COMPARATIVE EFFICACY AND SAFETY OF GRANISETRON AND RAMOSETRON IN PREVENTING POSTOPERATIVE NAUSEA AND VOMITING AFTER LAPAROSCOPIC CHOLECYSTECTOMY

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Abstract

Postoperative nausea and vomiting (PONV) is one of the most bothersome events that can happen after any laparoscopic cholecystectomy, causing a possibility of a severe impact on the well-being of patients and their recovery. The aim of the research was to differentiate between usefulness and the safety of the Granisetron and Ramosetron in preventing PONV within 24 hours after the surgery was carried out. A prospective, randomized, controlled study was executed as a single-blinded parallel-group prospective study using 250 patients (125 in each group) who were undergoing elective laparoscopic cholecystectomy. Only before induction they were given intravenously either Granisetron (75 mcg) or Ramosetron (4 mg). The main outcome was the total number of PONV attacks over the 24-hour period, and the secondary outcomes were: severity of nausea (with the help of Visual Analogue Scale), the use of rescue antiemetic medication, and the satisfaction of patients. Results: No significant differences were also observed between both groups based on the prevalence of nauseas, retching or vomiting incidences where the two drugs demonstrated close efficacy on the prevention of PONV. Granisetron was, however, safer possessing less adverse effect than Ramosetron. Conclusion: Granisetron and Ramosetron cannot be said to be better than each other in the laparoscopic cholecystectomy-induced PONV. Granisetron, however, is safer in the sense there are fewer side effects thus may be more effective than a prevention of PONV. Future research should prove these results by a larger sample of the study and a double-blind model.

Keywords: Postoperative nausea and vomiting (PONV), Granisetron, Ramosetron, Laparoscopic cholecystectomy.

Introduction

In addition to being a common and distressing addiction that occurs after using general anesthesia surgery, an example of treating nausea is postoperative nausea and vomiting (PONV).

Its total prevalence among high-risk patients is up to 80%. [1] PONV after laparoscopic cholecystectomy still has unacceptably high occurrence (40-75 percent, within 24 hours, with no active intervention).

PONV depends on numerous aspects, such as characteristics of the patient, surgical procedure and kind of anesthesia that is used. When 5-hydroxytryptamine (5-HT) is released, it causes a series of cascades of neurons processes impacting the central nervous system and gastrointestinal system. In particular, the role of 5-HT subtype 3 (5-HT3) receptor stimulation is connected with the emetic effect.

The recent developments in the prevention of PONV have been the introduction of non-pharmacological methods of decreasing baseline risk, using less emetogenic care techniques of using anesthetics and the newer antiemetic agents. Although curative measures have been achieved, antiemetic medications remain an essential part of the PONV management, either standalone or combinatorial. In such a case, there is a range of medicines in use, i.e., metoclopramide, haloperidol, dexamethasone, as well as some particular 5-HT3 receptors antagonists. Among the most conspicuous ones, there are the 5-HT3 receptor antagonists which have become a first-line treatment as well as they are quite effective and show few side effects. The most researched 5-HT3 receptor antagonist is Ramosetron, which demonstrates successful application in the care of chemotherapy-related nausea and vomiting as well as prevention and treatment of PONV. Nevertheless, other drugs have replaced Ramosetron such like granisetron, tropisetron, dolasetron as well as ramosetron.

Granisetron is the latest entry to this category of drugs in India as recorded on 25.04.2009. Compared to all the 5-HT3 receptor antagonists used so far, Granisetron is reported to be an alternative receptor antagonist, which has different mechanism of action, which enables different binding affinity and longer duration of action. The half-life of a single intravenous (IV) dose is about 40 hours thus effects lasts less than 24 hours with a possible 48 hours.

The use of granisetron and placebo has also been compared on determining the effects of these two on determining the prevention of PONV among surgery patients in the open abdominal surgery gynecology surgeries. But little is also carried out in Granisetron and other antiemetics in various surgical operations. Therefore, in this research we have attempted to compare the use of pre-induction of Granisetron intravenous injection in patients subjected to laparoscopic cholecystectomy with the antiemetic protection ability of the same drug during a period of 24 hours in the post-surgical time. The comparator drug was a popular 5-HT3 receptor blocker ramosetron.

METHODOLOGY

In the study, single-dose Granisetron (75 mcg) or Ramosetron (4 mg) was given intravenously and the objective was to determine the efficacy of the given dose of Ramosetron or Granisetron before the induction of anaesthesia in a patient (age 18 yrs or above) of either gender undergoing an elective surgery requiring laparoscopic cholecystectomy admitted to a tertiary care hospital.

All the participants were requested to sign an informed consent and the research was sanctioned by an institutional Ethics Committee.
Pregnant patients, patients with a body weight exceeding 30 percent of the ideal body weight, patients with a recent history of nausea, vomiting or retching over the last 24 hours, patients with a history of use of corticosteroids, psycho active drugs or any other medication that might have the capacity of producing an emetic reaction or an antiemetic effect in the 24 hours preceding surgery were to be excluded. Moreover, those patients with significant organ diseases (such as liver, kidney, heart, lungs, or bone marrow disorders), the already recognized hypersensitivity to the medications under the study, alcohol or drug abuse, or that had participated in another clinical trial within the last month were not allowed.

The randomization procedure involved the utilisation of computer based random number list where the allocation ratio 1:1 was used. Assigning of treatment thoroughness was blind to the end of the drug administration and achieved through the use of envelopes assigned sequential numbers, opaque, and sealed. A single-blind procedure was followed when using this medicine such that the patients did not know the exact composition of the antiemetic drug when it was given to them prior to the 24-hour period after the surgery.
The entire participants shared a common pre-anesthetic protocol, a technique of anesthesis as well as a laparoscopic method. Upon arrival in the operating room, the regular monitoring process was declared and the arterial pressure was measured in a non-invasive manner, the capnography was implemented, the ECG was tuned and the pulse oximetry. The suitable periphery vein was put to cannula to provide intravenous fluids and anesthesia medication. Tests drugs were prepared and the study group was subjected to the administration of Granisetron (75 mcg IV) or Ramosetron (4 mg IV) one minute before the anaesthetic induction based on the randomization codes.

To induce anesthesia, thiopental (5-7 mg/kg IV) was administered and intubation of trachea was facilitated by use of succinylcholine (2 mg/kg IV) or intermediate-acting muscle relaxant (i.e., vecuromium 0.08 mg/kg IV or atracurium 0.5 mg/kg IV). General anaesthesia was under nitrous oxide and sevoflurane 1-2% in oxygen and the muscle relaxation was boluses of vecuronium or atracurium occasionally. The analgesic regimen they used is fentanyl (2 mcg/kg IV) coupled with close ventilatory surveillance with an end-tidal partial pressure of CO2 being maintained at 4.7-5.3 kPa (35-40 mmHg). The use of the video allowed the process of cholecystectomy to be conducted laparoscopically and four holes into the abdomen were created during the procedure. The patient has been taken in reverse Trendelenburg position where the right side of the bed is elevated up to 30 degrees' angle. A Veress needle was applied to insufflate CO2 into the abdomen until the intra-abdominal pressure was maximized (i.e., total of 17 mmHg). Following the surgery, residual neuromuscular block reversal was undertaken through application of IV-glycopyrrolate and neuroxigmine after which the patient was extubated. All the patients received

20 minutes of 75 mg IM diclofenac sodium protocol a few minutes before the point of surgery termination.

The occurrence of PONV in this study was an incident of nausea, retching (inability to vomit without any contents of the stomach being thrown up), or a vomiting (expelling of stomach contents). As a primary outcome measure, the total amount of PONV episodes after the surgery within 24 hours was taken.

Second outcome measures that were included were:

- Single episodes of nausea, retching and vomiting during the 24-hour post procedure period.
- The severity of nausea (Visual Analogue Scale, 10 cm) at the second, 6 th, and 24 th postoperative hour.
- Use of rescue antiemetic drug (10 mg of metoclopramide by mouth).
- The full responders (patients with zero emetic incidents and no need of precipitation medicine).
- Patient satisfaction with the experience of nausea and vomiting, measuring agreement with a statement about satisfaction with the experience scale (dissatisfied, neutral, satisfied and highly satisfied) on a 4-point Likert scale with 24 hours post-surgery..

Should the severity of nausea be at 5 cm or above with the help of Visual Analogue Scale (VAS), a rescue medication was administered to the patients Metoclopramide 10 mg orally, or forced by the patient. Vital signs, oxygen saturation and ECG signals were monitored to assess the safety of the study medications, as well as adverse events that came out within 24hours of the surgery.

The main outcome was used as the basis of estimating the size of the sample, and it was deemed that the sample must consist of 125 patients per group to achieve a decrease in the prevalence of PONV of 2/3 (40 percent to 15 percent) with an 80 percent power and 5 percent Type I error rate. The case report forms were used to collect data. Analysis of the continuous data was performed by means of a Student t-test and the data with deviations of the normal distribution were compared using the Mann-Whitney U test. In categorical variables, Fisher exact test was used. No imputation of Missing data was made or all the statistical tests were two-tailed with a level of significance as $p < 0.05$. The raw data were recorded onto a Microsoft Excel spreadsheet and data were analyzed utilizing Statistica version 6 (StatSoft Inc., Tulsa, Oklahoma) as well as GraphPad Prism version 4 (GraphPad Software Inc., San Diego, California).

RESULT

To examine the effectiveness and safety of Granisetron and Ramosetron in prophylaxis of the postoperative nausea and vomiting (PONV) during laparoscopic cholecystectomy, 250 patients (125 patients in both groups) were taken into account in this research. As revealed in Table 1, the baseline characteristics were fairly comparable in the study participants in both groups. The diagnoses of the Granisetron group were 43.3 +14.25 years and the Ramosetron group had 44.9 + 13.36 years. Parallel weight distributions, time of surgery and anesthesia and insufflation also

existed in both the groups. These baseline characteristics made sure that the variation in the postoperative outcomes was not able to be explained by the existing variation in the baselines. Table 2 and Table 3 indicates that the number of nausea and retching and vomiting incidences was comparable between the two groups in each post-operation period. As regards to nausea, Granisetron group averaged 0.6 * 0.99 in the initial 2 hours and were compared to the Ramosetron group that averaged 0.7 * 1.01. Nausea cases between the two groups have the exact likelihood value of P = 0.670 citing that the two variables tested have no significant difference. A similar trend was also there wherein the outcome between retching or vomiting to be very close to the two groups was also not significant with the P-values of 0.929 and 0.262, respectively.

In particular, the results presented in Table 3 regarding the frequency of the PONV in the 24-hours follow-up after surgery showed that Granisetron group reported 1.5 +/- 2.06 instances of nausea compared to Ramosetron group with 1.4 +/- 2.38 instances of nausea, producing a p-value of 0.809 which did not hold any statistical significance. On the same note, the rate of retching and vomiting did not management significant variations in the two groups.

As far as safety profile was concerned, Table 4 indicated that Ramosetron group is associated with more adverse events than what is the case in Granisetron group. The unfortunate occurrences experienced with the Ramosetron group were throat itching (4.00%), dry mouth (8.00%) and having a bitter taste (1.60%). Granisetron group, on the contrary, presented fewer adverse events, such as a lesser degree of abdominal distension (1.60%) and sinus bradycardia (1.60%). Ramosetron group even registered 32 total adverse events as compared to 4 in Granisetron group which implies that Granisetron is safer than Ramosetron group.

Lastly, Granisetron and Ramosetron, which are used to avert postoperative nausea, retching and vomiting was equally successful among the patients who underwent laparoscopic cholecystectomy. Nevertheless, Granisetron showed better safety, as its adverse effects are not widely reported, implying that it can be preferred in the prevention of PONV in this respect since it has a lower chance of resulting in adverse events.

Table 1: Predictors of Granisetron Versus Ramosetron in Patients Undergoing Laparoscopic Cholecystectomy Preoperative Characteristics of Patients Who Had Granisetron Plus Ramosetron Used on a Prevention Basis in Lap Chole

Parameter	Granisetron (n = 125)		Ramosetron (n = 125)	
	Mean ± SD	Median	Range	Mean ± SD
Age (years)	43.3 ± 14.25	42.0	20.0 - 70.0	44.9 ± 13.36
Weight (kg)	57.1 ± 9.61	56.0	32.0 - 82.0	60.4 ± 9.99
Man: Women	44: 5			37: 12
Surgery Duration (min)	68.0 ± 36.34	55.0	30.0 - 190.0	56.2 ± 22.14

Anesthesia Duration (min)	90.0 ± 37.07	90.0	40.0 - 215.0	79.2 ± 24.33
Duration of insufflation (min)	59.7 ± 32.63	46.0	25.0 - 160.0	49.0 ± 21.47
Peak insufflation pressure (mmHg)	13.4 ± 1.76	13.0	10.8 - 17.0	13.0 ± 1.66
CO_2 quantity insufflated (L)	151.0 ± 134.55	118.0	32.8 - 818.0	153.6 ± 103.08
Group	**0 - 2 h**	**2 - 6 h**	**6 - 24 h**	**Total in 24 h**
	Mean ± SD	**Median (IQR)**	**Mean ± SD**	**Median (IQR)**
Granisetron (n = 49)	1.8 ± 2.40	1 (0.0 - 3.0)	1.3 ± 2.22	1 (0.0 - 2.0)
Ramosetron (n = 49)	1.3 ± 1.56	1 (0.0 - 2.0)	1.2 ± 2.25	1 (0.0 - 1.0)
P value	**0.619**		**0.329**	

Table 2: The Postop Episodes (Restricted to 1st 24hrs) of Postoperative Nausea, Retching and Vomiting on Granisetron and Ramosetron Groups

Group	**0 - 2 h**	**2 - 6 h**	**6 - 24 h**	**Total in 24 h**
	Mean ± SD	**Median (IQR)**	**Mean ± SD**	**Median (IQR)**
Nausea				
Granisetron (n = 125)	0.6 ± 0.99	0 (0.0 - 1.0)	0.5 ± 0.84	0 (0.0 - 1.0)
Ramosetron (n = 125)	0.7 ± 1.01	0 (0.0 - 1.0)	0.6 ± 1.32	0 (0.0 - 1.0)
P value	0.670		0.771	
Retching				
Granisetron (n = 125)	0.4 ± 1.14	0 (0.0 - 0.0)	0.3 ± 0.78	0 (0.0 - 0.0)
Ramosetron (n = 124)	0.3 ± 0.67	0 (0.0 - 0.0)	0.3 ± 0.90	0 (0.0 - 0.0)
P value	0.929		0.733	
Vomiting				
Granisetron (n = 125)	0.7 ± 1.38	0 (0.0 - 1.0)	0.6 ± 1.21	0 (0.0 - 1.0)
Ramosetron (n = 125)	0.3 ± 0.88	0 (0.0 - 0.1)	0.3 ± 0.91	0 (0.0 - 0.9)
P value	0.262		0.176	

Table 3: Incidences of Nausea, Retching and Vomiting during the Significant Time period surrounding the initial 2 Director Post-surgery of Granisetron and Ramosetron Groups

Group	**0 - 2 h**	**2 - 6 h**	**6 - 24 h**	**Total in 24 h**
	Mean ± SD	**Median (IQR)**	**Mean ± SD**	**Median (IQR)**

Nausea				
Granisetron (n = 125)	0.6 ± 0.99	0 (0.0 - 1.0)	0.5 ± 0.84	0 (0.0 - 1.0)
Ramosetron (n = 125)	0.7 ± 1.01	0 (0.0 - 1.0)	0.6 ± 1.32	0 (0.0 - 1.0)
P value	0.670		0.771	
Retching				
Granisetron (n = 125)	0.4 ± 1.14	0 (0.0 - 0.0)	0.3 ± 0.78	0 (0.0 - 0.0)
Ramosetron (n = 124)	0.3 ± 0.67	0 (0.0 - 0.0)	0.3 ± 0.90	0 (0.0 - 0.0)
P value	0.929		0.733	
Vomiting				
Granisetron (n = 125)	0.7 ± 1.38	0 (0.0 - 1.0)	0.6 ± 1.21	0 (0.0 - 1.0)
Ramosetron (n = 125)	0.3 ± 0.88	0 (0.0 - 0.1)	0.3 ± 0.91	0 (0.0 - 0.9)
P value	0.262		0.176	

Table 4: Adverse Events in Patients Receiving Granisetron and Ramosetron (n = 250)

Adverse Event	Granisetron (n = 125)	Ramosetron (n = 125)
Abdominal distension	2 (1.60%)	2 (1.60%)
Bitter taste in mouth	–	2 (1.60%)
Chest discomfort	–	2 (1.60%)
Constipation	2 (1.60%)	2 (1.60%)
Cough	2 (1.60%)	2 (1.60%)
Dizziness	2 (1.60%)	2 (1.60%)
Dryness of mouth	–	10 (8.00%)
Pain while swallowing	2 (1.60%)	2 (1.60%)
Sinus bradycardia	2 (1.60%)	–
Throat irritation	–	5 (4.00%)
Total	4	32

Figure 1: Granisetron vs Ramosetron in Laparoscopic Cholecystectomy

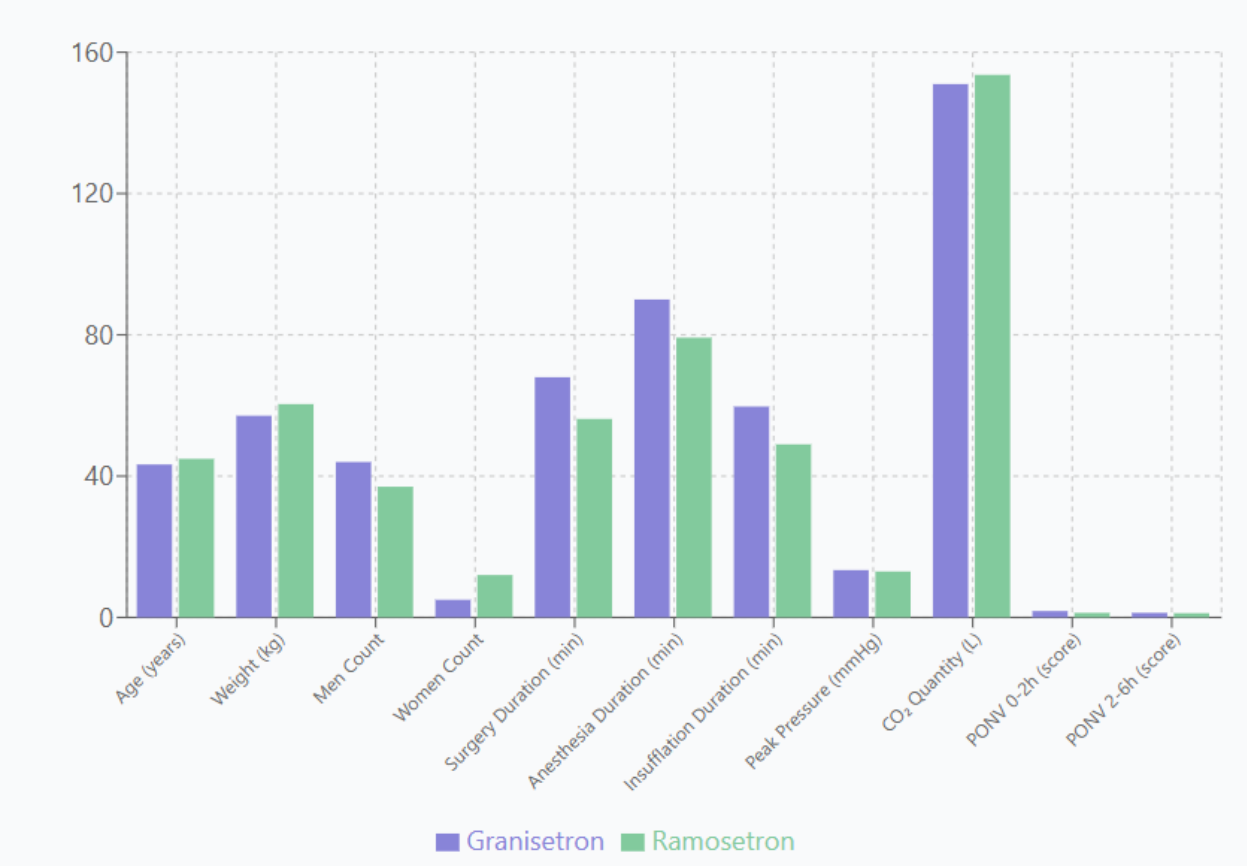


Figure 2: Postoperative PONV Episodes: Granisetron vs Ramosetron (First 24 Hours)

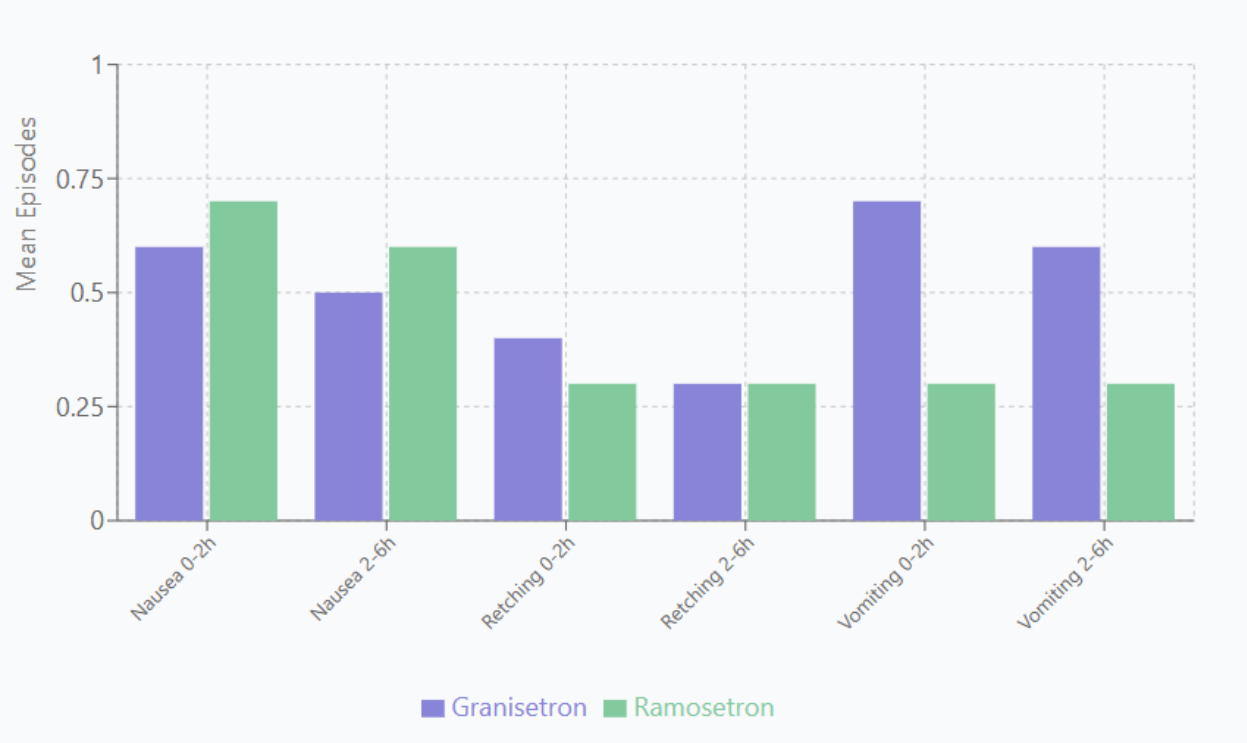


Figure 3: PONV Incidences During Post-Surgery Periods: Granisetron vs Ramosetron

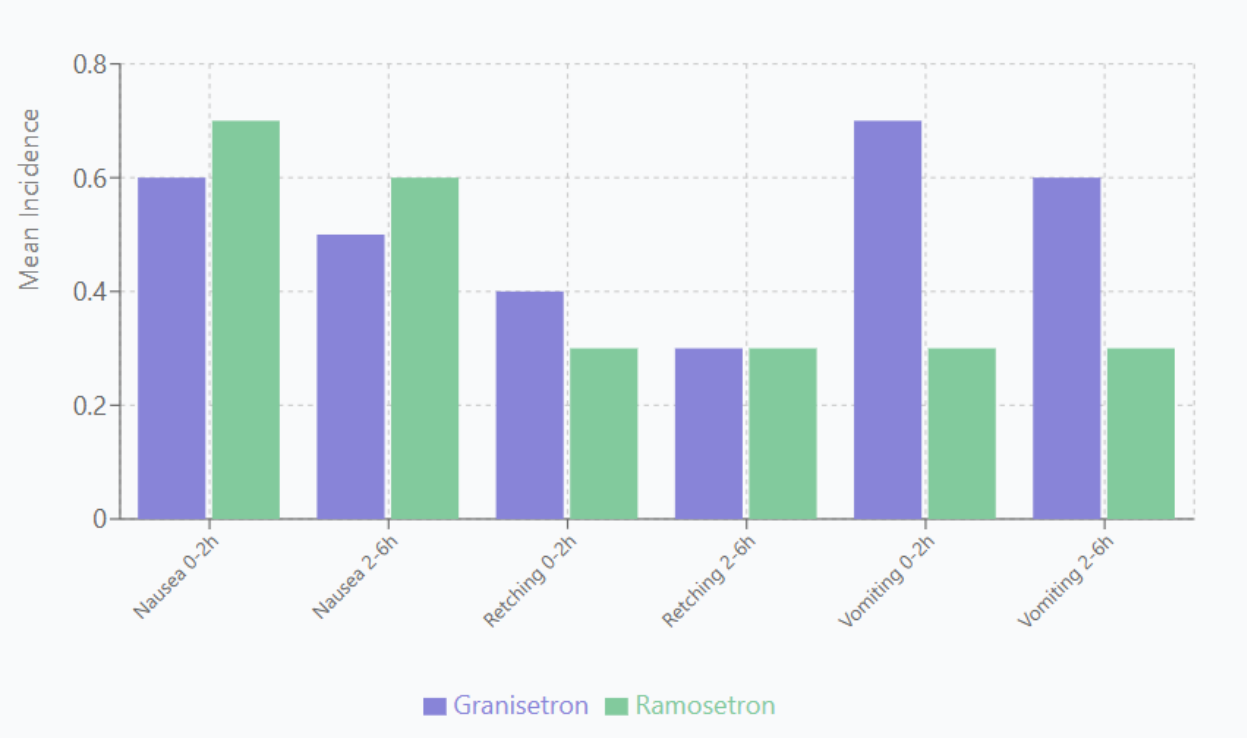
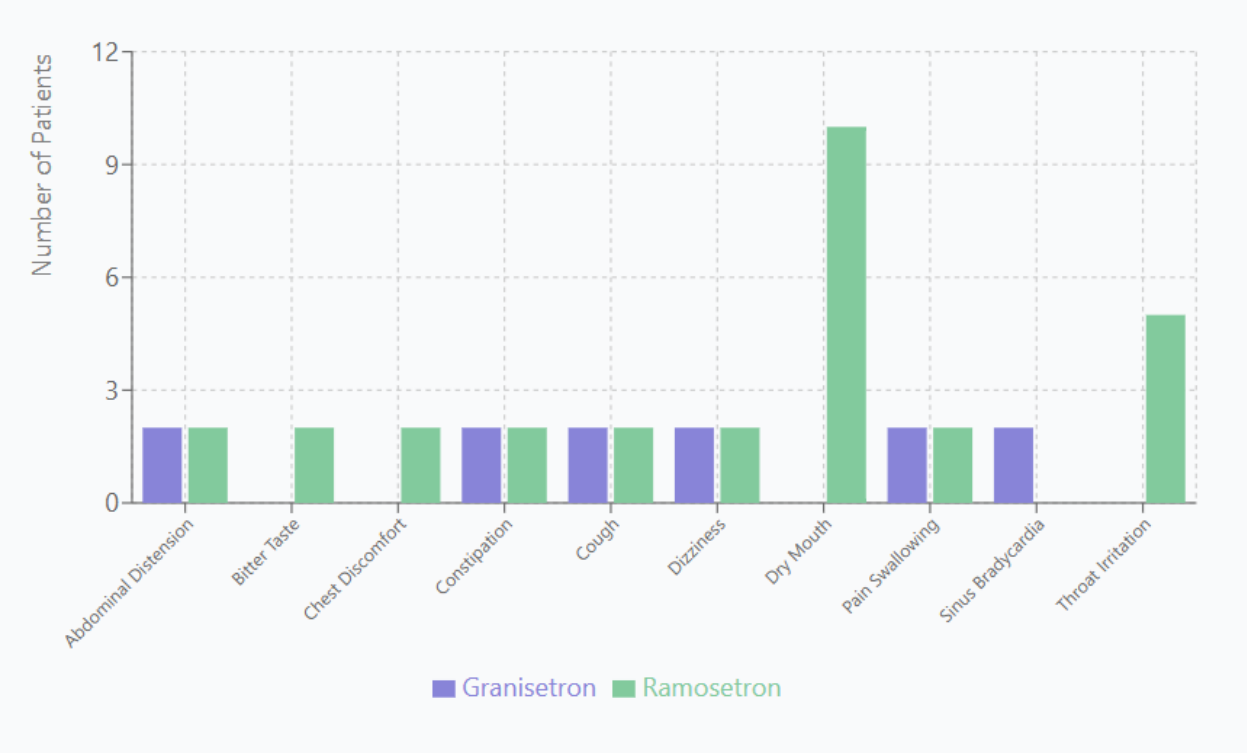


Figure 4: Adverse Events: Granisetron vs Ramosetron (n=250)



DISCUSSION

Nausea and vomiting during the early postoperative process are usually accompanied by different incidences, and they depend on several variables, and these include the duration of the procedure and the kind of anesthetic agents (and the doses, inhalational compounds, and opioids), and lastly smoking [9]. Activation of the 5-HT3 receptors can be considered as the primary mechanism of the vomiting reflex activation [10]. This reflex can that way occur due to the effects the anesthetic agents have on the central receptors (5-HT3 receptor) that are found in the medullary chemoreceptive trigger zone (CTZ) and also due to the releasing of serotonin by the enterochromaffin cells of the small intestine. The possible 5-HT3 receptor at vagal afferent nerve is then excited by this release in the emetic process [11].

The rate of postoperative nausea and vomiting (PONV), which develops as an aftermath of laparoscopic surgery, is actually soaring and PONV is a multifactorial response, that is, a response of many factors. The predisposing factors are the age, obesity, a prior history of a PONV, the surgical procedure during which it was performed, the techniques of the anesthesia and management of postoperative pain [12-16]. Patient groups in the work were generally similar in relation to demographic factors, surgical intervention, used anesthesia, antibiotic and analgesic intake after the surgery. Thus any perceived variations in the results may be brought about by the study medications.

Granisetron is quite a new 5-HT 3 receptor blocker, and it was initially used as a chemotherapy-induced nausea and vomiting treatment. Another advantage of granisetron over the older 5-HT3 antagonists is that it possesses a higher binding affinity as well as a long half-life and this alteration of trait could influence the pharmacokinetics and the mechanism involved in binding to receptors [17,18,7]. Although the specific mechanism of action by which PONV is prevented is still under study, it is thought that the mechanism of action may be similar to that of agent ramosetron, though its long half-life and the specific receptor actions may be advantages not seen by the ramosetron agent.

The ramosetron dose that was chosen in this study (4 mg before induction dose by IV route) is a dose that has been reported to be within its effective range [19]. The dosage of granisetron (75 mcg IV) entered failed to be strongly identified and was predicted after other clinical studies [20,21]. Kovac et al. have established that an effective dose of 75mcg worked better than the low doses (25mcg and 50mcg) in preventing PONV in the major gynaecology, and laparoscopic surgeries [21]. Placebo group was not involved as it was also indicated that placebo-controlled trials might be unethical in the case of having active drugs since PONV following laparoscopic surgery is distressing [22].

This trial implies that there is no significant antiemetic difference between Granisetron and Ramosetron in the predetermined prevention of PONV during the first 24 hours of liver extraction procedures that are performed using the laparoscopic surgery techniques and the effect of both medications is the same as far as the complete response (no PONV, no rescue medication) is concerned. Although Granisetron and Ramosetron respond differently pharmacokinetically as they do in their binding profiles (Ramosetron possesses the 3.5 - 5.5-hour

half-life, whereas Granisetron has up to 40 hours of a half-life), use different mechanisms to interact with their receptor, Granisetron has failed to produce better antiemetic properties than Ramosetron. Such results differ with other recent studies like Moon et al. [23] who favoured the significance of Granisetron relative to Ramosetron during life-threatened cases as well as those who underwent thyroidectomy procedure and those who received patient-controlled analgesia on fentanyl basis. Also Granisetron has proven better than Ramosetron in preventing PONV during middle ear surgery [24], during day care surgery [25], and during gynecological laparoscopic surgery [26]. It may turn out that the efficiency of the drugs is different in regard to the kind of surgery, where the two drugs are equally effective in case of laparoscopic cholecystectomy. In an examination Bhattacharjee et al. [27] found out that compared to Granisetron, was more effective in the interval 24-48 hours but not within 24 hours, after laparoscopic cholecystectomy in the prevention of PONV.

In terms of safety, both of the drugs were noted to be tolerated well, and no meaningful difference was observed in the prevalence of such typical side effects as a headache, dizziness, or drowsiness. Although there has been concern regarding the possibility of Ramosetron to increase the QTc interval and consequently raising the ventricular tachycardia risk [28,29], in the current study there were no signs of increased QTc interval or other ECG abnormalities. Both Granisetron and Ramosetron showed little side effects on being applied in the way described. Later on, the absence of any serious adverse effects could be cited as one of the reasons ensuring that the study was completed successfully by all the participants.

Conclusion

The outcome of the current study will definitely add up to the existing body of support of using Granisetron as a safe and dependable treatment of PONV during laparoscopic surgery despite the absence of placebo group. This study could be improved in the future by using a larger sample size and a double-blind design that will facilitate a further confirmation of these results and investigate a possible difference in efficacy regarding other types of surgeries.

References

1. Islam, S., & Jain, P. N. (2004). Post-operative nausea and vomiting (PONV): A review article. *Indian Journal of Anaesthesiology*, 48, 253–258.
2. Turkistani, A., Abdullah, K., Manaa, E., Delvi, B., Khairy, G., Abdulghani, B., et al. (2009). Effect of fluid preloading on postoperative nausea and vomiting following laparoscopic cholecystectomy. *Saudi Journal of Anaesthesia*, 3, 48–52.
3. Grover, V. K., Mathew, P. J., & Hegde, H. (2009). Efficacy of orally disintegrating ramosetron in preventing postoperative nausea and vomiting after laparoscopic cholecystectomy: A randomized, double-blind placebo-controlled study. *Anaesthesia*, 64, 595–600.

4. Wallenborn, J., Eberhart, L. H., & Kranke, P. (2009). Postoperative nausea and vomiting – what's new in anti-emetic pharmacotherapy. *Anasthesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie*, 44, 296–304.
5. Kloth, D. D. (2009). New pharmacologic findings for the treatment of PONV and PDNV. *American Journal of Health-System Pharmacy*, 66(1 Suppl 1), S11–S18.
6. Navari, R. M. (2006). Granisetron: A second-generation 5-hydroxytryptamine receptor antagonist. *Future Oncology*, 2, 591–602.
7. Rojas, C., Stathis, M., Thomas, A. G., Massuda, E. B., Alt, J., Zhang, J., et al. (2008). Granisetron exhibits unique molecular interactions with the 5-HT3 receptor. *Anesthesia & Analgesia*, 107, 469–478.
8. Muchatuta, N. A., & Paech, M. J. (2009). Management of postoperative nausea and vomiting: Focus on granisetron. *Therapeutic Clinical Risk Management*, 5, 21–34.
9. Lerman, J. (1992). Surgical and patient factors involved in postoperative nausea and vomiting. *British Journal of Anaesthesia*, 69(7 Suppl 1), 24S–32.
10. Bunce, K. T., & Tyers, M. B. (1992). The role of 5-HT in postoperative nausea and vomiting. *British Journal of Anaesthesia*, 69(7 Suppl 1), 60S–62.
11. Watcha, M. F., & White, P. F. (1992). Postoperative nausea and vomiting: Its etiology, treatment, and prevention. *Anesthesiology*, 77, 162–184.
12. Gan, T. J. (2007). Mechanisms underlying postoperative nausea and vomiting and neurotransmitter receptor antagonist-based pharmacotherapy. *CNS Drugs*, 21, 813–833.
13. Apfel, C. C., Kranke, P., Katz, M. H., Goepfert, C., Papenfuss, T., Rauch, S., et al. (2002). Volatile anaesthetics may be the main cause of early but not delayed postoperative vomiting: A randomized controlled trial of factorial design. *British Journal of Anaesthesia*, 88, 659–668.
14. Tramer, M., Moore, A., & McQuay, H. (1996). Omitting nitrous oxide in general anaesthesia: Meta-analysis of intraoperative awareness and postoperative emesis in randomized controlled trials. *British Journal of Anaesthesia*, 76, 186–193.
15. Sinclair, D. R., Chung, F., & Mezei, G. (1999). Can post-operative nausea and vomiting be predicted? *Anesthesiology*, 91, 109–118.
16. Koivuranta, M., Laara, E., Snare, L., & Alahuhta, S. (1997). A survey of postoperative nausea and vomiting. *Anaesthesia*, 52, 443–449.
17. Gan, T. J. (2005). Selective serotonin 5-HT3 receptor antagonists for postoperative nausea and vomiting: Are they all the same? *CNS Drugs*, 19, 225–238.
18. Ho, K. Y., & Gan, T. J. (2006). Pharmacology, pharmacogenetics, and clinical efficacy of 5-hydroxytryptamine type 3 receptor antagonists for postoperative nausea and vomiting. *Current Opinion in Anaesthesiology*, 19, 606–611.
19. Helmers, J. H., Briggs, L., Abrahamsson, J., Soni, J., Moodley, J., Forrler, M., et al. (1993). A single i.v. dose of ramosetron 8 mg prior to induction of anaesthesia reduces postoperative nausea and vomiting in gynaecological patients. *Canadian Journal of Anaesthesia*, 40, 1155–1161.

20. Candiotti, K. A., Kovac, A. L., Melson, T. I., Clerici, G., Joo Gan, T. (2008). A randomized, double-blind study to evaluate the efficacy and safety of 3 different doses of granisetron versus placebo in preventing postoperative and postdischarge nausea and vomiting. *Anesthesia & Analgesia*, 107, 445–451.
21. Kovac, A. L., Eberhart, L., Kotarski, J., Clerici, G., Apfel, C. (2008). A randomized, double-blind study to evaluate the efficacy and safety of three different doses of granisetron versus placebo in preventing postoperative nausea and vomiting over a 72-hour period. *Anesthesia & Analgesia*, 107, 439–444.
22. Aspinall, R. L., & Goodman, N. W. (1995). Denial of effective treatment and poor quality of clinical information in placebo-controlled trials of ramosetron for postoperative nausea and vomiting: A review of published trials. *British Medical Journal*, 311, 844–846.
23. Moon, Y. E., Joo, J., Kim, J. E., & Lee, Y. (2012). Antiemetic effect of ramosetron and granisetron in thyroidectomy: A prospective, randomized, double-blind study. *British Journal of Anaesthesia*, 108, 417–422.
24. Basu, A., Saha, D., Hembrom, B. P., Roy, A., Naaz, A. (2011). Comparison of granisetron, granisetron, and ramosetron as anti-emetics for prevention of postoperative nausea and vomiting in patients undergoing middle ear surgery. *Journal of Indian Medical Association*, 109, 327–329.
25. Bajwa, S. S., Bajwa, S. K., Kaur, J., Sharma, V., Singh, A., Singh, A., et al. (2011). Granisetron: A novel approach to control postoperative nausea and vomiting in day care surgery. *Saudi Journal of Anaesthesia*, 5, 19–24.
26. Park, S. K., & Cho, E. J. (2011). A randomized, double-blind trial of granisetron compared with ramosetron in preventing postoperative nausea and vomiting after gynecological laparoscopic surgery. *Journal of International Medical Research*, 39, 399–407.
27. Bhattacharjee, D. P., Dawn, S., Nayak, S., Roy, P. R., Acharya, A., Dey, R. (2010). A comparative study between granisetron and granisetron to prevent postoperative nausea and vomiting after laparoscopic cholecystectomy. *Journal of Anaesthesiology & Clinical Pharmacology*, 26, 480–483.
28. Charbit, B., Albaladejo, P., Funck-Brentano, C., Legrand, M., Samain, E., & Marty, J. (2005). Prolongation of QTc interval after postoperative nausea and vomiting treatment by droperidol or ramosetron. *Anesthesiology*, 102, 1094–1100.
29. McKechnie, K., & Froese, A. (2010). Ventricular tachycardia after ramosetron administration in a child with undiagnosed long QT syndrome. *Canadian Journal of Anaesthesia*, 57, 453–457.