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Original Research Article

Comparison of ramosetron with ondansetron for prevention of postoperative nausea and vomiting in patients undergoing lower abdominal surgery

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Abstract

Background: The goal of PONV management is to reduce or eliminate PONV and discomfort with minimum side effects. 5-HT antagonists work by blocking one of the pathways that lead to vomiting. Ondansetron is the most commonly used drug for this purpose. Ramosetron has a higher affinity for the 5-HT3 receptor than the older 5-HT3 antagonists, with an optimal dose of 0.6 mg and maintains its effects over two days.

Objectives: To compare the efficacy of ondansetron and ramosetron in the control of postoperative nausea and vomiting and to determine the occurrence of adverse effects with ondansetron and ramosetron.

Material and Methods: Fifty patients aged between 20-60 years posted for lower abdominal surgeries were divided into two groups (Group A & Group B) on the basis of the random sampling method. Group A received the first dose of Ramosetron in the intraoperative period 30min-1 hour before expected end of surgery. Group B received the first dose of Ondansetron in the intraoperative period 30min-1 hour before the expected end of surgery. Both groups were postoperatively monitored for incidence of nausea, the severity of nausea, the incidence of vomiting and use of rescue antiemetics, for 24 hours.

Data Analysis: The mean and Standard Deviation (SD) in each group was calculated. The data were analyzed by student t-test. For qualitative data, Chi-Square test was used for analysis. P-value less than 0.05 was considered statistically significant.

Result: The present results revealed that ramosetron is more effective than ondansetron in preventing late postoperative nausea and vomiting. Ramosetron is more potent and longer acting as compared to ondansetron. Incidences of side effects and use of rescue antiemetic are statistically not significant in both the groups.

Conclusion: This study concludes that the prophylactic intravenous administration of ramosetron is more effective than ondansetron for controlling late postoperative nausea and vomiting.

Keywords: Ondansetron, ramosetron, postoperative nausea and vomiting, antiemetic, $5HT_3$ antagonist

Introduction

The most common and distressing symptoms after surgery are pain, nausea and vomiting [1]. Pain causes suffering and draws first attention. Sometimes, especially after minor and ambulatory surgery, nausea and vomiting might be more uncomfortable, delaying hospital

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discharge [2]. However, in the last two decades, postoperative pain management has gained far more attention than postoperative nausea and vomiting. Incidence of postoperative nausea and vomiting is still very high in spite of few newer medications in our armament.

The vomiting lasted only a few minutes in most cases, but it could extend for hours or even days in others. PONV was claimed to be as common as 75-80% during the ether era. Changes in anaesthesia technique from opioid and deep ether anaesthesia to non-opioid or opioid-supplemented anaesthesia, use of fewer emetic anaesthetic drugs and better pre-and post-operative treatment slightly reduced the PONV. Despite these advancements, nausea and vomiting are still unacceptably common side effects of surgery and anaesthesia [3].

Persistence nausea vomiting can have serious medical consequences to the patient as well as financial implications in delayed discharge from the hospital. Now a day's number of acceptable surgical procedures has increased in the field of ambulatory anaesthesia, the need to find more effective alternatives to the options available, has become more urgent [4]. An unforeseen postoperative stay for severe nausea may overshadow the potential cost savings of conducting these procedures on an outpatient basis. In addition, although intractable nausea is distressing possibly dehydrating and not easily manageable at home, the expense of a hospital stays is disproportionate to the actual morbidity of nausea for most healthy outpatients. Finally, the therapy is unsatisfactory for the patient, the anesthesiologist and the surgeon. Even mild postoperative nausea and vomiting are sometimes regarded as failures of therapy rather than unavoidable perioperative effects. Antihistamines, anticholinergics, and dopamine antagonists have all been used in pharmacological attempts to lower the incidence or severity of emesis. Physical manoeuvres have included imposing various "Nothing per os" regimens, pre-anaesthetic suctioning of gastric contents, application of cricoid pressure, avoiding inflation of the stomach during ventilation by mask and ingestion of antacid solutions [5]. None of the aforementioned measures, alone or in combination, have proven to be totally effective in reducing the disturbing occurrence of emesis and its possible consequences. The relative ineffectiveness and associated adverse effects of traditional antiemetic agents led to a search for a newer and better antiemetic agent.

Ondansetron is a selective 5 hydroxytryptamine subtype 3 (5HT.) receptor antagonists were introduced into the market in 1991 which lack effects on cholinergic, adrenergic, dopaminergic or histaminergic receptors. Ondansetron is structurally related to serotonin [6]. Ondansetron has an effect on oesophageal or gastric motility, or small bowel transit time, lower oesophageal sphincter pressure. By 5-HT; selectivity, the undesirable side effects of using antagonists of dopaminergic, cholinergic or histaminergic receptors as antiemetic agents, such as dysphoria, sedation and extrapyramidal symptoms, are avoided. It has been shown to be an effective antiemetic with no major side effects in patients taking cytotoxic chemotherapy [7-10]. The use of ondansetron for the treatment of PONV has now become common. Extensive trials employing oral and intravenous ondansetron in a variety of patients undergoing various procedures have validated the drug's efficacy while also reducing the drug's side effects. This is now the gold standard by which all future antiemetic drugs will be evaluated. Ramosetron, a selective serotonin 5-hydroxytryptamine type 3 (5-HT3) receptor antagonist, has better inhibitory activities than those of formerly available antagonists such as ondansetron, granisetron and Tropisetron. Ramosetron is more potent and has longer-lasting antiemetic effects than older agents because of a slower rate of dissociation from the target receptor and higher binding affinity [11, 12]. In the postoperative period, since nausea, retching and vomiting may last for 24 hours or even more, a longer-acting drug may be essential and

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useful. Instead of a shorter acting drug like ondansetron, a longer-acting, ramosetron may be liked by physicians, patients or staff nurses who are involved in postoperative care [13]. Based on this, the present study was carried out to compare the effect of ramosetron with ondansetron for postoperative nausea and vomiting.

Materials and Methods

Study was conducted in Rajagiri Hospital, Kochin, Kerala, India.
Fifty patients aged between 20 to 60 years posted for lower abdominal surgeries were randomly divided into two groups i.e. Group A and Group B.

Inclusion criteria

Patients of ASA grade 1 between the age group of 20-60yr posted for lower abdominal surgeries under anaesthesia.

Exclusion criteria

1. Patients allergic to the study drugs.
2. Pregnancy.
3. Body weight more than 30% above the ideal body weight.
4. Vomiting or retching within 24 h before the operation.
5. Administration of antiemetics or steroids or psychoactive medications within 24h before the operation.
6. Respiratory, cardiovascular, renal, hepatic, endocrine, gastrointestinal or neurological disease.
7. Previous history of Postoperative nausea and vomiting.

Pre-operative examination

A routine pre-operative examination of general condition, CVS, CNS, RS and per abdomen, history of allergy to study medication of all the patients who were included in the study was done on the previous day of surgery for the assessment. Required investigations like complete haemogram, random blood sugar, urine-sugar, albumin, microscopy, electrocardiogram, chest x-ray done before the day of surgery.
All selected patients were pre-medicated with tab. alprazolam 0.25mg and tab. ranitidine hydrochloride 150 mg orally on the previous night. All the patients were explained about the visual analogue scale of 0 to 10, with 0 representing as no nausea and vomiting, 10 as severe nausea and vomiting. Group A and Group B were received the first dose of ramosetron and ondansetron respectively in the intraoperative period 30min to 1hour before the expected end of surgery. Both the groups were postoperatively monitored for incidence of nausea, the severity of nausea, incidence of vomiting and use of rescue antiemetics, for 24 hours.
Complete response is defined as 'no nausea, no retching, no vomiting' in both groups. Rescue medication was given for the patients who had severe nausea and vomiting. Drug, dose and frequency of rescue medication given were noted and also any analgesics given in the observation period was also noted.
All the patients were monitored for vitals as routine protocol, postoperatively. Any hemodynamic variations in blood pressure or heart rate of more than 30% of baseline were recorded following antiemetic medication. If any Side effects like constipation, headache, diarrhoea, fatigue, insomnia, dizziness, abdominal pain was recorded.

ISSN 2515-8260 Volume 09, Issue 04, 2022

Statistical analysis

The data collected were presented as mean, SD for quantitative observations and proportions (%) for qualitative observations. Quantitative data and qualitative data were analyzed by student's t-test and Chi-Square test respectively. A probability (P) value of < 0.05 was considered statistically significant.

Results

34 yr and 41 yr are the average age of the patients in ondansetron and ramosetron groups respectively. 59kg and 60kg are the average weight of the patients in ondansetron and ramosetron groups respectively. There was no statistical difference between age, weight and gender in the two groups (Table-1).

Table 1: Demographic details

Demographic details	Ondansetron	Ramosetron	p-value
Age (Yr)	34	41	$p>0.05$
Weight (Kg)	59	60	$p>0.05$
Male	12	12	$p>0.05$
Female	13	13	$p>0.05$

The mean duration of surgery in ondansetron and ramosetron groups are 99min and 93 min respectively. There was no statistical difference in the duration of surgery between the two groups. Duration of anaesthesia in ondansetron and ramosetron groups are 134 min and 138 min respectively. There was no statistical difference in the duration of anaesthesia between the two groups. 97.92µg, 100µg of fentanyl was used in ondansetron and ramosetron groups respectively. There was no statistical difference in the use of intraoperative fentanyl between the two groups. 157 mg, 146 mg of tramadol was used in ondansetron and ramosetron groups respectively. There was no statistical difference in post-op tramadol consumption between the two groups.

Percentage of patients who had a complete response to nausea and vomiting at early post-op (0-4hr) are 84%, 84%, mid post-op (4-12hr) are 88%, 96%, late post-op (12-24hr) are 88%, 100% respectively in ondansetron and ramosetron-treated groups. There was no statistical difference in overall complete response to nausea and vomiting between the two groups (Figure-1).

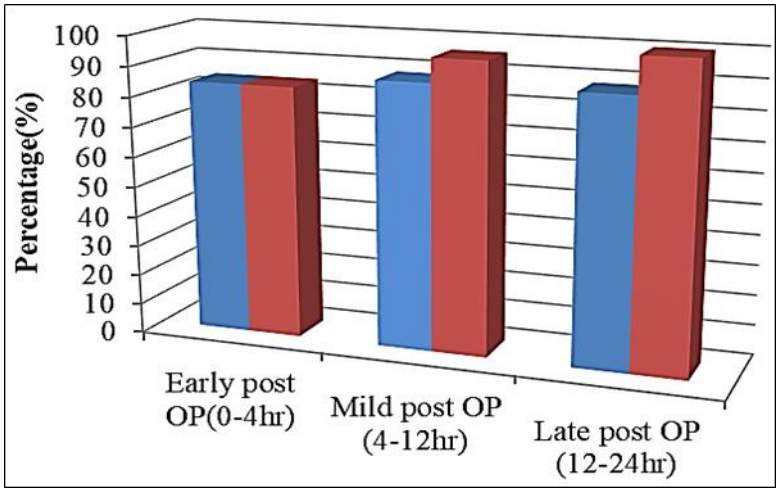

Fig 1: Complete response to nausea and vomiting

ISSN 2515-8260 Volume 09, Issue 04, 2022

Rescue antiemetics were used in 12% and 8% of patients in ondansetron and ramosetron treated groups respectively. But there was no statistical difference between the two groups in the need for rescue anti emetics. Side effects observed in ondansetron and ramosetron treated groups were 20%, 16% respectively. But there was no statistical difference between the two groups. Side effects observed in ondansetron and ramosetron treated groups were constipation in 40%, 25%, headache 20%, 25%, dizziness 40%, 50% respectively. 12%, 8% of patients had vomiting with general anesthesia in ondansetron and ramosetron treated groups respectively. There was a statistically significant difference in nausea in patients who received general anesthesia between the two groups. 8%, 8% of patients had vomiting with a subarachnoid block in ondansetron and ramosetron treated groups respectively. There was no statistical significance difference of nausea in patients who received subarachnoid block between the two groups.

Discussion

Postoperative nausea and vomiting (PONV) are associated with a number of factors. The incidence of PONV after anesthesia is still found to be relatively high despite the advances in antiemetic therapy. Factors affecting PONV include patient-related factors (age, sex, phase of the menstrual cycle), anesthesia-related factors (use of volatile anesthetic agents, N20, Opioid) and surgery-related factors [14]. In comparison to male patients, female patients had a higher incidence of PONV [15, 16]. On average, female patients suffer three times more often from PONV than men. In this direction, a continuous search for a need of optimal efficacious drugs was required. According to a study by Pearman *et al*., postoperative nausea and vomiting are more common in young patients and those who are fat [14]. Paxton *et al*., observed that nausea and vomiting are more common in the first 6 hours postoperative period [17]. When 5HT antagonists are given during the induction time, Janknegt *et al*., found that they are ineffective in preventing PONV [18]. Based on that study drugs were given half an hour before termination of the surgery. This makes the drugs to be more effective postoperatively for a longer time. The present study results are similar to Sinha *et al*., [19].

The dose of ondansetron, 4 or 8 mg I.V. has been recommended for preventing PONV. Tramer *et al*., Ryu *et al*., studies suggest that ondansetron, 8 mg is more effective than a dose of 4 mg. Therefore, ondansetron 8 mg was selected as an optimal dose in the present study [20, 21]. Kim *et al*., study reveals that ramosetron is effective in preventing PONV after gynecological surgery and a dose of 0.6 mg is an effective dose for preventing PONV [22]. Based on this ramosetron 0.6 mg dose was selected for the present study. The present study reveals ondansetron, ramosetron has an equal response of up to 84% in reducing the PONV. Fuji *et al*., showed that ramosetron showed a complete response of up to 90% with a dose either of 0.6mg [23].

Kim *et al*., claims the higher incidence (33% following antiemetics, for Ramosetron) in patients who underwent gynecological surgeries who received general anaesthesia [22]. However the present study subjects received either general anaesthesia or regional anaesthesia. As a known fact, general anaesthesia is known to induce perioperative nausea due to the use of nitrous oxide, intravenous opioids and intravenous antibiotics. Lee *et al*., study showed higher incidences of nausea and vomiting than the present study, possibly owing to the use of post-operative opioid PCA use in their study subjects [24].

The efficacy of the ondansetron, ramosetron during the early part of the study i.e. up to 4 hours are equal efficacy which was similar to the study of Fuji *et al*., [23].

However, during Mid post-op (4-12hr) and late post-op (12-24hr) ramosetron is more efficacious when compared to ondansetron with respect to nausea or retching. This could be explained by the pharmacological action of ramosetron. Ramosetron act on 5-HT receptors with demonstrated antiemetic effects. It exhibits significantly greater binding affinity for

SHT, receptors with a slower dissociation rate from receptor binding, resulting in more potent and longer receptor antagonizing effects compared with older 5-HT, receptor antagonists. Its half-life is 5.8+1.2 hours.

Noda *et al*., study reveals that adverse effects with a single therapeutic dose of granisetron or ramosetron against emesis induced by anticancer drugs are extremely rare and generally minor [25]. In the present study, the prophylactic use of ramosetron for preventing PONV reveals no sedative, dysphoria and extrapyramidal signs. The adverse events observed were not clinically serious and there were no differences in the incidence of headache, dizziness, and drowsiness between the two groups. Thus, ramosetron, like ondansetron, is devoid of clinically important side effects. No severe hemodynamic changes during the study period between the 2 groups. In developing countries cost of anesthesia is an ever-debatable factor. Considerable costs of anesthesia for patients can be a financial burden. Multiple efforts need to be made to reduce the cost of anesthesia. In India, ramosetron comes at a base price of Rs. 35 whereas ondansetron has a base price of Rs. 23. Since the dose of ramosetron is O.D. and ondansetron is T.I.D a total reduction of around 30% per 24 hours would be observed with its use. Incidences of nausea in patients who received general anaesthesia. This could be attributed to the fact that general anaesthesia triggers the CTZ and area postrema to induce nausea. Therefore, the use of rescue antiemetics was more in these patients.

In the present study the factors that might have contributed to nausea and vomiting are lower abdominal surgery, use of postoperative tramadol, use of intraoperative fentanyl etc. The limitation of this study design is the failure to include a control group receiving a placebo. Aspinall and Goodman 130 have also suggested that placebo-controlled trials may be unethical if active drugs are available because PONV are common and distressing symptoms against which there is an effective treatment. [26] Therefore, a control group was not included in our study. Also, individual variation in expressing the severity of nausea, opioid sensitive patient, observer errors, etc. all may contribute to bias and limitations for our study.

Conclusion

The present study concludes that the prophylactic intravenous administration of ramosetron is more effective than ondansetron for controlling late postoperative nausea and vomiting.

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Declarations

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ISSN 2515-8260 Volume 09, Issue 04, 2022

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