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Comparison of Clinical Efficacy and Safety of Ramosetron with Ondansetron for the Prevention of Postoperative Nausea and Vomiting in Patients Undergoing Surgery Under Spinal Anesthesia

KEYWORDS: PONV; Ramosetron; Ondansetron; Spinal anesthesia

DR Pankaja R MD	DR AnilKumar M R MD	DR N S ShashiKumar MD
Department of pharmacology, Mandya institute of medical sciences, Mandya.Karnataka	Assistant Professor, Department of Anaesthesiology and critical care, JSS Medical College, JSS University, Mysuru.Karnataka	Associate Professor, Department of Pharmacology, Mandya institute of medical sciences, Mandya.Karnataka.

ABSTRACT ***Background and Objectives of the Study*** *Nausea and vomiting are the most common distressing symptom in the post operative period. This study was undertaken to evaluate the clinical efficacy and safety of prophylactic use of intravenous Ramosetron 0.3mg with intravenous Ondansetron 4mg in preventing Post Operative Nausea and Vomiting (PONV) after surgery under Spinal anesthesia and to determine the incidence of adverse effects with Ramosetron and Ondansetron.*

Materials and Methods: *In this randomized, open-label study, 80 patients (age, 18-60 years) of ASA I-II, received intravenous Ramosetron 0.3mg or Ondansetron 4mg (n = 40 of each) immediately before induction of anesthesia. Postoperatively the incidences of nausea, vomiting, retching and safety assessments were performed at 0, 2, 6, 24 and 48hour during the first 48hour after surgery.*

Results: *The percentage of patients who had complete response was 80% (32/40) with Ramosetron and 37.5% (15/40) with Ondansetron (P < 0.001). The proportion of patients requiring rescue antiemetics was significantly lower with Ramosetron (5%) when compared with the Ondansetron group (15%) during the 48 hr after surgery (P<0.05). There was no significant difference in the incidence of side effects between the two groups.*

Conclusion*: Ramosetron (0.3mg) was more effective than Ondansetron (4mg) in preventing PONV in patients undergoing surgery under Spinal anesthesia.*

INTRODUCTION

Postoperative nausea and vomiting (PONV) is one of the most unpleasant and distressing symptoms which follow anesthesia and surgery. Many patients state that PONV is an undesirable postoperative outcome with a higher priority than incisional pain.(1) Postoperative nausea and vomiting, defined as nausea and/or vomiting occurring within 24 hours after surgery, affects between 20% and 30% of patients, as many as 70% to 80% of patients at high risk may be affected(2).

Until recently, PONV was considered a relatively unimportant postoperative complication, but the growing emphasis on day-care surgery has focused attention on complications. Hence, prophylactic antiemetic therapy is needed for all these patients (3). In spite of plenty of anti-emetic drugs available no single drug is 100% effective in prevention of PONV and combination therapy has got a lot of side effects (4, 5).

Ondansetron was the first 5-HT3 receptor antagonist to become clinically available for the treatment and prevention of PONV. However, Ondansetron is less selective for the 5-HT3 receptor compared with the other 5-HT3 antagonists. It binds to 5HT1B, 5HT1C, α-adrenergic and opioid receptors with low affinity. Systematic reviews have revealed that Ondansetron's prophylactic effect on vomiting is good, but the effect on preventing nausea is less pronounced (6).

Ramosetron is a newly developed 5-HT3 receptor antagonist with a higher affinity and longer duration of action compared with other 5-HT3 receptor antagonists.

OBJECTIVES OF THE STUDY

1. To evaluate the clinical efficacy and safety of prophylactic use of intravenous Ramosetron 0.3mg with intravenous Ondansetron 4mg in preventing Post Operative Nausea and Vomiting (PONV) after surgery under spinal anesthesia.
2. To determine the incidence of adverse effects with Ramosetron and Ondansetron.

METHODOLOGY

Method of collection of Data:

After obtaining Institutional Ethical Committee approval and patients written, informed consent, a Prospective Randomized Open Labeled Active Controlled Parallel Group Clinical Study was conducted in 80 ASA physical status I and II patients in the age group of 18 to 60 years who were scheduled for surgery under spinal anesthesia.

Inclusion criteria: All adult patients of both sexes between age group 18 to 60 years who fulfil American Society of Anesthesiologists (ASA) grade I and II were included.

Exclusion criteria: Subjects with known history of allergy to the study drugs, Subjects who fall under ASA grade III and IV, H/o Motion sickness or PONV, Administration of antiemetics or steroids or psychoactive medications within 48 h before the operation were excluded.

Standard anaesthesia technique was followed throughout the study. Two to three minutes before induction of anesthesia, patients were randomly allocated to two groups to receive the study drugs intravenously: IV Ondansetron 4 mg (Group 1) or IV Ramosetron 0.3 mg (Group 2).

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Postoperative vital score (PVS): Heart rate, noninvasive blood pressure and respiratory rate were considered as the measures of postoperative vitals. Scores were allotted 2 - When all the three parameters were within 20% of the preoperative value, 1 - If any one or more of the three parameters ranged between 20-40% of the preoperative value, 0 - If atleast one of the three parameters was more than 40% of preoperative value.

Numeric rating scale used for scoring PONV was as follows: Grade 0: No nausea / vomiting, Grade 1: Nausea only, Grade 2: Vomiting once, Grade 3: Vomiting more than once in the postoperative ward. Blood pressure, pulse rate, respiratory rate and urine output were monitored for 48 hours. Patients were assessed for incidence of nausea, retching, vomiting and side–effects at 0, 2, 6, 24, 48 hr postoperatively.

Efficacy assessment: Complete response is defined as the absence of nausea, retching or vomiting and no need for rescue antiemetic during the 48-hour observation period. Rescue antiemetic Inj. Metoclopramide 10 mg IV was given in the event of two or more episodes of vomiting.

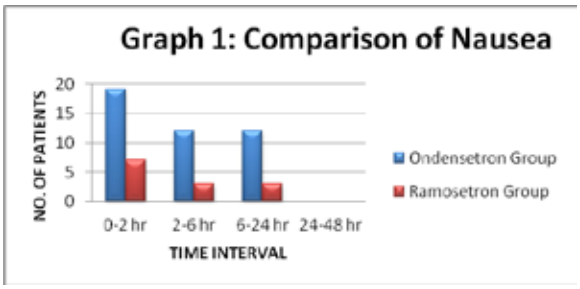
Nausea is defined as a subjectively unpleasant sensation associated with awareness of the urge to vomit. Severity of nausea was graded as 0, 1, 2 and 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe). Intensity of nausea was assessed at 0, 2, 6, 24 and 48th hours period by verbal rating scale (VRS)

An emetic episode is defined as forceful expulsion of gastrointestinal contents through the mouth. Repeated vomiting within 1 to 2 minutes period is recorded as single episode .it is scored as Complete control when No emesis, Partial control for 1 Episode, Failure if More than 1 episode or receipt of rescue antiemetic.

Safety evaluation: Evaluation for adverse reactions like Headache, Sedation, Dizziness, Diarrhea was monitored for 48 hour post operatively.

Statistical analysis:
Continuous data, expressed as the mean ± SD, were compared using the 'Z' test. For qualitative data, X2 (Chi-square) test was applied. The level of significance was taken as $P > 0.05$ - not significant, $P < 0.05$ – significant, and $P < 0.01$ – highly significant.

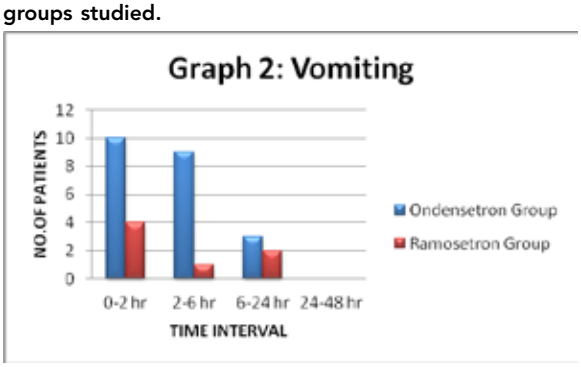
RESULTS:
There was no significant difference between the two groups with regard to age, gender, duration of surgery, type of surgery, the ASA status and level of block. All the study subjects in both the groups had a post-operative vital score of 2 which indicates that all the three parameters (Heart rate, non-invasive blood pressure and respiratory rate) were within 20% of the preoperative value.



Graph 1 Comparison of nausea grading among 2 study groups

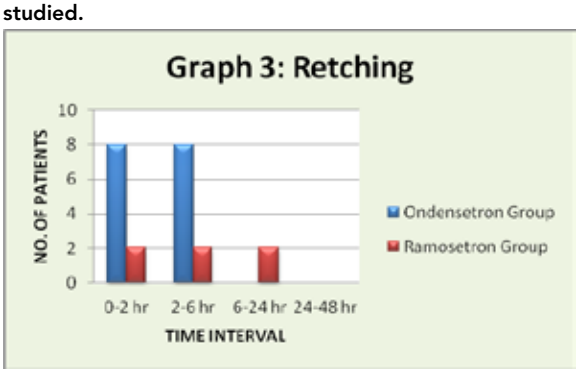
The nausea grading was significantly low in the Ramosetron group compared to Ondansetron group at 0-2, 2-6 and 6-24 hr (graph 1).

Graph 2 Comparison of episodes of vomiting among 2 groups studied.



90% of the patients in Ramosetron group did not experience vomiting in the time interval of 0-2 hr post operatively when compared to 75% of the patients in Ondansetron group. Also there was a significant reduction of vomiting in the Ramosetron group between 2-6 hr postoperatively compared to Ondansetron group.(graph 2).

Graph 3 Comparison of retching among 2 groups studied.



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There was a significant reduction in incidence of retching in Ramosetron group compared to Ondansetron group between 0-2 hr and 2-6 hr postoperatively (graph 3).

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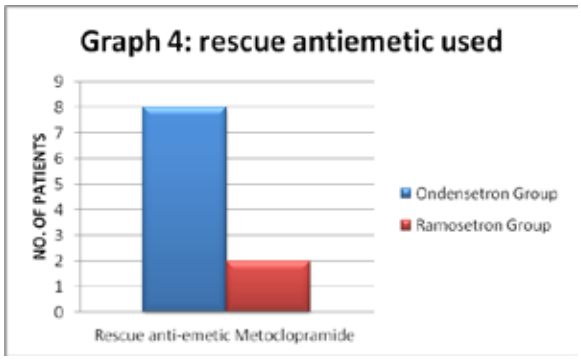
Graph 4: Rescue anti-emetic used for the study subjects



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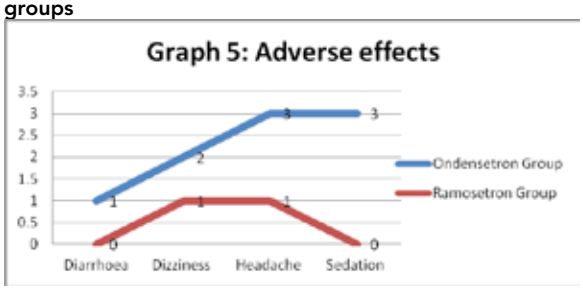
The proportion of patients requiring rescue antiemetics was significantly lower with Ramosetron (5%) when compared with the Ondansetron group (15%) during the 48 h after surgery (P<0.05)(graph 4).

Graph 5: Comparison of adverse effects among 2 study groups



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The frequency of adverse effects was not statistically significant between the two groups. In Group I one patient complained of diarrhoea, two patients complained of dizziness, three patients had headache and three patients complained of sedation. In group II one patient had dizziness, one had headache (graph 5). All the patients in the Ondansetron group had moderate pain following surgery while in the Ramosetron group two patients had mild pain and thirty eight patients had moderate pain following surgery. There was no statistically significant difference between the two groups with regard to severity of pain.

Table 1 Comparison of overall efficacy of the drugs among 2 study groups

Overall Efficacy of the Drugs	Ondensetron Group (n=40)		Ramosetron Group (n=40)	
Complete Response	15	37.5	32	80.0
Nausea	11	27.5	3	7.5
Vomiting	8	20.0	3	7.5
Anti-emetics	6	15.0	2	5.0
P Value = 0.002				

In comparing the overall efficacy of the drugs among the two groups, Ramosetron showed statistically significant efficacy (P < 0.05). In the Ondansetron group eleven patients complained of nausea, eight patients had vomiting and six patients required rescue antiemetic. In the Ramosetron group three patients complained of nausea, three patients had vomiting and two patients required rescue antiemetics(table 1). Complete response was very significantly higher in the Ramosetron group (80%) when compared to Ondansetron group (37.5%).

DISCUSSION

The most common and distressing symptoms, which follow anesthesia and surgery, are pain and emesis. PONV has been characterized as big 'little problem and has been a common complication for both inpatients and outpatients undergoing virtually all types of surgical procedures (4). It is often associated with increased morbidity of postoperative bleeding, wound dehiscence, pulmonary aspiration of gastric contents, fluid and electrolyte imbalance, dehydration, delayed hospital discharge, unexpected hospital admission, and decreased satisfaction in surgical patients. PONV without prophylaxis is a serious and common cause of significant problems (7).

Most research on the 5-HT3 receptor antagonists has been on Ondansetron, and its antiemetic efficacy has been well established in chemotherapy-induced emesis and the prevention and treatment of PONV (8). Ramosetron is a recently developed selective 5-HT3 receptor antagonist. It exhibits significantly greater binding affinity for 5-HT3 receptors with a slower dissociation rate from receptor binding, resulting in more potent and longer receptor antagonizing effects compared with older 5-HT3 receptor antagonists (8).

In our study all the factors were well balanced between the two groups, all patients underwent the same preoperative fasting, premedication and same standardized balanced anesthesia and postoperative care. The groups were similar with respect to age, weight, duration of surgery, type of surgery and postoperative analgesia.

Tachycardia and hypertension are the reflection of pain which in turn can influence the incidence of emesis in early post operative period. In our study scoring system was used to quantify the haemodynamic changes during surgery and in postoperative period. There was no difference in haemodynamic changes between the two groups as compared to the preoperative value, both during intraoperative and postoperative period. The postoperative pain scores and requirement of analgesic were essentially comparable without any significant difference between the groups.

In a study conducted by Lee JW et al, there were no significant differences in complete response, incidence of nausea/vomiting and rescue anti-emetic during < 2 h and 2-24 h postoperatively. A complete response 24-48 h after surgery was significantly higher in the Ramosetron group (98.3%) compared with the Ondansetron group (86.7%). There was no difference in the use of rescue anti-emetics during postoperative 24-48 h (6).

Hahm TS et al compared the prophylactic anti-emetic efficacy of Ramosetron and Ondansetron in patients at high-risk for PONV after total knee replacement. There were no differences between the groups in the first 2 h after surgery. More patients in the Ramosetron group had a complete response between 2 and 48 h compared with the Ondansetron group (9).

In our study complete response after surgery was significantly higher in the Ramosetron group (80%) compared with the Ondansetron group (37.5%). Only 7.5% of pa-

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tients in Ramosetron group had vomiting, compared to 20% of Ondansetron group. Incidence of vomiting was significantly low at 2-6 hour in the Ramosetron group compared to Ondansetron group. Requirement of rescue antiemetic in the Ramosetron group (5%) was significantly low (P=0.042) than the Ondansetron group (15%). The incidence of retching was less in Ramosetron group than Ondansetron group. 95% of patients experienced no retching in Ramosetron group while it was 80% in Ondansetron group. This observation was significant at 0-2 hour (P=0.043) and 2-6 hour (P=0.042). 'No nausea' in Ramosetron group was 82.5% as compared to 52.5% in Ondansetron group. The incidence of nausea was significantly less in the Ramosetron group compared with Ondansetron group at 0-2 hr (P=0.012), 2-6 hr (P=0.023) and at 6-24 hr (P=0.035).

Kim SI et al conducted a study on 162 patients undergoing gynaecological operation and concluded that there were no statistically significant differences in the incidence of adverse events between Ramosetron, Ondansetron and placebo. The most frequently reported adverse events were dizziness and headache (8). There was no significant difference in the side effects between the two groups in our study.

Thus, Ramosetron was more effective in decreasing the PONV in patients undergoing surgery under spinal anesthesia as compared to Ondansetron with low side effect profile.

CONCLUSION

IV. Ramosetron 0.3mg, administered immediately before induction, significantly decreased the incidence and severity of nausea, retching and vomiting, and the need for rescue antiemetic therapy compared with IV. Ondansetron 4mg. There was no significant difference in haemodynamic changes (heart rate, blood pressure, and respiratory rate), and incidence of side effects between the two groups. No serious complications were observed in either group. Prophylactic therapy with Ramosetron is more effective and safe than Ondansetron in preventing PONV in patients undergoing surgery under Spinal anesthesia.

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