

RAMOSETRON: PREVENTION FOR POST OPERATIVE NAUSEA AND VOMITING AFTER LAPAROSCOPIC CHOLECYSTECTOMY- A PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND COMPARISION WITH ONDASETRON

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ABSTRACT: BACKGROUND: Postoperative nausea and vomiting (PONV) frequently hampers implementation of laparoscopic surgery in spite of so many antiemetic drugs and regimens. This study was to compare the efficacy of Ramosetron and Ondansetron in (PONV) after Laparoscopic Cholecystectomy. **MATERIALS & METHODS:** 124 adult patients of either sex, of ASA physical status I and II, scheduled for Laparoscopic Cholecystectomy operation, were randomly allocated into Group A (n=62) patients received IV Ondansetron 4mg and Group B (n=62) patients received IV Ramosetron (0.3 mg). Drug was administered prior to induction of GA. Episodes of PONV were compared between the groups at 4 hrs,4.5 hrs,5 hrs,5.5 hrs and 6 hrs post- operatively. **STATISTICAL ANALYSIS:** The raw data analyzed by SPSS[®] statistical package version 18.0 (SPSS Inc., Chicago, IL, USA). Numerical variables were compared by independent sample t test. Chi square test, Officers exact test and Fischer's exact test were used to compare categorical variables between groups. All analysis were two tailed and a P<0.05 was considered statistically significant **RESULTS:** Statistically significant difference between groups A and B (P <0.05), was found showing that Ramosetron was superior than Ondansetron in antiemetic efficacy and Ramosetron emerged as a better antiemetic than Ondansetron in 1st12 hrs post-operative period. The post-operative mean Visual Analogue Scale(VAS) scoring for the severity of PONV between the two study groups at 4 hrs and 6 hrs post operative period, revealed that there was statistically significant difference between the two groups , showing that severity of nausea was more in case of Ondansetron than Ramosetron. **CONCLUSION:** So, it was evident that single dose preoperative administration of IV Ramosetron (0.3 mg) has better efficacy than IV Ondansetron (4 mg) in reducing the episodes of PONV over 12 hours postoperative period in patients undergoing Laparoscopic Cholecystectomy under GA.

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INTRODUCTION: Postoperative nausea and vomiting (PONV), one of the most common and distressing adverse events experienced by patients after an anaesthesia and surgery [1,2], may prolong recovery, delay patient discharge, and increase hospital costs [1,2]. Prevention and treatment of PONV help to accelerate post-operative recovery and increase patient satisfaction [3, 4]. Post operative nausea and vomiting is common after Laparoscopic Cholecystectomy with a high incidence of 40-75% [5, 6]. S. Chatterjee et al (2011) mentioned [7] in a review article "High rate of PONV in laparoscopy may be caused by the gas used to "inflate" the abdomen to create work place for the instruments. This puts pressure on the vagus nerve, which has a connection to the brain's nausea and vomiting center." Other patients like gynaecological laparoscopy, ENT surgeries, Neurosurgery are the other surgeries which can induce risk for PONV. Numerous studies have investigated the prevention and treatment of PONV for patients scheduled to undergo Laparoscopic Cholecystectomy by a variety of antiemetics including anticholinergics [8, 9], antihistamines [10], phenothiazines [11], butyrophenones [12], and benzamide [6, 13]. However, these agents may cause undesirable adverse effects such as excessive sedation, hypotension, dry mouth, dysphoria, hallucinations, and extrapyramidal signs [14]. 5-HT₃ antagonists prevent serotonin from binding to 5-HT₃ receptors on the ends of the vagus nerve's afferent branches, which send signals directly to the vomiting center in the medulla oblongata and in the chemoreceptor trigger zone of the brain [15]. By preventing activation of these receptors, 5-HT₃ antagonists interrupt one of the pathways leading to vomiting [15]. . Ondansetron, the most commonly used prophylactic 5-HT₃ antagonist, was found to be more effective than traditional antiemetics, like droperidol and metoclopramide, in reducing the incidence of PONV [16, 17, 18]. Ramosetron, a new 5-HT₃ receptor antagonist, has higher potency and prolonged activity than previously developed 5-HT₃ antagonists as an antiemetic after chemotherapy [19, 20] or surgery [21,22,23] Laparoscopic Cholecystectomy is the commonest surgery in our institution that occur as planned surgery. So our effort is to eliminate this commonly occurring side effect of Laparoscopic cholecystectomy ie PONV. So we have tried it with most newly developed HT₃ antagonist (Ramosetron) and commonly used agent (Ondansetron). The aim and objective of this study was to compare the antiemetic efficacy of the two drugs in the 1st 12hours post-operative period. The severity of PONV was recorded using VAS with choice options ranging from 0 (no nausea) to 10 (worst possible nausea).

MATERIALS AND METHODS: After obtaining permission from institutional ethics committee, written informed consent was taken. Total 124 adult patients were randomly allocated to two equal groups (n = 62 in each group) using computer generated random number list. Group A comprised patients who received single dose IV Ondansetron (4 mg) and group B comprised those who received single dose IV Ramosetron (0.3mg) 5 min before induction.

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EXCLUSION CRITERIA: Patient refusal, any contraindication to any of the two drugs, history of allergy to any of the two drugs, pregnancy, lactating mothers and children (<13 yrs), subjects who vomited or received antiemetics within 24 hours before surgery, hepatic, renal or cardiac abnormality, alcoholism, diabetes, significant gastrointestinal disorders (e.g. peptic ulcer disease or gastro esophageal reflux disease) and motion sickness.

In preoperative assessment, patients were enquired about heartburn, belching, abdominal discomfort, history of motion sickness, any antiemetic treatment received, history of previous exposure to anaesthesia and history of PONV. The patients were enquired about any history of drug allergy, previous operations or prolonged drug treatment. General examination, Systemic examinations and Assessment of the airway were done. Preoperative fasting of minimum 6 hours was ensured before operation in all cases. All patients received premedication of tablet diazepam 5mg orally the night before surgery and in the morning of operation; 2hr before surgery; to allay anxiety, apprehension and for sound sleep. The patients also received tablet ranitidine 150 mg in the previous night and in the morning of operation. Pre-loading was done with 10 ml/kg body weight of Ringer lactate solution to compensate overnight fasting deficit. Group A patient received single dose IV Ondansetron (4 mg) and group B patients received single dose IV Ramosetron (0.3mg) 5 min before induction.

The patients were pre-oxygenated with 100% oxygen for a period of 5 minutes. Injection fentanyl (2µg/kg) and glycopyrrolate (0.01mg/kg) were given intravenously 3 minutes before induction of anaesthesia. All the patients were induced with IV injection of Thiopentone Sodium 2.5% (5mg/kg) titrated till the loss of eyelash reflex. After that, atracurium (0.5mg/kg) was given to facilitate laryngoscopy and intubation. Controlled ventilation was maintained with 33% oxygen in 67% nitrous oxide using Boyle's apparatus. Laryngoscopy, intubation and cuff inflation were completed within 15 seconds in all cases. Muscle relaxation was maintained with intermittent intravenous atracurium (0.2 mg/kg) as and when required. Intraoperatively, pulse rate, respiratory rate, arterial oxygen saturation, ECG, capnography, systolic and diastolic pressure, were monitored continuously. Ventilation was controlled manually and adjusted to maintain the end tidal partial pressure of CO₂ (ET_{CO₂}) between 35-45 mmHg. Maintenance and loss of fluid was compensated with Lactated Ringer's solution. Laparoscopic Cholecystectomy was performed under video guidance and involved four punctures of the abdomen and abdomen insufflated with CO₂ through a veress needle to a maximum intra-abdominal pressure of 15 mmHg. At the completion of surgery, residual neuromuscular blockade was antagonized at TOF ratio > 0.7 with neostigmine 0.05mg/kg and atropine 0.02mg/kg intravenously and patient was extubated in awake condition. All the patients received tramadol 2 mg/kg IV 20 minutes before the end of surgery. The patients were then sent to the post-operative recovery unit. Post operative analgesia was provided with (NSAIDS) injection diclofenac 50mg intramuscularly. All patients received moist oxygen supplementation (3 liter/min) for 4 hours and standard minimum monitoring standards were used. All the patients were on intravenous drip and did not have any oral fluid during the study period of 24 hours.

Throughout the 12 hours postoperative period, all the parameters were recorded first at 2 hrs and then every half hourly for 4 hrs and then at every 1 hourly up to 12 hrs post-operative period. All episodes of nausea, retching and vomiting were recorded by using score (vomiting=3, retching=2, nausea=1, none=0) of Bellville and co-workers (1959)⁽²⁴⁾ which was the primary assessment parameter. Severity of PONV was observed by VAS scoring (0 represent "no nausea" and 10

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represents “worst possible nausea”) at 2 hrs, 4 hrs, 6 hrs and 12 hrs post-operative period. The time to first administration of rescue antiemetic and the total dose of rescue antiemetic were also recorded. If the patient experienced emetic episodes or requested for treatment, rescue antiemetic was given with IV Metoclopramide (10mg).

STATISTICAL ANALYSIS: The raw data were entered into Microsoft excel spread sheet & analyzed by appropriate statistical software. Normally distributed numerical variables were compared between groups by independent sample t test. Chi square test, Officers exact test and Fischer’s exact test were used to compare categorical variables between groups. All analysis was two tailed and a $P < 0.05$ was considered statistically significant.

RESULTS AND ANALYSIS: There were no statistically significant differences between the two groups in terms of demographic characteristics of the patients namely age, sex and body weight, ASA status ,anaesthesia duration, surgery duration.(as shown in Table1).

TABLE 1: Comparison of demographic data between the two study groups

Parameter	Ondansetron(A)n=62	Ramosetron(B) n=62	p value
Age (years)	43.0323±11.0705	42.2258±11.0845	0.6860
Bodyweight (Kg)	56.0968 ± 3.17113	56.2097 ± 3.60845	0.8534
Sex	101.2903±0.4576	101.2097±0.4104	0.3036
Male	18(9.03%)	13(20.97%)	
Female	44(70.97%)	49(79.03%)	
ASA physical status (I/II)	40/22	37/25	0.59
Surgery time (min)	40 (20-99)	44 (24-85)	0.776
Anesthesia time (min)	47 (25-106)	50 (29-100)	0.547

During the 12 hours post-operative study period, the comparison of mean pulse rate, respiratory rate, systolic and diastolic blood pressure showed that there was no clinically significant difference between the groups.

Comparison of the post-operative mean PONV episodes in 1st 12hrs post-operative period between the two study groups at succeeding time intervals (as shown in Table 2) showed that at 4 hrs, 4.5 hrs, 5 hrs, 5.5 hrs and 6 hrs, there was statistically significant difference between the groups ($p < 0.05$), showing that Ramosetron is better than Ondansetron as an antiemetic. In case of total PONV episodes, there is significant statistical difference between the groups ($p < 0.05$), showing that Ramosetron is better than Ondansetron in case of antiemetic efficacy in 1st 12hrs post-operative period.

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TABLE 2: Comparing the post-operative mean PONV episodes (in 12 hrs post operative period) between the two study groups at succeeding time intervals.

Time	PONV (episodes)	Ondansetron (A)	Ramosetron (B)	p value
4hrs	Mean ± SD	0.161±0.578	0.00±0.00	0.0299
	Range	0 - 3	0 - 0	
4.5hrs	Mean ± SD	0.225±0.663	0.00±0.00	0.0083
	Range	0 - 3	0 - 0	
5hrs	Mean ± SD	0.145±0.507	0.00±0.00	0.0260
	Range	0 - 3	0 - 0	
5.5hrs	Mean ± SD	0.225±0.733	0.00±0.00	0.0168
	Range	0 - 3	0 - 0	
6hrs	Mean ± SD	0.096±0.348	0.00±0.00	0.0308
	Range	0 - 2	0 - 0	
Total episodes of PONV	Mean ± SD	1.177±1.769	0.612±1.310	0.0457
	Range	0 - 5	0 - 5	

Comparison of the post-operative mean VAS Scoring (in 12 hrs post-operative period) for the severity of PONV between the two study groups at succeeding time intervals (as shown in Table 3) showed that at 4 hrs and 6 hrs post operative period, there was statistically significant difference between groups A and B ($P < 0.05$), showing that severity of PONV is more in case of Ondansetron than Ramosetron.

TABLE 3: Comparing the post-operative mean VAS Scoring (in 12 hrs post operative period) for severity of PONV between the two study groups at succeeding time intervals.

Time	VAS Score	Ondansetron (A)	Ramosetron (B)	p value
4 hrs	Mean ± SD	0.709±1.702	0.00±0.00	0.001
	Range	0 - 8	0 - 0	
6 hrs	Mean ± SD	1.032±2.165	0.290±0.947	0.014
	Range	0 - 6	0 - 4	

Comparison of the rescue antiemetic (Metoclopramide 10 mg) use frequency between the study groups (as shown in Table 4), showed that the use of rescue antiemetic was comparatively less in case of Ramosetron(19.35%) than Ondansetron(32.26%), which was not statistically significant (Fisher's exact test 2-tailed p value 0.150).

TABLE 4 : Comparison of rescue antiemetic (Metoclopramide) use frequency between the study groups

Group	Metoclopramide not used	Metoclopramide used	Totals
Ondansetron (A)	42 (67.74%)	20 (32.26%)	62
Ramosetron (B)	50 (80.65%)	12 (19.35%)	62
Totals	92	42	124

Fisher's exact test 2-tailed p value 0.150.

DISCUSSION: The complex act of vomiting involves coordination of the respiratory, gastrointestinal, and abdominal musculature and is controlled by the emetic center. The area situated in the lateral reticular formation close to the tractus solitarius in the brain stem is thought to be the emetic center.^[1,2,25] Stimuli from several areas within the central nervous system can affect the emetic center.^[1] These include afferents from the pharynx, gastrointestinal tract and mediastinum, as well as afferents from the higher cortical centers (including the visual center and the vestibular portion of the eighth cranial nerve) and the chemoreceptor trigger zone (CTZ) in the area postrema. The area postrema of the brain is rich in dopamine, opioid, and serotonin or 5-hydroxytryptamine (5HT₃) receptors. Four major neuro transmitter systems appear to play important roles in mediating the emetic response viz. dopaminergic, histaminic (H1), cholinergic, muscarinic and 5HT₃.^[1] As there are four different types of receptors, there are at least four sites of action of the antiemetic drugs. Antiemetic agents may have actions at more than one receptor, but they tend to have a more prominent action at one or two receptors.^[1,25]

The 5-HT₃ receptor antagonists bind competitively to the 5-HT₃ receptor in the chemoreceptor trigger zone and gastrointestinal tract to inhibit emetic symptoms ^[26]. Preoperative anxiety is known to be related with the increase of emesis. α -adrenergic activation by catecholamine release is thought to be related ^[27] and excessive air swallowing due to anxiety may also contribute.

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 5HT_{1B}, 5HT_{1C}, α -adrenergic and opioid receptors with low affinity ^[26]. Systematic review revealed that ondansetron's prophylactic effect on vomiting is good, but the effect on preventing nausea is less pronounced ^[28]. 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 ^[29]. The elimination half-life of ramosetron (9.3 h) is longer than that of ondansetron (3.5 h), granisetron (4.9 h) and absetron (3.0 h) ^[26, 29]. Ramosetron has a higher affinity (K_i = 0.091) and slower dissociation rate for 5-HT₃ receptors compared with other 5-HT₃ receptor antagonists ^[30]. Also, the active metabolite M1 maintains high receptor occupancy and prolongs action duration. ^[29] Ayuhara et al. ^[31] reported that the occupancy of the 5-HT₃ receptor correlated with the clinical efficacy of 5-HT₃ receptor antagonists. Our study is based on ramosetron and ondansetron.

There were no statistically significant differences between the two groups in terms of demographic characteristics of the patients namely age, sex and body weight (Table 1). The study conducted by Fujii Y, et al (2003), ^[32] in a total of 100 patients yielded similar results.

The post-operative mean PONV episodes (in 12 hrs post-operative period) between the two study groups at succeeding time intervals showed statistically significant difference between the groups (P < 0.05), suggesting that Ramosetron is better than Ondansetron (Table 2). Similar study conducted by Ryu J et al (2009)^[33] in 120 patients scheduled for Laparoscopic Cholecystectomy, were randomized (in double blind fashion) to receive 4 mg of Ondansetron(group O4), 8 mg of Ondansetron(group O8) or 0.3 mg of Ramosetron (group R) iv after surgery. The results were assessed at 2 hrs, 24 hrs, and 48 hrs after surgery. They concluded that Ramosetron 0.3 mg was as effective as Ondansetron 8 mg for the prophylaxis of PONV after Laparoscopic -Cholecystectomy.

Choi YS, et al (2008) ^[34], compared the effect of Ramosetron with that of Ondansetron on opioid-based IV patient-controlled analgesia (PCA) related postoperative nausea and vomiting

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(PONV) in highly susceptible patients after lumbar spine surgery and found that moderate to severe degree of nausea was significantly more in the group Ondansetron (34%) than in the group Ramosetron (13%) 6 to 24 hours after surgery. Overall incidence of vomiting 6 to 24 hours after surgery was significantly lower in the group Ramosetron (30% vs. 11% respectively). They concluded that Ramosetron was superior to Ondansetron in terms of preventing vomiting. T. S. Hahm, et al (2010)^[35]. compared the prophylactic anti-emetic efficacy of Ramosetron and Ondansetron in patients at high-risk for postoperative nausea and vomiting after total knee replacement surgery and found that more patients in the Ramosetron group had a complete response (no postoperative nausea and vomiting and no rescue anti-emetic) between 2 and 48 h. The incidence of nausea between 2 and 24 h was also less in the Ramosetron group. They concluded that Ramosetron was more effective than Ondansetron in preventing postoperative nausea and vomiting.

The post-operative mean VAS Scoring (in 12 hrs post-operative period) between the two study groups at succeeding time intervals was compared which showed statistically significant difference between groups A and B ($p < 0.05$), (as revealed in Table 3) suggesting that severity PONV was more in case of Ondansetron than Ramosetron.

Similar study conducted by Choi YS, et al (2008),^[34] in 94 female nonsmoker patients (aged 18-65 years), randomly allocated into either Ondansetron group (group O, $n = 47$) or Ramosetron group (group R, $n = 47$) after lumbar spine surgery. They concluded that Ramosetron was superior to Ondansetron in terms of preventing vomiting and reducing the severity of nausea related to Fentanyl-based IV PCA. Kim Sl, et al (2009)^[36] studied the comparison of Ramosetron with Ondansetron for prevention of postoperative nausea and vomiting in patients undergoing gynaecological surgery. The incidence of nausea was lower in the Ramosetron (50%) and Ondansetron (44%) groups than placebo (69%) groups. Also, the incidence of vomiting was lower in both the Ramosetron (17%) and the Ondansetron (20%) groups than in the placebo group (44%) during the first 24 hrs after surgery ($P < 0.05$). The visual analogue scale score for nausea was also lower in the Ramosetron and Ondansetron groups compared with the placebo group. They concluded that Ramosetron 0.3 mg IV was as effective as Ondansetron 8 mg IV in decreasing the incidence of PONV and reducing nausea severity in female patients during the first 24 hrs after gynaecological surgery. T. S. Hahm, et al (2010)^[35] compared the prophylactic antiemetic efficacy of Ramosetron and Ondansetron in patients at high-risk for postoperative nausea and vomiting after total knee replacement. The incidence of nausea between 2 h and 24 h and the severity of nausea between 2 and 48 h were less in the Ramosetron group.

The authors conclude from the study that Ramosetron is a very effective, safe antiemetic in the prevention of PONV and preoperative prophylactic administration of single dose IV Ramosetron (0.3 mg) has better efficacy than single dose IV Ondansetron (4 mg) in reducing the incidence of PONV over 12 hours postoperative period, in patients undergoing Laparoscopic Cholecystectomy under general anaesthesia. However a larger study with large sample size needs to be conducted to establish the author's point of view with solidarity. The study being conducted in a developing country, the authors could not measure some of the biochemical parameters of nausea and vomiting like C reactive protein, urea, aldehydes, and ketones.

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