A randomized clinical trial comparing the efficacy and safety of ramosetron versus ondansetron in patients undergoing abdominal surgery under general anesthesia

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ABSTRACT

Background: Post-operative nausea and vomiting is one of the most common and distressing complications after anesthesia and surgery. It may lead to serious post-operative complications. Ramosetron is a newer 5-HT3 receptor antagonist and has more potent and longer duration of antiemetic effects compared to first generation 5HT3 receptor antagonists. The purpose of this study was to compare the efficacy of Ramosetron for the prevention of post-operative nausea and vomiting with that of Ondansetron in patients undergoing abdominal surgeries under general anesthesia. **Methods:** In this randomized, double-blind study, 60 patients, 18-60 years of both genders falling under ASA I-II category scheduled for abdominal surgery were included. Group I received I.V ramosetron 0.3 mg while group II received I.V Ondansetron 4 mg at the time of extubation. The standard general anesthetic technique was used throughout. Postoperatively the incidences of nausea, vomiting, and safety assessments were performed at 1, 2, 6, and 24 h during the first 24 h after surgery. **Results:** There were no differences between groups with respect to patient demographics. The percentage of patients who had complete response (no PONV, and no need for another rescue antiemetic) from 0 to 24 h after anesthesia was 56% with ramosetron and 33% with ondansetron. The corresponding rates at 1, 2, 6, and 24 h after anesthesia were 76% and 63%, 76% and 50%, 100 and 83%, 100 and 93%, respectively. Safety profiles of the two drugs were comparable, as no clinically serious adverse effects caused by study drugs were observed in either of the groups. **Conclusion:** Our study concludes that prophylactic therapy with ramosetron is highly efficacious than ondansetron in preventing PONV in patients undergoing abdominal surgery under general anesthesia.

Key words: *General anesthesia, ondansetron, postoperative nausea, post-operative vomiting, ramosetron*

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INTRODUCTION

Postoperative nausea and vomiting (PONV) is one of the most unpleasant and distressing symptom associated with anesthesia and surgery.[1]

The overall incidence of emetic sequelae after a balanced anesthesia remains between 20 and 30%, approaching 70% in patients in certain high risk categories.[2] With the change in emphasis from an inpatient to outpatient hospital care there has been increased interest in the "big little problem" of PONV.[3] PONV is a continuing concern in surgical patients and the management of this problem is still confusing.[4] Patients often perceive PONV as one of the most bothersome peri-operative complication and may consider it as distressing as the pain associated with the surgical procedure.[5] Development of effective antiemetic therapy has been hampered by the multifactorial nature of PONV.[6] Of the many different modes of intervention to prevent PONV, antiemetic drugs play an important role in therapy of PONV. Metoclopramide, domperidone, phenothiazines, butyrophenones, anticholinergics, and antihistamines are the commonly used drugs to prevent PONV. Presently, there is no single PONV antiemetic medication or

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technique that is 100% effective for all patients[3] and a search for better drug continues.

The management of nausea and vomiting has improved greatly in recent years, with the introduction of 5-Hydroxytryptamine (5-HT_3) – receptor antagonists, which are widely regarded as most efficacious antiemetics available today and are currently recommended as the agents of first choice to control nausea and vomiting in most instances.[7] Ramosetron is a potent and selective 5-hydroxytryptermine (5-HT_3) receptor antagonist indicated for the prevention and treatment of nausea and vomiting, associated with cytotoxic chemotherapy and radiotherapy, and post-operative vomiting.[8] Ondansetron is also a serotonin 5-HT_3 receptor antagonist. It reduces the activity of the vagus nerve, which deactivates the vomiting center in the medulla oblongata, and also blocks serotonin receptors in the chemoreceptor trigger zone.[9]

The present study aims to compare the efficacy and safety of prophylactic ondansetron and ramosetron on the incidence of post-operative nausea and vomiting in patients undergoing elective/emergency abdominal surgery under general anesthesia and to assess the requirement of rescue anti emetics in the post-operative period.

METHODS

After obtaining institutional ethics committee approval and written informed consent, the present study was conducted in 60 ASA physical status I and II hospitalized patients in the age group of 18 to 60 years who were scheduled for major abdominal surgeries under general anesthesia during the period January 2011 to June 2012. Patients having gastrointestinal (GI) diseases, such as hiatus hernia, gastroesophageal regurgitation disorder, peptic ulcer disease, and autonomic dysfunction disorder were excluded from the study also excluded were pregnant, lactating women, patients with renal, hepatic, neurological impairment, patients who had received any antiemetic medication within 24 h prior to surgery, patients with history of motion sickness, PONV in previous surgery, history of vomiting, and or Ryle's tube *in situ* in the last 24 h.

Subjects were randomized to the two groups by using random number tables. Group I received ramosetron 0.3 mg IV and Group II received ondansetron 4 mg IV before extubation.

Sample size of 54 was calculated by nMaster software which was estimated to give 80% power to the study with a α error of 5%, *P*-value of <0.05 was considered significant. Considering 10% as the dropout rate, 60 patients were recruited for the study.

Preoperative visit was conducted one day before surgery. Detailed history of patient's complaints was noted. General and systemic examination of cardiovascular and respiratory systems was done.

Basic laboratory investigations, hemoglobin level, total count and differential count, urine routine, and screening of chest X-ray, ECG, blood urea, and serum creatinine were evaluated prior to surgery. Patients were advised to remain nil orally for 8 h.

Anesthesia

All patients were premedicated with ranitidine 50 mg I.V 2 h before the procedure and glycopyrollate 5 mcg/kg. General anesthesia (GA) was induced with propofol (2 mg/kg), intubated with succinyl choline (2 mg/kg), with endotracheal tube of size (7.0/7.5/8.0/8.5). Maintained with fentanyl (2 mcg/kg) and atracurium loading dose of (0.5 mg/kg) and maintenance dose of (0.1 mg/kg), N_2O:O_2:5:3 and inhalational agents. At the end of the surgery after thorough oral suctioning, reversal was done with neostigmine (0.05 mg/kg) glycopyrollate (10 mcg/kg) and before extubating Ramosetron (0.3 mg i.v) was given in group-I and ondansetron (4 mg i.v) in group-II patients and then extubated.

Heart rate, blood pressure, oxygen saturation, and respiratory rate were monitored intraoperatively and postoperatively at 1, 2, 6, and 24 h. Postoperative analgesia was provided with diclofenac sodium 75 mg intramuscularly for mild pain and repeated every 8 h if mild pain persisted; tramadol 100 mg in 100 ml of normal saline by slow i.v infusion for moderate to severe pain and repeated every 8 h if moderate pain persisted.

Nausea was defined as a subjectively unpleasant sensation associated with awareness of the urge to vomit. It was graded as 0, 1, 2, 3 indicating none, mild, moderate, and severe, respectively, which was assessed retrospectively by verbal rating scale (VRS).

An emetic episode was defined as forceful expulsion of GI contents through the mouth. Repeated vomiting within 1 -2 min period was recorded as a single episode. No emesis was taken as complete control, 1 episode as Partial control, >1 episode or receipt of rescue antiemetic as failure of prophylaxis.

PONV numerical score of Grade 0 indicated no nausea/vomiting, Grade 1 as nausea only, Grade 2 as vomiting once, and Grade 3 as vomiting more than once. Complete response (CR) was defined as no nausea, vomiting, and no need for rescue antiemetic. Ramosetron 0.3 mg i.v. was given as rescue antiemetic in case of vomiting episode

more than once and in moderate-severe nausea in both groups. Patients were assessed for incidence of nausea, vomiting, and other side effects at 1, 2, 6, and 24 h postoperatively.

Simplified risk score from Apfel *et al.*[10] was used to predict the risk for PONV. The points given were females = 1, non-smoker = 1, history of PONV/motion sickness, postoperative opioids, total ranging from 0 to 4. When the score was 0,1,2,3, or 4 the risk of PONV was 10, 21, 39, 61, and 79%, respectively.

Statistical analysis

All the observations and particulars of each patient were recorded in a performa. The comparison of data among the two groups was performed using two tailed *t*-test and "Z" scores were obtained. $P < 0.05$ was taken as significant and $P < 0.01$ as highly significant. All values were expressed as means with standard deviation (SD).

RESULTS

Sixty patients were recruited and randomized to the two groups with 30 subjects in each. Mean age in group I and group II was 43.2 years and 42.7 years, respectively. Mean weight of patients in group – I was 48.3 and in group – II it was 48.67. Mean duration of surgery in Group I was 88.67 min and in group II it was 87.67 min. Most common surgeries encountered during the study period in both groups were laparotomy followed by cholecystectomy and abdominal hysterectomy.

Incidence of emesis was significantly more at 1st hour in group I and in 1st and 2nd hour in group II [Figure 1].

A complete control during the first 24 after anesthesia occurred in 90 and 70% of Group I and Group II patients, respectively ($P < 0.05$). Incidence of emesis was highly significant in Group II compared to Group I ($P < 0.01$). Failure was more in Group II than Group I ($P < 0.05$) [Figure 2].

Incidence of nausea was more at 1st, 2nd h in both the groups. Mean episode was not significant statistically at different time intervals [Figure 3].

There was highly significant reduction in severity of nausea in group I compared to group II. A total of 67% of group I patients did not experience nausea, while in group II this was 33%. When major nausea episodes were considered (score of 2 or more), significantly less number of patients in group I had major nausea (13 *vs.* 43%) [Figure 4].

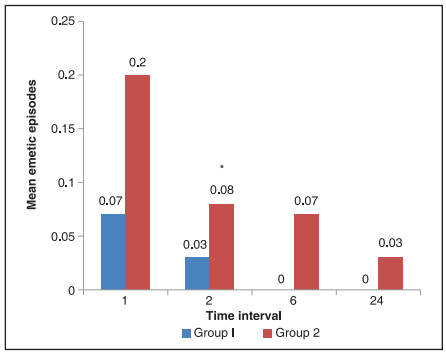

Figure 1: Incidence of Emesis *$P < 0.05$, **$P < 0.01$

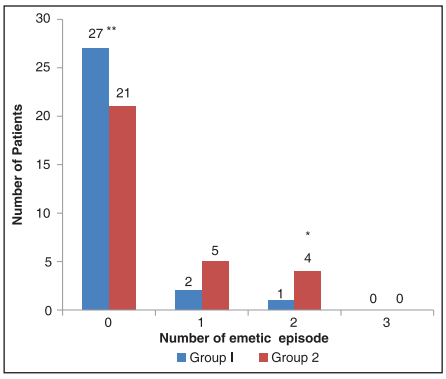

Figure 2: Complete Response Rate

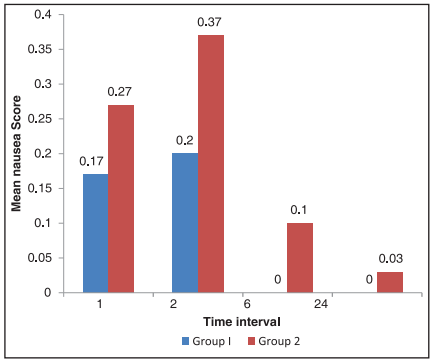

Figure 3: Incidence of nausea *$P < 0.05$

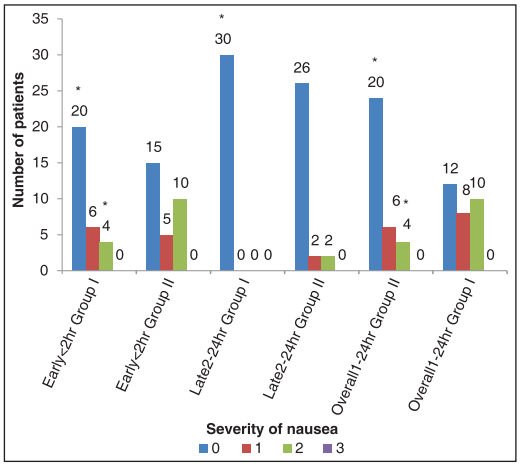

Figure 4: Severity of nausea

Percentage of patients requiring rescue antiemetic at 0-1 h was 3 and 16%. Percentage of patients requiring rescue antiemetic at 1-2 h was 10 and 20%. Frequency of nausea and vomiting was low after 2 h in both the groups. Observation of PONV score at 2-6 h was significantly different among the groups. Postoperative analgesic requirements were not significantly different at any point of time among the two treatment groups [Table 1].

Overall adverse effects were not significant statistically between the groups. In Group I three patients complained of headache and two complained of dizziness. In group II two patients had headache, three had dizziness [Table 2].

DISCUSSION

Post-operative emesis leads to dehydration, electrolyte imbalances, venous hypertension, bleeding, hematoma formation, suture dehiscence, oesophageal rupture, aspiration pneumonitis, delayed post-anesthesia care unit (PACU) discharge, and unanticipated hospital admission, leading to increased health care costs.[2]

In our study, the various confounding factors such as age, gender, obesity, gastroparesis, anxiety, history of motion sickness and PONV, type and duration of surgery, post-op analgesia were well balanced between the two groups. All patients underwent preoperative 8 h fasting, premedication, standardized balanced anesthesia, and postoperative care.

Sinclair *et al.* reported that the incidence of PONV decreased after the age of 50 years and age decreased the likelihood of PONV by 12% for each 10 years increase.[11] Average age in our study was 43.2 in group I and 42.17 years in group II. Incidence of PONV was more in younger patients in both groups. Studies have also taken into consideration about the duration of surgery and anesthesia having an effect on PONV.[12] Similar observations were made in our study which showed increased incidence of nausea and vomiting with the increase in the duration of surgery. There was no difference in hemodynamic changes between the two groups as compared to 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. The study done by Fujii *et al.* on 120 women undergoing gynaecological surgeries concluded that ramosetron was more effective than ondansetron in preventing post-operative nausea and vomiting.[13] Suh *et al.* concluded that prophylactic therapy with ramosetron is effective and severity of post-operative nausea and vomiting was less compared to ondansetron in early post-operative period.[14]

In our study, grade 0 nausea was observed in 40 and 66% subjects in group I and group II, respectively. Postoperative nausea scores were lower in the ramosetron group than the ondansetron group at all the times till 24 h but the scores did not achieve statistical significance. There was no significant difference in the incidence of nausea between

Table 1: Postoperative analgesics, PONV, and rescue antiemetic

Postoperative period	0-1h		1-2 h		2-6 h		6-24 h	
	Group I	Group II	Group I	Group II	Group I	Group II	Group I	Group II
Postoperative analgesics used								
Diclofenac	23	24	00	00	24	23	24	23
Tramadol	07	06	—	—	—	—	—	—
PONV								
No nausea/vomiting	23	19	23	15	30	25	30	28
Nausea only	05	05	06	11	0	03	0	1
Vomiting once	02	06	00	04	0	02	0	1
Vomiting more than once	00	00	01	00	0	00	0	0
Rescue antiemetics used*	01	05	03	06	—	02	—	—

Table 2: Adverse effects

Postoperative period	0-1h		1-2 h		2-6 h		6-24 h	
	Group I	Group II	Group I	Group II	Group I	Group II	Group I	Group II
Headache	01	01	01	—	—	—	01	01
Dizziness	01	01	—	01	01	01	—	—
Drowsiness	—	—	—	01	—	—	—	—
EPS	—	—	—	—	—	—	—	—
Others	—	—	—	—	—	—	—	—
Total	02	02	01	02	01	01	01	01

the two groups both in early and late postoperative period. When the severity of nausea was compared between the two groups, they were found to be significantly less in ramosetron group than in ondansetron group. When major nausea episodes were considered (Score of 2 or more), significantly less number of patients in group I had major nausea (13% in group I and 40% in group II, $P < 0.05$).

In our study ,88% patients in group I were emesis free while in group II 72% patients experienced no emesis. The incidence of vomiting was more at 1st and 2nd h in both groups and it was less in group I at both time intervals. A total of 6% of patients in group I had vomiting as compared to 20% in group II. This difference was seen to be statistically highly significant ($P < 0.01$). Severity of vomiting was also found to be less in group I than in group II. One patient of group I had more than 1 emetic episode, while four patients of group II had this, which is highly significant statistically. A total of 33% of Group II patients had early emesis and only 10% had late emesis whereas in group I corresponding values were 10 and 0%, respectively. Difference in requirement of rescue antiemetic was statistically significant at 1 h (3% *vs.* 16%) and 2 h (10 *vs.* 20%) in group I and II, respectively.

CONCLUSION

Postoperative vomiting was significantly less with ramosetron group compared to ondansetron. Incidence of vomiting during first 2 h was significantly high in ondansetron group than in ramosetron group ($P < 0.01$). Incidence of major vomiting (>1 episode) was also significantly high in group II (13%) compared to group I (3%). Use of ramosetron led to better control of both early (<2 hour) and late (2-24 h) nausea. There was no significant difference in hemodynamic changes (heart rate, blood pressure, and respiratory rate), and incidence of side effects between the two groups (except for mild headache, dizziness, drowsiness). No serious adverse events were observed in either of the groups. We conclude that prophylactic therapy with ramosetron is highly efficacious and safe than ondansetron in preventing PONV in patients undergoing abdominal surgery with general anesthesia.

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