There were no significant grade 3 or 4 toxicities. In the study done by Navari [9] there were no grade 3 or 4 toxicities. The studies were comparable to present study as there were no significant toxicities.

The average FLIE scores on day 1 and day 6 in OPD group were 30.34 and 32.47 while average FLIE scores on day 1 and day 6 in APD group were 32.47 and 39.18.

A cross sectional study done by Aksu et al. [12] included sixty patients with Non-Small Cell Lung Cancer receiving chemotherapy regimen consisting of Cisplatin and Docetax el. The patients were randomized to two groups. Patients in Group A (31 patients) received 3 daily doses of Aprepitant along with oral Ondans tron and Dexamethasone. Group B patients (29 patients) received only Ondansetron and Dexamathasone. The efficacy of both regimens was evaluated by modified Turkish version of FLIE scale consisting of 18 questions. Median FLIE score in group A was 24.97 (± 12.45) while it was 38.1 (± 26.987) in group B and the difference was statistically significant (p=0.022). The study concluded that Aprepitant in combination with other drugs was better compared to others in prevention of CINV.

Conclusion

The study showed that both APD and OPD regimens were equally efficacious in controlling CINV in acute and delayed period. However OPD regimen was better in overall period compared to APR. There were no significant grade 2 or 3 adverse effects in both the groups. Requirement of rescue medications were more in APD regimen. OPD regimen had less impact on Quality Of Life compared to APD regimen. However, more randomized studies with larger sample size are required to confirm the efficacy and safety of OLN.

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