Prevention Of Post-Operative Nausea And Vomiting In Females Following Laparoscopic Cholecystectomy: Is Ramosetron Superior To Granisetron?

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Citation

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Abstract

Aims and objectives: This study was designed to study the efficacy of ramosetron in prevention of postoperative nausea and vomiting in females following laparoscopic cholecystectomy and to compare it with that of granisetron.
Methods : 100 female patients of physical status ASA I and II, aged 25-55 years scheduled for elective laparoscopic cholecystectomy were recruited. Patients with a history of smoking, drug or alcohol abuse, peptic ulcer disease, patients who had received antiemetics within 24 hours before surgery, menstruating, pregnant or lactating women, patients with history of motion sickness or patients in whom laparoscopic cholecystectomy was converted into open surgery were excluded from study. Patients were divided into two equal groups of 50 each. Patients in group A (granistron group) received 2mg of granisetron diluted in saline to make a total volume of 4ml and patients in group B (ramosetron group) received 0.3mg of ramosetron diluted in saline to make a total volume of 4ml towards the end of surgery.
Observations and results: There was no significant difference in postoperative nausea and vomiting (PONV) scores between the two groups immediately after extubation and up to 12 hours postoperatively, however a statistically significant difference was observed in PONV scores 12-18 hours and 18-24 hours postoperatively between the two groups.
Conclusion: Ramosetron is a better antiemetic and is superior to granisetron in providing prolonged relief from postoperative nausea and vomiting following laparoscopic cholecystectomy in females.

INTRODUCTION

Laparoscopic cholecystectomy has emerged as a popular alternative to traditional open cholecystectomy in the management of cholelithiasis but it has been experienced that laparoscopic surgical procedures are associated with excessive episodes of nausea and vomiting in the postoperative period[1]. Postoperative nausea and vomiting (PONV) is one of the main complaints after laparoscopy (40-75% of patients), and the most important factor determining the length of hospital stay after ambulatory anesthesia [1] .

Postoperative nausea and vomiting (PONV) remains an unpleasant and persistent clinical problem in the surgical patients after anesthesia [2] .

Persistent vomiting may lead to disturbances in the electrolytes, dehydration, minor incisional pain to more severe hematoma, delayed wound healing, wound dehiscence and bleeding, aspiration of vomitus, esophageal rupture, raised intracranial pressure and bilateral pneumothorax. Furthermore discharge from post-anesthetic care unit (PACU) may be delayed and hospital stay prolonged, thereby increasing the overall medical cost [2,3,4].

The main patient related factors are age, gender, history of motion sickness, previous nausea and vomiting, pregnancy [2,5], surgery within 1-7 days of menstrual cycle [3,6], patients not smoking [2,3,4]. Women are more sensitive to all emetic stimuli. The mechanism of postoperative nausea and vomiting in them is complicated by the prevailing hormonal status [3]. Hence the incidence of emetic episodes (PONV) is 2-3 times more prevalent in women than men[3] and four times higher during menses[3], four times higher in the menstrual age group than post menopausal, as the changing environment sensitizes the brainstem to the action of other emetic stimuli[2,3,4,5].

Various drugs used for preventing PONV include the anticholinergics (glycopyrollate, scopalamine), phenothiazines (promethazine, prochloperazine),

antihistamines (hydroxyzine, diphenhydramine), butyrophenones (droperidol), benzamides (metochlorpramide) and steroids (betamethasone, dexamethasone). Some of these antiemetics are associated with adverse effects such as restlessness, dry mouth, sedation, hypotension, extrapyramidal symptoms and dystonic effects [7]. Three major groups of drugs, among the traditional antiemetics, that remain in use for PONV are the benzamides, butyrophenones and steroids. The newer antiemetic group of drugs, 5-HT3 receptor antagonists, is generally superior to the traditional antiemetic agents for preventing PONV. These antiemetics do not have the adverse effects of the traditional antiemetics. Headache and dizziness are the main side effects of 5-HT3 antagonists in the dosage used for PONV[2,3,7] .

Popularly used drugs nowadays for prevention of postoperative nausea and vomiting include Ondansetron and Granisetron. However these drugs are also not without side effects. The unwanted effects of Ondansetron are headache, dizziness, musculoskeletal pain, drowsiness, sedation, shivers, malaise, fatigue, injection site reaction, urinary retention, chest pain, hypotension, fever, pruritus, paraesthesia, raised liver enzymes, slight QT-prolongation and reduced heart rate [3,7,8]. The adverse effects of Granisetron include decreased gastrointestinal motility resulting in mild transient constipation (thus patients with subacute intestinal obstruction should be monitored)[3,8], headache, diarrhea, somnolence, dizziness, dyspepsia, transient increase in hepatic transaminases [3]. Granisetron lacks dysphoric, sedative and extrapyramidal side effects. No safety profile is available for its use in neonates and pregnant women and therefore may be avoided in them [7,9].

An ideal antiemetic used for prevention of postoperative nausea and vomiting should have quicker onset and longer duration of action and should have least undesired side effects.

Therefore to have the above-mentioned properties and to overcome the side effects of previously used drugs for post-operative nausea and vomiting, a need was felt to try a new drug with a better clinical profile and less side effects. Ramosetron, a newer antiemetic drug is a 5-HT3 blocker. It has been shown by various investigators that Ramosetron has a longer duration of action [2,9,10,11,12,13,14] and least unwanted side effects as compared to the previously used antiemetics for prevention of postoperative nausea and vomiting.

Therefore the present study was conducted to study the efficacy of Ramosetron and to compare it with Granisetron in prevention of post operative nausea and vomiting following laparoscopic cholecystectomy in female patients.

MATERIAL AND METHODS

After institutional ethical committee approval and written informed consent, this study was conducted on 100 female patients of ASA physical status I and II in the age group of 25-55 years scheduled for elective laparoscopic cholecystectomy under general anaesthesia. Patients with a history of smoking, history of drug or alcohol abuse, history of peptic ulcer disease, patients with impaired kidney or liver function, patients who had received anti-emetics within 24 hours before scheduled surgery, menstruating, pregnant or lactating women, patients who had history of motion sickness and history of previous post-operative nausea and vomiting, patients on whom laparoscopic cholecystectomy was converted into open cholecystectomy were excluded from study.

Patients were randomly allocated to two groups of 50 patients each. Patients enrolled in the Granisetron group received 2 mg IV of Granisetron and those in the Ramosetron group received 0.3 mg IV of Ramosetron towards the completion of the surgical procedure .The drugs were prepared by a single person in 5ml syringes and all study medication was diluted in normal saline to make 4ml of total medication in order to ensure blinding.

Group A: Patients received 2 mg of Granisetron diluted to make 4ml in normal saline.

Group B: Patients received 0.3 mg of Ramosetron diluted to make 4ml in normal saline.

On the day before the surgery all the patients were clinically evaluated, assessed and investigated as per the protocol. The study protocol was explained to the patient and written informed consent was taken from each participant. No pre-anesthetic medication was given.

Anesthesia was induced with 5mg/kg of sodium thiopentone IV and 100 mcg/kg of morphine. Intubation of trachea was facilitated with atracurium 0.5 mg/kg. Anesthesia was maintained with 66% N2O and 0.5 % halothane in oxygen. Intra operative muscle relaxation was achieved with atracurium as required. Ventilation was mechanically controlled and adjusted to maintain an end-tidal CO2(ETCO2) at 30-40 mm Hg. A nasogastric tube was inserted and suction applied to empty stomach of air and other contents. Before extubation of trachea the nasogastric tube was again suctioned and then removed.

During surgery patients were positioned in the reverse

Trendelenburg position with the right side of the table elevated. The abdomen was insufflated with carbon dioxide, to an intra-abdominal pressure of 10-14 mmHg. Intraoperative monitoring included ECG, pulse oximetry,ETCO2,systolic, diastolic and mean blood pressure, which was recorded every 5 minutes. Ketorolac 0.5 mg /kg i/m was given towards end of surgery. Duration of anesthesia, surgery and carbon dioxide insufflations was recorded in every patient.

After completion of surgery neuromuscular blockade was reversed neostigmine 0.04 mg/kg and glycopyrolate and patients were extubated when adequate spontaneous ventilation was established.

The post-operative nausea and vomiting (PONV) was defined as a subjective unpleasant sensation associated with an urge to vomit (Retching and Vomiting was grouped together).

The incidence of nausea and vomiting was recorded every 6-hours for a period of 24 hours by direct questioning to the patient or to her attendant by the same anesthetist. No distinction was made between vomiting and retching (retching event was considered as vomiting event). Nausea and vomiting was evaluated on a three point scale.

0 = none

1 = nausea

2 = vomiting.

Rescue antiemetic medication, if required, was given in the form of Granisetron 2mg, repeated, if the patient experienced severe nausea, if there were more than 3 emetic episodes within a period of 15 minutes or if the patient asked for it.

The data obtained was statistically evaluated and analyzed using unpaired students t-test, chi-square and Fisher's exact test.

RESULTS

The two groups were comparable with respect to age, weight, duration of anaesthesia and duration of surgery. The average age of the patients in the granisetron group was 38.44 years and 38.50 years in the ramosetron group. Average weight of the patients in the granisetron group was 63.0 kgs against 63.74 kgs in the ramosetron group. The mean duration of anaesthesia in the granisetron group was 60.8 minutes and 62.40 minutes in the ramosetron group. Average surgical time in the granisetron group was 55.28 minutes against 56.42 minutes in the ramosetron group. The duration of CO2 insufflation did not differ between the two groups. The mean duration of CO2 insufflation in the granisetron group was 51.10 minutes while as it was 52.2 minutes in the ramosetron group.

There was no statistically significant difference in PONV scores immediately after extubation and up to 12 hours postoperatively.

Table 1

Showing PONV scores immediately after extubation.

PONV Score	Granisetron group		Ramosetron group		P value	Remark
	No.	%	No.	%		
Nausea	4	8	3	6	1.000	NS
Vomiting	1	2	0	0	1.000	NS
Rescue antiemetic required	1	2	0	0	1.000	NS

NS = Not significant, PONV = Post-operative nausea and vomiting.

Table 2

Showing PONV scores 0-6 hours after extubation.

PONV Score	Granisetron group		Ramosetron group		P value	Remark
	No.	%	No.	%		
Nausea	9	18	6	12	0.0576	NS
Vomiting	5	10	2	4	0.4360	NS
Rescue antiemetic required	1	2	1	2	1.000	NS

NS = Not significant.

Table 3

Showing PONV scores 6-12 hours after extubation.

PONV Score	Granisetron group		Ramosetron group		P value	Remark
	No.	%	No.	%		
Nausea	11	22	7	14	0. 4360	NS
Vomiting	6	12	2	4	0.2690	NS
Rescue antiemetic required	5	10	2	4	0. 4360	NS

NS = Not significant.

However a statistically significant difference was observed in PONV scores 12-18 hours after extubation between the two groups.

The incidence of nausea was 30% in the granisetron group and only 12% in the ramosetron group. The difference was statistically significant.18% of patients in the granisetron

group had vomiting while as only 2% of patients in the ramosetron had episodes of vomiting. The difference was statistically significant. The incidence of rescue antiemetic needed was 20% in the granisetron group and only 2% in the ramosetron group with a statistically significant difference between the two groups.

Table 4

Showing PONV scores 12-18 hours after extubation.

PONV Score	Granisetron group		Ramosetron group		P value	Remark
	No.	%	No.	%		
Nausea	15	30	6	12	0. 0479	S
Vomiting	9	18	1	2	0.0157	S
Rescue antiemetic required	10	20	2	4	0. 0277	S

S = Significant.

After 18-24 hours of extubation, a statistically significant difference was observed in PONV scores between the two groups.

The incidence of nausea was 34% in the granisetron group and only 10% in the ramostron group. The difference was highly significant. Episodes of vomiting occurred in 20% of patients in the granistron group and only 4% in the ramostron group with a statistically significant difference.24% of patients in the granisetron group required rescue antiemetic while as only 6% of patients required rescue antiemetic in the ramostron group. The difference was statistically significant.

Table 5

Showing PONV scores 18-24 hours after extubation.

PONV Score	Granisetron group		Ramosetron group		P value	Remark
	No.	%	No.	%		
Nausea	17	34	5	10	0. 007	HS
Vomiting	10	20	2	4	0.0277	S
Rescue antiemetic required	12	24	3	6	0. 0226	S

HS = Highly Significant.

DISCUSSION

Despite the latest advances in anesthesia and the introduction of new class of antiemetics, postoperative nausea and vomiting (PONV) is still one of the most common complaints of patients in the post-operative period. One and a half century is over since the first anesthesia was administrated and despite the remarkable advances in this specialty and the development of newer anesthetics the incidence of postoperative nausea and vomiting has been unacceptably high. Generally, one-third of patients undergoing surgery are known to suffer from postoperative nausea, vomiting, or both, and often rate PONV as worse than postoperative pain[4]. After Laparoscopic Cholecystectomy its incidence has been reported to be as high as 40-75%[1].

With the idea of safety and comfort in mind, it is expected that efforts would be made to reduce the chances of vomiting associated with anesthesia and surgery, therefore many nonspecific and therapeutic measures have been applied to prevent sickness during and after the operation.

Several studies have been conducted to know the mechanism and causes of postoperative nausea and vomiting and to find out the safe and satisfactory antiemetic or emesis free anesthesia strategy. The problem is multifactorial in origin, including patient characteristics, nature of underlying disease, the type of surgery, as well as the anesthetic agents and postoperative care. The main patient related factors are age, gender, history of motion sickness, previous nausea and vomiting and pregnancy. The incidence of PONV in females has been reported to be very high and is approximately two to three times more prevalent in adult women than in men, with greater severity of vomiting in women[3]. Women are more sensitive to all emetic stimuli. The mechanism of postoperative nausea and vomiting in them is then complicated by the prevailing hormone status. Hence the incidence of emetic episodes are four times higher in the menstrual age group than post-menopausal[15], as the changing endocrine environment sensitizes the brainstem emetic mechanism to the action of other emetic stimuli[3].

There are numerous antiemetic drugs available having different mechanisms of action and target sites with varying potency and pharmacokinetic profiles. Routinely employed drug classes are prokinetics, dopaminergic antagonists, 5HT3 antagonists, butyrophenones, anticholinergic, phenothiazines, antihistaminics, benzamides and steroids. Most of the antiemetics are known to cause drowsiness,dysphoria,hallucinations,dry mouth and extrapyramidal side effects[7,16].

Though hazards associated with a single dose of an anti-emetic are small, as compared to the hazards and inconvenience of vomiting yet efforts are always on to develop drugs which can be used safely as antiemetics without having untoward side effects, especially on the

cardiovascular and respiratory system. As a result of this continuous search for better antiemetics, 5HT3 receptor antagonists were introduced with an idea of good margin of safety.

In our study, we found no statistically significant difference in PONV scores in two groups immediately after extubation and upto 12 hours postoperatively, meaning thereby that Ramosetron is as effective as Granisetron in preventing PONV in female patients undergoing laparoscopic cholecystectomy.

Precise mechanism of Granisetron for prevention of PONV remains unclear, but it has been suggested that Granisetron acts as a 5-HT3 receptor antagonist. Similar mechanism has been suggested for Ramosetron.

Our results are in accordance with the results obtained by Yoshita Fuji, Yuhji Saitoh, Hiroyoshi Tanaka, Hidenori Toyooka, who in their study found no statistically significant difference in the PONV scores in the two groups immediately after extubation and upto 12 hours postoperatively[5].

However a statistically significant difference was observed in postoperative nausea and vomiting scores in our study 12-18 hours and 18-24 hours after extubation.

Our results are in accordance with the results obtained by Yoshita Fuji, Yuhji Saitoh, Hiroyoshi Tanaka, Hidenori Toyooka, who in their study concluded that Ramosetron is more effective than Granisetron for prevention of postoperative nausea and vomiting during 0-48 hours after anaesthesia for laparoscopic cholecystectomy[5].

Our results are also in accordance with the results obtained by Feng Yi Feng, Pin Zhang, You Jian He, Yu Hong Li, Mei Zhen Zhou, Gang Cheng, Minoru Yamamoto, who in their study observed that, 18-24 hours after administration of chemotherapy, patients given Ramosetron had significantly better scores for nausea than the patients given Granisetron [12].

We observed that Ramosetron is more potent than Granisetron and the need for rescue antiemetics in the Ramosetron group was less than that in the Granisetron group.

Ramosetron is a newly developed 5-HT3 receptor antagonist with a more potent and longer antagonizing effect compared with older 5-HT3 receptor antagonists[17]. The elimination half life of Ramosetron (9 hours) is longer than that of Granisetron (4.9 hours) [18]. Because of these pharmacological properties, Ramosetron is clinically reported to be more potent with a longer duration of action than older 5-HT3 receptor antagonists [17,18]. Ramosetron has also been known to be equivalent to Granisetron in the overall antiemetic effect and even superior to Granisetron in the no-vomiting (emesis free) rate for patients receiving chemotherapy[19].

We also observed that Ramosetron has a longer antiemetic duration than Granisetron and was associated with longer emesis free periods in the study group than in the Granisetron group.

Ramosetron has been found to be 58 times more potent than Granisetron and its antiemetic effect lasts 10.7 times longer than that of Granisetron in ferrets treated with cisplatin [12]. The more potency and longer duration of action of Ramosetron could be the reasons that gave us favorable results for Ramosetron over Granisetron in prevention of PONV.

It has been also seen that Ramosetron has high pharmacological bioavailability[20]. The high bioavailability of Ramosetron results in antagonism at maximum number of 5-HT3 receptors which explains its better efficacy and superiority over Granisetron in prevention of PONV.

Ramosetron has been seen to have a higher affinity for 5HT3 receptors than Granisetron with a significantly higher efficacy 6-48 hours after treatment[18].

Besides, as we studied only female patients, the bias of gender was eliminated in our study.

References

1. Jean L. Joris; Anesthesia for laparoscopic surgery. Millers Anesthesia, 6th edition, chapter 57, p. 2294.
2. Ky Ho, J W Chiu : Multimodal antiemetic therapy and emetic risk profiling ; Annals Academy of Medicine Singapore 2005;34:196-205.
3. Alex S. Evers, Mervyn Maze: Antiemetics. Anesthetic pharmacology (physiologic principles and clinical practices), a companion to Millers anesthesia. Chapter 45; p.777.
4. Eun Jin Kim, Justin Sang Ko, Chung Su Kim, Sang Min Lee, Duck Hwan Choi: Combination of antiemetics for prevention of post operative nausea and vomiting in high risk patients : J Korean Med Sci 2007; 22: 878-82.
5. Fuji Y, Saitoh Y, Tanaka, H. Toyooka H: Ramosetron versus Granisetron for prevention of post operative Nausea and Vomiting after laparoscopic cholecystectomy; Can J Anesth 1999 ;46: 991-93.
6. J. Lance Lightor. Intraoperative management of postoperative nausea and vomiting: Ambulatory Anesthesia:Clinical Anesthesia by Paul G. Barash, Bruce F. Cullen, Robert K. Stoelting, Michael K. Cahalan, M.Christine Stock; 6th edition: chapter 32; p.841.
7. Helms, Quan, Herfindal, Gourley: Textbook of therapeutics (Drugs and Disease Management),Lippincott and Williams, Section xiii-Gastrointestinal Diseases, p.1287-88.
8. Hardman, Limbird, Gilman: Prokinetic and antiemetic drugs : Pharmacology by Gillman and Goodman-10th edition, chapter-38 : p.1029-30.
9. Y. Fuji, Y. Saitoh, H. Tanaka, H. Toyooka: Camprison of Ramosetron and Granisetron for preventing postoperative

nausea and vomiting in women after gynaecolgic surgery; Anesth Analg 1999; 89:476-9.
10. Fuji, Y. Saitoh, H. Tanaka, H. Toyooka: Ramosetron for preventing postoperative nausea and vomiting in women ater gynaecologic surgery; Anesth Analg 2000; 90: 472-5.
11. Fuji, H. Tanaka, M. Ito: A randomized clinical trial of a single dose of Ramosetron for prevention of vomiting after strabismus surgery in children; Arch Ophthalmol 2005 ; 123: 25-28.
12. Feng Yi Feng, Pin Zhang, You Jian He, Yu Hong Li, Mei Zhen Zhou, Gang Cheng and Minoru Yamamoto . Comparison of the selective serotonin-3 antagonist in treating acute chemotherapy induced emesis, nausea and anorexia : A single blind, randomized, crossover study. Current Therapeutic Research 2000 ; 61 :901-9.
13. Arkom Cheirsilpa, Tanadej Sinthusake, Apinya Songsakkaesorn, Somchit Visawaprasit, Kemachit Chulaka and Nunchaporn Changkuingdee. Comparison of Ramosetron and Granisetron for prevention of acute and delayed emesis in cisplatin based chemotherapy: A randomized controlled trial: Jpn J Clin Oncol 2005; 35 : 695-99.
14. Kyubo Kim, Eui Kyu Chie, Jin-young Jang, Sun Whe Kim, Do-Youn Oh, Seock-Ah Im, et al : Ramosetron for the prevention of nausea and vomiting during 5-fluorouracil based chemo-radiotherapy for pancreatico-biliary cancer: Jpn J Clin Oncol 2009; 39 :111-15.
15. Lindbald T, Bucklers DN, Forrest JB: The incidence of postoperative nausea and vomiting in women undergoing laparoscopy is influenced by the day of menstrual cycle. Can J Anesth 1991; 38 : 298.
16. Watcha MF, White PF. Postoperative nausea and vomiting :Its etiology,treatment and prevention. Anesthesiology 1992; 77: 162-84.
17. Kim SI, Kim SC, Baek YH, Ok SY, Kim SH. Comparison of Ramosetron with Ondansetron for prevention of postoperative nausea and vomiting in patients undergoing gynaecological surgery.Br J Anaesth. 2009 ; 103: 549-53.
18. Rabasseda X. Ramosetron, a 5-HT3 receptor antagonist for the control of nausea and vomiting. Drugs of Today 2002 ; 38: 75-89.
19. Kang YK, Park YH, Ryoo BY, Bang YJ, Cho KS, Shin DB,et al. Ramosetron for the prevention of cisplatin-induced acute emesis: a prospective randomized comparison with Granisetron; J Int Med Res 2002; 30 :220-9.
20. Kamato T, Ito H, Nagakura Y, et al. Mechanism of cisplatin- and m-chlorophenylbiguanide-induced emesis in ferret. Eur J Pharma- col 1993; 238:369–76.

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