

EFFICACY, SAFETY AND QUALITY OF LIFE OUTCOMES OF PALONOSETRON, RAMOSETRON AND GRANISETRON AS A PART OF ANTIEMETIC THERAPY IN PREVENTION OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING- A RANDOMISED COMPARATIVE TRIAL

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ABSTRACT

BACKGROUND

5-HT₃ receptor antagonists have potent antiemetic effect in chemotherapy induced nausea and vomiting. The present study was conducted to study and compare the efficacy and safety of ramosetron, palonosetron and granisetron in preventing acute and delayed nausea and vomiting in cancer patients receiving moderately emetogenic chemotherapy, and the impact of these drugs on daily living of these patients.

MATERIALS AND METHODS

It was an open label, randomised, prospective, comparative, parallel study. A total of 59 patients were enrolled in the study. They were divided into 3 groups: palonosetron (0.25mg i.v and 0.5mg orally daily; n=18) group, ramosetron (0.3 mg i.v and 0.1 mg orally daily; n=22) group, and granisetron (1mg i.v and 2mg orally daily; n=19). The drugs were given for 5 days after chemotherapy cycle. In addition, all the three groups received inj. dexamethasone (16mg) prior to chemotherapy and tab. domperidone 10mg orally before chemotherapy and 3 times daily till day 5. The incidence and severity of nausea and vomiting, use of rescue antiemetics and the impact on daily living were evaluated for 7 days. Emetic episodes were recorded on a diary on a daily basis and nausea was measured on a visual analogue scale. Complete response rates (no emesis and no need of rescue antiemetics) were measured as the primary end point. The quality of life outcomes were measured using the functional life index – emesis (FLIE) questionnaire. Safety was evaluated by monitoring the adverse drug reactions of the test drugs.

RESULTS

The complete response rate in ramosetron group (72.7% in acute; 68.2% in delayed) were numerically better than palonosetron (66.7%; 61.1%) and granisetron (42.1%; 36.8%). The results didn't achieve statistical significance. The impact on daily living was numerically better in ramosetron than palonosetron and granisetron but the results didn't show a statistical significance. All the three drugs were well tolerated.

CONCLUSION

All the three drugs were effective and well tolerated. However, ramosetron showed numerically better complete response rates and better quality of life outcomes as compared to palonosetron and granisetron.

KEYWORDS

Emetogenic chemotherapy, nausea and vomiting, serotonin, quality of life, FLIE, CINV.

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BACKGROUND

Nausea and vomiting are the most distressing side effects of cancer chemotherapy. Chemotherapy induced nausea and vomiting (CINV) have a negative impact on patient's quality of life and frequently considered as a major factor for treatment abandonment.¹ Without appropriate prophylaxis, 70-80% patients experience CINV.² Numerous neurotransmitters have been established as important mediators of CINV, including dopamine, serotonin, substance P, neurokinin etc. Various agents like steroids, dopamine antagonists, serotonin antagonists, neurokinin

inhibitors etc. have been tried and have shown variable efficacy in controlling CINV. However, there is no single neurotransmitter responsible for all forms of CINV, and no single clinically available antagonist to these neurotransmitter receptors is able to provide complete protection against all forms of CINV. As per international guidelines, these drugs have to be used in combination for the control of CINV.³

Of the various antiemetics being used in CINV, the serotonin antagonists have been extensively studied and used for the last 2 decades and have shown to be very effective and safer as compared to the earlier antiemetics. The first generation 5-HT₃ antagonists like ondansetron, granisetron, dolasetron and tropisetron have been widely used for combating emesis in combination with steroids.⁴ These drugs act by inhibiting serotonin 5-HT₃ receptors which are found in abundance in the chemoreceptor trigger zone (CTZ), vomiting centre (VC) and the gastrointestinal tract. These congeners have comparable efficacies in preventing acute chemotherapy induced nausea and vomiting.

Of late the second generation 5-HT₃ antagonists are the preferred options for managing chemotherapy induced emesis. Palonosetron, a newer member of this generation, is a potent and highly selective serotonin 5-HT₃ receptor antagonist. Intravenously administered palonosetron has a linear pharmacokinetic profile, with a long terminal elimination half-life that approximately equals 40 hours⁵ and moderate (62%) plasma protein binding.⁶ Ramosetron is another highly selective 5-HT₃ antagonist developed in Japan.^{7,8,9} It has shown to have a longer action owing to its slow dissociation from the 5-HT₃ receptor.

Due to scanty data regarding the efficacy and safety of palonosetron and ramosetron in Indian setup, and none from our region, the present study was intended to study and compare the efficacy and safety of the 2nd generation 5-HT₃ antagonists palonosetron and ramosetron with the widely used 1st generation agent granisetron in combination with dexamethasone and domperidone in acute and delayed CINV due to moderately emetogenic chemotherapy. As the 1st generation 5-HT₃ antagonists have only modest effect in preventing delayed CINV, newer antiemetics that are claimed to prevent delayed CINV more effectively are highly desirable to maintain daily life activities and quality of life. So a more robust data needs to be generated and the present study was an endeavour in this regard.

MATERIALS AND METHODS

The study was conducted by the Postgraduate Department of Pharmacology and Therapeutics in collaboration with the Department of Radiotherapy and Oncology, GMC Jammu, in north India, for a period of one year. It was a prospective, randomised, open label, comparative, parallel study.

The approval of the institutional ethics committee for conducting the study was obtained.

Patients attending the Radiotherapy and Oncology OPD, of either sex, aged 18-75 years with histologically confirmed cancer who were scheduled to receive their first course of

moderately emetogenic chemotherapy were included in the study. Written informed consent was obtained from the patients after explaining them the nature and purpose of the study.

The exclusion criteria were radiotherapy within 2 weeks prior to chemotherapy, presence of concurrent illness other than cancer, occurrence of nausea or vomiting within 72 hours prior to chemotherapy, pregnant and lactating females, history of allergy to the study drugs, history of intake of antiemetics, antipsychotics or sedatives within 72 hrs of chemotherapy, biochemical criteria namely liver function tests >3 times normal, serum creatinine >2.5 mg/dl, platelet count <1 lakh/mm³, haemoglobin <8.5 g/dl, patients with gastro-intestinal obstruction or any other condition that could provoke emesis and Karnofsky score <60%.

A detailed history was taken from the patients followed by a detailed general physical examination and systemic examination prior to the chemotherapy. They underwent various investigations namely complete haemogram, liver function tests, renal function tests, blood sugar (random) and electrocardiography as the baseline investigations prior to chemotherapy.

The enrolled patients were then randomly allocated to one of the 3 groups:

Group A: inj. dexamethasone (16mg) i.v. + tab. domperidone (10mg) oral + inj. palonosetron (0.25mg) i.v. 30 minutes before chemotherapy followed by tab. palonosetron (0.5mg) once daily + tab. domperidone (10mg) thrice daily orally from day 2 to day 5.

Group B: inj. dexamethasone (16mg) i.v. + tab. domperidone (10mg) oral + inj. ramosetron (0.3mg) i.v. 30 minutes before chemotherapy followed by tab. ramosetron (0.1mg) once daily + tab. domperidone (10mg) thrice daily orally from day 2 to day 5.

Group C: inj. dexamethasone (16mg) i.v. + tab. domperidone (10mg) oral + inj. granisetron (1mg) i.v. 30 minutes before chemotherapy followed by tab. granisetron (2mg) once daily + tab. domperidone (10mg) thrice daily orally from day 2 to day 5.

The patients were followed up for 7 days from the day of chemotherapy. They recorded the number of emetic episodes on a daily basis on the diary provided to them. They were provided with visual analogue scales to register their experience of nausea on daily basis. They were interviewed regarding the quality of life using an appropriate questionnaire.

The antiemetic efficacy of the drugs was evaluated on the basis of the frequency of emetic episodes and intensity of nausea.

An emetic episode was defined as a single incidence of vomiting (expulsion of stomach contents through the mouth) or retching (an attempt to vomit but without expulsion of stomach contents). The response criteria for emesis were as

follows: completely effective (no emesis), moderately effective (1-2 episodes), slightly effective (3-5 episodes) and not effective (>5 episodes).¹⁰ The emesis was classified as acute (occurring within 24 hours of chemotherapy) and delayed (occurring beyond 24 hours upto 7 days after chemotherapy). The need for rescue antiemetics also served as a response criterion. No emesis and no need of rescue antiemetics was defined as a complete response which served as the primary end point.

Nausea was defined as an unpleasant sensation with an urge to vomit. It was classified as acute (occurring within 24 hours of chemotherapy) and delayed (occurring beyond 24 hours upto 7 days after chemotherapy). Nausea was measured on the 100 mm visual analogue scale (VAS) daily.¹¹ Due to its subjective nature, the intensity of nausea was not included in the primary efficacy endpoint i.e. complete response.

The safety profile of the drugs was studied and compared on the basis of adverse drug reactions.

The quality of life outcomes were measured by using a modified Functional Life Index- Emesis (FLIE) questionnaire.^{12,13} The questionnaire was filled up by the patients on day 2 and day 6. Higher scores are more favourable and indicate greater ability to maintain daily life.

A total score of ≥ 108 was considered as 'no impact on daily living' (NIDL) which signifies an average item score of ≥ 6 .

Statistical Analysis

Data was analysed with the help of computer software MS Excel and SPSS for Windows. Baseline comparability was evaluated using chi square test/ one way analysis of variance (ANOVA) as deemed appropriate. Results were presented as proportions and statistical significance between the groups was assessed using chi square test and Kruskal Wallis analysis of variance. All the analyses were undertaken according to the intention to treat principle. A p-value of < 0.05 was considered as statistically significant. All p-values reported were two-tailed.

RESULTS

A total of 59 patients were enrolled and all completed the study after fulfilling the inclusion criteria. 18 patients were enrolled under palonosetron group (group A), 22 under ramosetron group (group B) and 19 under granisetron group (group C) (Figure 1). The three groups were comparable as per the baseline characteristics of age and sex (Table 1).

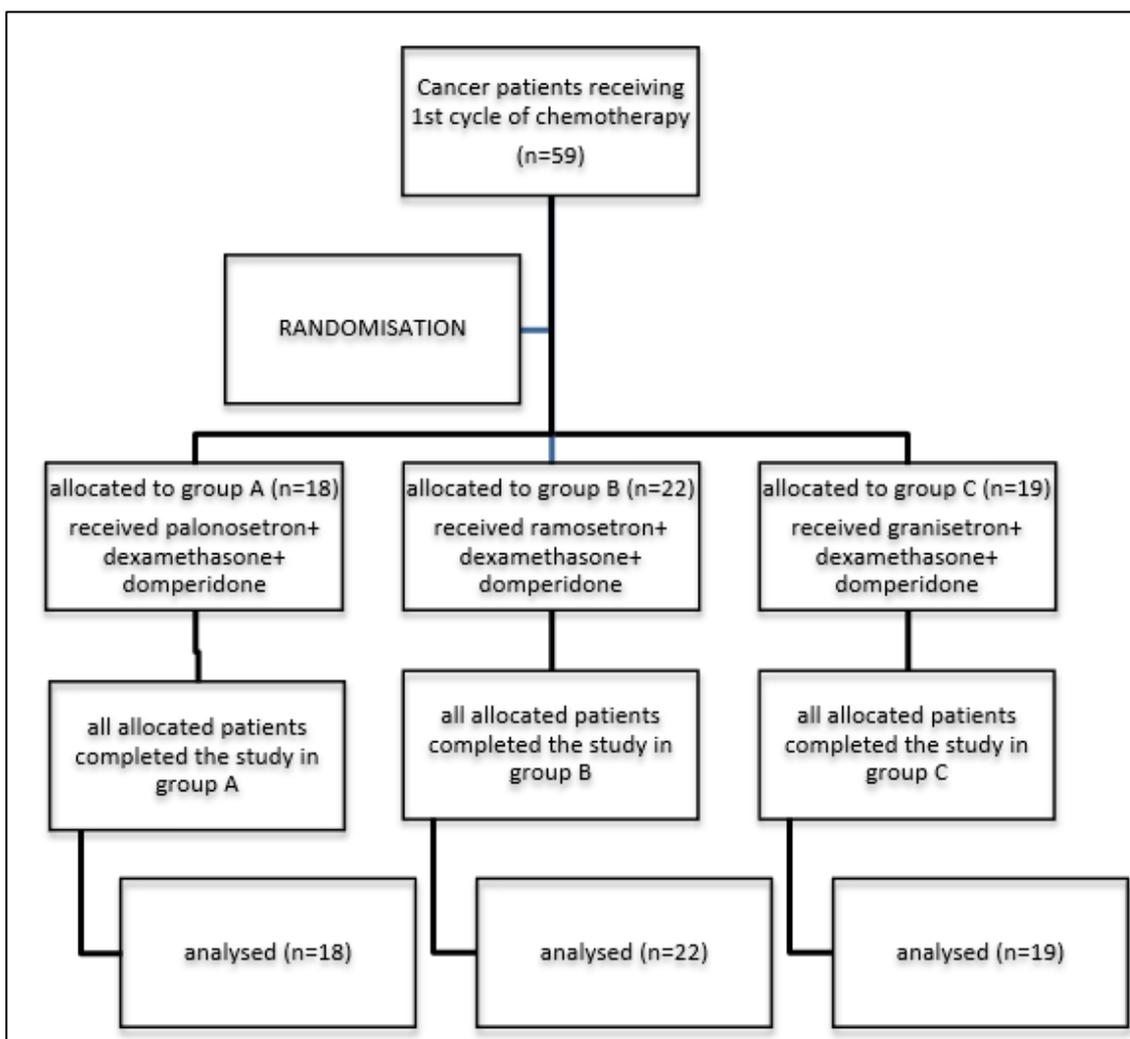


Figure 1. Consort Flow Diagram

Characteristics	Group A (Palonosetron) (n=18)	Group B (Ramosetron) (n=22)	Group C (Granisetron) (n=19)	Statistical Inference
AGE	50.72±2.89	51.82±2.32	47.05±2.89	F-0.88 p-0.42, NS
SEX				χ ² -2.10 p-0.35, NS
Male	5	10	5	
Female	13	12	14	

Table 1. Demographic Characteristics of the Study Groups (NS= Non-Significant)

Of the 59 patients, 39 were females and 20 were males with a female to male ratio of 1.95: 1. Mean age was 49.95±1.54 years. Out of 59, majority of patients were of carcinoma (CA) breast (42.4%), followed by CA lung (15.3%), CA ovary (11.9%), non-Hodgkin lymphoma (10.2%), CA endometrium (3.4%) and others (16.8%). (Table 2).

Diagnosis	Group A (Palonosetron) (n=18)	Group B (Ramosetron) (n=22)	Group C (Granisetron) (n=19)
CA breast	9	7	9
CA cervix	0	0	1
CA colon	0	1	0
CA endometrium	2	0	0
CA larynx	0	1	0
CA lung	2	4	3
CA ovary	2	1	4
CA parotid	1	1	0
CA rectosigmoid	0	1	0
CA rectum	0	1	0
CA urinary bladder	0	1	0
Malignant ascites	0	2	0
Non-hodgkin lymphoma	2	2	2

Table 2. Cancer Types in the Study Groups

The most common chemotherapy regimens used were paclitaxel + carboplatin (37.3%), followed by cyclophosphamide + adriamycin + 5-fluorouracil (22.0%), cyclophosphamide + epirubicin + 5-fluorouracil (15.3%), cyclophosphamide + adriamycin + vincristine (8.5%), oxaliplatin (6.8%) and others (10.1%). (Table 3).

Chemotherapy Regimens	Group A (Palonosetron) (n=18)	Group B (Ramosetron) (n=22)	Group C (Granisetron)(n=19)
5-fluorouracil, cyclophosphamide, adriamycin	7	3	3
5-fluorouracil, cyclophosphamide, epirubicin	1	2	6
Carboplatin, cyclophosphamide	0	0	1
Cyclophosphamide, adriamycin, vincristine	2	2	1
Cyclophosphamide, epirubicin, docetaxel	0	1	0
Cyclophosphamide, mitoxantrone, vincristine	0	0	1
Doxorubicin, paclitaxel	0	1	0
Gemcitabine, carboplatin	1	0	0
Oxaliplatin	0	4	0
Paclitaxel, carboplatin	6	9	7
Paclitaxel, carboplatin, 5-fluorouracil	1	0	0

Table 3. Various Chemotherapy Regimens Used in the Three Groups

When the results of the efficacy parameters of the three groups were compared and assessed by chi square test to know the level of significance between them, the statistical analysis revealed no statistical difference between the groups studied (p>0.05). However, the analysis of data revealed that the complete response rates produced by

ramosetron (72.7% in acute; 68.2% in delayed) were numerically better than palonosetron (66.7%; 61.1%) and granisetron (42.1%; 36.8%). Similarly, palonosetron provided greater efficacy numerically than granisetron, though these differences did not attain statistical significance (Fig. 2).

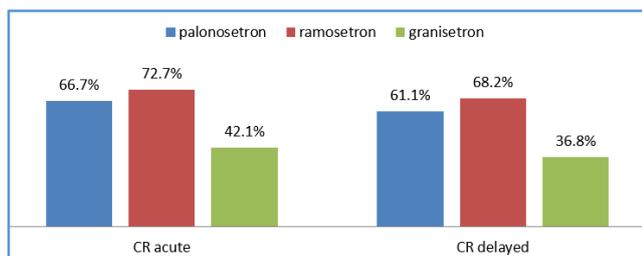


Figure 2. Comparative Effect of the Three Drugs on Acute and Delayed Complete Response (CR) Rates

The control of nausea in the acute and delayed phases was found to be numerically better with ramosetron (59.1% in acute; 45.5% in delayed) as compared to palonosetron (33.3%; 22.2%) and granisetron (26.3% in both acute and delayed). These results also did not demonstrate any statistical significance (Fig. 3).

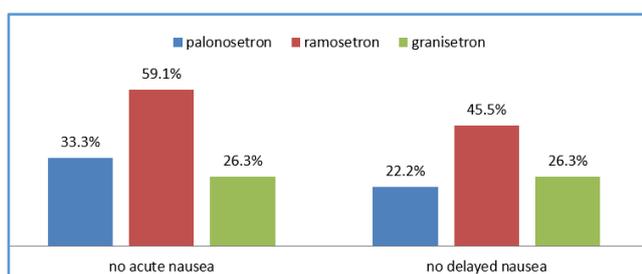


Figure 3. Comparative Effect of the Study Drugs in Controlling Acute and Delayed Nausea

The mean nausea scores in the acute and delayed phases were lesser in the ramosetron group (2.09±0.58 cm in acute; 3.00±0.63 cm in delayed) than palonosetron (3.56±0.67 cm; 4.50±0.69 cm) and granisetron (4.21±0.65 cm; 4.58±0.68 cm) groups.

A greater proportion of patients had no impact on daily living (FLIE score >108) in the acute and delayed phase with the use of ramosetron (59.1% in acute phase; 45.5% in delayed) as compared to palonosetron (33.3%; 22.2%) and granisetron (26.3% in both acute and delayed). Statistical analysis did not reveal any statistical significance between the groups.

The mean FLIE scores in the patients on ramosetron (109.95±4.56 in acute; 105.00±4.67 in delayed) were better than patients on palonosetron (100.22±5.39; 97.56±4.87) and granisetron (93.11±5.25; 92.68±4.99), indicating a better quality of life in patients on ramosetron. However, these results also did not show any statistical significance.

The safety evaluation was based on recording of adverse events upto 7 days of chemotherapy. Total number of adverse drug events reported by patients during the entire study period was 13 in a total of 59 patients (22.03%). The various ADRs reported were constipation and headache. Maximum number of ADRs of constipation (n=3) were reported in group A (palonosetron), followed by group B (ramosetron) and group C (granisetron) with 2 ADRs each. There was a total of 7 ADRs of constipation (53.85% of total ADRs) (Fig. 4). The ADRs were self-limiting and mild in nature.

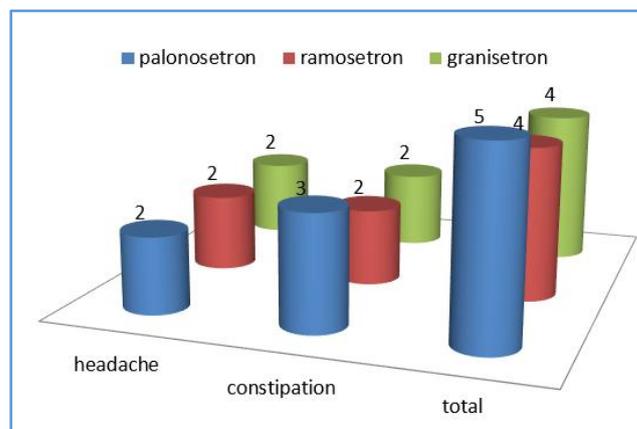


Figure 4. ADR Profile of the Study Drugs

DISCUSSION

Effective prevention of chemotherapy induced nausea and vomiting is a key in improving the quality of life of patients receiving cancer chemotherapy as nausea and vomiting are rated as the most troublesome and distressing adverse effects of cancer chemotherapy. Combination of drugs acting through various mechanisms in CINV helps to improve the response rates as no single mediator is responsible in the aetiology of CINV. 5-HT₃ antagonists are a cornerstone of management of CINV in combination regimes.

The present study aimed at evaluating and comparing the three 5-HT₃ receptor antagonists palonosetron, ramosetron and granisetron for their efficacy in preventing acute and delayed CINV, their safety and their impact on quality of lives of the patients during the week following chemotherapy.

The antiemetic efficacy of the drugs in preventing acute and delayed vomiting was evaluated as the proportion of patients having a complete response (CR) i.e. no vomiting and no need of rescue antiemetics. The results revealed that ramosetron produced better CR rates in both acute and delayed phases in terms of proportions than palonosetron and granisetron. Palonosetron in turn produced better CR rates than granisetron. Application of statistical analysis did not reveal any statistical significance between the acute and delayed CR rates. Previous studies comparing ramosetron and granisetron for prevention of acute and delayed emesis have revealed similar efficacies and concluded that the two drugs may be used interchangeably for preventing CINV.^{11,14} In a study of palonosetron compared with granisetron for the prevention of chemotherapy-induced nausea and vomiting in Chinese population, palonosetron consistently produced numerically higher complete response rates than granisetron in the acute phase and delayed phase, though the differences were not significant.¹⁵ In a comparative study of antiemetics for the prevention of postoperative nausea and vomiting after laparoscopic gynaecologic surgery, the number of complete responders at 48 h after the surgery was maximum for ramosetron, though the differences between the groups were not statistically significant.¹⁶

In all the three groups, the complete response rates in the acute phase were seen to be better as compared to the

respective complete response rates in the delayed phase in the terms of proportions. In a phase II trial of ramosetron and dexamethasone in the prevention of cisplatin-induced nausea and vomiting, the prevention of acute emesis seemed to be more effective than the prevention of delayed emesis.¹⁷ Some comparative trials have also corroborated these findings.^{14,15}

Chemotherapeutic agents release 5-HT from enterochromaffin cells which activate 5-HT₃ receptors on visceral afferent fibres to induce emesis. 5-HT₃ receptor antagonists block the activity of 5-HT₃ receptors in gut as well as in area postrema, CTZ and vomiting centre. Therefore such 5-HT₃ antagonists possess both peripheral and central action and result in significantly improved control rates of nausea and vomiting associated with emetogenic chemotherapy.

The control of nausea was not as effective as the control of vomiting in all the three groups. A lesser proportion of patients in all the groups were nausea free as compared to the corresponding CR rates. Similar observations were made on measuring the impact of delayed chemotherapy-induced nausea and vomiting on patients, health resource utilization and costs in German cancer centres where more patients reported nausea than vomiting.¹⁸ Ramosetron showed a better control of nausea than palonosetron and granisetron in both the acute and delayed phases. The mean nausea scores on VAS were lower in ramosetron group compared to palonosetron and granisetron. Comparative analysis did not demonstrate any statistical significance among the groups. The control of nausea was better in the acute phase as compared to delayed phase within the groups.

The ADRs reported during the study were mild in nature and did not warrant discontinuation of therapy. In all the three groups the most commonly reported ADRs were constipation and headache. There difference in the safety profile of the treatment groups was not statistically significant. All the three treatment groups were well tolerated. Similar findings have been observed in other trials as well.^{11,14}

In the present study, the ramosetron group showed a better impact on the quality of life than palonosetron and granisetron in both the acute and delayed phases which can be correlated with better complete response rates in the acute and delayed phases and better control of nausea than palonosetron and granisetron. The mean FLIE questionnaire scores in the acute and delayed phases were better in ramosetron group and a higher proportion of patients showed no impact on daily living (NIDL) as defined by a FLIE score of >108 in both the acute and delayed phases. Statistical analysis failed to demonstrate significant difference in the proportions. Very few studies have been conducted for measuring the maintenance of daily life activities in patients receiving moderately emetogenic chemotherapy using the FLIE questionnaire.¹⁹ The results have demonstrated the impact of a better control of CINV on the functional status of the patients using the FLIE instrument and established a correlation between the efficacy and the ability of patients to continue to conduct

their daily lives. However, the current study suffers from few limitations as the sample size was small and it was not a placebo-controlled study due to ethical considerations.

CONCLUSION

From the results of the present study, we conclude that all the three groups are efficacious and safe in preventing CINV. On intergroup comparison, the results were found to be statistically non-significant. But ramosetron scored better numerically on all the efficacy parameters and also had a better impact on the quality of life. The ADRs in all the three groups were comparable and mild. Considering these facts, ramosetron can be considered as a better choice in prevention of CINV, though further studies with larger sample sizes need to be done to substantiate these findings.

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