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Olanzapine versus aprepitant for the prophylaxis of Chemotherapy-induced nausea and vomiting in patients receiving Taxane/ Adriamycin/ Cyclophosphamide (TAC) regimen for post-mastectomy breast cancer

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ABSTRACT

Breast cancer is mainly formed in the tissues of the breast, and it spreads through the lymphatic system. They are mostly found in women rather than men. The breast cancer incidence has been increasing globally, with 1 in 8 women developing cancer in their lifetime. This prospective observational study was conducted to determine the Chemotherapy-Induced Nausea and Vomiting (CINV) in post-mastectomy breast cancer patients for nine months in a tertiary care hospital. Sixty patients were divided into two groups where one arm received Olanzapine, and the other received aprepitant. Both the arms were analysed for the severity of nausea and vomiting. Aprepitant (APT) is a neurokinin one receptor antagonist (NK1RA) which is used as antiemetic in the prophylaxis of CINV. Olanzapine (OLP) is a second-generation antipsychotic agent, which works by blocking the serotonin receptor. The objective of the study is to Evaluate the Safety and Efficacy of APT versus OLP in preventing CINV in breast cancer patients on Docetaxel-Adriamycin-Cyclophosphamide regimen. The OLP is more effective than APT in antiemetic therapy.

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INTRODUCTION

Breast cancer is mainly formed in the tissue of the breast, and it spreads mainly through the lymphatic system. They are mostly found in women and rarely in men. It is the second most common cancer in women (Zhang *et al.*, 2018; Chow *et al.*, 2016). Chemotherapy-Induced Nausea and Vomiting is one of the most common ADRs in a patient undergoing chemotherapy with any drug regimen. The occurrence is about 90%. (Rumyantsev *et al.*, 2018). It is still a clinical problem, and its pathophysiology is not entirely understood (Einhorn *et al.*, 2017).

The predisposing factors of CINV are mostly due to the emetogenic potential of the drug and admin-

istration of the chemotherapy schedule. In post-chemotherapy, the antineoplastic drugs show either acute or delayed phase of nausea and vomiting (Chanthawong *et al.*, 2011; Zhang *et al.*, 2018). The receptors responsible for nausea and vomiting are Muscarinic receptor, Histamine H_1, Dopamine $D_{2,}$ $5HT_3$ and Opioid receptor.

These receptors, in turn, activate the Chemoreceptor Trigger Zone, thereby inducing the vomiting centre in the medulla (Babu *et al.*, 2016; Dennert *et al.*, 1997).

APT is an NK1RA which is mainly used as antiemetic prophylaxis in chemotherapy-induced nausea and vomiting. These drugs are prescribed only for the CINV and not for common nausea and vomiting. This drug is usually given along with a corticosteroid and serotonin 5-HT receptor blockers for better efficacy (Navari, 2014). Olanzapine (OLP) is the second generation antipsychotic agent, which works by blocking the serotonin receptor. It is more effective in controlling CINV in Chemotherapy patient (Chiu *et al.*, 2016). Taxane — Adriamycin — cyclophosphamide regimen is usually given in the breast cancer patient at different stages based on the severity of cancer. This regimen was selected for this study because they are highly emetogenic anticancer drugs defined by Hesketh. They are Level 4 and Level 5 drugs associated with emesis-producing frequency of 60%–90% and more than 90%, respectively (Hesketh, 2014).

The study aims to Evaluate the Safety and Efficacy of Olanzapine and Aprepitant in breast cancer patient talking Taxane — Adriamycin — Cyclophosphamide. The primary objective is to study the breakthrough emesis and complete response after the prophylaxis**.** The secondary objective of the study is to study the severity of nausea, vomiting, acute and delayed phase of emesis in the chemotherapy cycle.

MATERIALS AND METHODS

Study site

The study was conducted in a tertiary care 1000 bedded multi-speciality Teaching Hospital.

Study period

This study was performed for nine months.

The study design is a comparative prospective Observational study. Sixty patients were enrolled in the study, and their demographic data were collected. The patients selected were divided into two groups. The post-mastectomy drug regimen selected in this study was Taxane/ Adriamycin/ cyclophosphamide.

The Docetaxel (Taxane) is administered 120 mg, intravenously for about an hour. This was immediately followed by Doxorubicin (Adriamycin) 600 mg administered as an IV infusion every 21 days. Cyclophosphamide 400 mg was administered in divided doses for 4 -5 days.

Group A

Day 1- Patients on treatment with Olanzapine (10mg- P/o), Dexamethasone (12mg- P/o) and palonosetron (0.25mg- IV). Day 2 and 3- Olanzapine (10mg- P/o) and dexamethasone (8mg — P/o).

Group B

Day 1- Patients on treatment with Aprepitant (120mg- P/o), Dexamethasone (12mg- P/o) and palonosetron (0.25mg- IV). Day 2 and 3- Aprepitant (80mg- P/o) and dexamethasone (8mg – P/o).

On day 5, both the groups will be observed for complete response and breakthrough emesis. Multinational Association for Supportive Care in Cancer (MASCC) Assessment tool was used to understand the prevention, severity and control of nausea.

Common Terminology Criteria Adverse Event (CTCAE) scale is a grading system where it accesses the severity of vomiting. The 100 mm visual analogue scale is used for the severity of nausea. The data are analysed, and the results are collated.

Patient selection

Inclusion criteria

Patients who have undergone mastectomy and are given chemotherapy in this regimen, Adults, aged 18 years and above, Post-mastectomy breast cancer patient undergoing the Docetaxel-Doxorubicin-Cyclophosphamide, Breast cancer patient who is either on Olanzapine and Aprepitant antiemetic prophylaxis and patient who were given under antibiotics and motility enhancers were given a washout period before included in the study.

Exclusion criteria

Patients were receiving other than palonosetron, dexamethasone, Olanzapine and Aprepitant as antiemetic prophylaxis regimen were excluded, Patients diagnosed with severe psychiatric conditions and taking antipsychotic drugs like risperidone, clozapine etc., Patients suffering from tumours of metastasis and node involvement, acutely ill patients such as the severe liver and renal disorders, Serious cardiac disorders with left ventricular ejection fraction <50%, Pregnant and lactating women and Women in a childbearing stage.

Ethical number

VISTAS-SPS/IEC/II/2019/02

Statistical analysis

The study will be analysed using the student t-test with a 95% level of significance, and 'p' value of <0.05 is considered significant. The obtained data will be statistically analysed with the help of SPSS.

RESULTS AND DISCUSSION

This study was carried out to understand the severity of nausea and vomiting in CINV in patients taking the TAC regimen. The study instruments that were used are the MASCC Assessment tool, 100 mm scale and CTCAE scale. The severity of nausea and vomiting was assessed in the acute and delayed phase of post — Chemotherapy. A study conducted by Shivaprakash *et al.* proved that Olanzapine outweighed aprepitant in mild to moderate emetogenic drugs (Shivaprakash *et al.*, 2017). Our study was carried in moderate to high emetogenic anticancer drugs, and the emesis producing frequency was about 90%. It was observed in our study that the groups showed statistical differences. Though aprepitant was considered as an essential drug in the prophylaxis regimen by all the major international guidelines (American Society of Clinical Oncology, National Comprehensive Cancer Network and Multinational Association of Supportive Care in Cancer (MASCC)), the Olanzapine was proved to have better efficacy (Jordan *et al.*, 2015; Sapkota *et al.*, 2017).

Figure 1 shows the administration of antiemetic, 5^{th} day from the chemotherapy, showed a surprising result that none of the chemotherapy patients who were taking TAC regimen showed no nausea and no vomiting. The percentage of the Olanzapine was more in both 0 -24 hr no nausea (84%) and no vomiting (87%). Values are expressed as a percentage.

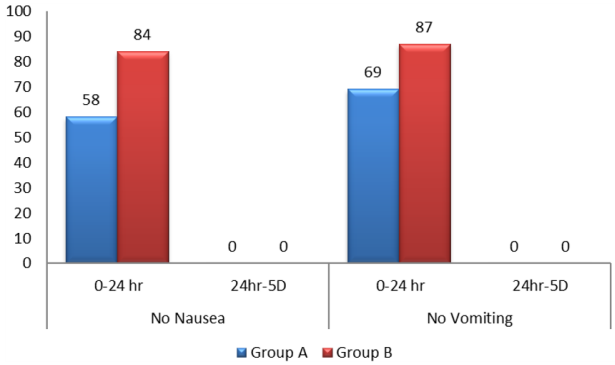

Figure 1: Percentage of Patients who achieved no-nausea and no-vomiting

$P \leq 0.05$ is considered statistically significant. D5: Day 5 of Chemotherapy.

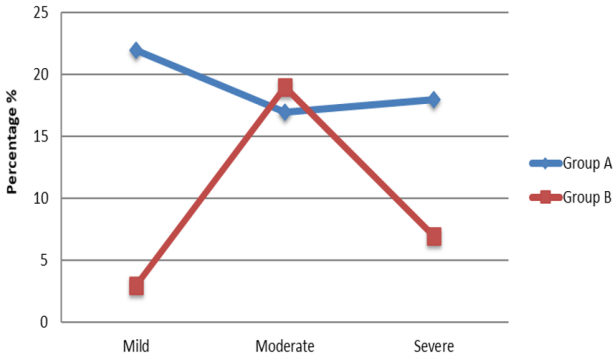

Figure 2: Percentage of patients showing the severity of nausea

Figure 2 shows the percentage of patients reporting the severity of nausea where Group A and Group B showed statistical significance. Mild — according to the MASCC Antiemesis Tool (MAT) was given a score of 1-4, Mod- was given a score of 5–7 and severity were given a score of score 8–10.

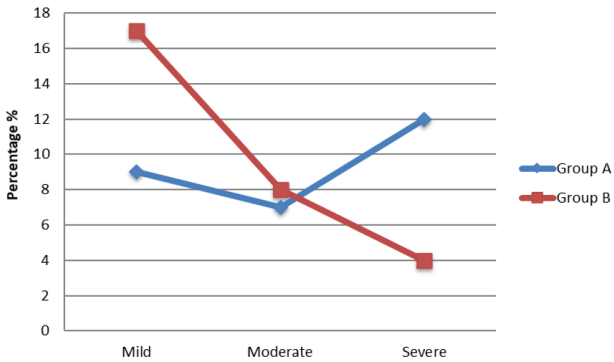

Figure 3: Percentage of patients showing the severity of vomiting

Figure 3 shows the percentage of people reporting the severity of vomiting. Both the group showed a statistical difference. The severity of vomiting was reported less in Group B. According to the CTCAE (Common Terminology Criteria for Adverse Events), which is mainly used in chemotherapy to witness the severity of vomiting in patients. Mild-Grade I Moderate-Grade II; Severe — Grade III.

Table 1 shows the age distribution of patients who are enrolled in this study. 60 – 65 years (22.80%) were more in the study, and 45-50 years (15.7%) were reported the least.

Table 2 shows co-morbidities that are present in the patients. Musculoskeletal/ rheumatic arthritis (31.57%) were reported more, and peripheral vascular diseases (5.26%) were reported the least.

Table 3 shows the staging of breast cancer in patients. In group A, Stage III a (12) was reported

Table 1: Age distribution

S. No	Age group	No of patients (n = 57)	Percentage %
1	45-50	9	15.7%
2	51-55	12	21.05%
3	56-60	11	19.29%
4	60-65	13	22.80%
5	>66	12	21.05%

Table 2: Co-Morbidity

S No	Co-Morbidity	No of Patients (n = 57)	Percentage %
1	Musculoskeletal/ rheumatic arthritis	18	31.57%
2	Coronary artery disease	7	12.28%
3	peripheral vascular disease	3	5.26%
4	DiabetesMelitus	11	19.29%
5	Hypertension	9	15.7%
6	Diabetes and Hypertension	6	10.52%
7	Others	3	5.26%

Table 3: American Joint Committee on Cancer – TNM scale

S No	Staging	Group A (n=28)	Group B (n=29)
1	TNM Stage II b	7	8
2	TNM Stage III a	12	15
3	TNM Stage III b	9	6

Table 4: Association for Democratic ReformsADR Reported

ADR	Group A	Group B	P-Value
Hiccups	13	5	0.0632
Dizziness	3	6	0.0852
Headache	7	3	0.0921
Skin rash	0	1	0.0832
Breathing Trouble	2	4	0.7214
Tiredness	8	9	0. 3451

more, and stage II b (7) was the least. Whereas in group B stage, III b (9) was the least.

Table 4 shows the ADR that was reported in the study. Hiccups (13) were the maximum reported ADR and the least was breathing difficulty(2) in Group A. whereas in Group B the maximum was Tiredness (9) and the minimum was the skin rash (1).

The drug olanzapine is more potent than aprepitant because it works by blocking several receptors such as alpha-1, dopamine, histamine H-1, muscarinic, and serotonin type 2 (5-HT2) receptors which are responsible for triggering the chemoreceptor trigger zone which in turn causes the activation of vomiting centre.

The antagonist action of Olanzapine at these receptors is responsible for its efficacy in CINV. In comparison, the aprepitant crosses the blood-brain barrier and blocks only the neurokinin 1 receptor in the brain.

In terms of the adverse drug reactions, there was no statistical difference between both the groups except for the hiccups, which was reported more in Group A. The results showed clinical superiority in Olanzapine when compared to the aprepitant.

CONCLUSION

There was a statistical difference in the data obtained from the score scale, such as MAT and CTCAE. The Olanzapine and Aprepitant showed better safety and efficacy in the patients taking Docetaxel, Doxorubicin and Cyclophosphamide regimen. Though major international guidelines recommend aprepitant, Olanzapine outweighs the same in terms of better safety, efficacy and cost-effectiveness. It can be used as an alternate for the drug aprepitant.

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Conflict of Interest

The author declare that they have no conflict of interest for this study.

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