A Comparative Study of Ramosetron versus Ondansetron in Post-Operative Nausea and Vomiting after Laparoscopic Cholecystectomy

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ABSTRACT

BACKGROUND

Post-Operative Nausea and Vomiting (PONV), is one of the most common and distressing adverse events experienced by patients after an anaesthesia and surgery. It may prolong recovery, delay patient discharge and increase hospital costs. PONV is common after laparoscopic cholecystectomy with a high incidence of 40-75%. In this study, we used conventional 5-HT_3 receptor antagonist ondansetron and a newer 5-HT_3 receptor antagonist, Ramosetron as a prophylaxis for PONV after laparoscopic cholecystectomy (LC) under general anaesthesia in two different groups of patients and we compared the efficacy and tolerability of the two drugs. This study was carried out to compare the efficacy of Ramosetron and Ondansetron in preventing PONV after laparoscopic cholecystectomy under general anaesthesia.

METHODS

This is a prospective randomized controlled study conducted among 124 adult-patients of either sex, aged between 25 and 55 yrs., of ASA physical status 1 and ii scheduled for laparoscopic cholecystectomy, who were randomly allocated into Group A (n=62) receiving (IV) Ondansetron (4 mg) and group B (n=62) receiving IV Ramosetron (0.3 mg) prior to the induction of general anaesthesia in a double-blind manner. Episodes of PONV were noted at 0.5, 1, 2, 4, 6, 12 hours postoperatively.

RESULTS

Statistically significant difference between Groups A and B ($p<0.05$) was found showing that Ramosetron was superior to Ondansetron as antiemetic with regard to frequency and severity.

CONCLUSIONS

It was evident that preoperative prophylactic administration of single dose IV Ramosetron (0.3 mg) has a better efficacy than single dose IV ondansetron (4 mg) in reducing the episodes of PONV over 12 hrs postoperatively in patients undergoing laparoscopic cholecystectomy under general anaesthesia.

KEYWORDS

Laparoscopic Cholecystectomy, Ramosetron, Ondansetron, Postoperative Nausea and Vomiting

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BACKGROUND

Post-Operative Nausea and Vomiting (PONV), is 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. Prevention and treatment of PONV help to accelerate post-operative recovery and increase patient satisfaction.[3,4] laparoscopic cholecystectomy (LC) is routinely performed for cholelithiasis. Post-operative nausea and vomiting is common after LC with a high incidence of 40-75%.[5-7] Numerous studies have investigated the prevention and treatment of PONV for patients scheduled to undergo LC by a variety of antiemetic's including anticholinergics[8,9] antihistaminic,[10] phenothiazines,[11] butyrophenones,[12] and benzamide.[13] However these agents may cause undesirable adverse effects such as excessive sedation, hypotension, dry mouth, dysphoria, hallucinations and extrapyramidal signs.[14] Serotonin subtype 3($5\text{-}HT_3$) antagonists prevent serotonin from binding to $5\text{-}HT_3$ on the ends of 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, $5\text{-}HT_3$ antagonist interrupt one of the pathways leading to vomiting.[15] Findings have demonstrated that several $5\text{-}HT_3$ antagonists (ondansetron, granisetron, tropisetron dolosetron and Ramosetron) currently available are highly efficacious for PONV. Ondansetron, the most commonly used prophylactic $5\text{-}HT_3$ antagonist was found to be more effective than traditional antiemetics, including droperidol and metoclopramide in reducing the incidence of PONV.[16-18] Ramosetron, a new $5\text{-}HT_3$ receptor antagonist has higher potency and prolonged activity than previously developed $5\text{-}HT_3$ antagonists as an antiemetic after chemotherapy[19,20] or surgery.[21-23] In this study, we used conventional $5\text{-}HT_3$ receptor antagonist, ondansetron and a newer $5\text{-}HT_3$ antagonist, Ramosetron as a prophylaxis of PONV after laparoscopic cholecystectomy (LC) operation under general anaesthesia two different groups of patients (one group received ondansetron 4 mg I.V. and another group received Ramosetron 0.3 mg I.V. before operation) and we compared the efficacy and tolerability of the two drugs. The rescue antiemetic used was metoclopramide 10 mg IV for patients who experienced an episode of vomiting. The severity of nausea was recorded using a visual analogue scale (VAS) with choice options ranging from 0 (no nausea) to 10 (worst possible nausea). Other postoperative adverse effects, such as headache, also were recorded.

We wanted to compare the antiemetic efficacy and adverse effects of Ondansetron and Ramosetron in the 1st 12 hours postoperative period.

METHODS

After obtaining permission from institutional ethics committee, written consent was taken. The study was done at Murshidabad Medical College and Hospital on and from 1st July 2019 to 15th February 2020. Total 124 adult patients (with 95% confidence level) 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 (0.3 mg). Patient refusal, any known allergy or contraindication to any of the two drugs, pregnancy, lactation and children, subjects who vomited or received antiemetics within 24 h before surgery, hepatic, renal or cardiopulmonary abnormality, alcoholism, diabetes, significant gastrointestinal disorders and motion sickness were excluded. In preoperative assessment, patients were enquired about heartburn, belching and abdominal discomfort, h/o motion sickness, any antiemetic received, h/o previous exposure to anaesthesia and h/o PONV, h/o drug allergy or prolonged drug treatment. General and systemic examination and assessment of the airway were done. All patients received premedication of tablet diazepam 5 mg orally the night before surgery to allay anxiety, apprehension and for sound sleep. The patients were preoxygenated with 100% oxygen for a period of 5 minutes. Injection fentanyl (2 mcg) and glycopyrrolate (0.01 mg/Kg) were given intravenously 3 mins before induction of anaesthesia. All the patients were induced with IV injection of Thiopentone 2.5% (5 mg/Kg) titrated till the loss of eyelash reflex. Inj. Atracurium (0.5 mg/Kg)) was given was given to facilitate laryngoscopy and intubation. Controlled ventilation was maintained with 33% oxygen and 67% nitrous oxide. Muscle relaxation was maintained with intermittent intravenous atracurium (0.2 mg/Kg) as when required. Intraoperatively, the pulse rate, respiratory. arterial oxygen saturation, ECG, Capnography, systolic and diastolic pressure continuously. Laparoscopic surgeries were performed under video guidance and involved four punctures of the abdomen and the abdomen insufflated with carbon dioxide through a Veress needle to a maximum intraabdominal pressure of 14 mmHg. At the completion of surgery, residual neuromuscular blockade was antagonized with neostigmine 0.05 mg/Kg and atropine 0.02 mg/Kg intravenously and patient was extubated in conscious condition. Postoperative analgesia was given Tramadol 2 mg/Kg IV 20 mins before the end of surgery and inj. Diclofenac 50 mg postoperatively. All patients received moist oxygen supplementation (3 L/min) for 2h. All the patients were on intravenous drip and did not have any oral fluid during the study period of 12h. Throughout the 18h of postoperative period, all the parameters were recorded on 0.5, 1, 2, 4, 6, 12h. Severity of PONV was observed by VAS scoring (0 represent 'no vomiting' and 10 represents 'worst possible vomiting'). Rescue antiemetic was given with IV metoclopramide (10 mg) slowly.

Statistical Analysis

The raw data were entered into Microsoft excel spread sheet and analysed by appropriate statistical software SPSS statistical package version 18.0 (SPSS Inc, Chicago. ii, USA). 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 will be two tailed and p value of less than 0.05 was considered statistically significant.

RESULTS

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, duration of anaesthesia and surgery. There was statistically no significant difference in age, body weight and sex. From Table 2 it is clear that at 2h and 12 hour episodes of PONV are not significantly different among the two groups but other readings show Ramosetron has controlled PONV more significantly than Ondansetron.

Parameter		Ondansetron (A)	Ramosetron (B)	p
Age (yrs.)	Mean ± SD Range	43.0323±11.07052 25.00-65.00	42.2258±11.08450 25.00-64.00	0.68600
Body Weight (Kg)	Mean ± SD Range	56.0968 ± 3.17113 50.00-64.00	56.2097 ± 3.60845 50.00-65.00	0.853489
Sex	Mean ± SD Male Female	101.2903±0.45762 29.03% 70.97%	101.2097±0.41040 20.97% 79.03%	0.303627

Table 1. Comparison of Demographic Data between the Two Study Groups

Time	PONV (Episodes)	Ondansetron (A)	Ramosetron (B)	p
2 hrs (PV1)	Mean ± SD Range	0.00±0.00 0 - 0	0.00±0.00 0 - 0	0.000
2.5 hrs (PV2)	Mean ± SD Range	0.00±0.00 0 - 0	0.00±0.00 0 - 0	0.000
3 hrs (PV3)	Mean ± SD Range	0.00±0.00 0 - 0	0.00±0.00 0 - 0	0.000
3.5 hrs (PV4)	Mean ± SD Range	0.080±0.375 0 - 2	0.00±0.00 0 - 0	0.0932
4 hrs (PV5)	Mean ± SD Range	0.161±0.578 0 - 3	0.00±0.00 0 - 0	0.0299
4.5 hrs (PV6)	Mean ± SD Range	0.225±0.663 0 - 3	0.00±0.00 0 - 0	0.0083
5 hrs (PV7)	Mean ± SD Range	0.145±0.507 0 - 3	0.00±0.00 0 - 0	0.0260
5.5 hrs (PV8)	Mean ± SD Range	0.225±0.733 0 - 3	0.00±0.00 0 - 0	0.0168
6 hrs (PV9)	Mean ± SD Range	0.096±0.348 0 - 2	0.00±0.00 0 - 0	0.0308
7 hrs (PV10)	Mean ± SD Range	0.145±0.596 0 - 3	0.064±0.306 0 - 2	0.3455
8 hrs (PV11)	Mean ± SD Range	0.096±0.392 0 - 2	0.177±0.558 0 - 2	0.3544
9 hrs (PV12)	Mean ± SD Range	0.00±0.00 0 - 0	0.209±0.630 0 - 3	0.0099
10 hrs (PV13)	Mean ± SD Range	0.00±0.00 0 -0	0.145±0.473 0 - 2	0.0173
11 hrs (PV14)	Mean ± SD Range	0.00±0.00 0 - 0	0.016±0.127 0 - 1	0.3192
12 hrs (PV15)	Mean ± SD Range	0.00±0.00 0 -0	0.00±0.00 0 - 0	0.00
sum PVTot	Mean ± SD Range	1.177±1.769 0 - 5	0.612±1.310 0 - 5	0.0457

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	VAS Score	Ondansetron (A)	Ramosetron (B)	p
2 hrs (V2)	Mean ± SD Range	0.032±0.254 0 - 2	0.00±0.00 0 - 0	0.319
4 hrs (V4)	Mean ± SD Range	0.709±1.702 0 - 8	0.00±0.00 0 - 0	0.001
6 hrs (V6)	Mean ± SD Range	1.032±2.165 0 - 6	0.290±0.947 0 - 4	0.014
12 hrs (V12)	Mean ± SD Range	0.00±0.00 0 - 0	0.225±0.733 0 - 4	0.016

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

- At V4 and V6 (4 hrs and 6 hrs post-operative period), there is statistically significant difference between groups A and B ($p<0.05$), indicating that severity of nausea (PONV) is more in case of Ondansetron than Ramosetron.
- But at V12 (12 hrs post-operative period), there is also statistically significant difference between groups A and B ($p<0.05$), indicating that severity of nausea (PONV) is more in case of Ramosetron.

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

Table 4. Comparison of Rescue Antiemetic (Metoclopramide) Use Frequency between the Study Groups

The use of rescue antiemetic is less in case of Ramosetron (19.35%) than Ondansetron (32.26%). Fisher's exact test 2-tailed p value 0.150. So, there is no statistically significant difference between the two study groups. There is no difference in total dose of rescue anti-emetic (i.e., 10 mg of Metoclopramide used) between the groups.

Time	Adverse Effects	Ondansetron (A)	Ramosetron (B)	2- tailed p
4 hrs (AE5)	Present Absent	1.61% 98.39%	0% 100%	1.000
4.5 hrs (AE6)	Present Absent	3.23% 96.77%	0% 100%	0.496
5 hrs (AE7)	Present Absent	1.61% 98.39%	0% 100%	1.000
5.5 hrs (AE8)	Present Absent	1.61% 98.39%	0% 100%	1.000
6 hrs (AE9)	Present Absent	1.61% 98.39%	0% 100%	1.000
7 hrs (AE10)	Present Absent	1.61% 98.39%	0% 100%	1.000
8 hrs (AE11)	Present Absent	1.61% 98.39	1.61% 98.39%	1.000
9 hrs (AE12)	Present Absent	0% 100%	4.84% 95.16%	0.244
10 hrs (AE13)	Present Absent	0% 100%	3.23% 96.77%	0.496

Table 5. Comparing the Post-Operative Treatment Emergent Adverse Effects between the Two Study Groups at Succeeding Time Intervals

There is statistically no significant difference between the two study groups. AE1, AE2, AE3, AE4, AE14 and AE15 were not encountered in either group. Again, during the 12h postoperative 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.

DISCUSSION

Postoperative nausea and vomiting (PONV) are among the most distressing and common complaints that patients have following general anaesthesia and surgery and its control is still a big challenge for the anaesthesiologists. Persistent nausea and vomiting causes not only patient discomfort, but also may result in dehydration, electrolyte imbalance, wound dehiscence, bleeding, venous hypertension, increased intracranial pressure and increased risk of pulmonary aspiration of vomitus[24] It also delays post-operative recovery and increases cost of hospital stay.[25,26] Post-operative nausea and vomiting is common after laparoscopic cholecystectomy with a high incidence of 40-75%.[5-7] The

aetiology of PONV is not entirely known. It is probably multifactorial in origin, with risk factors including age, sex, obesity, history of motion sickness, previous PONV, operative procedure, anaesthetic technique, and post-operative pain.[1] Published evidences suggest that appropriate antiemetic treatment is recommended for patients with more than two risk factors.[2] Ondansetron, the most commonly used prophylactic 5-HT_3 antagonist, was found to be more effective than traditional antiemetics, including droperidol and metoclopramide, in reducing the incidence of PONV.[16-18] Ramosetron, a new 5-HT_3 receptor antagonist, has higher potency and prolonged activity than previously developed 5-HT_3 antagonists as an antiemetic after chemotherapy[19,20] or surgery.[21-23] Ondansetron is a highly selective antagonist at 5-HT_3 receptors. The drug antagonises 5-HT_3 receptors both centrally and peripherally. Ramosetron hydrochloride is considered to exert its antiemetic action by blocking 5-HT_3 receptors present in the afferent vagal nerve-endings in the gastrointestinal mucosa. The present study compared the efficacy and tolerability of Ramosetron and Ondansetron as a prophylaxis of PONV after laparoscopic cholecystectomy (LC) operation under general anaesthesia in two different groups of patients (one group received Ondansetron 4 mg iv and another group received Ramosetron 0.3 mg iv before operation). The study was carried out with 124 patients of either sex, weighing 25-65 kg, of ASA physical status I and II, so that other risk factors which may contribute to the increased incidence of PONV could be eliminated. The patients were randomly divided into two equal groups of 62 patients each (n=62). In our study, we have observed number of patients who had episodes of nausea and vomiting in laparoscopic cholecystectomy under general anaesthesia. Ramosetron, recently developed 5-HT_3 receptor antagonist. It shows significantly greater affinity for 5-HT_3 receptors, resulting more potent, longer receptor antagonizing effects compared to older 5-HT_3 antagonist.[24,25] Ramosetron is more potent and longer duration of action granisetron in prevention of emesis after cis-platin therapy and prevention of PONV.[26] Choi and Colleagues reported that Ramosetron IV was better than Ondansetron I.V. in reducing the severity of nausea, incidence of vomiting and the rescue antiemetics at 6-24 hrs after operation in patients who undergone spinal surgery.[27] In our study, there is statistically significant difference between groups A and B ($p<0.05$) indicating that severity of nausea (PONV) is more in case of Ondansetron than Ramosetron at 4 hrs and 6 hrs postoperative period. Kim et al performed similar study in Gynaecological surgery and they have observed similar results as well. The use of rescue antiemetic is less in case of Ramosetron (19.35%) than Ondansetron (32.26%) in our study. But there is no difference in total dose of rescue antiemetic (i.e. 10 mg of Metoclopramide used) between the groups. The most frequently reported adverse events of 5-HT_3 receptor antagonists are dizziness and headache.[28] Up to 8 hrs postoperative period, adverse effects of Ramosetron are absent, but after that fewer side effects are seen. In case of Ondansetron, few adverse effects are seen up to 9 hrs postoperative period, but after that no effects are seen.

CONCLUSIONS

Ramosetron is a very effective and safe antiemetic in the prevention of PONV. Preoperative prophylactic administration of single dose of IV Ramosetron (0.3 mg) has better efficacy than single dose of IV Ondansetron (4 mg) in reducing the incidence of PONV over the first 12 hrs. postoperative period in patients undergoing laparoscopic cholecystectomy under general anaesthesia.

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