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Aprepitant versus Palonosetron as add-on therapy for the Prophylaxis of Chemotherapy induced Nausea and Vomiting (CINV) in patients with Carcinoma Breast: A Prospective Observational Study

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***Abstract*:**
BACKGROUND: *Nausea is the first and vomiting the third most distressing side-effect of cancer chemotherapy. With the introduction of neurokinin-1 receptor antagonist aprepitant, additional improvement in CINV control is observed. However, breakthrough CINV persists in 30%–40% patients receiving prophylactic antiemetics. Also amongst breast cancer patients only 33% achieve complete absence of nausea despite using aprepitant (APT).Long acting 5-HT_3 receptor antagonist palonosetron (PAL) is the first and only antiemetic effective in the prevention of delayed CINV. Also PAL prophylaxis is less costly than APT. However data regarding head-to-head comparison of both these drugs are lacking.*
OBJECTIVE: *Hence this study was undertaken to compare the efficacy, safety of aprepitant versus palonosetron in the prophylaxis of CINV in breast cancer patients.*
METHOD: *A prospective, observational study was conducted in the Department of Radiotherapy and Pharmacology, VIMSAR, Burla. A total of 51 patients were recruited with 24 in APT group and 27 in PAL group. Data regarding complete remission of nausea and vomiting were collected using MAT tool from day 1-5 of chemotherapy. Severity of nausea and vomiting was assessed using VAS scale and CTCAE criteria.*
RESULTS: *Complete response (no nausea or vomiting) was achieved in 91.67% of APT group and 88.89% of PAL group in the acute phase. Among the APT patients, 66.67% had moderate and 33.33% had severe nausea, while in the PAL group all patients had mild nausea.VAS score in PAL group was significantly higher than APT group in the acute phase.*
CONCLUSION: *PAL was found to be equally effective to APT in the prophylaxis of CINV in breast cancer patients receiving chemotherapy.*
Keywords: *CINV, Breast cancer, Aprepitant, Palanosetron*

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I. Introduction

Nausea is the first and vomiting the third most distressing side-effect of cancer chemotherapy[1]. With the introduction of neurokinin-1 receptor antagonist, aprepitant, additional improvement in CINV control is observed. However, breakthrough CINV persists in 30%–40% patients in spite of receiving prophylactic antiemetics[2].Amongst breast cancer patients receiving highly emetogenic chemotherapy like cyclophosphamide+ doxorubicin/epirubicin, only 33% achieve complete absence of nausea despite using aprepitant (APT)[3].Long acting 5-HT_3 receptor antagonist palonosetron(PAL) is the first and only antiemetic effective in the prevention of delayed CINV. Also PAL therapy is less costly than APT. However data regarding head-to-head comparison of both these drugs are lacking.

Emetogenicity of the chemotherapy combination for acute emesis is classified as Level 1–5 by Hesketh[4]. Level 1 being the least, it is defined as the proportion of patients who experience emesis in the absence of effective antiemetic prophylaxis <10%; level 2, 10%–30%; level 3 ,30%–60%; level 4, 60%–90%, and level 5 90%.[4]

In our setup, almost all the breast cancer patients receive emetogenic chemotherapy combination regimen which are graded Level 4 and Level 5, such as doxorubicin, widely used in breast carcinoma, and

cyclophosphamide, an alkylating agent used broadly in lymphoma, ovarian carcinoma, and along with doxorubicin in breast cancer[5]. Cyclophosphamide in combination with an anthracycline like doxorubicin or epirubicin is considered as highly emetogenic[4] resulting in distressing side-effects at many times.

Although significant progress has been made in terms of prevention, chemotherapy-induced nausea and vomiting (CINV) still remains a potentially severe and distressing adverse effect of cancer treatment. The CINV risk also depends on patient characteristics, such as gender, age, and history of tobacco intake. It has been reported that female patients are at greater risk of CINV[6]. Uncontrolled CINV limits the dose intensity of chemotherapy and seriously compromises the patient's quality of life.

Three categories of drugs with the highest therapeutic index for CINV management include: (1) 5-HT_3 receptor antagonist (palonosetron and granisetron), (2) NK-1 receptor antagonists (aprepitant), and (3) glucocorticoid (dexamethasone)[7]. The administration of three antiemetic agents is recommended in patients treated with highly emetogenic chemotherapy (HEC) according to the updated antiemetic guidelines of the Multinational Association of Supportive Care in Cancer (MASCC), American Society of Clinical Oncology (ASCO) [8,9] and guidelines published by the Japan Society of Clinical Oncology (JSCO) in 2010[10].

II. Objective

Hence this study was undertaken to compare the efficacy and safety of aprepitant versus palonosetron in the prophylaxis of CINV in breast cancer patients receiving cyclophosphamide and doxorubicin and epirubicin chemotherapy regimen.

III. Methodology

A prospective, Observational study was carried out over a period of 3 months (Aug 2019–Oct 2019) in the Department of Radiotherapy and Pharmacology at VIMSAR, Burla. The study was conducted after obtaining informed consent from all the participants and institutional human ethical committee clearance (Letter No. IEC 19-I-S-0 148/147/Dt.20.09.19).

Subject selection

Inclusion criteria-

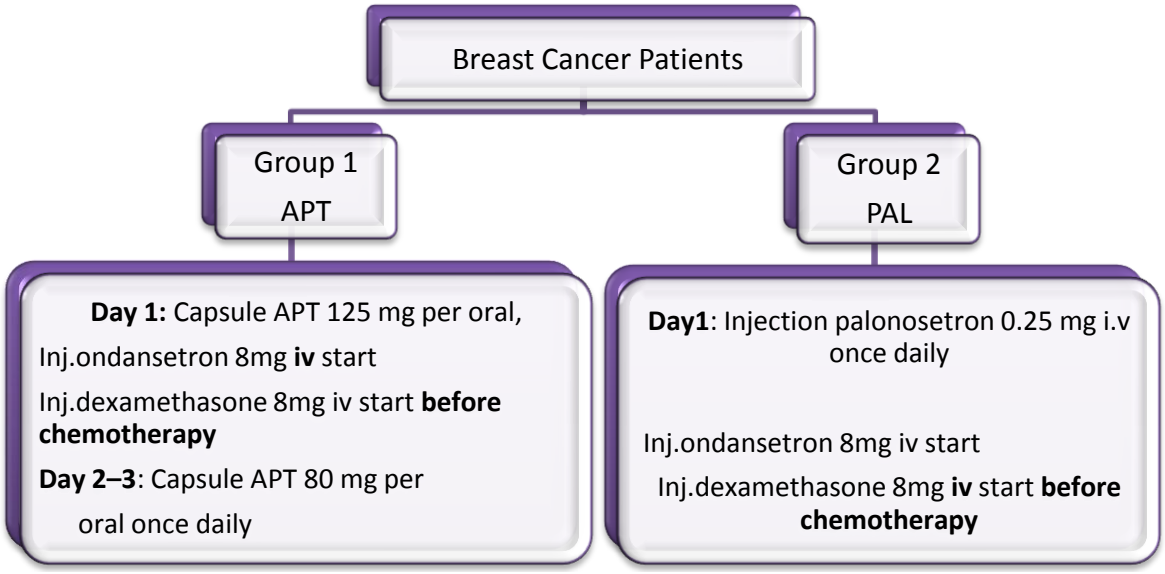
1. Adults aged 18 years and above.
2. Patients who are histopathologically proven to be have breast cancer and are chemotherapy naïve.
3. Patients who have been prescribed highly emetic chemotherapy combination of cyclophosphamide and doxorubicin/ epirubicin.
4. Performance status of >60

Exclusion criteria-

1. Patients who are on antiemetics other than palonosetron, dexamethasone, and APT as an antiemetic prophylaxis regimen
2. Patients suffering from tumors with brain metastasis, gastrointestinal tumors
3. Patients diagnosed with serious psychiatric conditions and on antipsychotic drugs
4. Patients with acute surgical conditions such as small bowel obstruction, appendicitis, and pancreatitis.
5. Acutely ill patients such as serious liver and renal disorders and serious cardiac disorders.
6. Pregnant and lactating women.

Method

Data were collected using a predesigned format and MAT tool from chemotherapy naive patients admitted in the IPD of Dept of Radiotherapy, VIMSAR, Burla. Those patients who satisfied the selection criteria were included in the study**.** They were grouped alternately into two groups receiving aprepitant and palonosetron as follows:



The patients were observed for 5 days post chemotherapy for nausea and vomiting; between 0-24h for acute/early phase and 24h-5days for delayed phase. They were assessed for complete response (CR) i.e., absence of any episode of nausea or vomiting and not requiring the use of rescue medication (T. Ondansetron 8-16 mg). The assessment was done using MASCC Antiemesis Tool (MAT), a standardized and established method. Also the severity of vomiting was assessed by VAS scale and was graded as (mild, moderate and severe) by Common Terminology Criteria for Adverse Events (CTCAE version 4.03) incorporating details such as no. of episodes of vomiting, need for Total parenteral nutrition etc. Besides this, rest details such as demographic characteristics of age, history of smoking, tobacco consumption, comorbid illness were also obtained from all the patients

The patients were followed up in their second cycle of chemotherapy after 21 days and data collection was done in the similar way as mentioned above.

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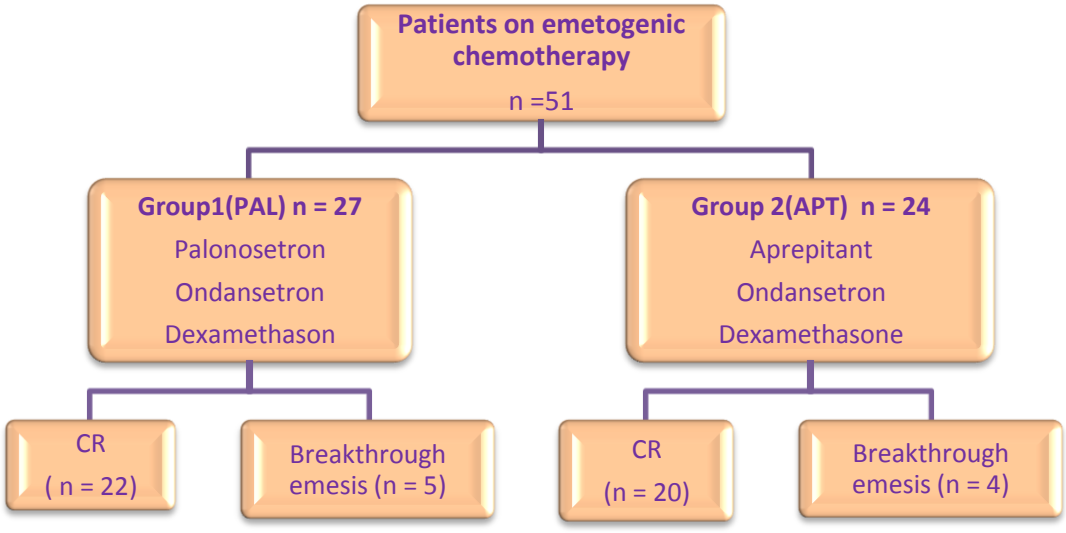
Statistical analysis

Categorical data were expressed as a percentage and continuous data as mean ± standard deviation. Statistical analysis was performed by Graphpad prism ver6.. using appropriate statistical tests, p value <0.05 being considered significant.

IV. Results

Figure 1: Distribution of patients with CR and breakthrough emesis in different groups.



51 patients participated in the study. 24 patients received APT, 27 patients received PAL. All the patients had completed the study and participated in both the initial and follow up phase of the study.

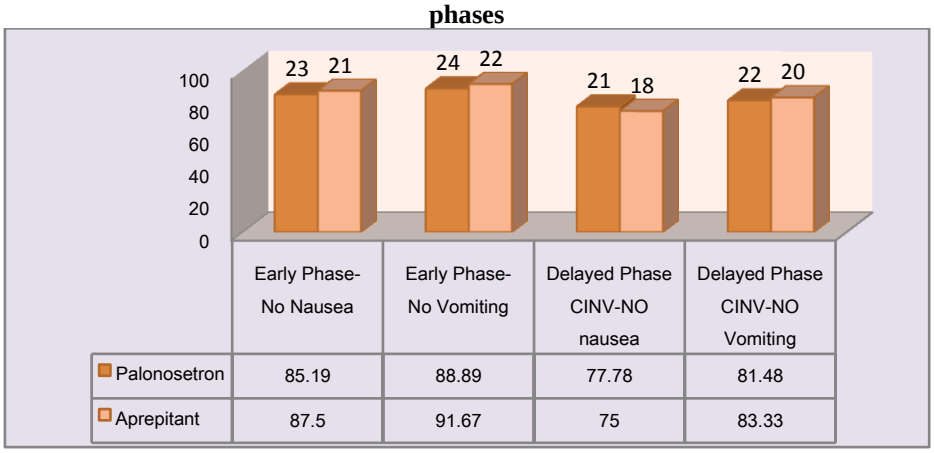
Table 1: Demographic status of breast cancer patients

Character	Palonosetron (n=27)	Aprepitant (n=24)	Total (n=51)
Age in years	46.81±8.55	45.25±8.45	46.03±8.45
TNM STAGING (%)			
T2N0M0	11 (40.74)	10 (41.66)	21 (41.17)
T2N0MX	2 (7.40)	3 (12.5)	5 (9.80)
T3N0M0	8 (29.62)	4 (16.66)	12 (23.52)
T4N0M0	6 (22.22)	7 (29.1)	13 (25.49)
Comorbidity (%)			
No comorbidity	24(88.90)	21(87.5)	45(88.24)
DM	1 (3.70)	2 (8.33)	3 (5.88)
HTN	1 (3.70)	1 (4.17)	2 (3.92)
Others	1 (3.70)	0	1 (1.96)
Habits (Tobacco intake / Smoking) (%)			
NO	25(92.59)	23(95.83)	48(94.12)
YES	2 (7.41)	1 (4.17)	3 (5.88)

Data expressed as mean±std dev (percentage values)

The breast cancer patients included in our study were aged between 35-65 years with an average age of 46 years. According to the TNM staging of breast cancer 41.17% patients were diagnosed as T2N0M0 (40.74% among PAL and 41.66% among APT). 88.90% of PAL group and 87.5% patients of APT group patients had no comorbidities. 94.12% of total no. of patients had no habits of tobacco chewing and smoking.

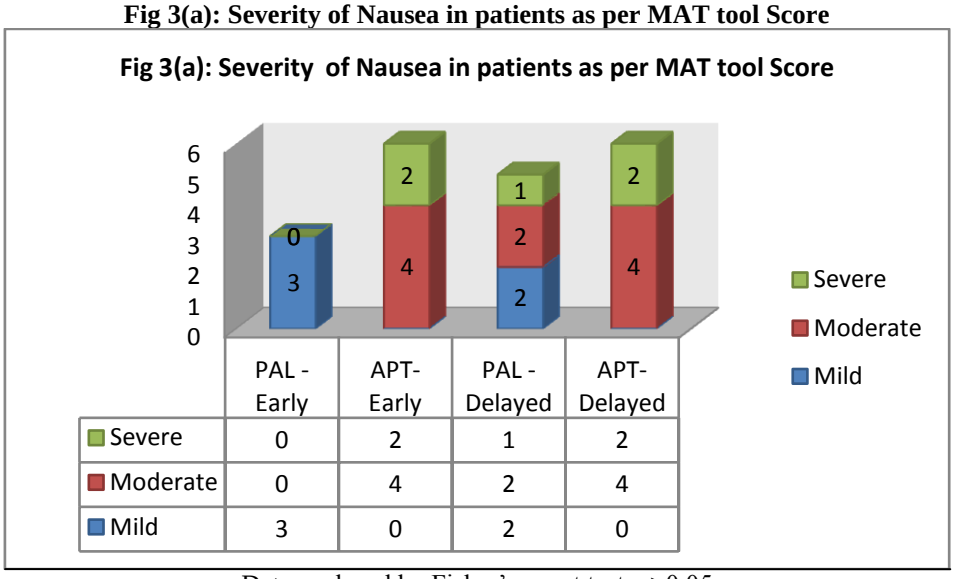
Fig 2: Proportion of patients with no nausea and no vomiting (Complete Response) at different study phases



Data analysed by Fisher's exact test, p>0.05

Out of a total of 27 patients, 23 patients of PAL group had no nausea and 24 had no vomiting. (CR=85-89%). On the other hand, out of 24 patients of APT group, 21 patients had no nausea and 22 had no vomiting in the first 24 hrs (CR=87-92%). In the delayed phase of PAL group, 21 patients had no nausea and 22 had no vomiting. (CR=78-82%) while 18 patients of APT group had no nausea and 20 had no vomiting in the same phase (CR=75-83%). [fig 1]

Fig 3(a): Severity of Nausea in patients as per MAT tool Score

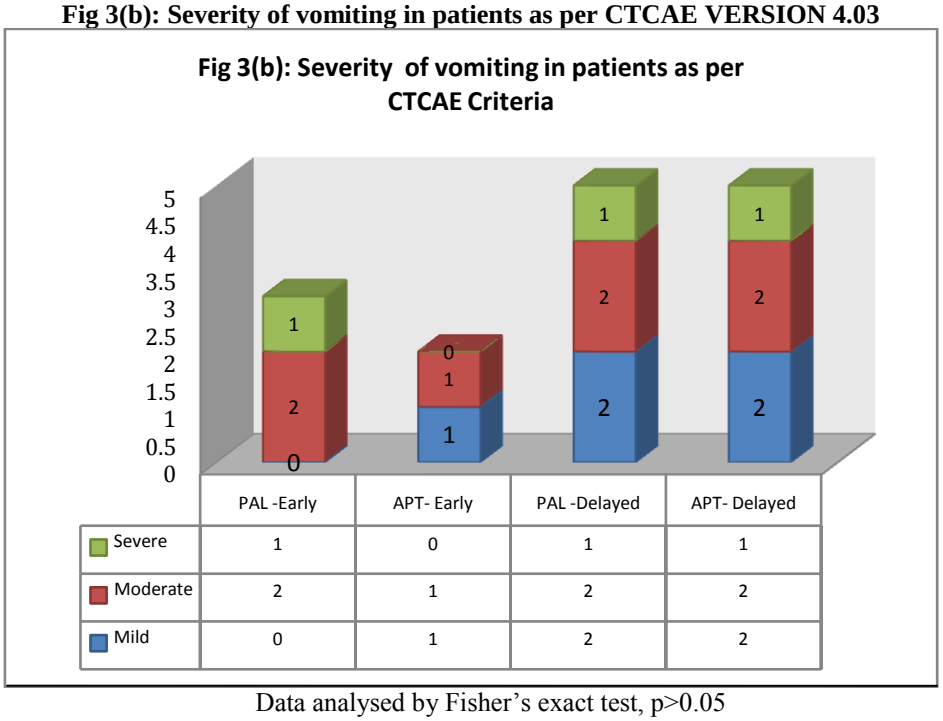


	PAL - Early	APT- Early	PAL - Delayed	APT- Delayed
Severe	0	2	1	2
Moderate	0	4	2	4
Mild	3	0	2	0

Data analysed by Fisher's exact test, p>0.05

Severity of nausea was graded from MAT scale as mild, moderate, and severe having score as 1-4, 5-7and 8-10 respectively. In the early phase a total of 3 patients of PAL group had nausea of mild severity while in the APT group a total of 6 patients had nausea (4 – moderate, 2- severe). In delayed phase 5 patients of PAL group had nausea of which 2 had mild, 2moderate and 1 had severe nausea while out of total 6 patients of APT group having nausea, 4 had moderate and 2 patients had severe nausea. The difference in number of patients having nausea in both the study groups was not statistically significant. [fig 3(a)]

Fig 3(b): Severity of vomiting in patients as per CTCAE VERSION 4.03



	PAL -Early	APT- Early	PAL -Delayed	APT- Delayed
Severe	1	0	1	1
Moderate	2	1	2	2
Mild	0	1	2	2

Data analysed by Fisher's exact test, p>0.05

Severity of vomiting was graded from CTCAE guidelines as mild (grade1), moderate (grade2) and severe (grade3 and above). In the early phase, a total of 3 patients had vomiting of which 2 had moderate and one had severe grade in PAL group while in APT group total of 2 patients had vomiting (1- mild,1-moderate). In delayed phase, in PAL group total of 5 patients had vomiting (2- mild, 2-moderate, 1- severe)and it was the same case with the APT group with 5 patients having severe vomiting(2mild, 2moderate and 1severe).Here too there was no statistically significant difference in severity of vomiting in patients of both the study groups.[fig 3(b)].

Table2: VAS score of patients for nausea and vomiting receiving PAL and APT (Mean±SEM)

Criteria	Palonosetron	Aprepitant	P value
VAS score- 24 hrs	79.11±1.94	72.13±3.14	0.012*
VAS score- 2-5 days	75.19±3.22	69±4.26	0.23

Data analysed by Mann Whitney U test, *p<0.05

Table 2 shows the VAS score of patients for nausea and vomiting receiving APT and PAL.A significant difference was found in the Vas score of PAL as compared to APT in the early phase while no such difference was seen in the delayed phase.

Table 3: CR, Severity and VAS scores of patients of PAL vs APT in the 2ndcycle of chemotherapy

Sl no	Tool	Subcategory	Palanosetron		Aprepitant	
			Early	Delayed	Early	Delayed
1	MAT Tool	No Nausea	100	96.29	100	91.66
		No Vomiting	100	92.59	100	100
2	CTCAE Severity (Nausea)	Mild	0	66.67	0	100
		Moderate	0	33.33	0	0
		Severity	0	0	0	0
3	VAS score	VAS 24HR	81.88±1.81		80.71±0.61	
		VAS2-5DAYS	83.14±1.52***		80±0.82	

***p<0.001, Data expressed as Mean±SEM, analysed by Mann Whitney test for VAS score

When the patients were followed up after 21 days for their subsequent chemotherapy cycle, it was observed that 100% complete response was achieved in the early phase in both the groups, while in the delayed phase 66.67%mild and 33.33% moderate grade in PAL group while 100 %of mild grade in APT group.

It was observed that the VAS score of PAL group was significantly higher than APT in the delayed phase of CINV and in the 2nd cycle of chemotherapy.

As per the Safety profile we found that diarrhoea (14.81%) was the commonest ADR in Palonosetron group followed by weakness and tingling sensation (11%).Similarly in the APT group diarrhoea was again found to be the commonest ADR (12.5%) followed by 1 case each of other ADR like vertigo and increased urinary frequency(<1%).

V. Discussion

As per the demographic status presented in Table 1, breast cancer patients studied were aged between 35-65 years of age with an average age of 46 years. Similar observations were made by **G. Shivaprakash et al**[11], with a mean age of 46 years. From the same table it is observed that majority of the breast cancer patients (41.17%) receiving chemotherapy were of stage T2N0M0.This finding is in contrast to the previously cited study where majority of the patients belongs to AJCC T3N0M0. 88.90% of PAL group patients and 87.5% of APT group had no comorbidities [Table 1]. 94.12% of patients had no habits of tobacco chewing and smoking. Only 4.17% in APT group and 7.41% in PAL group had habits of tobacco chewing and smoking. This all is due to lower prevalence of bad habits in Indian female. Studies have shown that prevalence of tobacco intake is only 15% and alcohol and smoking prevalence is <1% in Indian women.[12]

Proportion of patients with no nausea and no vomiting (complete response) in PAL and APT group in acute and delayed periods following chemotherapy is presented in figure 2. 85.19% in PAL group and 87.5% in APT group shows no nausea in early phase while 77.78% in PAL group and 75% in APT group shows no nausea in delayed phase, showing that in the early phase APT shows better control of CINV, but in delayed phase PAL was more effective in CINV. Similar results were shown by **Ohzawa et al**[13] whereby palonosetron showed better control of CINV in the delayed phase. The properties of palonosetron, a second-generation 5-HT3 receptor antagonist, include a prolonged half-life of approximately 40 hours and effects on receptor internalization. These properties underlie the effectiveness of this drug in the management of delayed nausea and vomiting.

Some international guidelines for antiemesis, generally recommend the use of a 5-HT3 receptor antagonist and dexamethasone with or without the neurokinin-1 receptor antagonist aprepitant, as it is believed that APT enhances the ability to prevent CINV in patients receiving HEC, mainly those involving cisplatin in select patients, although the characteristics of these select patients are unclear [14]. However, no clinical study has evaluated whether palonosetron or aprepitant is the best antiemetic therapy for MEC/HEC.

Severity of Nausea in patients as per MAT tool Score (Fig 3 (a)), Severity of vomiting in patients as per CTCAE criteria (Fig 3(b)) showed that there was no difference in the severity of breakthrough emesis in both the groups. Only comparison of VAS scores showed better results with PAL than APT in early phase. One study by **Yoshida et al** showed similar results whereby there was no improvement in severity for CINV with use of APT along with standard regimen of 5HT-3 antagonist+ Dexamethasone when compared to two drug therapy of 5HT-3 antagonist+ Dexamethasone only.[15] In contrast another study Japanese crossover study showed total control rate for **severe to mild** nausea was lower for palonosetron+Dexamethasone (46%) than APT +5HT-3 antagonist+ Dexamethasone ($p = 0.235$)[16].

It is seen that when the same antiemetic prophylaxis is administered in multiple cycles of HEC there is a better response regarding the prevention of CINV as they help in counteracting anticipatory vomiting. In our study we found that PAL showed better effect than APT w.r.t. severity management (VAS score) in the management of CINV in the second cycle of chemotherapy. In contrast the study by **Abdel-Malek et al** showed that patients receiving Aprepitant recorded less nausea in subsequent cycles that those given without Aprepitant reflecting decrease in the anticipatory nausea. The continuance of the initial high anti-emetic effects of 5HT3 and dexamethasone is sometimes declined through subsequent cycles[17].

Thus, a large prospective randomized study should be performed to prove which antiemetic prophylaxis is better for controlling CINV.

VI. Conclusion

PAL and APT were comparable, and PAL was found efficacious equally efficient in preventing CINV compared to APT. But the cost of therapy of APT is very high (Rs 1215/cycle) compared to PAL (Rs 100/cycle). Due to prolonged action of PAL in preventing CINV and low cost, it can be used as effective alternative to APT for CINV in breast cancer patients on doxorubicin-cyclophosphamide regimen.

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