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Original Research Article

Satisfaction Level of Cancer Patients using Ramosetron and Ondansetron: A Comparative Study

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Abstract

Background: To compare level of satisfaction of the patients receiving Ramosetron and ondansetron in prevention of acute and delayed nausea and vomiting associated with chemotherapy.

Methods: 60 patients were recruited in the study and were allocated to two groups (Ondansetron and Ramosetron group). Patients were initially screened and then study visits included clinic visits on day 8, day 9 and day 14. Patient diaries were used to record patients' satisfaction which was based on severity of nausea and vomiting using visual analogue scale (VAS).

Results: VAS score was significantly lower in Ramosetron group as compared to Ondansetron group in acute phase of nausea and vomiting indicating level of satisfaction higher in Ramosetron group. Similarly, in delayed and overall phase Ramosetron group experienced lower range of scoring on VAS scale as compared to Ondansetron group. The difference was statistically significant ($p<0.01$).

Conclusions: Level of overall satisfaction of the patients in Ramosetron group was significantly higher as compared to Ondansetron group in patients receiving the two drugs for prevention of nausea and vomiting caused by cisplatin chemotherapy in head and neck cancer patients.

Keywords: Satisfaction, Ondansetron, Ramosetron, Visual Analog Score.

Introduction

Chemotherapy, though unfortunately has side effects, is seen as a life saver for those diagnosed with carcinoma/cancer. One of the common side effects is chemotherapy-induced nausea and vomiting, (CINV). The nausea and vomiting induced by

chemotherapies occur mostly within the first few hours of getting the treatment (acute nausea and vomiting) while others cause nausea and vomiting followed by another period of nausea and vomiting a day or more after chemotherapy has been initiated (delayed nausea and vomiting)[1]. Nausea and Vomiting continue to remain a concern for patients receiving cancer treatment. Cancer patients often give higher ranking to the nausea and vomiting as the most severe side effects of chemotherapy[2]. It has been reported that the frequency of chemotherapy induced nausea and vomiting, particularly delayed nausea and vomiting, is underestimated by treating oncology physicians and nurses[3].

The consequences of not controlling the nausea and vomiting induced by chemotherapy may lead to complications as well as poor compliance with treatment with the cancer therapy and follow-up, and a diminished quality of life[4].

A number of drugs are available to manage nausea and vomiting. These drugs (antihistaminic, phenothiazine derivatives, anticholinergics and dopamine receptor antagonist) have unwanted side effects like sedation, dysphoria, extrapyramidal symptoms, dry mouth, restlessness and tachycardia[5].

Newer drugs, Selective serotonin 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonists (5- HT_3RA) are devoid of such side effects and are highly effective and thus the first line choice in prevention of Chemotherapy induced nausea and vomiting[6]. These Serotonin antagonists are believed to be effective in acute CINV because of rapid release of serotonin in the gastrointestinal tract in the first 24 h[7]. In humans, a peak in the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) is observed in urine at 4 h, with levels returning to baseline within 24 h[8,9]. These drugs include ondansetron, granisetron, dolasetron and tropisetron. Currently introduced $5HT_3$RA include ramosetron and palonosetron. The antiemetic efficacy of ondansetron has been well established in the prevention and treatment of CINV.

Ramosetron hydrochloride, is a relatively newer 5HT3 receptor antagonist with an affinity higher than ondansetron, granisetron and tropisetron[10]. Ramosetron has been introduced for the treatment of irritable bowel syndrome (IBS), chemotherapy (cisplatin)-induced nausea and vomiting and late in post-operative nausea and vomiting, with almost no study done for comparing the level of satisfaction of patients receiving this drug with other antiemetics[11-13].

Patient satisfaction is of utmost importance in health care delivery. Though, the satisfaction level is difficult to assess, one of the methods is by using visual analogue scale (VAS) scoring[14].

Since the literature available is scarce and contradicting, the currenmt study was planned to evaluate and compare the level of satisfaction of patients receiving ramosetron and ondansetron as antiemetics for cisplatin chemotherapy induced nausea and vomiting in treatment of head and neck cancers.

Methods:

Study design: This was prospective, comparative study.

Sample size: All the cases of head and neck cancer reporting to the department during the study period were included in the study. A total of 60 eligible cases reported to the department and were recruited in the study. They were further divided into two groups receiving Ramosetron or Ondansetron. These drugs were prescribed by their treating clinician and out of 60 patients, 35 patients (Group 1) received Ondansetron while remaining 25 received Ramosetron (Group 2).

Study Period: 18 months (1st march, 2018 to 31st October,2019)

Study Unit: Cancer patients undergoing Chemotherapy

Study Place: This clinical study was done in collaboration with the department of Radiotherapy and Oncology of a premier Medical Institute.

Patients were recruited in the study according to the following inclusion and exclusion criteria

Inclusion criteria:

- Male or female, age ≥18 yrs, with histologically confirmed malignant disease
- Patients naïve to chemotherapy, with a Karnofsky index ≥70%
- Scheduled to receive a single dose cisplatin as a single drug or in combination
- Recurrent cases of head and neck cancers, who had taken radiation therapy 6 months back and thus planned for palliative chemotherapy.
- Patients with hepatic function and renal function in normal limits.

Exclusion criteria

- Nonconsenting, Inability to understand or cooperate with study procedures.
- Scheduled to receive any drug with antiemetic efficacy from 24 hrs before to 5 days after treatment.
- Emesis, retching, or Grade 2 or 3 nausea ≤24 hrs before chemotherapy (Grading of nausea as per the National Cancer Institute Common Toxicity Criteria, version3).[14]
- Ongoing emesis due to any organic etiology.
- Contraindications to 5-HT3 receptor antagonists.
- Patient having Hb <9gm%, TLC <4000/cu.mm and Platelet Count<1,00,000/ cu.mm. in the screening visit.
- Patients on concurrent chemo-radiotherapy.

Study conduction

Brief description of methods/procedures in the study:

Screening visit- (Day1-7)-The consenting patients were initially screened for eligibility between day 1 and day 7 and the following were recorded: history of nausea and vomiting, physical examination; vital signs; Investigations like haematology, blood chemistry and urine analysis; complete past medical history; concomitant medications; and history of nausea and vomiting. Then Study visits included clinic visits on day 8, day 9 and day 14.

Patient diaries were used to record the satisfaction of patients at particular time based on severity of nausea and vomiting using VAS scale daily until day 12 starting from day 8 (days on which chemotherapy has to be given). On 14th day the Patient Diary Cards were collected back.

Study visit (visit 1): (Day 8)

One hour before the start of chemotherapy, the following parameters were recorded in the enrolled patients: BP measurement, Heart Rate, Pre-dose Nausea/vomiting, any drug administration, concomitant medications, adverse events recorded.

Patient diary cards were distributed and explained about the relevant entries to be made.

Study visit II: (Day 9)

The following test and procedures were carried on patients on second day after chemotherapy that would mean 9th day of study: physical examination and vital signs, haematology, blood chemistry, urine analysis, adverse events recorded, concomitant medications recorded

Study visit III: (Day - 14)

The following test and procedures were carried on patients on 14th day of the study. Physical examination and vital signs, haematology, blood chemistry, adverse

events recorded, concomitant medications recorded, patient diary cards collected

Study treatment

- Group 1- Ondansetron (Osetron), a clear colourless, nonpyrogenic, sterile solution available in 2ml and 4ml vials with strength of 2mg/ml. A total dose equivalent to 16 mg of ondansetron was administered intravenously 30 minutes prior to chemotherapy.
- Group 2- Ramosetron (Nozia) (supplied by Zydus (Alidac Corza) administered intravenously over 30 seconds in the recommended dosage of 0.3mg. It was administered 30 minutes before administration of each course of chemotherapy

Assessments:

Level of Satisfaction: Visual Analogue scale was plotted to record patients' overall assessment of satisfaction on control of nausea and vomiting.[14,15]

Safety assessment*:* Safety was assessed by the following: adverse event (AE) reporting for a period of 15 days (30 days for serious AEs); vital sign measurements; laboratory tests performed; physical examination, and electrocardiogram (ECG) recordings performed at specified time points.

Adverse event monitoring: The expected adverse event for the drugs under consideration as reported in literature are headache, dizziness and constipation with a reported incidence of less than 2%. The adverse events were evaluated as per the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE).[16]. If any adverse event occurred, it was evaluated by the investigator and recorded in case record form stating the onset, severity, duration, likely cause, action taken reference to the study drugs and outcome. For all adverse events, the onset, duration, symptoms and sign, treatment, relationship to the study drug were noted in the adverse event page of case record form

Statistical analysis*:*

The student's 't' test (to assess significance in demographic profile between the groups) and Z test (to observe significance between two proportions) were used to measure the difference among the result, expressed in the form of P value.

Results:

The demographic data and baseline characteristics of the patients (Table 1) of both the groups were comparable i.e. difference between the age, weight, height, BSA and Karnofsky index in the patients of two groups was not statistically significant (P>0.05). There was no significant (P >0.05) association between the history of nausea and vomiting of both the groups.

Table 1: Showing the demographic and behavioural characteristics.

Demographic characteristics	**Group 1 receiving Ondansetron**	**Group 2 receiving Ramosetron**
	(mean ± SD)	**(mean ± SD)**
Age (in years)	55.2±11.18	57.53±10.81
Weight (in Kgs)	61.17±09.66	56.5±7.14
Height (in cms.)	161.4±10.82	163.7±9.61
BSA	1.40±0.17	1.42±0.12
Karnofsky index, %	84.32±5.63	86±3.00
Behavioral and clinical characteristics(N=60)	**n_1= 35 (%)**	**n_2=25(%)**
Smoker	12(33.33)	09(36.66)

Alcoholic	06(16.67)	04(16.67)
Other	06(16.67)	03(13.33)
Nausea and vomiting history: N=60 (%) *	**n_1= 35 (%)**	**n_2=25(%)**
Present	06(16.67)	02(08.00)
Absent	29(83.33)	23(92.00)
***** X^2 =1.07, p>0.05		

Visual analogue scale (VAS) for overall satisfaction

It was observed that VAS score was significantly lower in Group 2 as compared to Group 1 (p<0.01) in acute phase of nausea and vomiting indicating level of satisfaction higher in Group 2(Ramosetron) group. Similarly, in delayed and overall phase Group 2 experienced lower range of scoring on VAS scale as compared to Group-1. The difference was statistically significant (p<0.01) (Table 2).

Table 2: Showing Phase wise Visual Analog Score for overall satisfaction

Phases	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	t-test	p value
Acute Phase (0-24h)	63.7±5.06 (n=30)	46.2±4.95 (n=30)	13.54	P<0.01
Delayed Phase (24-120h)	63.0±8.49 (n=120)	49.57±14.63 (n=120)	8.69	P<0.01
Overall Phase (0-120h)	63.10±7.38 (n=150)	48.9±12.91 (n=150)	11.69	P<0.01

The results on Day 1 were same as that of acute phase. On day 2, day 3, day 4 and day 5, the group 2 VAS score were significantly less as compared to Ondansetron group (Group-1)(p<0.01) (Table 3). The difference between the Phase wise VAS score was highly statistically significant (P <0.01) for all the phases i.e. acute, delayed and overall phase in favour of Group 2. The difference between the Day wise VAS score was highly statistically significant (P <0.01) for all the days in favour of ramosetron group.

Table 3: Showing the Day wise VAS for overall satisfaction.

Day (time period in hrs)	Group 1(Mean ± SD)	Group-2 (Mean ± SD)	t-value	P-value
Day 1 (0-24h)	62.7±5.01	45.2±4.75	12.54	P<0.01
Day 2 (24-48h)	70.4±4.35	63.20±3.16	9.15	P<0.01
Day 3 (48-72h)	70.13±4.17	53.30±3.57	15.45	P<0.01
Day 4(72-96h)	67±3.60	45.8±3.15	22.17	P<0.01
Day 5 (96-120h)	41.7±3.95	35.90±4.32	5.08	P<0.01

The details of adverse events (whether or not related to the study drug) are shown in Table 4 both ramosetron and ondansetron were well tolerated, and no adverse event related withdrawals were reported during the study. In the Ondansetron group (group-1) 53.33% of patients and in Ramosetron group-2,50% of patients experienced at least one adverse event. Most of the adverse events, 81.25% in Ondansetron group and 60% in Ramosetron group were mild in intensity with the majority of adverse events assessed as associated with the

patient's disease and/or chemotherapy treatment. The number of patients reporting headache and diarrhea were higher in ramosetron group (14 and 4) as compared to ondansetron group (12 and 2). Whereas the number of patients reporting dizziness and fatigue were higher in ondansetron group (3 and 2) compared to ramosetron group (0 and 1) respectively. Overall, the difference in the proportion of patients with patients with possible adverse events was not significant (P >0.05).

The common adverse events (whether or not related to the study drug) in ramosetron group were headache (46.66%), diarrhoea (13.33%), fever and abdominal pain (6.66%) whereas in ondansetron group, the common adverse events were Headache (40%), Fatigue and diarrhoea (6.66%). Constipation and dyspepsia was equal in both the groups (3.33%) Tinnitus was present only in Ondansetron group (3.33%). Fever was less in Ondansetron group (3.33%) as compared to Ramosetron group.

Post hoc analysis revealed no differences in the duration of adverse events commonly associated with 5-HT3 receptor antagonist therapy (i.e. headache, fatigue and constipation) in patients treated with ramosetron compared with ondanserton. No serious adverse event was reported in the study.

Table 4: Showing the frequency of reported possible adverse events.

Reported Adverse Event	Group 1(Ondansetron Group)	Group-2 (Ramosetron Group)	Z-value	P-value
Headache	15(40)	12(46.66)	0.52	P>0.05
Diarrhoea	03(6.66)	03(13.33)	0.86	P>0.05
Dizziness	04(10)	00(0)	1.77	P>0.05
Fatigue	03(6.66)	01(3.33)	0.59	P>0.05
Constipation	01(3.33)	01(3.33)	0	P>0.05
Tinnitus	01(3.33)	00(0)	1	P>0.05
Fever	01(3.33)	02(6.66)	0.59	P>0.05
Cough	01(3.33)	01(3.33)	0	P>0.05
Asthenia	00(0)	01(3.33)	1	P>0.05
Dyspepsia	01(3.33)	01(3.33)	0	P>0.05
Abdominal Pain	01(3.33)	02(6.66)	1.43	P>0.05

No statistically significant differences were found between both the groups with respect to physical examination, Vital parameters, laboratory parameters i.e. haematology, liver function tests and urine analysis. Overall, no significant safety concerns were identified in the study. After applying 'Z' test of difference between two proportions, there is no significant difference (P >0.05) between proportions of possible adverse events in both the groups.

Discussion:

The 5-HT_3 receptor antagonist is considered as the gold standard anti-emetic treatment providing effective control of acute nausea and vomiting. They offer a substantial tolerability benefit over older other conventional antiemetic. Ondansetron is the most widely used drug for the prevention of chemotherapy-induced nausea and vomiting (CINV). Structure of ramosetron results in more potent blocked of $5HT_3$ receptor. This effect has been demonstrated both in vitro and in animal studies and in the latter, it appears to prevent vomiting associated with cisplatin chemotherapy.17 The efficacy of

the ramosetron has been supported by several clinical trials comparing antiemetic efficacy of ramosetron with that of granisetron in 76 patients receiving cisplatin chemotherapy[16]. Results are strongly in favour of ramosetron. In some other comparative clinical studies, ramosetron had superior efficacy into the acute and delayed than other first generation $5HT_3$ receptor antagonist[10,18].

In the present study, the demographic data and baseline characteristics like age, height and Karnofsky index were comparable with the observations reported by J Jayesh et al and Kim et al except weight which was higher in these studies[13,19]. We could not make out the sex differences among all characteristics because the enrolled study patients were only males.

Regarding VAS score, highly significant ($p<0.01$) results were found in favour of ramosetron starting from day 1 to day 5. Acute, delayed and overall phases also showed highly significant results indicating that level of satisfaction is significantly higher with patients treated with ramosetron group as compared to Ondansetron. Similar results were shown by Park et al that is level of satisfaction was higher in ramosetron group as compared to Palonosetron, though it was not statistically significant ($p>0.05$).20 Another study revealed no significant difference between level of satisfaction in between two groups ($p>0.05$)[21]

Safety:

Both the study drugs were well tolerated by all the patients in the study. During the study period, 9 adverse events were reported in both the groups. Study conducted by Jayesh J showed almost same pattern of adverse events i.e. 8 and 5 in ramosetron and ondansetron group respectively suggesting ramosetron as a safer alternative, but the difference was not statistically significant[19]. Another study done by Shi Y et al concluded ramosetron as safer drug as compared to ondansetronin in terms of controlling appetite loss[22]. Ramosetron tended to be more effective than ondansetron in its antiemetic action.

In present study, the common adverse events in both the groups (whether or not related to the study drug) were headache, diarrhoea, fatigue, constipation, fever, cough and dyspepsia. Dizziness and tinnitus were reported only in ondansetron group. Abdominal pain and asthenia reported only in ramosetron group. No serious adverse event reported in present study.

Jayesh J reported bodyache as common adverse event of ramosetron group[18]. While weakness was common in ondansetron groups. Overall no safety concerns were raised in this study which is consistent with the results other two studies.

Conclusion:

Level of satisfaction (assessed by VAS score) of the patients in ramosetron group was higher as compared to ondansetron group.

Limitations of the study- The small sample size is the limitation of the current study. Hence future studies should be planned with more number of patients considering the limitations in the present study.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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