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Study Comparing Ramosetron, Granisetron and Ondansetron in Laparoscopic Surgeries Under General Anaesthesia

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ABSTRACT

Backgound: *Postoperative nausea and vomiting (PONV) is one of the most common and distressing complications after anaesthesia and surgery.*

Aim: *Compare the antiemetic efficacy of intravenous Ramosetron, Granisetron and Ondansetron for prophylaxis of post operative nausea and vomiting after laparoscopic surgeries under General Anesthesia.*

Methodology: *It is a prospective study include 50 patients undergoing laproscopic surgery under general anesthesia. Study is done for a period of 6 months. Patients were randomly divided into three groups, Group-A received Ondansetron 8mg, Group-B received Granisetron 3 mg and Group-C received Ramosetron 0.3mg*

Results: *However, there were no significant differences in the incidence of nausea and vomiting, severity of nausea, and required rescue PONV between the groups in first 24 hours. Between 24-48 hrs the incidence of nausea and vomiting is significantly(p value=0.05) less in Group C compared to group-A. Ramosetron is giving longer protection against PONV up to 48 hours.*

Conclusion: *Study therefore concludes that prophylactic therapy with Ramosetron is more effective than with Ondansetron and Granisetron for the long term prevention of PONV after laparoscopic surgeries under general anaesthesia.*

Keywords: *Ondansetron, Granisetron , Ramosetron, General anesthesia*

INTRODUCTION

Postoperative Nausea and Vomiting (PONV) are common distressing complications of surgery and anaesthesia.[1] The syndrome of nausea, retching and vomiting is known as 'sickness' and each part of it can be distinguished as a separate entity. PONV (Post operative nausea and vomiting) has been characterized as big little problem and has been a common complication for both inpatients and outpatients undergoing virtually all types of surgical procedures.[2] In the present scenario it is estimated that 22% to 30% of adult patients will develop post operative emesis which is consistently lower when compared to 75% - 80% incidence reported during the 'ETHER ERA'.

As per the statistical data, incidence of post operative nausea and vomiting ranges from 25% to 55% following inpatient surgery and 8% to 47% for outpatient surgery. Along with pain, this is often listed by the patient as their most important peri-operative concerns.[3] Severe and persistent post operative nausea and vomiting can cause tension on suture lines, bleeding at operative sites and wound dehiscence, venous hypertension, esophageal tear and rupture, rib fractures, gastric herniation and muscular fatigue.[4, 5] Their costs may result from longer time to recover, extended stay in the hospital, added attention required from nurses and physicians.

There are various types of procedures that may be viewed as possible risk factors include intra-abdominal, laparoscopic, orthopedic, major gynecological, ear, nose and throat (ENT),thyroid, breast and plastic surgery as well as neurosurgery[6]and in children hernia repair, adeno-tonsillectomy, strabismus or penile surgery and orchiopexy. [7]

Laparoscopic surgeries are associated with an appreciably high rate of PONV, because of the creation of pneumoperitonium during the procedure.[8] Its incidence being as high as 50%.[9]

So far several drugs have been used for preventing PONV. Most of them act as antagonist at the receptors which are involved in emesis. The traditional anti emetics include antihistamines, anticholinergics and dopamine-receptor antagonists.[10] Early ambulation and reduced morbidity are the advantages of the drug therapy. However, they have limited efficacy in PONV and are associated with side effects such as sedation and extra pyramidal signs.

Newer class of drugs, such as the Serotonin Receptor Antagonists (SRA) provides better efficacy and safety as compared to the traditional drugs.[11].The present study is to compare the antiemetic effects of intravenously administered ramosetron, granisetron and ondansetron for prophylaxis of post-operative nausea and vomiting in patients undergoing laparoscopic surgeries under general anesthesia.

MATERIALS & METHODS

Present study is a randomized prospective study include 75 patients undergoing laproscopic surgery under general anesthesia. Study is done for a period of 6 months from January 2014 to june 2014 admitted in our hospital.

Inclusion criteria: ASA I-II male & female patients, aged 18-65 years, undergoing elective laparoscopic surgeries under general anaesthesia.

Exclusion criteria: gastrointestinal disease, smokers, who had history of motion sickness, postoperative nausea and vomiting, pregnant, menstruating and those who had taken antiemetic medication within last 24 hrs.

Patients were divided into three groups and following drugs were given

Group	No. of patients in each group	Study drug	Dose Of drug
Group – A	25 Patients	Ondansetron	8 mg
Group – B	25 Patients	Granisetron	3 mg
Group – C	25 Patients	Ramosetron	0.3mg

The study protocol was approved by the institution ethical committee and informed consent was obtained from every patient .Based on the previous studies advocating use of the minimum recommended doses, ondansetron in a dose of 8 mg and granisetron in a dose of 3mg, ramosetron in a dose of 0.3 mg were administered for prevention of PONV in the present study. Medications were prepared by paramedical personnel who are not involved in the study in identical syringes with study drugs and 0.9% normal saline was added to the granistron and ramosetron to make desired volume (4ml) and was administered according to the randomization list.

All patients were kept fasting after midnight. In the operation room, routine monitoring (ECG, pulse oximetry, NIBP) were attached and baseline vital parameters like heart rate (HR), blood pressure (systolic, diastolic and mean) and arterial oxygen saturation (SpO2) were recorded. An intravenous line was secured. All patients were premedicated with study drug and inj. Glycopyrrolate 0.2 mg as a anti sialogogue, inj.Midazolam 0.03 mg/kg as a sedative and inj. Tramadol 2 mg/kg intravenously as a analgesic before induction.

After preoxygenation for 3 minutes, induction of anaesthesia was done with inj. Thiopental 5mg/kg. Patients were intubated with inj. Succinylcholine 2 mg/kg with appropriate size endotracheal tube. Anaesthesia was maintained with 33% oxygen, nitrous oxide 67%. Muscle relaxation was maintained with inj. vecuronium bromide with a dose of 0.1mg/kg and intermittent bolus doses of vecuronium bromide and supplemented with sevoflurane. The patients were mechanically ventilated to keep $EtCO_2$ between 32-35 mm Hg. A nasogastric tube was inserted to empty the stomach. For laparoscopic surgical procedure, peritoneal cavity was insufflated with carbon dioxide. Intra abdominal pressure was kept <14 mm Hg. At the end of surgical procedure, residual neuromuscular block was adequately reversed using intravenous glycopyrrolate 0.01mg/kg and neostigmine 0.05mg/kg and subsequently extubated. Before tracheal extubation, the nasogastric tube was suctioned and removed. For postoperative analgesia, injection diclofenac sodium-75 mg intramuscular was given when pain score was > 4(VAS). All patients were observed postoperatively by resident doctors who were unaware of the study drug. Patients were transferred to post anaesthesia care unit and blood pressure, heart rate and oxygen saturation were monitored. All episodes of PONV (nausea, retching and vomiting) were recorded at different intervals of 4, 8, 12, 16, 20, 24, 36 and 48 hours in postoperative ward.

Nausea was defined as unpleasant sensation associated with awareness of the urge to vomit. Retching was defined as the laboured, spastic, rhythmic contraction of the respiratory muscles without the expulsion of gastric contents. Vomiting was defined as the forceful expulsion of gastric contents from mouth. Complete response (free from emesis) was defined as no PONV and no need for any rescue medication injection metoclopramide10 mg i.v. was given as rescue medication if they vomited more than twice.

At the end of each interval we registered whether vomiting has occurred and asked the patients whether they felt nausea, retching. The result was scored as no PONV-0, nausea-1, retching-2 and vomiting-3 and Fisher's and Chi-Square test analyzed a 2x2 contingency table, P value < 0.05 was considered significant.

RESULTS

The present study was under taken on 75 ASA grade I-II male and female patients, aged 18-65 years, undergoing elective laparoscopic surgeries under general anesthesia.

These patients were randomly divided into three groups, Group-A received Ondansetron 8mg, Group-B received Granisetron 3 mg and Group-C received Ramosetron 0.3mg.

In our study data was analyzed using Fisher's and chi-square Analyze a 2x2 contingency table. Demographic data was expressed as mean ± standard deviation and analyzed data using one way analysis of variance (ANOVA). Probability values < 0.05 were considered as statistically significant.

Table 1: Demographic Data

Characterisitic	Group-A (Ondansetron)	Group-B (Granisetron)	Group-C (Ramosetron)	P value
Age (yrs)	28.8 ± 9.92	30.5 ± 12.8	30.20± 8.99	0.83
Weight (kg)	51.48±5.6	50.64± 5.39	50.64± 5.28	0.82
Duration of surgery (min)	58.48±13.81	58.64±14.43	56.44±11.36	0.81

Table shows the demographic distribution (age, weight, duration of surgery) is comparable between the above three groups which is statistically insignificant (p>0.05).

Table -2: Demographic Data (Gender)

Gender	Group-A (Ondansetron)	Group-B (Granisetron)	Group-C (Ramosetron)
Female	18	17	17
Male	7	8	7

The gender distributions of patients were similar between Group-A (Ondansetron), Group-B (Granisetron) and Group-C (Ramosetron).

Table -3: Incidence Of Nausea Among Three Groups In First 48 Hrs.

Group	0-4 Hrs	4-8 Hrs	8-12 Hrs	12-16 hrs	16-20 hrs	20-24 hrs	24-36 hrs	36-48 hrs
A	1	1	1	2	2	3	9	10
B	0	1	1	1	2	2	2	4
C	0	0	1	1	1	1	1	1
	P value	P value	P value	P value	P value	P value	P value	P value
A/C	1.0	1.0	1.0	1.0	1.0	0.61	0.03*	0.02
A/B	1.0	1.0	1.0	1.0	1.0	1.0	0.09	0.22
B/C	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.35

*Significance(P<0.05) Group- A (Ondansetron), Group-B (Granisetron) and Group- C (Ramosetron)

Table shows first 24 hrs after surgery the incidence of nausea is less and comparable in all the above three groups (p>0.05). But between 24-48 hrs the incidence of nausea is significantly less in Group C with p<0.05 ie with significant when compared to group-A and the incidence nausea is also less in Group-B compared to Group-A but statistically insignificant (p>0.05). The incidence of nausea is little more in Group-B compared to Group-C but statistically insignificant (p>0.05).

Table 4: Incidence Of Retching Among 3 Groups In First 48 Hrs.

Group	0-4 Hrs	4-8 Hrs	8-12 Hrs	12-16 hrs	16-20 hrs	20- 24 hrs	24-36 Hrs	36-48 hrs
A	1	1	1	1	2	3	3	4
B	0	0	0	1	1	2	2	3
C	0	0	0	0	1	1	1	1
	P value	P value	P value	P value	P value	P value	P value	P value
A/C	1.0	1.0	1.0	1.0	1.0	0.61	0.61	0.35
A/B	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
B/C	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.61

*Significance(P<0.05) Group- A (Ondansetron), Group-B (Granisetron) and Group- C (Ramosetron)

It shows first 24 hrs after surgery the incidence of retching is less and comparable in all the above three groups (p>0.05). Between 24-48 hrs the incidence of retching is little more in Group-A compared to Group B and C but statistically insignificant (p>0.05). The incidence of retching is almost comparable between Group-Band C.

Table -5: Incidence Of Vomiting Among 3 Groups In First 48 Hrs.

Group	0-4 Hrs	4-8 Hrs	8-12 Hrs	12-16 hrs	16-20 hrs	20- 24 hrs	24-36 hrs	36-48 hrs
A	1	1	1	2	2	3	9	11
B	0	0	0	1	2	2	3	5
C	0	0	0	1	1	1	1	1
	P value	P value	P value	P value	P value	P value	P value	P value
A/C	1.0	1.0	1.0	1.0	1.0	0.61	0.03**	0.01
A/B	1.0	1.0	1.0	1.0	1.0	1.0	0.19	0.25
B/C	1.0	1.0	1.0	1.0	1.0	1.0	0.61	0.20

*Significance(P<0.05) Group- A (Ondansetron), Group-B (Granisetron) and Group- C (Ramosetron)

Above table shows first 24 hrs after surgery the incidence of vomiting is less and comparable in all the above three groups (p>0.05). But between 24-48 hrs the incidence of vommiting is significantly less in Group C with p<0.05 compared to group-A and less in Group-B compared to Group-A but statistically insignificant (p>0.05). The incidence of vomiting is little more in Group-B compared to Group-C but statistically insignificant (p>0.05).

Table-6: Total And Net Incidence Of Vomiting In 0-48 Hrs

Group	Total Incidence	No. Patients who vomited twice	No. Patients who vomited once	Net Incidence
A	30	10	10	20
B	13	4	5	9
C	5	1	3	4

Group- A (Ondansetron), Group-B (Granisetron) and Group- C (Ramosetron)

DISCUSSION

This study compared the antiemetic efficacy of intravenous ramosetron, granisetron and ondansetron for prophylaxis of post operative nausea and vomiting after laparoscopic surgeries under General Aneasthesia. Although laparoscopic surgeries decreased surgical morbidity and have become an accepted procedure for the treatment of many surgical procedures, the high incidence of PONV remains a major clinical problem.

The etiology of PONV after laparoscopic surgery performed under general anesthesia is not fully understood, but is probably multifactorial. Several factors, including age, sex, smoking, history of motion sickness, intraoperative use of isoflurane, residual pneumoperitoneum after CO_2 insufflations ,[12] peritoneum distension, diaphragm irritation and visceral organ irritation and manipulation,[13] have been considered to influence the incidence of PONV.

In this study, however, treatment groups were similar with respect to demographic data and duration of anesthesia, and CO_2 insufflations, where as those with a history of motion sickness and smoking were excluded from the study. Therefore, the difference in the incidence of PONV among the groups could be attributed to the variation in the antiemetic drugs administered. Although ondansetron 4 or 8 mg has been recommended for preventing PONV, the meta-analysis by Tramer and colleagues[14] suggested that an 8 mg dose of ondansetron was optimal for prevention of PONV. Therefore, ondansetron 8 mg was chosen for this study. Our results demonstrated that ondansetron 8 mg was effective in decreasing the incidence of PONV during the 24 h after surgery, which is comparable with the previous reports of ondansetron use for the prevention of PONV.

Granisetron is effective for the treatment of emesis induced by cancer chemotherapy. The precise mechanism of granisetron for the prevention of PONV remains unclear, but it has been suggested that granisetron may act on sites containing 5-HT_3 receptors with demonstrated antiemetic effects. Ramosetron is a newly developed 5-HT_3 receptors antagonist with a more potent and longer receptor antagonizing effect compared with older 5-HT_3 receptors antagonists.[52]In addition, the elimination half-life of ramosetron (9 h) is longer than that of ondansetron (3.5 h) or granisetron (4.9 h).[16] Because of these pharmacological properties, ramosetron is reportedly more potent with a longer duration of action than older 5-HT_3receptor antagonists clinically

The reported efficacy of ramosetron is similar to that of granisetron in the prevention of cisplatin-induced emesis. However, ramosetron appears to have a longer duration of action during the 24 h after cisplatin chemotherapy. In addition, it has been reported that ramosetron was comparable with granisetron to prevent PONV 0–24 h after surgery, but ramosetron was more effective than granisetron for preventing PONV 24–48 h after surgery.[17] Our study results also showed that Ramosetron was comparable with granisetron to prevent PONV 0-24hr after surgery, between 24–48 h after surgery there is a decreased incidence of PONV in Ramosetron group compared with granisetron group but, statistically insignificant.

According to Fujii and colleagues, [18] ramosetron is effective in preventing PONV after major

gynaecological surgery, and ramosetron 0.3 mg is an effective dose for preventing PONV. In addition, the manufacturer's recommended dose is 0.3 mg i.v. once a day. Therefore, ramosetron at 0.3 mg dose was chosen for this study. Our results demonstrated that ramosetron 0.3 mg was effective in decreasing the incidence of PONV up to 48 h after surgery.

Rhu J et al [19]reported that ramosetron 0.3 mg and ondansetron 8mg are more effective than ondansetron 4mg for prevention of PONV (2hrs). Ramosetron 0.3mg is as effective as ondansetron 8mg for prophylaxis of PONV after laparoscopic cholecystectomy.

Kim SI et al[20] reported that Ramosetron 0.3mg was as effective as ondansetron 8mg iv in decreasing the incidence of PONV and reducing nausea severity in female patients during the first during the first 24hrs after gynecological surgery.

Although the efficacy of ramosetron was shown to be similar to ondansetron in reducing the incidence of PONV and severity of nausea, ramosetron appeared superior to ondansetron in minimizing the need for additional rescue antiemetic during the first 24 h after operation. Ramosetron significantly reduced the need for additional rescue antiemetic over the 48 h after operation (0–24 h and 24–48h). Ondansetron also significantly reduced the need for additional rescue antiemetic during 0-24 h after operation. However, it did not significantly decrease the need for additional rescue antiemetic use during after 24 hrs after operation and, consequently. As a result, it appears that ramosetron has a more potent, longer lasting antiemetic effect when compared with ondansetron which is statistically significant. Therefore, we suggest ramosetron is a more favorable antiemetic than ondansetron in the prevention of PONV.

The most frequently reported adverse events of 5-HT_3 receptor antagonists are dizziness and headache [21]Adverse events observed minimal in our study were similar among all three groups Many medications given to participants under anesthesia care are also known to cause QTc prolongation, such as inhaled anesthetics, propofol, thiopental, succinylcholine, and neuromuscular blocker antagonists. Most currently available antiemetic also cause QTc prolongation, including phenothiazines, antihistamines, and $5HT_3$ antagonists such as Ondansetron.

In one study Chan MT et al was observed that, a 2.7-3.5% QT prolongation recorded at 5 min after injection of pre-induction medications was equal to 11.3 ± 24.3 ms with 1.25 mg droperidol alone, 9.9 ± 34.7 ms with 4 mg Ondansetron alone.[22] but in our study QTc changes were not monitored.

In our study we compare the antiemetic efficiency of ondansetron, granisetron and ramosetron post operatively for laparoscopic surgeries for first 48 hours. Our study demonstrate that in first 24 hours antiemetic efficiency of three groups of drugs (Ondansetron, Granisetron and ramosetron) are similar and statistically not significant

Bhattacharya D et al[23] reported that Granisetron is superior than ondansetron for prevention of PONV results showed that incidence of PONV to be less with Granisetron when compared with ondansetron. With in first 6 hours post operatively in patients undergoing day care gynecological laparoscopy these findings are in agreement with our study where incidence of PONV was less with ondansetron and Granisetron in first 6 hours postoperatively

Raihan Uddin Md, et al[24] did study on comparison of ondansetron and granisetron for prevention of PONV following elective cesarean section and concluded that both the drugs have reduced the PONV significantly but comparison between these two drugs for prevention of PONV following elective cesarean section is similar. Our study is also correlating with their study in early prevention of PONV with ondansetron and granisetron.

Our study therefore concludes that ramosetron is safe and has a more potent antiemetic effect as compare to ondansetron and granisetron in patients undergoing laparoscopic surgeries and

confirms the observations of Fujii and associates.[17,18]

CONCLUSION

All the three drugs are effective in preventing nausea and vomiting in first 24 hours. Ramosetron is giving longer protection against PONV up to 48 hours, So prophylactic therapy with Ramosetron is more effective than with Ondansetron and Granisetron for the long term prevention of PONV after laparoscopic surgeries under general anaesthesia.

LIMITATIONS

The limitation of this study was that we compared the efficacy of ramosetron and ondansetron by their known optimal doses because their equipotent doses were unknown at the time of study commencement. Further studies are needed to investigate the equipotency of ramosetron and ondansetron to prevent PONV.

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