Comparative Study of Ramosetron and Ondansetron for Prevention of Chemotherapy Induced Nausea and Vomiting In Head & Neck Cancers

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Abstract: Objective: To compare efficacy of Ramosetron and Ondansetron in the prevention of acute & delayed nausea and vomiting associated with cisplatin chemotherapy. Methods: 60 patients were recruited in the study. Patients were randomly allocated to ramosetron(R) & ondansetron group (O). Patients were initially screened for eligibility between day 1 and day 7. Study visits included clinic visits on day 8, day 9 and day 14. Patient diaries were used to record emetic episodes and severity of nausea, which were recorded daily until day 12 starting from day 8. On 14th day the patient diary cards were collected back. Results: Complete Response Rate (CRR) during the first 24 hours (acute phase) was non significantly higher in the R group (86.66%) as compared to O group (76.66%) ($p > 0.05$). For the delayed phase (24-120 hr.) & overall phase (0-120hrs), the proportion of patients achieving CRR was significantly higher for R group (86.66% for both phases) as compared to O group (78.33%, 78%, respectively) ($p < 0.10$, $p<0.05$, respectively) . Complete Control (CC) rate was higher in O group (90%) in acute phase as compared to R group(86.66%) but in delayed & in overall phase CC rate was greater in R group (87.6%, 87.3%) as compared to O group (81.6%, 83.33%)($p>0.05$). Conclusion: Ramosetron and Ondansetron are equally effective in the prevention of cisplatin induced nausea and vomiting in acute phase (0-24 hrs). Ramosetron came out to be significantly more effective antiemetic agent in the prevention of delayed phase (24-120 hrs) and overall phases of CINV(0-120 hrs).

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Key words: Ondansetron, Ramosetron, Cisplatin, Vomiting, Delayed.

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Introduction: Chemotherapy can be seen as a life saver for those diagnosed with cancer. Unfortunately, chemotherapy often has side effects. One of them is chemotherapy-induced nausea and vomiting, (CINV). Some chemotherapies cause nausea and vomiting mostly within the first few hours of getting the treatment (acute nausea and vomiting). Others cause acute nausea and vomiting followed by another period of nausea and vomiting a day or more after chemotherapy has been given (delayed nausea and vomiting)[1] . In a study, cancer patients ranked nausea and vomiting as the first and second most severe side effects of chemotherapy, respectively[2].

CINV continue to remain a concern for patients receiving cancer treatment. It has been observed that the frequency of chemotherapy – induced nausea and vomiting, particularly delayed nausea and vomiting, is underestimated by oncology physicians and nurses[3].
The consequences of not controlling the nausea and vomiting induced by cancer treatment may lead to many complications, a failure of the patient to comply with the cancer therapy and follow-up, and a diminished quality of life[4].

There are a number of drugs that are used to manage nausea and vomiting. These drugs are generally antihistaminics, phenothiazine derivatives, anticholinergics and dopamine receptor antagonist with unwanted side effects like sedation, dysphoria, extrapyramidal symptoms, dry mouth, restlessness and tachycardia.[5]

Recently introduced selective serotonin 5-hydroxytryptamine type 3 (5HT3) receptor antagonists ($5HT_3RA$) are devoid of such side effects and are highly effective and thus the first line therapies in prevention of CINV.[6]

Serotonin antagonists are believed to be effective in acute CINV because serotonin is released rapidly from the enterochromaffin cells 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 $5HT_3RA$ include ramosetron and palanosetron. 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)[11], chemotherapy (cisplatin)-induced nausea and vomiting[12] and late in post-operative nausea and vomiting[13], with very few studies done for comparing the efficacy of this drug with other antiemetics.

Considering the above mentioned facts and the incidence of CINV, and also that very few comparative studies of ramosetron has been carried out, that too in a western population, the present study was planned to evaluate and compare the efficacy and safety of ramosetron and ondansetron in both acute and delayed phases of CINV in patients receiving moderately emetogenic cancer chemotherapy.

Methods: This clinical study was done in collaboration with the department of Radiotherapy and Oncology, SRMSIMS, Bareilly. Patients were recruited in the study according to the subject eligibility

Inclusion criteria:

- Provision of written informed consent.
- 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:

- 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- HT_3 receptor antagonists.
- Patient having Hb< 9 gm%, TLC < 4000/cu.mm and Platelet Count<1,00,000/ cu.mm. in the screening visit.
- Patients on concurrent chemo-radiotherapy were excluded from the study.
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Study Design: This was an open-label, randomized, parallel group, prospective and comparative study. The study was performed after the protocol approval by Institutional Ethical Committee.

Study Groups: Depending on the treatment received, there were two study groups.

- Patients were randomized either to the ramosetron group [R] or in the ondansetron group [O] according to the randomization.
- Randomization was done in such a way that eligible patients coming to the OPD were alternately placed in ramosetron group [R] and ondansetron group [O] respectively.

Study Population: 60 diagnosed cases of head & neck cancer, 30 subjects in each group were recruited in the study. 6 drop outs were replaced.

Study duration:

- ✓ The expected duration for participation of each subject enrolled in the study was 14 days.
- ✓ The study was carried out from 10/10/2014 to 20/06/2015

Study Conduct: Brief description of methods/procedures in the study: Consenting patients were initially screened for eligibility during any time between day 1 and day 7. Within 7 days prior to study commencement the following were recorded: physical examination; vital signs; Investigations; past medical history; concomitant medications; and history of nausea and vomiting.Study visits included clinic visits on day 8, day 9 and day 14.

Patient diaries were used to record the following - emetic episodes; and severity of nausea, which were recorded 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.
Physical examination and vital signs included Height & Weight, body temperature, blood pressure, heart rate. Investigations performed.

Screening Visit: [Day 1-Day 7]: At any time point during the week before administration of

investigational drugs, patients were screened. History of nausea & vomiting, complete past medical history & physical examination was done and had undergone following tests: haematology , blood chemistry and urine analysis

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.

Patient Diary Cards: Cards were distributed to patients and the following were recorded:

1. Number of emetic episodes, every day from 1st to 5th day at 2, 12 and 24 hours time points from the start of chemotherapy.
2. Degree of nausea, every day from 1st to 5th day at 2, 12 and 24 hours time points from the start of chemotherapy.
3. The patients were asked to bring the patient diary cards at each visit.

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 & vital signs, haematology, blood chemistry, urine analysis, adverse 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 & vital signs, haematology, blood chemistry, adverse events recorded, concomitant medications recorded, patient diary cards collected

Study treatment: 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

- 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.

Study Assessment -The primary end point of the study was the proportion of patients achieving a complete response (CR; defined as no emetic episode and no use of rescue medication) during the first 24h following chemotherapy administration (i.e. efficacy in preventing acute CINV). Secondary end points included the following: the proportion of patients achieving a CR during the delayed 24-120-h time period and the cumulative overall 0-120-h time period, as well as CR rates during successive 24-h time periods (i.e. 24-48, 48-72, 72-96, 96-120 h); the proportion of patients achieving complete control (CC; defined as no emetic episode, no need for rescue medication and no nausea) for the 0-24, 24-120 and 0-120 h intervals; number of emetic episodes daily and cumulatively for the 24-120 and 0-120 h intervals

Efficacy assessment: Efficacy for acute (0-24) and delayed (24-120h) CINV were determined. Therapeutic response was evaluated by recording the occurrence of an emetic episode, the degree of nausea, and the need for rescue medication. Treatment was considered a failure (i.e. unsatisfactory therapeutic response) if a patient has at least one emetic episode or received rescue medication.

Statistical Analysis: The student's 't' test (to assess significance in demographic profile between the groups) & 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. the difference between the age, weight, height, BSA and Karnofsky index in the patients of two groups was not statistically significant (P>0.05).

Complete response (CR) rate in acute phase: Complete Response rate during the first 24 hours was numerically higher in the R group as compared to O group but the difference was statistically not significant (P > 0.05). (Table 3)

Complete response rate in delayed phase & overall phase: For the delayed phase (24-120 hr.) time period, the proportion of patients achieving a CR rate was significantly higher for R group as compared to O

group (P < 0.10) (Table 3). For the overall phase (0-120hr.) time period, the proportion of patients achieving a CR rate was significantly higher for R Group as compared O group (P < 0.05) (Table3).

Complete Control Rates (CC Rates): Study Days 1-5 (acute and delayed CINV): CC Rates for R group was numerically lesser as compared to O group in acute phase. In delayed phase & in overall phase, CC rates for R group was numerically higher as compared to O group. These differences were not statistically significant.(p>0.05) (Table 4)

Vomiting Assessment: The number of vomiting episodes were less with ramosetron as compared to ondansetron, during the acute (0-24 h)(6,18 respectively), delayed (24-120 h)(30, 57 respectively) and overall (0-120 h)(36, 75 respectively) phase. The difference was highly significant (P<0.01)(Table 2)

In addition, there was highly significant difference in the incidence of number of vomiting episodes in Ramosetron group as compared to Ondansetron group (P < 0.01 on day 1 (0-24 h), day 2 (24-48 h), day 3 (48-72 h) but not statistically significant on day 4(72-96h) and day 5(96-120h)(fig 1)

Nausea Assessment: The proportion of patients with no nausea was numerically higher for R group in delayed phase & in overall phase as compared to O group (p>0.05). However, in acute phase, the proportion of patients with no nausea in both the group was almost same.(P>0.05).

Table no. 1: Demographic Data and Baseline Characteristics

Characteristics	O Group	R Group
Age, Years [mean± SD]	52.5±7.96	50.13± 12.64
Weight, kg [Mean± SD]	52.73 ± 5.87	51.60 ± 7.46
Height, cm [Mean± SD]	162.93 ± 7.06	164.90 ± 7.54
BSA [Mean± SD]	1.55 ± 0.18	1.53 ± 0.12
Karnofsky Index, % [Mean± SD}	77.33± 5.83	80.54 ± 3.05
Addiction: n [%] Tobacco Addiction Smoker Alcoholic Others	 7 [23.33] 10[33.33] 05 [16.66] 05 [16.66]	 11[36.66] 11[36.66] 05[16.66] 04 [13.33]
Nausea and Vomiting History: n [%] Present Absent	 02 [6.66] 28 [93.33]	 01 [3.33] [96.67]

n = Number of Patients ; [%] = Percentage of Patients

The difference between the age, weight, height, BSA and Karnofsky index & history of nausea & vomiting in the patients of two groups was not statistically significant (P>0.05) by applying student's test.

Table No. 2: Total Number of Vomiting Episodes (Phase wise)

Phase (Time Period, hrs)	O Group No. [%]	R Group No. [%]	'Z' Value	'P' Value	Result
Acute Phase (0-24h)	18[60] n=30	06[20] n=30	3.16	P<0.01	HS
Delayed Phase (24-120h)	57[47.5] n=120	31[25.83] n=120	3.48	P<0.01	HS
Overall Phase (0-120h)	75[50] n=150	37[24.6] n=150	4.53	P<0.01	HS

n – Number of vomiting episodes , HS - Highly Significant, NS - Not Significant. After applying 'Z' test of difference between two proportions, there was a highly significant difference (P < 0.01) between proportions of vomiting episode (day wise and phase wise in favour of 'R' group as compared to 'O' except on day 5 which was not significant (P > 0.05).

Table No. 3: Complete Response [CR] Rates (Phase Wise)

Phase (Time Period, hrs)	O Group (CR, %)	R Group (CR, %)	'Z' Value	'P' Value	Result
Acute Phase (0-24h)	76.66% n=30	86.66% n= 30	1.03	P>0.05	NS
Delayed Phase (24-120h)	78.33% n=120	86.66% n=120	1.69	P<0.10	S
Overall Phase (0-120h)	78 % n=150	86.66% n=150	1.96	P<0.05	S

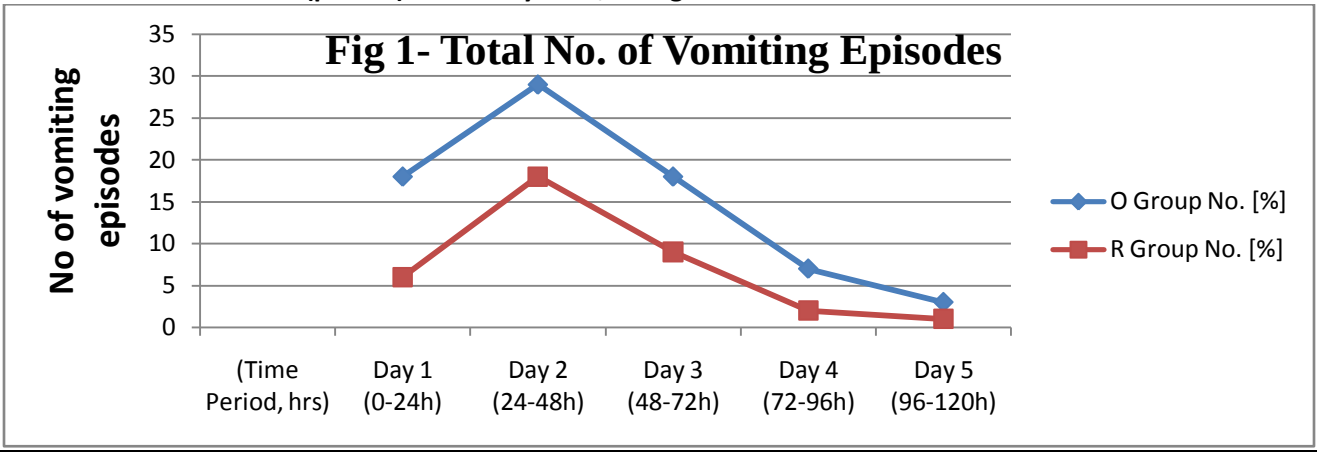
NS – Not Significant, on applying 'Z' test of difference between two proportion, there is no significant difference (P > 0.05) between proportion of complete response rate (Day wise and Phase wise) in acute phase between both the groups however, there is significant difference between two groups in delayed phase (p<0.05) and overall phase (p<0.05) in favour of ramosetron

Table No.4: Complete Control [CC] Rates (Phase wise)

Phase (Time Period, hrs)	O Group (CR Rate, %)	R Group (CR Rate, %)	'Z' Value	'P' Value	Result
Acute Phase (0-24h)	90% (n=30)	86.66% (n=30)	0.402	p>0.05	NS
Delayed Phase (24-120h)	81.6% (n=120)	87.60% (n=120)	1.25	p>0.05	NS
Overall Phase (0-120h)	83.33 (n=150)	87.33% (n=150)	0.97	p>0.05	NS

After applying 'Z' test of difference between two proportions, there was no significant difference (p>0.05) between proportions of complete control rates in the two groups

Fig 1- Significant difference was observed in number of vomiting between the two groups on day 1,day 2 & day 3(p<0.01) but at day 4& 5, no significant difference was seen



Discussion: The 5-HT_3 – receptor antagonist are currently perceived as the gold standard antiemetic treatment providing effective control of acute nausea and vomiting, offering a substantial tolerability benefit over older conventional antiemetic. Ondansetron is the most widely used drug for the prevention of chemotherapy-induced nausea and vomiting. 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.[15]

The efficacy of the ramosetron has been supported by several clinical trial [16] comparing antiemetic efficacy of ramosetron with that of granisetron in 76 patients receiving cisplatin chemotherapy. 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.[10,17]

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[18] and Kim et al.[13],except weight which was higher in these studies.In our study patients enrolled were only males. So, we could not make out the gender differences among all characteristics.

Efficacy assessment: Complete response rates (CRR) observed in this study were superior for ramosetron (86.66%) as compared to ondansetron (76.66%) during acute phase. However, these figures did not reach statistical significance (p>0.05). Similar results were obtained by Jayesh J et al.[18], 2014 where CRR for ramosetron 68% and that of ondansetron was 63 % (p>0.05).[18] While studies conducted by Kang Y K et al.[16], 2002 proved high CRR for ramosetron (90.4%) as compared to granisetron (87 %). Both the studies proved noninferiority of ramosetron over ondansetron & granisetron respectively.Ramosetron

was as effective as ondansetron in acute phase in our study.

In delayed phase (24-120hrs), the CRR observed for ramosetron (85.83%) in our study was superior to ondansetron (78.33%) and this difference was found to be statistically significant ($p<0.01$) indicating that ramosetron was more effective as compared to ondansetron in delayed phase. These findings were in accordance with Jayesh et al.[18], 2013. Results obtained by Kang YK et al.[16], in delayed phase showed no significant difference.

In our study, ramosetron produced numerically superior CRR (86%) as compared with ondansetron (78%) in over all phase (0-120hrs) and this difference came out to be significant ($p<0.05$) suggesting that ramosetron was more effective as ondansetron in over all phase. These findings were in accordance with Jang G et al.[19], 2013.

Regarding no. of episodes of vomiting in our study, patients treated with ramosetron has significantly less no. of vomiting episodes compared to patients treated with ondansetron in acute, delayed and over all phase ($p < 0.01$). In addition, the number of vomiting episodes was significantly less on day 1-5 ($p < 0.01$) in ramosetron group as compared to ondansetron group. The results were comparable with the studies of Jayesh J et al.[18], 2014, Kim et al.[13], 2014 and Kang YK et al[16], 2002.

In the present study, CC rates were more in ondansetron (90%) as compared to ramosetron (86.66%) in acute phase but statistically not significant. Numerically higher Complete Control (CC) rates were observed for ramosetron (87.6% & 87.3%) as compared to ondansetron (81.6% & 83.33%) in, delayed and overall phase respectively but it did not reach statistically significant indicating that ramosetron was as effective as ondansetron ($p>0.05$). Hence, from the above data, although achieved in an open label trial, it proves that ramosetron and ondansetron are equally effective antiemetic agents in acute phase while ramosetron is more effective in delayed CINV.

The significantly higher CR rates and prolonged efficacy of ramosetron can be explained by the fact that ramosetron exhibits a pharmacologically distinct profile from other 5HT3 receptors antagonists that is 5HT3 receptors binding affinity of ramosetron is greater than others in its class, making it more potent than other receptor antagonists (pKi for Ramosetron is 9.67 vz 8.39 for ondansetron, 8.9 for granisetron and 7.6 for dolasetron).[10,,20] Despite the high costs associated with prophylaxis against CINV, the direct cost of care was higher for patients who did not receive adequate CINV prophylaxis. Indirect costs related to lost work hours were also higher for patients with uncontrolled CINV.[21]In our study, we could not make out gender differences as far as safety & efficacy of both the drugs were concerned.

The sample size in the current study was 60 (for both ramosetron & ondansetron) which was less. Hence future studies should be planned with more number of patients considering the limitations in the present study.

Conclusion: Ramosetron and ondansetron in single, fixed, doses of 0.3 mg and 16 mg respectively, are equally effective antiemetic agents in the prevention of cancer chemotherapy induced nausea and vomiting (CINV) in patients undergoing cisplatin chemotherapy in acute phase (0-24 hrs) of CINV. Ramosetron in the dose of 0.3 mg came out to be significantly more effective antiemetic agent in the prevention of delayed phase (24-120 hrs) and overall phase of CINV(0-120 hrs).There was no significant difference in complete control rate between the ramosetron & ondansetron group .

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