International Journal of Medical and Pharmaceutical Research

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Website: https://ijmpr.in/

Research Article

Efficacy of Granisetron and Dexamethasone with and Without Neurokinin 1 Receptor Antagonist In Prevention of Chemotherapy Induced Nausea and Vomiting: A Prospective Study

Radha A[1*], Anuradha H V[2], Vinayak V Maka[3]

[1] Associate Professor, Department of Pharmacology, Sri Madhusudan Sai Institute of Medical Sciences and Research, Muddenahalli, Chikkaballapur, Karnataka 562101, India.
[2] Professor & HOD. Department of Pharmacology, M S Ramaiah Medical college, Bangalore, Karnataka 560054, India.
[3] Professor, Department of Medical Oncology, M S Ramaiah Memorial Hospital, Bangalore, Karnataka 560054, India.

OPEN ACCESS

Corresponding Author:

Dr Radha A,
Associate Professor,
Department of Pharmacology,
Sri Madhusudan Sai Institute of Medical Sciences and Research,
Muddenahalli, Chikkaballapur,
Karnataka, India

Received: 18-01-2025
Accepted: 15-02-2025
Published: 28-02-2025

ABSTRACT

Background: Chemotherapy induced nausea & vomiting (CINV) is the most distressing side effects which significantly affect the patient's quality of life and adherence to the scheduled treatment. The introduction of a Neurokinin 1 (NK1) receptor antagonist with older drugs seems to show an enhanced protection against acute and strikingly improved protection against delayed phase of emesis.
Objectives: To assess the efficacy & adverse effects of granisetron and dexamethasone with and without NK-1 receptor antagonist in the prevention of CINV.
Material and Methods: Total of 120 inpatients receiving cancer chemotherapy in the medical oncology wards on high to moderate chemotherapy were recruited. One group received NK-1 antagonist along with granisetron & dexamethasone & other group received granisetron & dexamethasone without NK1 antagonist. All the demographic data were recorded & episodes of nausea, vomiting, any rescue medications used and adverse effects if any in both the study groups were recorded.
Results: The percentage of Complete Response in NK1 group and control group in the overall phase (95% versus 56.6%; p value 0.000) and delayed phase (95% versus 58.3%; p value 0.000) was significantly higher, whereas in acute phase it was not significant (100% versus 88.3%; p value 0.06). The adverse effects addressed in the NK1groups & control were headache {6 (10%) versus 5 (8.3%) subjects} and fatigue {6(10%) versus 3(5%) subjects} & were comparable (p value 0.53).
Conclusion: The NK1 antagonist in combination with granisetron and dexamethasone was more effective and tolerated in preventing CINV in participants receiving high to moderate chemotherapy.

Keywords: Chemotherapy induced nausea and vomiting, chemotherapy, NK1 antagonist, granisetron and dexamethasone.

INTRODUCTION

Chemotherapy Induced Nausea and Vomiting (CINV) is the most distressing side effects which significantly affect the patient's quality of life and adherence to the scheduled treatment.[1] It results in poor nutrition, weight loss, dehydration and electrolyte imbalance leading to delay or discontinuation of a potential advantageous treatment regimen.[1] Based on the percentage of emesis occurrence/experience without antiemetic prophylaxis to antineoplastic drugs in patient, antineoplastic agents are classified as Highly Emetogenic Chemotherapy (HEC) >90 %, Moderately Emetogenic Chemotherapy (MEC) is 30 %–90 %, low emetogenic 10 % -<30 % and minimal emetogenic <10 %.[2,3,4,5,6] CINV can occur within the acute (0–24 hours) or delayed (25–120 hours) phases of chemotherapy, with increased severity in the delayed phase.[7]

Antiemetic prophylaxis for CINV is an important aspect of cancer treatment management which depends on the type of chemotherapy administered and specific patient characteristics.[2] The drugs used for prophylaxis of CINV are serotonin receptor-3 (5-HT3) antagonist, corticosteroid, dopamine 2 antagonist such as domperidone etc. The older antiemetic regimen in cancer chemotherapy is a combination of 5-HT3 antagonist and corticosteroid which does not show much improvement both in the acute and particularly in delayed phase of vomiting.[8]

The introduction of a Neurokinin 1 receptor antagonist with older drugs seems to show an enhanced protection against acute and strikingly improved protection against delayed phase of emesis.[8]

There is certainly a need for improvement in protection against CINV particularly in the delayed phase. As there are very few studies done in this regard in the Indian population the present study aims to evaluate the role and efficacy of NK1 receptor antagonist in early and delayed phase of emesis when administered with granisetron and dexamethasone versus granisetron and dexamethasone combination for prevention of CINV.

MATERIAL AND METHODS

Primary objective:

1. Assess the efficacy of granisetron and dexamethasone with and without NK1 receptor antagonist in the prevention of CINV.

Secondary objectives:

1. Assess the adverse effects in both the study groups during the 5 days post-chemotherapy

Source of data

Data was collected from inpatients diagnosed with cancer admitted to the Medical Oncology ward in Tertiary care teaching hospital and who were on moderate to high emetogenic chemotherapy.

Method of collection of data

A prospective observational study of cancer patients admitted to Medical Oncology ward and on antiemetic regimens for moderate to high emetogenic chemotherapy. After obtaining the Ethics committee approval, one hundred and twenty patients who fulfilled the inclusion and exclusion criteria were divided into two groups based on the antiemetic regimens received by them as shown in Figure 1. Patients'demographic data with respect to age, gender, family, and drug history were recorded on a predesigned proforma.

The respective groups received these regimens 30 minutes before chemotherapy and episodes of nausea, vomiting, any rescue medications used and adverse effects if any in both the study groups were recorded for a period of 5 days post chemotherapy. Follow up was done for a period of 5 days post chemotherapy by phone call to the patients/caregiver. Grading of nausea and vomiting documented according to National Cancer Institute Common Terminology Criteria for Adverse Effects (NCI CTCAE version 4.03).[9]

Primary endpoint

1. Efficacy was measured in terms of Complete Response (CR- no incidents of vomiting and no need for rescue medications) in both the study groups.

Secondary endpoint

1. Total Control (TC- no incidents of nausea, vomiting & no need for rescue medication) and Complete Protection (CP- no incidents of vomiting, no need for rescue medication & mild nausea) in both the study groups.
2. Percentage of participants with no incidents of emesis, nausea and no need for rescue medication in both the study groups.
3. Adverse effects addressed in both the study groups.

Inclusion criteria

1. Males and females aged 18 to 75 years.
2. Eastern Co-operative Oncology Group (ECOG) performance status <2.[10]
3. Biopsy proven cancer.
4. Chemotherapy naive patients planned to receive moderate to high chemotherapy.
5. Patients with no nausea and vomiting 24 hours prior to chemotherapy.
6. Patients who have given written inform consent.

Exclusion criteria

1. Patients with active infection, severe heart disease, uncontrolled Hypertension or uncontrolled Diabetic Mellitus, active gastric or duodenal ulcers.

2. Pregnant and lactating women.
3. Patients with symptomatic primary or secondary Brain cancer.
4. Patients receiving radiotherapy on brain, abdomen or pelvis 2 weeks before chemotherapy.
5. Patients who have known allergy or reported severe side effects to any of the study drugs.
6. Patients with abnormal liver and renal function tests.

Sample size calculation

Based on a previous study conducted by Nishimura et al[11], it was found that the proportion of no incidents of emesis was 95 % in NK1 receptor antagonist combination regimen compared to 83 % without NK1 receptor antagonist. The sample size was calculated assuming a superior margin of 25 % to achieve the power of 80 % considering an alpha error of 5 % and the sample size was estimated to be 60 patients in each group.

Statistical analysis

All the quantitative parameters such as age, sex was presented in terms of descriptive statistics such as mean and standard deviation. Qualitative variables like nausea, emesis etc were summarized using frequency and percentage. The percentage of complete response, no incidents of emesis, no need for rescue therapy & total control was compared separately in acute, delayed and overall phase between the two groups and was tested for statistical significance using chi square test of significance. Adverse effects in both the groups were tabulated.

RESULTS

The study was conducted for a period of two years and six months. One hundred and twenty participants admitted in the Oncology ward, Department of Medical Oncology, in tertiary care teaching hospital were included in the study according to inclusion and exclusion criteria. Out of 210 participants screened, 120 participants met the inclusion criteria, and 60 participants were present in each study group and there was no loss to follow-up (Figure 1). Table 1 shows the baseline demographic characteristics of participants including age, sex, primary cancer diagnosis and type of emetogenic agents. The study groups were comparable. Majority of the participants in the study group were in the age range of 35-55 years. The gender distribution of control and NK1 group was 18.4% male versus 81.6% female and 8.4% male versus 91.6% female, respectively. Majority of the participants were female because most common cancer type was breast cancer. Majority of cancers seen in this study were breast cancer followed by carcinoma cervix, carcinoma ovary and others (Figure 2). The number of participants treated with HEC was more in NK1 group (50) compared with control group (36) and number of participants treated with MEC was more in control group (24) compared with NK1 group (10) in this study. The majority of chemotherapeutic regimen in the study group were AC (Adriamycin + Cyclophosphamide) followed by cisplatin, paclitaxel/docetaxel+carboplatin, cisplatin+others, oxaliplatin+others, carboplatin, cyclophosphamide+bortezomib and adriamycin (Table 2).

The Complete Response (CR) of NK1 group was significantly higher than control group in the overall phase (95% versus 56.6%; p value 0.000) and delayed phase (95% versus 58.3%; p value 0.000). The CR in acute phase (100% versus 88.3%; p value 0.06, Figure 3) showed good response though not statistically significant. The Total Control (TC) in the overall phase showed significant difference between the NK1 group and control group (46.6% versus 28.3%; p value 0.038). The TC in acute (76.6% versus 73.3%; p value 0.673) and delayed phase (48.3% versus 30%; p value 0.120) were not statistically significant. The complete protection in overall phase between NK1 and control group was statistically significant (95% versus 56.7%; p value 0.000). The percentage of participants with no incidents of emesis in NK1 versus control group in overall phase (95% versus 43.3%; p value 0.000) and delayed phase (95% versus 35%; p value 0.000) were statistically significant but in acute phase it was not significant. A significant association was observed with percentage of participants with no incidents of nausea in control group versus NK1 group in overall phase (28.4% versus 46.7%, p value 0.038), whereas in acute phase (73.4% versus 76.7%, p value 0.673) and delayed phase (35% versus 51.7%, p value 0.120) were non-significant. The percentage of participants who didn't require rescue medications in NK1 versus control group in overall phase (75% versus 45% p value 0.001) was statistically significant. The side effects addressed in the participants of control and NK1groups were headache (5 versus 6 participants) and fatigue (3 versus 6 participants) and were comparable (p value 0.53).

The percentage of participants treated with HEC presented with nausea and vomiting were significantly less in NK1 group than the control group (52 % versus 83.3 %; p value 0.002 and 4 % versus 63.8 %; p value 0.000), whereas the percentage of participants treated with MEC presented with nausea and vomiting didn't show significance (54.1% versus 60% and 12.5% versus 10%)

Figure 1. Study flow chart

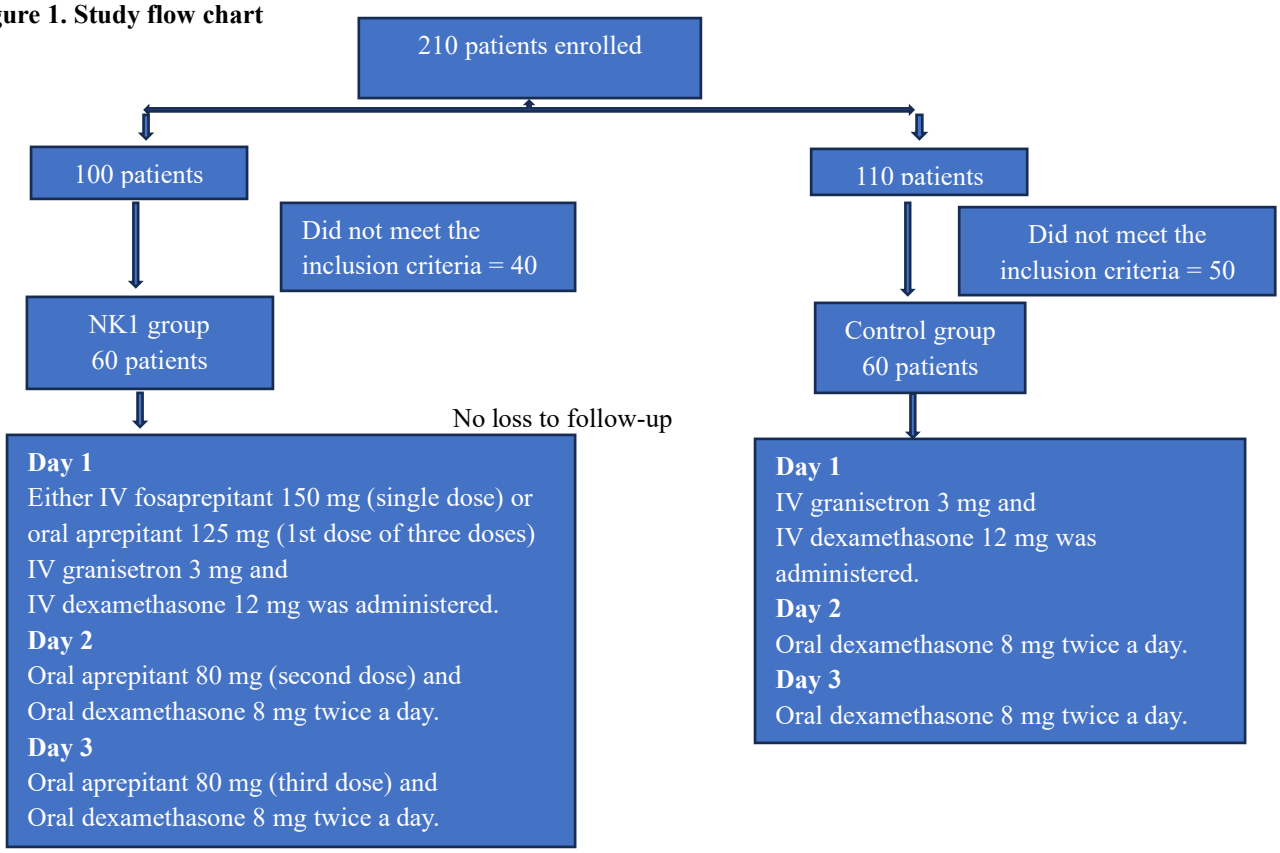


Table 1. Baseline demographic data

Serial number	Characteristics		Control group n (%)	NK1 group n (%)
1	Age (mean ± SD) in years		49.63±12.5	52.03±10.3
2	Gender	Male	11 (18.4)	5 (08.4)
		Female	49 (81.6)	55 (91.6)
3	Primary cancer diagnosis			
	Carcinoma Breast		23	30
	Carcinoma cervix		11	6
	Carcinoma ovary		7	1
	Others*		19	23

***Others include Carcinoma oral cavity, pyriform fossa, rectum, stomach, endometrium, prostate, lung, non hodgkins lymphoma, cholangiocarcinoma, multiple myeloma and osteogenic carcinoma.**

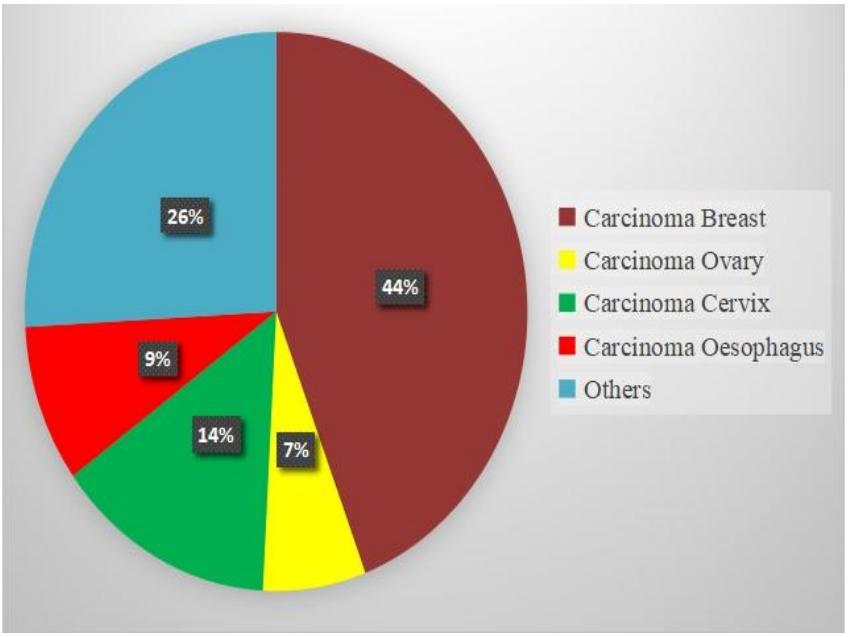


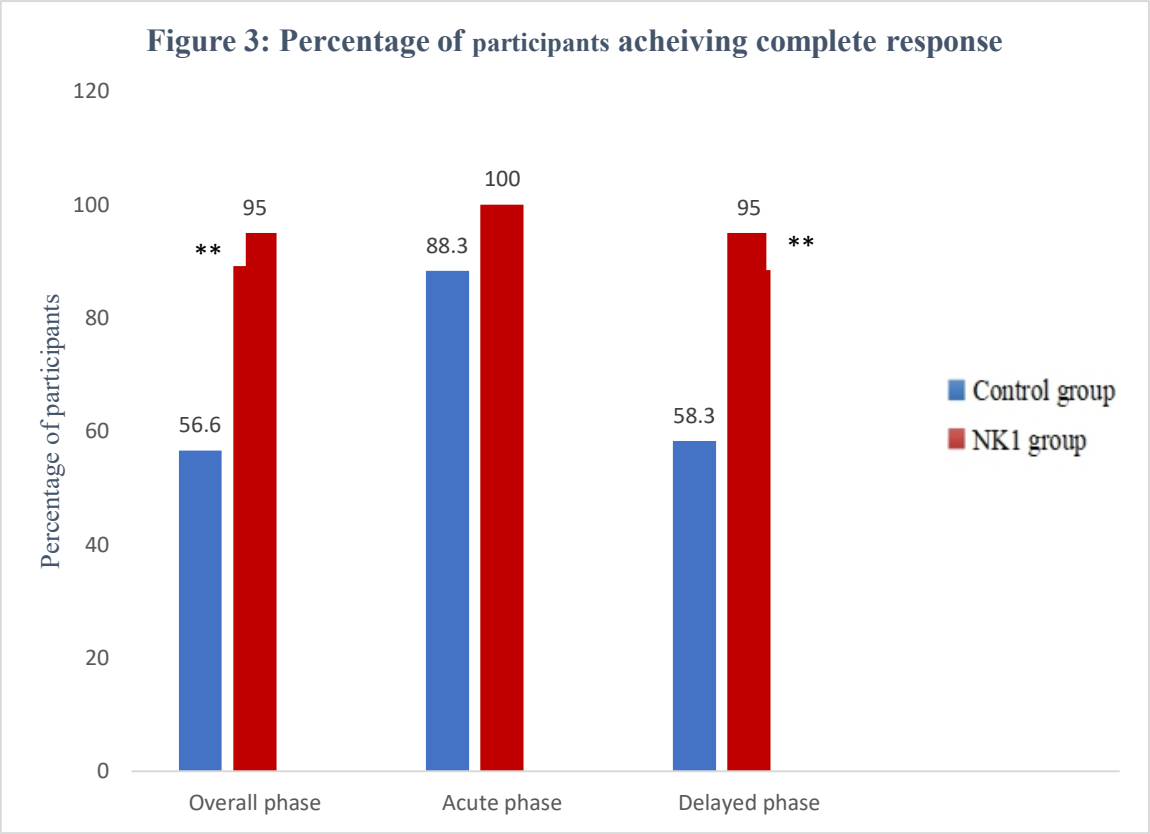
Figure 2. Types of cancer included in the study

***Others include Carcinoma oral cavity, pyriform fossa, rectum, stomach, endometrium, prostate, lung, cholangiocarcinoma, non hodgkins lymphoma, multiple myeloma and osteogenic carcinoma.**

Table 2. Pattern of chemotherapeutic agents

Class of antiemetic agents	Chemotherapeutic agents	Number of participants
HEC	Adriamycin/Epirubicin + Cyclophosphamide ± 5-Fluorouracil	51
	Cisplatin	30
	Cisplatin + Etoposide/ Pemetrexed /Gemcitabine / Docetaxel /5-Fluorouracil	5
MEC	Paclitaxel/Docetaxel + Carboplatin	28
	Oxaliplatin + Capecetabine/Gemcitabine	2
	Carboplatin	2
	Cyclophosphamide + Bortezomib	1
	Adriamycin	1
TOTAL		120

***HEC - high emetogenic chemotherapy, MEC - moderate emetogenic chemotherapy**



Complete response - no vomiting, no need of rescue medication.
Overall phase =0-120hr, acute phase = 0-24hr & delayed phase = 25-120hr.
Control group n=60 & NK1 group n=60.
**** p value - 0.000 (chi square test) was highly significant between the study groups in overall & delayed phase whereas p value - 0.06 was not significant in acute phase.**

DISCUSSION

The majority of the patients in the study groups were in the age range of 35-55 years with minimum age of 18yr and maximum of 75yrs because maximum number of patients were breast cancer and India accounts for the 3rd highest number of cancers cases among women after china.[12] Whereas in Nishimura et al[11] study, majority of the patients were >60 yr (72.4 % in NK1 group & 72.8 % in control group) because the patients included were colorectal cancers. The majority of the participants in the study were female because most common cancer type in India was breast cancer[12] which was contrast to the Poli-Bigelli et al[7] study 235 males versus 48 females in NK1 group and 237 males versus 49 females respectively, as most of the patients were diagnosed with respiratory, urogenital cancer and the study was conducted in Latin American countries. The number of participants treated with HEC was more in NK1 group (50) compared with the control group (36) and number of participants treated with MEC was more in control group (24) compared with NK1 group (10) and was contrast to Tsuji et al study where the proportion of MEC (30) was more compared to HEC (7).[13]

The percentage of CR in the study was comparable with the results obtained by Saito et al[14] and Poli-Bigelli et al[7] study. In Saito et al study, percentage of CR treated with HEC medication in the overall phase (64 % versus 47 %; p value 0.0015) and delayed phase (65 % versus 49 %; p value 0.0025) and in Poli-Bigelli et al study, ondansetron was used instead of granisetron and percentage of CR on HEC medication in overall phase (62.7 % versus 43.3 %; p value 0.001) and delayed phase (67.7 % versus 46.8 %; p value 0.001) was statistically significant. The percentage of CR in acute phase showed good response though not statistically significant may be due to NK1 antagonist strikingly improves delayed emesis. The results obtained were matching Nishimura et al[11] (94.7 % versus 92.4 %; p value 0.37) whereas percentage of CR in the Saito et al[14] and Poli-Bigelli et al[7] study on HEC medication in the acute phase showed statistically significant response (94 % versus 81 %; p value 0.0006 & 82.8 % versus 68.4 %; p value 0.001).

The percentage of Total Control (TC) in the overall phase was statistically significant between the group and the results were contrast to Saito et al[14] study (22.2 % versus 29.5 %) and Hesketh et al[15] study (70.7 % versus 64.2 %) because the participants included were Japanese and US so racial differences may exist. The results were comparable with Poli-Bigelli et al[7] study (44 % versus 32 %; p value <0.01).

The percentage of TC in acute and delayed phase were not statistically significant and it were aligning to acute phase (67.6 % versus 66.5 %) and delayed phase (30.1 % versus 22.9 %) in Saito et al[14] and acute phase in Poli-Bigelli et al[7] study (64 % versus 57 %) but TC in delayed phase was statistically significant (50 % versus 34 %; p value <0.01).

Significantly a greater number of participants in the NK1 group did not have emesis in overall and delayed phase than in the control group, which were same as Hesketh et al[15] and Nishimura et al[11] study (77.5 % versus 55 %; p value 0.01 & 80.8 % versus 58.8 %; p value 0.01 & 95.7 % versus 83.6 %; p value 0.0001 & 95.7 % versus 84.7 %; p value 0.0003 respectively).

The percentage of participants with no incidents of emesis in acute phase was not statistically significant, which were not matching Hesketh et al[15] and Nishimura et al[11] study (90.2 % versus 79.3 %; p value <0.01 & 100 % versus 96.7 %; p value 0.013 respectively).

The percentage of participants with no incidents of nausea in NK1 group and control group in overall phase was statistically significant and was comparable with Poli-Bigelli et al[7] study (49 % versus 39 %; p value <0.01) and was contrast to Saito et al[14] study (30.1 % versus 24.1 %) but in acute phase and delayed phase it was not statistically significant and results obtained were similar to, 67.6 % versus 67.5 % in acute phase and 30.6 % versus 24.7 % in delayed phase in Saito et al[14] study.

The percentage of participants who didn't require rescue therapy in NK1 versus control group in overall phase was statistically significant and comparable to Hesketh et al study[15] (80.8 % versus 70.8 %; p value 0.01) & Poli-Bigelli et al[7] study (82 % versus 73 %; p value <0.01) respectively.

The adverse effects addressed in the participants of NK1 groups & control group were headache and fatigue and were comparable (p value 0.53). The adverse effect observed were aligning with Hesketh et al study[15] (p value 0.1) and Poli-Bigelli et al[7] study. Adverse drug events like constipation, hiccups, anorexia, vomiting & nausea were also reported upto 14 days of chemotherapy.

The percentage of participants on HEC presenting with nausea and vomiting were less in NK1 group than control group and was statistically significant, even though patients on HEC were more in the NK1 group. This indicates NK1 antagonist may reduce nausea & vomiting when participants are treated with HEC. The results were comparable with Saito et al[14] study percentage of participants on HEC with vomiting (32.4 % versus 50.9 %; p value 0.001) but with nausea (69.9 % versus 75.9 %) it was not statistically significant.

The percentage of participants on MEC presenting with nausea and vomiting did not show significance may be due to a smaller number of participants on MEC. The results obtained were comparable with participants presenting nausea but not comparable with vomiting in Nishimura et al[11] study (34.8 % versus 40.4 %; p value 0.26 & 4.3 % versus 16.4 %; p value 0.0001).

The study showed addition of NK1 antagonist to the 5HT3 antagonist and dexamethasone, was effective and safe in preventing CINV who are on high to moderately emetogenic chemotherapy. However, the percentage of CR in acute phase and percentage of no incidents of nausea in acute and delayed phase were not statistically significant between the groups.

LIMITATION

The limitation of the study was small sample size, observational study so the lab parameters like liver function test not monitored and proportion of males, females and participants on HEC and MEC were not equal for subgroup analysis. Combination of NK1 antagonist, dexamethasone with 5HT3 antagonist palonosetron instead of granisetron, should be evaluated as palonosetron found to be effective in delayed nausea & vomiting.

ACKNOWLEDGEMENTS

Authors acknowledge the support extended by Dr Cuckoo Aiyappa, Dr Harish K and Mrs Radhika for statistical analysis.

DECLARATION OF CONFLICTING INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article**.**

FUNDING SOURCE

The authors received no financial support for the research, authorship, and publication of this article.

REFERENCES

1. Celio, L., Ricchini, & De Braud. (2013). Safety, efficacy, and patient acceptability of single-dose fosaprepitant regimen for the prevention of chemotherapy-induced nausea and vomiting. Patient Preference and Adherence, 7, 391-400. https://doi.org/10.2147/ppa.s31288
2. Weinstein, C., Jordan, K., Green, S. A., Camacho, E., Khanani, S., Beckford-Brathwaite, E., Vallejos, W., Liang, L. W., Noga, S. J., & Rapoport, B. L. (2016). Single-dose fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with moderately emetogenic chemotherapy: results of a randomized, double-blind phase III trial. Annals of Oncology, 27(1), 172–178. https://doi.org/10.1093/annonc/mdv482
3. Grunberg, S. M., Warr, D., Gralla, R. J., Rapoport, B. L., Hesketh, P. J., Jordan, K., & Espersen, B. T. (2011). Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity--state of the art. Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer, 19 Suppl 1, S43-47. https://doi.org/10.1007/s00520-010-1003-x
4. Berger, M. J., Ettinger, D. S., Aston, J., Barbour, S., Bergsbaken, J., Bierman, P. J., Brandt, D., Dolan, D. E., Ellis, G., Kim, E. J., Kirkegaard, S., Kloth, D. D., Lagman, R., Lim, D., Loprinzi, C., Ma, C. X., Maurer, V., Michaud, L. B., Nabell, L. M., & Noonan, K. (2017). NCCN Guidelines Insights: Antiemesis, Version 2.2017. Journal of the National Comprehensive Cancer Network, 15(7), 883–893. https://doi.org/10.6004/jnccn.2017.0117
5. Hesketh, P. J., Kris, M. G., Basch, E., Bohlke, K., Barbour, S. Y., Clark-Snow, R. A., Danso, M. A., Dennis, K., Dupuis, L. L., Dusetzina, S. B., Eng, C., Feyer, P. C., Jordan, K., Noonan, K., Sparacio, D., Somerfield, M. R., & Lyman, G. H. (2017). Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 35(28), 3240–3261. https://doi.org/10.1200/JCO.2017.74.4789
6. Roila, F., Molassiotis, A., Herrstedt, J., Aapro, M., Gralla, R. J., Bruera, E., Clark-Snow, R. A., Dupuis, L. L., Einhorn, L. H., Feyer, P., Hesketh, P. J., Jordan, K., Olver, I., Rapoport, B. L., Roscoe, J., Ruhlmann, C. H., Walsh, D., Warr, D., & van der Wetering, M. (2016). 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Annals of Oncology, 27(5), v119–v133. https://doi.org/10.1093/annonc/mdw270
7. Poli-Bigelli, S., Rodrigues-Pereira, J., Carides, A. D., Julie Ma, G., Eldridge, K., Hipple, A., Evans, J. K., Horgan, K. J., & Lawson, F. (2003). Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Cancer, 97(12), 3090–3098. https://doi.org/10.1002/cncr.11433
8. Maru, A., Gangadharan, V. P., Desai, C., Mohapatra, R., & Carides, A. D. (2013). A Phase 3, randomized, double-blind study of single-dose fosaprepitant for prevention of cisplatin-induced nausea and vomiting: Results of an Indian population subanalysis. Indian Journal of Cancer, 50(4), 285-292 https://doi.org/10.4103/0019-509x.123580
9. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. [Internet]. U.S Department of Health and Human Services; 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Referenc
10. Oken, M. M., Creech, R. H., Tormey, D. C., Horton, J., Davis, T. E., McFadden, E. T., & Carbone, P. P. (1982). Toxicity and response criteria of the Eastern Cooperative Oncology Group. AMERICAN JOURNAL of CLINICAL ONCOLOGY, 5(6), 649–656. https://doi.org/10.1097/00000421-198212000-00014
11. Nishimura, J., Satoh, T., Fukunaga, M., Takemoto, H., Nakata, K., Ide, Y., Fukuzaki, T., Kudo, T., Miyake, Y., Yasui, M., Morita, S., Sakai, D., Uemura, M., Hata, T., Takemasa, I., Mizushima, T., Ohno, Y., Yamamoto, H., Sekimoto, M., & Nezu, R. (2015). Combination antiemetic therapy with aprepitant/fosaprepitant in patients with colorectal cancer receiving oxaliplatin-based chemotherapy (SENRI trial): a multicentre, randomised, controlled phase 3 trial. European Journal of Cancer (Oxford, England: 1990), 51(10), 1274–1282. https://doi.org/10.1016/j.ejca.2015.03.024
12. Katzung, B. G. (2018). Basic and Clinical Pharmacology 14th Edition. McGraw Hill Professional.
13. Tsuji A, Kobayashi K, Hata Y, Negoro Y, Morita S. (2014). Aprepitant for Nausea and Vomiting Induced by Highly and Moderately Emetogenic Chemotherapy in Japanese Patients with Gastrointestinal Cancer: A Single-Center, Retrospective Study. J Pharmacol Clin Toxicol, 2(2), 1030.
14. Saito, H., Yoshizawa, H., Yoshimori, K., Katakami, N., Katsumata, N., Kawahara, M., & Eguchi, K. (2013). Efficacy and safety of single-dose fosaprepitant in the prevention of chemotherapy-induced nausea and vomiting in patients receiving high-dose cisplatin: a multicentre, randomised, double-blind, placebo-controlled phase 3 trial. Annals of oncology : official journal of the European Society for Medical Oncology, 24(4), 1067–1073. https://doi.org/10.1093/annonc/mds541
15. Hesketh, P. J., Grunberg, S. M., Gralla, R. J., Warr, D. G., Roila, F., de Wit, R., Chawla, S. P., Carides, A. D., Ianus, J., Elmer, M. E., Evans, J. K., Beck, K., Reines, S., Horgan, K. J., & Aprepitant Protocol 052 Study Group (2003). The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin--the Aprepitant Protocol 052 Study Group. Journal of clinical oncology: official journal of the American Society of Clinical Oncology, 21(22), 4112–4119. https://doi.org/10.1200/JCO.2003.01.095