EVALUATION OF NEWER ANTI-EMETIC DRUGS IN PROPHYLAXIS OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING IN CANCER PATIENTS

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Introduction

Recent times have seen an increase in the incidence of cancer. This is mainly attributed to urbanization, industrialization, lifestyle changes, population growth and increased life span (in turn leading to an increase in the elderly population).[1] Cancer prevalence in India is estimated to be around 2.5 million, with over 8,00,000 new cases and 5,50,000 deaths occurring each year due to this disease. More than 70% of the cases report for diagnostic and treatment services in the advanced stages of the disease, which has lead to a poor survival and high mortality rate.[2, 3]

Cancer Chemotherapy may be indicated as a primary, palliative, adjuvant, or neoadjuvant treatment modality.[4] Cancer chemotherapeutic agents have a major side effect of severe nausea and vomiting, hence most of the cancer patients receive antiemetic drugs with cancer chemotherapy. Chemotherapy induced nausea and vomiting (CINV) is a particular problem with moderately and highly emetogenic chemotherapeutic agents.

Chemotherapy induced nausea and vomiting (CINV) in cancer patients places a significant burden on patients' function and quality of life, their families and caregivers, and healthcare providers. Despite the advances in preventing CINV, a substantial proportion of patients experience persistent nausea and vomiting.[5]

Incidence of acute nausea and vomiting caused by highly emetogenic chemotherapy (HEC) ranges from 21-39% and 12-21% respectively. Incidence of acute nausea and vomiting caused by moderately emetogenic chemotherapy (MEC) ranges from 35-39% and 12-36% respectively. Incidence of delayed nausea and vomiting caused by highly emetogenic chemotherapy (HEC) ranges from 33-68% and 23-60% respectively. Incidence of delayed nausea and vomiting caused by moderately emetogenic chemotherapy (HEC) ranges from 21-68% and 19-39% respectively. [6, 7, 8]

5-HT_3 antagonists such as Ondansetron, Granisetron, Doalsetron, Dolasetron and Granisetron are effective against cytotoxic drug-induced nausea and vomiting (both acute CINV- occurring within 24 hours of therapy and delayed CINV- occurring more than 24 hours after administration of chemotherapy and persisting for up to 5–7 days 9) and have revolutionized chemotherapy.[10]

Dolasetron is a second generation 5-HT_3 receptor antagonist approved by the Food and Drug administration in the year 2003 as a single intravenous (IV) dose for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy and prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.[11]

Granisetron is a selective 5-HT_3 receptor antagonist. It has been on the market since 1996 in Japan and a number of other Asian countries as an antiemetic drug for cancer patients receiving chemotherapy.[12]

There are numerous studies comparing the various 5-HT_3 antagonist drugs in Chemotherapy induced nausea and vomiting (CINV) caused by moderate-highly emetogenic chemotherapeutic agents. However there are no known studies comparing the effectiveness of Dolasetron and Granisetron for the prevention of CINV. The aim of this study was- to compare the effectiveness of two 5-HT3 antagonists- Dolasetron and Granisetron, for the prophylaxis of Chemotherapy induced nausea and vomiting (CINV), in both acute (upto 24 hours) and delayed (upto 7 days) phases, when given for moderate to highly emetogenic anticancer drugs in single intravenous dose half an hour before starting chemotherapy.

Methodology

This was a prospective, randomized, double-blinded interventional study; spread over a period of 6 months, conducted at tertiary care teaching hospital. Patients (≥18 YEARS), of either sex who underwent chemotherapy in the Department of Oncology, using only moderately and highly emetogenic drugs were eligible to be included in the study. Patients suffering from gastrointestinal malignancy with obstruction of the GI tract, patients receiving radiotherapy to abdomen and pelvis and patients undergoing any surgical procedure or suffering from any disease causing vomiting were excluded from the study.

A total of hundred patients were selected randomly and were randomized into two groups (A and B) of 50 patients each. Randomization was done on the basis of a computer generated randomization table.

Of the two groups, group A received Inj Dolasetron 0.25 mg IV + Inj Dexamethasone 8 mg IV and group B received Inj Granisetron 0.3 mg IV + Inj Dexamethasone 8 mg IV. As the study was double-blinded, the investigator was blinded to the fact that group A received Dolasetron and group B received Granisetron. This was revealed at the end of study before analyses.

A total of two study visits were warranted. The first would be the day on which the study drug was administered wherein the patient was interviewed for approximately 10 minutes and the data was collected as per the Case Record Form. The second visit would be 1, 2 or 3 weeks after the first one, wherein the home cards were collected and few minutes were taken to fill up a questionnaire.

The primary end point was taken as proportion of patients with complete response. Complete response was taken as patient having no episodes of nausea and vomiting as well as not requiring any rescue medication. Various secondary efficacy parameters were taken into consideration: proportion of patients exhibiting episodes of immediate nausea, immediate vomiting, delayed nausea, delayed vomiting; need for rescue medication; time to emetic episode and assessment of severity of nausea and vomiting.

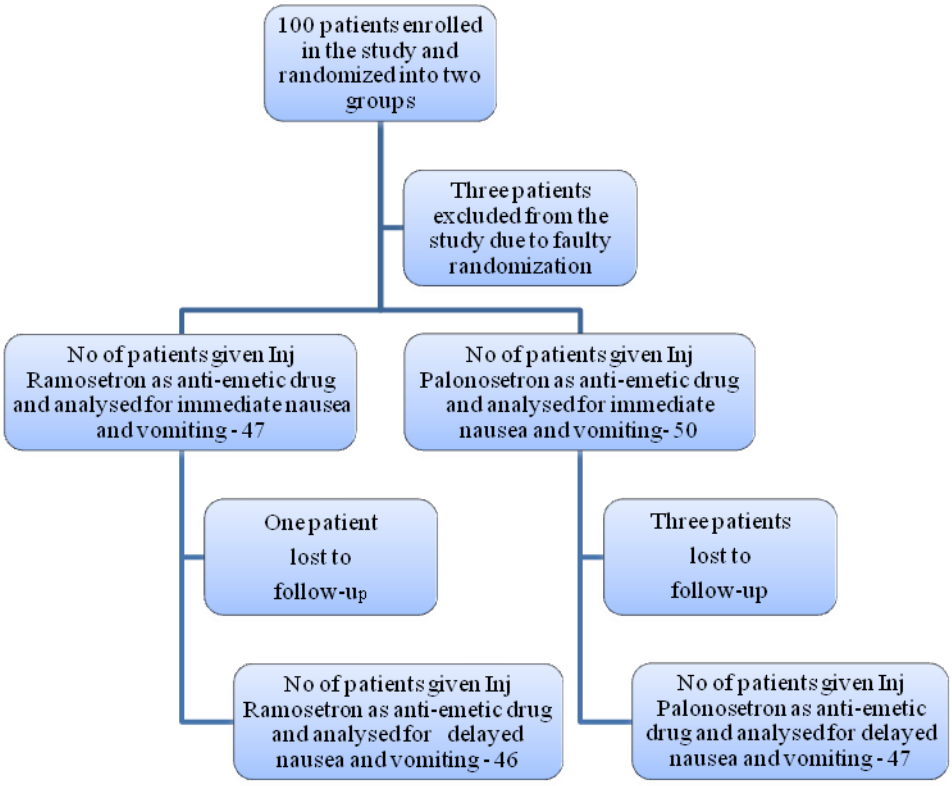
Z-test was applied to compare the response among the two groups receiving Dolasetron and Granisetron. Standard error of proportion was calculated.

The study was approved by the Human Research Ethics Committee (HREC), H M Patel Centre for Medical Care and Education, Karamsad. Written informed consent of all participants was taken after explaining the entire process, either in English or Gujarati, whichever the patient was comfortable with.

Results

Out of 100 patients enrolled, three cases were not taken into consideration for analysis as result of faulty randomization. Out of the 97 patients, four patients were lost to follow-up. The study profile of the patients is as follows:

Figure 1: Study Profile



Demographic profile of the patients:

There was no significant difference among the patients of the two different groups in terms of age distribution, sex of the patients and diagnosis of cancer according to its site. Table 1 shows the demographic profile of the patient.

Table 1: Demographic data

Parameter	No of patients who received Inj Dolasetron	No of patients who received Inj Granisetron	Total
N	**25**	**23**	**48**
Age (Years)			
21-30	1	0	1
31-40	6	1	7
41-50	6	4	10
51-60	7	11	18
61-70	5	7	12
Sex			
Male	15	18	33
Female	10	5	15
Diagnosis (according to site of cancer)			
Oral cavity	12	12	24
Lung	2	4	6
Cervix	4	0	4
Blood, lymph nodes	1	3	4
Breast	2	1	3
Urinary Bladder	1	0	1
Gall Bladder	0	1	1
Knee Joint	1	0	1
Larynx	0	1	1
Small Intestine	0	1	1
Rectum	1	0	1
Prostrate	1	0	1

Chemotherapeutic agents:

The following are the details regarding the chemotherapeutic agents prescribed and administered to the patients included in this study:

Drugs: Each patient was administered minimum of one chemotherapeutic agent to a maximum of 4 drugs. The most common drug given was Cisplatin. **[Table 2]**

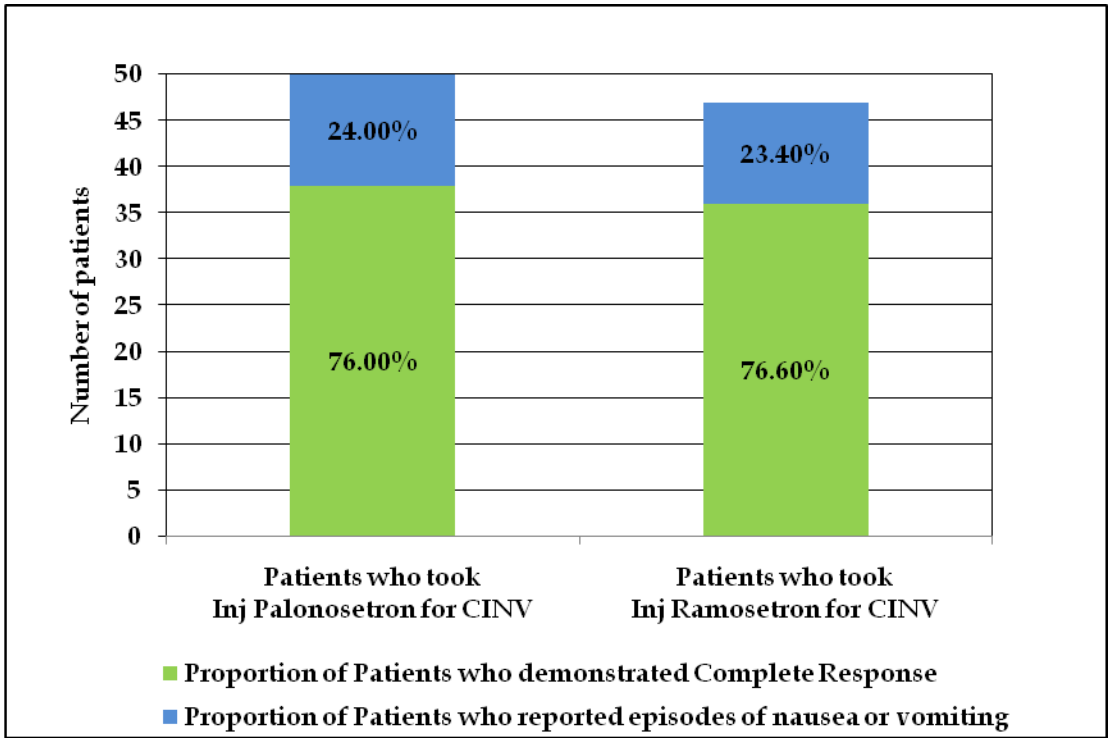
Table 2: Chemotherapeutic agents given to patients

Sr No	Name of Drug	No of patients
1	Cisplatin	15
2	Paclitaxel	8
3	Carboplatin	6
4	5 Fluorouracil	6
5	Doxorubicin	6
6	Gemcitabine	4
7	Cyclophosphamide	4
8	Pemetrexed	3
9	Oxaliplatin	3
10	Vincristine	2
11	Bleomycin	2
12	Vinblastine	2
13	Dacarbazine	2
14	Capecitabine	2
15	Epirubicin	1
16	Ifosfamide	1
17	Mesna	1
18	Docetaxel	1
	Total	69 doses

Primary Efficacy End point:

Out of the 50 patients in group A i.e. who were given Inj Dolasetron, 38 patients (76%) showed complete response (having no episodes of nausea and vomiting; not requiring any rescue medication). In group B i.e. who were given Inj Granisetron, 36 out 47 patients (76.6%) showed complete response. The standard error of difference between these two proportions is 0.07 which is insignificant if taking into consideration 95% confidence intervals. Hence we can conclude that there is no clinical difference in the effectiveness of the two drugs- Dolasetron and Granisetron, when used for the prophylaxis of CINV (Standard error= 8.63; taking 95% CI, Z value= 0.07<1.96). [Fig 2]

Figure 2: Patients who demonstrated complete response vs those who reported episodes of nausea & vomiting



Secondary efficacy End points:

No difference was found between the two drugs when proportion of patients who experienced acute and delayed nausea and emesis among both the groups were compared [Fig 3,4]. When calculating time to emetic episode it was seen that episodes of nausea and vomiting appeared earlier with Granisetron [Fig 5]. Need for rescue medication as well as severity of nausea and vomiting did not differ between the two groups [Table 3,4,5]. Severity of nausea has been assessed in the following two ways:- 1. Visual Analogue Scale (VAS) for Nausea and 2. Common Terminology Criteria for Adverse Events (CTCAE) grading of nausea and vomiting**.** No difference was found among the two groups in terms of assessment of severity in the above two ways.

Figure 3: Patients who exhibited immediate nausea & vomiting vs those who did not exhibit

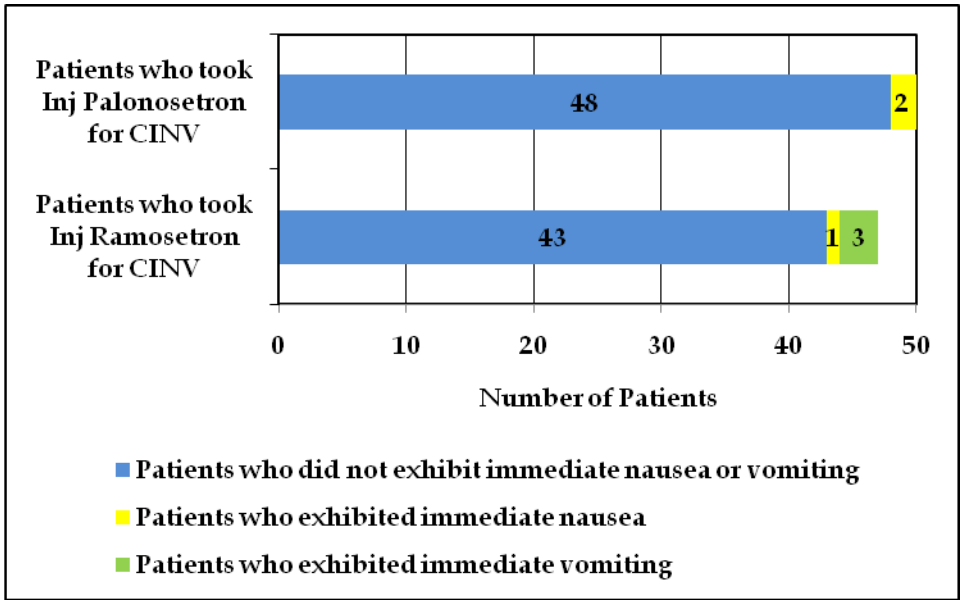


Figure 4: Patients who exhibited delayed nausea & vomiting vs those who did not exhibit

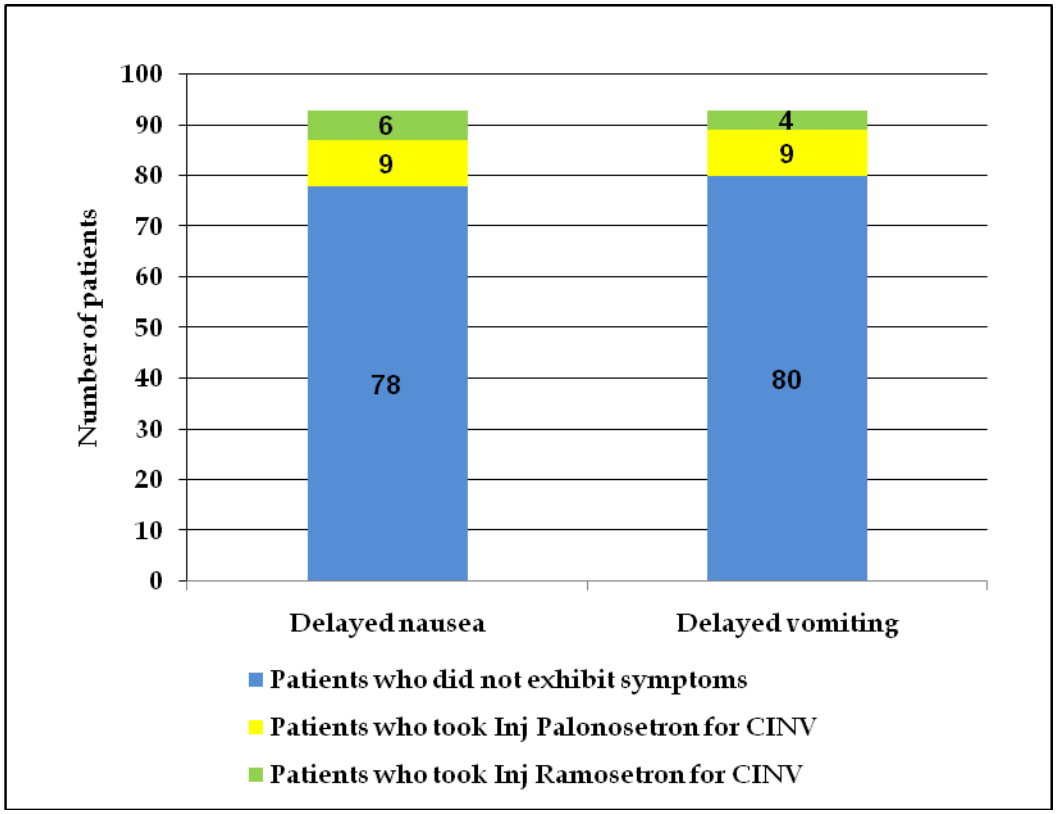


Figure 5: Episodes of nausea and vomiting and Time of emesis

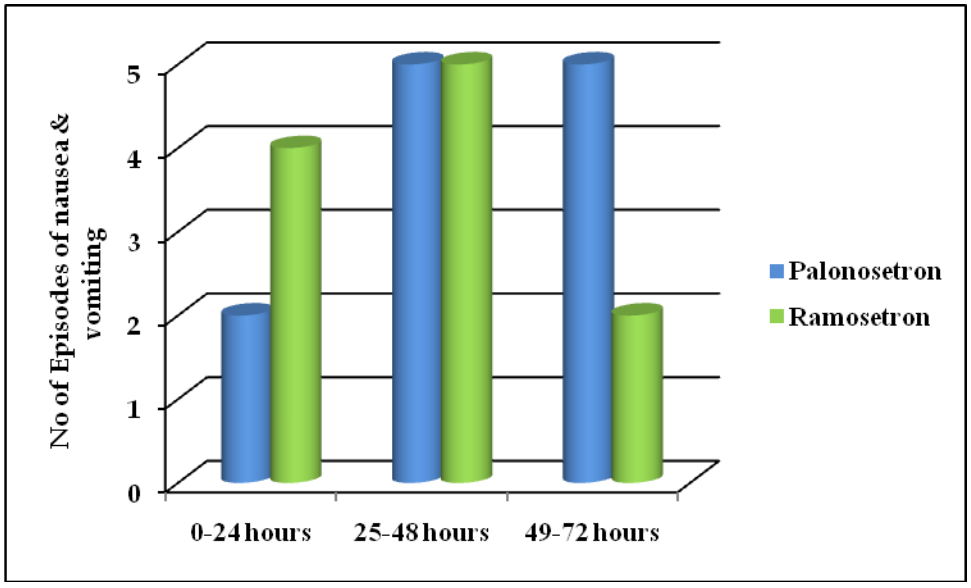


Table 3: Visual Analogue Scale for nausea

VAS score	No of patients in Group A	No of patients in group B
2	6	4
3	1	0
4	0	1
5	1	2
6	2	0

Table 4: Common Terminology Criteria for Adverse Events (CTCAE) grading for nausea

CTCAE grade	No of patients in Group A	No of patients in group B
1	5	4
2	2	1
3	3	2

Table 5: Common Terminology Criteria for Adverse Events (CTCAE) grading for vomiting

CTCAE grade	No of patients in Group A	No of patients in group B
1	8	7
2	1	0

Relation of chemotherapeutic agent with the anti-emetic drug:

The patients who were administered moderate-highly emetogenic chemotherapeutic agents were included in the study. A total of 39 doses of moderately emetogenic agents and a total of 67 doses of highly emetogenic agents were given to the patients.
[Table 6,7; Figure 6]

Table 6: Moderately emetogenic chemotherapeutic agents

Anti-emetic drug given along with moderately emetogenic chemotherapeutic agent	No of patients	No of patients who reported episodes of nausea and vomiting
Inj Dolasetron	18	4
Inj Granisetron	21	2

When compared the difference between the two groups was found to be insignificant.

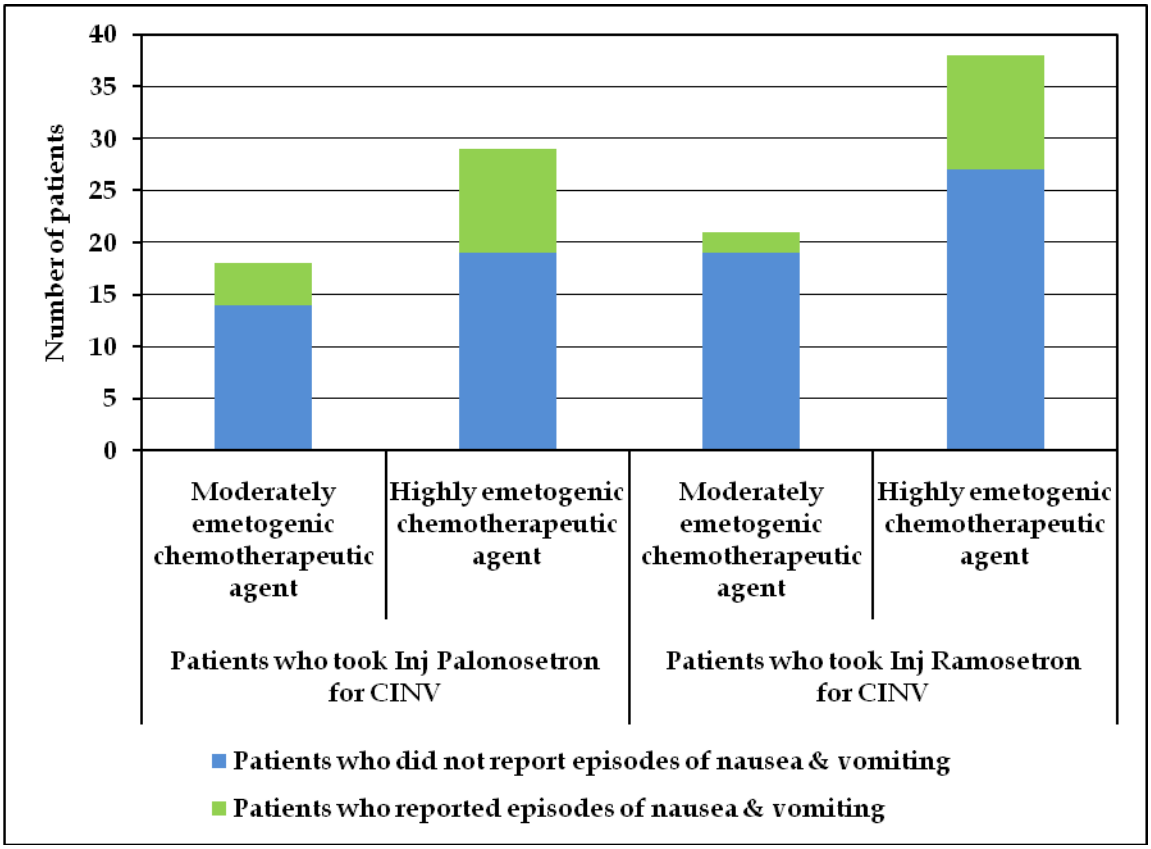
($z=1.086<1.96$)

Table 7: Highly emetogenic chemotherapeutic agents

Anti-emetic drug given along with highly emetogenic chemotherapeutic agent	No of patients	No of patients who reported episodes of nausea and vomiting
Inj Dolasetron	29	10
Inj Granisetron	38	11

When compared the difference between the two groups was found to be insignificant.
($z=0.48<1.96$)

Figure 6: Relation of chemotherapeutic agent with the anti-emetic drug



Discussion

The difference between the two groups- those who received Inj Dolasetron versus those who received Inj Granisetron for CINV was not significant. Hence the two drugs Dolasetron and Granisetron showed similar effectiveness as antiemetic drugs in chemotherapy induced nausea and vomiting. Comparison of the two groups in terms of the above four secondary parameters showed that there was no significant difference in proportion of patients who exhibited immediate nausea, immediate vomiting, delayed nausea and delayed vomiting among the patients receiving Dolasetron and Granisetron. A study carried out by Aapro et al, 2006[13], carried out in 667 patients, comparing Dolasetron and Ondansetron in CINV showed Dolasetron to have slightly higher complete response rates (66.7% CR rate with Dolasetron versus 46.7% CR rate with ondansetron). Gralla et al[14] and Kaushal et al[15] also showed superiority of Dolasetron over Ondansetron.

Mitsue et al, 2009[16] carried out a study comparing Dolasetron and Granisetron in 1114 patients and found that Dolasetron was non-inferior to Granisetron in terms of complete response (75.3%

for Dolasetron versus 73.3% for Granisetron); a finding which matches this study. A similar study comparing Dolasetron and Granisetron, carried out in 144 Chinese patients by Tian et al [17] also showed non-inferiority of Dolasetron to Granisetron.

Study comparing Granisetron and Granosetron by Ho et al, 2010[18] and Cheirsilpa et al, 2005[19] showed that Granisetron was non-inferior to that of Granisetron for the prevention of acute chemotherapy-induced nausea and vomiting.

In a study carried out by Yang et al, 2002[20], in 194 patients, Granisetron was found to prevent acute vomiting better than granisetron while undergoing cisplatin based therapy. Granisetron was found to be more potent and longer-lasting than granisetron in preventing chemotherapy-induced digestive disturbance in a study carried out in 111 patients by Feng et al, 2002[21]

Studies comparing Dolasetron with older antiemetic drugs (Aapro et al, 2006[13] and Mitsue et al, 2009[16]) found that incidence of acute nausea and vomiting was similar but incidence of delayed nausea and vomiting was significantly higher with older antiemetic drugs, Ondansetron and Granisetron. This could be attributed to the fact that Dolasetron has a significantly longer half life (upto 72 hours); hence its better response in preventing delayed nausea and vomiting. But, this fact did not have any impact on the incidence of delayed nausea and vomiting in this study.

Conclusion

This study showed that Dolasetron and Granisetron are equally effective in preventing chemotherapy induced nausea and vomiting with both moderate and highly emetogenic chemotherapeutic agents.

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