Clinical Investigation

Comparison of ramosetron with ondansetron for the prevention of post-operative nausea and vomiting in high-risk patients

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ABSTRACT

Background and Aims: Post-operative nausea and vomiting (PONV) has an 80% incidence in high-risk patients. This is despite the availability of several antiemetic drugs. Selective 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonists are considered first-line for prophylaxis, ondansetron being the most commonly used agent. Ramosetron, another selective 5-HT_3 receptor antagonist, is more potent and longer acting than ondansetron. This study was conducted to evaluate the antiemetic efficacy of ramosetron in comparison with ondansetron in patients at a high risk of PONV. **Methods:** This was a prospective randomised double-blind study carried out over a 6-month period in which 206 patients with at least two risk factors for PONV were randomised to receive ramosetron 0.3 mg or ondansetron 8 mg, 30 min before the end of surgery. The incidence of PONV, severity of nausea and need for rescue antiemetic were recorded over the next 24 h. Primary outcome was the incidence of PONV. Secondary outcomes included severity of nausea and need for rescue. The data were analysed using the Predictive Analytics Software (PASW, version 18: Chicago, IL, USA). **Results:** The incidence of PONV was found to be 35% in the ramosetron group as opposed to 43.7% in the ondansetron group ($P = 0.199$). Need for rescue antiemetic was 23.3% in the ramosetron group and 32% in the ondansetron group ($P = 0.156$) in the 24 h following surgery. **Conclusion:** Ramosetron 0.3 mg and ondansetron 8 mg were equally effective in reducing the incidence of PONV in high risk patients.

Key words: 5-hydroxytryptamine type 3, antiemetics, nausea, post-operative nausea and vomiting

INTRODUCTION

Post-operative nausea and vomiting (PONV) is a common complaint, with an incidence of up to 80% in high-risk patients.[1] This is despite the availability of several medications for prophylaxis and treatment of PONV. PONV is distressing and potentially detrimental to a patient's recovery as it can result in wound dehiscence, bleeding, aspiration of gastric contents, electrolyte imbalances, and delayed hospital discharge.[2] Multiple scoring systems to identify patients at risk have been developed such as Apfel's simplified score.[1] This scoring system includes four risk factors: Female sex, non-smoking status, history of PONV or motion sickness and post-operative opioid use.[1-4] The presence of none, one, two, three or all four risk factors is associated with a PONV incidence of 10%, 20%, 40%, 60% and 80%, respectively.[1] Presence of two or more risk factors pre-disposes the patient to a greater chance of PONV. Current consensus guidelines recommend prophylactic administration of an antiemetic to any patient with two or more risk factors.[5]

Selective serotonin [5 hydroxytryptamine type 3 (5 HT3)] receptor antagonists are considered first line in the prevention of PONV, due to their proven efficacy and favourable side-effect profile. Most research has been conducted on ondansetron, and its efficacy is well-established. Ramosetron is a selective 5-HT_3 antagonist. It exhibits a higher affinity for the receptors with a slower dissociation, resulting in a longer duration

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of action.[6-8] Few studies have compared the efficacy of ramosetron with ondansetron in the post-operative period. A recent meta-analysis by Mihara et al.[9] consisting of 6 well designed randomised controlled trials comparing 0.3 mg ramosetron with 4 mg ondansetron concluded that though ramosetron appeared as superior in preventing early and late post-operative vomiting, the clinical relevance was unclear since the number-needed-to-treat (NNT) was large.

We therefore designed a prospective, randomized, double-blind study to evaluate the antiemetic efficacy of ramosetron compared with ondansetron in high-risk patients.

METHODS

After Institutional Ethical Committee approval and an informed consent, 206 adult American Society of Anaesthesiologists (ASA) physical status I and II patients scheduled to undergo breast, parotid, thyroid or gynaecological surgeries, with at least two of the established risk factors, were recruited into the study over a 6-month period from April to September 2012. The risk factors taken for inclusion were female sex, non-smoking status, history of PONV or motion sickness and the perioperative use of opioids.[1] Pregnant or menstruating patients, those with a history of gastro-oesophageal reflux, those who had received antiemetic or suffered from nausea or vomiting in the 24 h preceding the scheduled operation and those undergoing major intra-abdominal, intra-thoracic, pelvic and reconstructive surgeries were excluded from the study.

The patients were randomised according to a computer generated random number table into two groups comprising 103 subjects each. One group received ramosetron 0.3 mg and the other received ondansetron 8 mg. The study drugs were drawn in identical syringes with 4ml volume each, labelled 'antiemetic'(ramosetron was diluted to 4 ml in normal saline) by a nurse who was not a part of the study and handed to the respective OT anaesthesiologist. The patient and investigators were blinded to the study medication.

A standardized anaesthesia regimen was followed. All patients received general anaesthesia and were induced with propofol (2 mg/kg). Vecuronium (0.1 mg/kg) intravenous (IV) was used to facilitate tracheal intubation. Anaesthesia was maintained with 0.5–2% isoflurane, 33% oxygen in nitrous oxide (N_2O). Intraoperative analgesia was provided with IV fentanyl (2–3 μg/kg) or morphine (0.1–0.2 mg/kg) and diclofenac (2 mg/kg) IV. At the end of surgery, residual neuromuscular block was reversed with neostigmine (0.05 mg/kg) and glycopyrrolate (0.01 mg/kg) IV. The study drug was administered IV 30 min before the end of surgery by the attending anaesthesiologist. Post-operative analgesia was provided with paracetamol or diclofenac.

The incidence of PONV, severity of nausea and need for rescue antiemetic were recorded over the next 24 h, which was divided into two intervals (early and late): 0–6 h and 6–24 h (h), respectively. An episode of vomiting was defined as either vomiting (expulsion of stomach contents) or retching (an involuntary attempt to vomit but not productive of stomach contents). Nausea was defined as the desire to vomit.

Patients were asked to rate the severity of nausea using a four-point scale[10] wherein, 0 = no nausea, 1 = mild, 2 = moderate and 3 = severe grade. Rescue medication for PONV (metoclopramide 10 mg IV) was administered on patient request or complaint of established nausea or vomiting. Patients were educated in the pre-operative period on how to request treatment if and when PONV occurred in the post-operative period.

The primary outcome measure was the incidence of PONV during the first 24 h; secondary outcome measures were severity of nausea and need for rescue medication.

The data were analysed using the Predictive Analytics Software (PASW, version 18: Chicago, IL, USA). Repeated measures ANOVA (with Bonferroni correction) was used to compare the continuous variables and Chi-square test or Fisher's exact test was used for comparing categorical variables. Values were considered significant when $P < 0.05$. A sample size of 206 subjects was estimated through PASS (NCSS; LLC) to achieve an 80% power to detect a 30% reduction in PONV between the groups.

RESULTS

A total of 206 patients with ASA physical status I or II were recruited into the study. 103 patients received ramosetron and 103 patients received ondansetron. The risk factors, duration of surgery and anaesthesia

and the dose of opioids received between two groups are as shown in Table 1. 68% (70/103) of the ramosetron group and 70.9% (73/103) of the ondansetron group had three risk factors.

The mean duration of surgery and anaesthesia and the intraoperative dose of fentanyl in both the groups were comparable. 19 (18.4%) patients in the ramosetron group and 20 (19.4%) patients in the ondansetron group also received morphine for perioperative analgesia after a 2 μg/kg dose of fentanyl at induction. These patients underwent surgery lasting >3 h and were therefore administered morphine for intraoperative analgesia as per the practice at the institution.

The overall incidence of PONV in the first 24 h was found to be 39.3%. In the ramosetron group, it was 35% as opposed to 43.7% in the ondansetron group ($P = 0.199$) [Figure 1]. There was no significant difference in the incidence of nausea between ramosetron and ondansetron groups (35% vs. 40.8%) ($P = 0.38$). The incidence of nausea in the first 6 h after surgery was higher than in the latter period in both groups [Table 2]. However, 15 patients (14.6%) from the ramosetron group and 13 patients (12.6%) from the ondansetron group had one episode of vomiting.

The incidence of PONV was lower (statistically insignificant) in the ramosetron group ($P = 0.199$) [Figure 1]. Rescue antiemetic requirement was similar in both groups; 23.3% and 32% in the ramosetron and ondansetron groups, respectively ($P = 0.156$). None in the ramosetron group required a rescue antiemetic in the 6–24 h period after surgery [Figure 2].

None of the patients suffered from severe nausea in either of the groups. No statistically significant difference was found in the nausea scores between the groups. Only 1 patient from the ondansetron group complained of moderate nausea in the 6–24 h time frame [Figure 3]. 22 (21.4%) patients in the ondansetron group had an episode of vomiting in comparison with 17 (16.5%) in the ramosetron group in the 24 h period ($P = 0.374$).

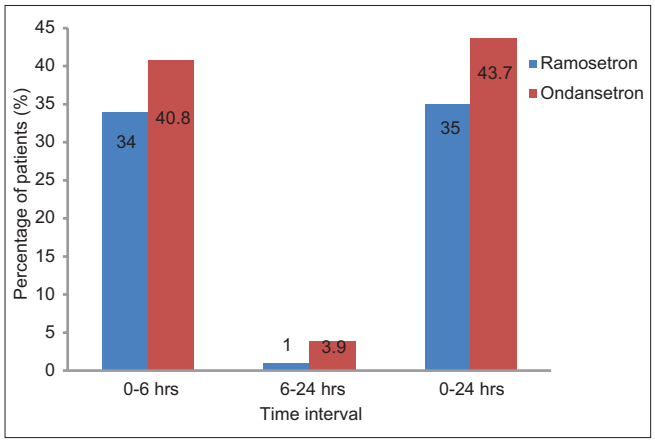

Figure 1: Incidence of post-operative nausea and vomiting

DISCUSSION

In this prospective, randomised, double-blind study comparing the antiemetic efficacy of ramosetron

Table 1: Demographics

Patient characteristics	*n*=103	
	Ramosetron	Ondansetron
Age in years	49.0 (±13.4)	47.3 (±13.8)
Sex		
Female	87 (84.5)	92 (89.3)
Duration of surgery in minutes	116.9 (±47.9)	116.5 (±50.3)
Duration of anaesthesia in minutes	140.0 (±54.6)	135.9 (±52.0)
Number of risk factors (%)		
2	31.1	26.2
3	68	70.9
4	1	2.9
Risk factors		
Female	87 (84.5)	92 (89.3)
Non-smoker	95 (92.2)	95 (92.2)
History of motion sickness or PONV	5 (4.9)	3 (2.9)
Perioperative opioids	91 (88.3)	96 (93.2)
Intraoperative fentanyl dose		
Fentanyl (μg)	162.6 (±47.3)	163.2 (±51.6)
Surgery (number of patients)		
Breast	34 (33)	38 (36.9)
Gynaecology	39 (37.9)	32 (31.1)
Thyroid	17 (16.5)	19 (18.4)
Parotid	6 (5.8)	2 (1.9)
TURBT	4 (3.9)	6 (5.8)
Neck dissection	3 (2.9)	6 (5.8)

Data are represented as mean (±SD) or number (%). SD – Standard deviation; PONV – Postoperative nausea and vomiting; TURBT – Transurethral resection of bladder tumour

Table 2: Incidence of nausea, retching, emesis and rescue

Incidence	*n*=103 each		*P*
	Ramosetron	Ondansetron	
Nausea			
0-6 h	36 (35)	40 (38.8)	0.564
6-24 h	1 (1.0)	4 (3.9)	0.174
Retching			
0-6 h	9 (8.7)	16 (15.5)	0.135
6-24 h	0 (0.0)	3 (2.9)	0.081
Emesis			
0-6 h	15 (14.6)	13 (12.6)	0.684
6-24 h	0 (0.0)	3 (2.9)	0.081
Rescue antiemetic			
0-6 h	24 (23.3)	30 (29.1)	0.342
6-24 h	0 (0.0)	3 (2.9)	0.246

Data represented as the number of patients (%)

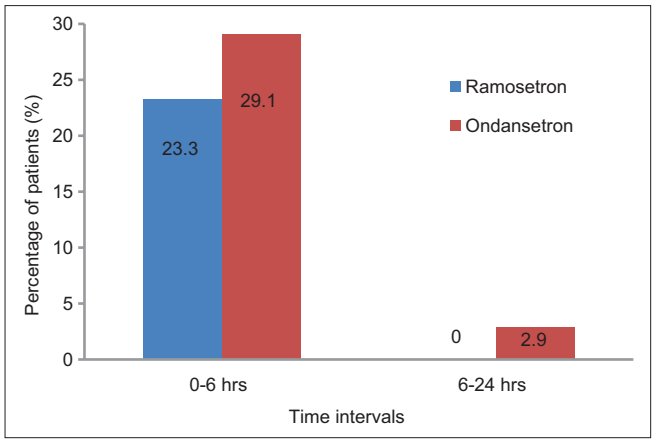

Figure 2: Rescue antiemetic requirement

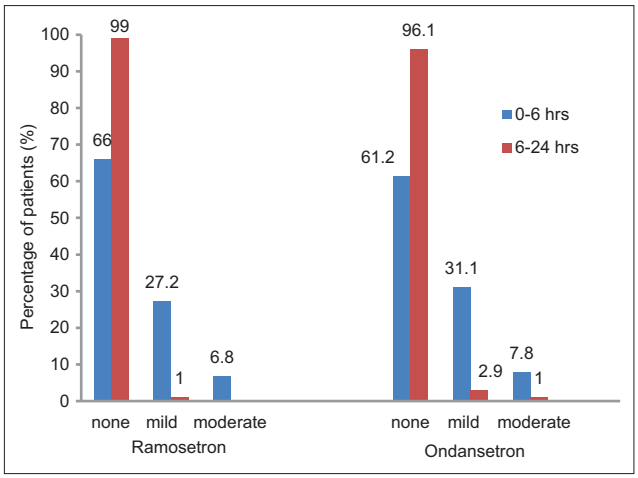

Figure 3: Severity of nausea

with ondansetron in patients at high risk of PONV, no significant difference was found in the incidence of PONV, severity of nausea and the need for rescue antiemetic between the two groups in the first 24 h following surgery. The incidence of PONV was obtained by combining the episodes of nausea, retching and emesis.

Ramosetron has been shown to be superior to other 5-HT_3 antagonists in previous studies.[11,12] However, a significant number of these studies appeared to be qualitatively poor[9,13,14] Mihara *et al.* conducted a meta-analysis after eliminating the controversial papers[9] and included only 12 well-designed studies of which six studies compared ramosetron with ondansetron. These six studies involved 637 patients, 317 receiving ramosetron and 320 patients who received ondansetron. The sample size was therefore relatively small. They further included only those studies in which ondansetron was used in a dose of 4 mg and concluded that, ramosetron was statistically better at preventing PONV in comparison with ondansetron though with unclear clinical relevance as the NNT was large. Ondansetron in doses of both 4 mg and 8 mg have been recommended for PONV. The meta-analysis by Tramèr *et al.* suggested 8 mg as the optimal dose of ondansetron.[15] At this dose, ondansetron has been found to be more effective even in patients with a previous history of PONV.[16] We therefore chose 8 mg as the prophylactic dose of ondansetron for those enrolled in this study. At this dose, ondansetron was found to be as effective as 0.3 mg of ramosetron in preventing PONV in high-risk patients. Ryu *et al.*[17] concluded that ramosetron 0.3 mg and ondansetron 8 mg were better than ondansetron 4 mg in reducing PONV following laparoscopic cholecystectomy. A similar study[18] in patients undergoing gynaecological surgery found ramosetron, 0.3 mg to be as effective as 8 mg ondansetron. Similarly, a study involving patients highly susceptible to PONV undergoing spine surgery and on a fentanyl patient-controlled analgesia (PCA) also found ramosetron prophylaxis to be as effective as ondansetron.[19] In a study[11] performed on highly susceptible patients undergoing abdominal hysterectomy, ramosetron (0.3 mg) was found to be more effective in preventing delayed PONV which is understandable considering the fact that it has an elimination half-life of 9 h which is much longer than that of ondansetron (3.5 h) with a higher affinity and a slower dissociation rate for 5-HT_3 receptors compared with other 5-HT_3 receptor antagonists.[20] This reported higher potency and longer duration of action, in comparison with other 5-HT_3 antagonists[7,21] might minimise the need for an additional rescue antiemetic in the first 24 h period after an operation.[18] However, in the present study, the effectiveness of ramosetron 0.3 mg and ondansetron 8 mg in the prevention of PONV and the need for a rescue antiemetic were similar in both the early (0–6 h) and late (6–24 h) periods. Though the need for a rescue antiemetic was lower in the ramosetron group in the 24-h period, it did not reach statistical significance. A few patients in the ondansetron group did have nausea in the 6–24 h period as opposed to just one patient in the ramosetron group. However, there was no statistically significant difference in the incidence or severity of nausea between the two groups in the 24 h period.

Despite the use of a prophylactic antiemetic and an anaesthetic agent propofol, known for its antiemetic properties, the overall incidence of PONV was 39.3%. This could be attributed to the fact that more female patients were part of the study, which is expected based

on the study design. The incidence of PONV is known to be higher in females.[1,3,5] It could be also attributed to the use of nitrous oxide (N_2O) for maintenance of anaesthesia as per regular practice at the hospital. N_2O is known for its emetogenic properties and omitting it would probably have been a better option.[22] However, according to a recent meta-analysis, the overall impact of N_2O on PONV is at best modest[23]; furthermore, propofol was found to negate the emetic effects of N_2O.

The incidence of PONV increases with the number of risk factors. We selected patients who had 2 or more risk factors for PONV using Apfel's simplified risk score,[1] a useful and simple tool for identification and stratification of patients at high risk for PONV. Of the 206 patients enrolled for the study, 59 (28.6%) had two risk factors, 143 (69.4%) had three while only 4 patients (1.9%) had four risk factors Current consensus guidelines[5] recommend the use of two or more antiemetics for a more effective control of PONV in patients with two or more risk factors, with 5-HT_3 antagonist and a second drug. In the present study, a single prophylaxis was used, and the addition of a second antiemetic such as dexamethasone would have probably reduced the incidence of PONV. Dexamethasone has been successfully used as an adjunct to 5-HT_3 antagonists, resulting in enhanced antiemetic efficacy with negligible side-effects.[24] Dexamethasone appears to be most effective when administered before the induction of anaesthesia.[25] However, in a recent study,[26] which compared ramosetron to ondansetron plus a single bolus of dexamethasone in high-risk patients undergoing spine surgery, the incidence of PONV was much higher than in the current study (50 and 60%, respectively). This high incidence could be attributed to the use of an opioid (fentanyl) PCA post-operatively.

Repeating the prophylactic or a similar class antiemetic in case of PONV within 6 h of surgery is considered futile.[5] Current consensus guidelines recommend the use of an agent belonging to a different class when prophylaxis fails[5]; we decided to use metoclopramide 10 mg as a rescue antiemetic. No significant adverse effects were noticed in either of the groups. In India, ramosetron is relatively more expensive than ondansetron. An ampoule of 0.3 mg ramosetron costs approximately Rs. 34.75 as opposed to Rs. 11.37 for an 8 mg ampoule of ondansetron (about 3 times less). Considering that there was no difference in the outcome on PONV with either of the drugs, the use of ramosetron would only add to the cost of treatment. The choice of the antiemetic agent should, therefore, be individualized with due consideration to the cost effectiveness and benefit to the patient.

There are a few limitations in the present study. Surgeries of 3-h duration or less were included; hence results may not be similar when extrapolated to surgeries of a much longer duration. Surgeries on the gut and those involving extensive bowel handling were excluded. The study also predominantly included female patients, which is expected based on the study design.

CONCLUSION

Ramosetron 0.3 mg and ondansetron 8 mg when used prophylactically, in a single dose in high-risk patients, were equally equally effective in reducing the incidence of PONV. There was no significant difference in the incidence of PONV, severity of nausea or the need for rescue antiemetic in either of the groups. Considering the cost difference with no added benefit to the patient, both in the current study as well as in the recent meta-analyses, there appears to be no great advantage to using ramosetron as a prophylaxis for PONV in place of ondansetron.

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