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Research Article

A COMPARATIVE STUDY OF ONDANSETRON WITH RAMOSETRON IN PREVENTION OF POST-OPERATIVE NAUSEA AND VOMITING IN PATIENTS UNDERGOING GENERAL ANESTHESIA

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ABSTRACT

Objective: Post-operative nausea and vomiting (PONV) is an unpleasant, distressing, and exhausting experience for patients. PONV may prolong recovery, delay patient discharge, and increase hospital costs. Prevention and treatment of PONV help to accelerate post-operative recovery and increase patient satisfaction. In this study, we compared the efficacy of Ondansetron and Ramosetron to prevent PONV in patients undergoing elective surgeries under general anaesthesia and also to study their side effects.

Methods: Eighty patients (American Society of Anesthesiologists [ASA] I and II) between the age group of 18 and 65 years scheduled to undergo elective surgeries under general anaesthesia were randomly allocated into two groups. Group O received Ondansetron 4 mg and Group R received Ramosetron 0.3 mg intravenously before induction of anaesthesia. Episodes of nausea, vomiting, and retching were determined and noted in first 24 h after surgery at time intervals of 0–3 h, 3–6 h, 6–12 h, and 12–24 h. The incidence of adverse effects and the use of rescue anti-emetics were also noted in the post-operative period. At the end of the surgery, results were compiled and statistical analysis was done using Student's "t" test and Chi-square test. $p<0.05$ was considered as significant.

Results: The incidence of nausea was lower in patients receiving Ramosetron when compared to patients receiving Ondansetron especially in the 0–3 h period (p=0.032). This was statistically significant. The incidence nausea was lower in Group R during 3–6 h, 6–12 h, and 12–24 h period which was not statistically significant (p=1.000, p=0.359, p=1.000 respectively). The incidence of vomiting was lower in patients receiving Ramosetron when compared to patients receiving Ondansetron in the 0–3 h, 3–6 h, 6–12 h, and 12–24 h period, but it was not statistically significant (p=0.712, p=1.000, p=0.241, and p=0.116, respectively). The use of rescue anti-emetics and the incidence of adverse side effects were more in patients receiving Ondansetron when compared to patients receiving Ramosetron with no significance.

Conclusion: Our study concludes that ramosetron was more effective than ondansetron in the prevention of post-operative nausea and was associated with fewer side effects comparatively.

Keywords: Ondansetron, Ramosetron, Post-operative nausea and vomiting.

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INTRODUCTION

Post-operative nausea and vomiting (PONV) is a frequent and unpleasant condition that occurs following a surgical treatment. PONV occurs in 20–30% of patients and is more common (70–80%) in high-risk patients [1,2].

Increased patient discomfort due to PONV is still a source of worry for surgeons and anesthesiologists, and it has some obvious implications for recovery. This frequently results in a delay in the discharge of these patients, putting an additional stress on the hospital. Most patients consider the anguish caused by PONV to be more unpleasant than the post-operative pain itself [3].

Although PONV is typically non-fatal and self-limiting, it can cause wound dehiscence, haemorrhage, aspiration of gastrointestinal contents, dehydration, and electrolyte imbalances [4].

PONV risk factors include both anesthesia-related and non-anesthesia-related variables. According to clinical investigations, the use of volatile anesthetics and post-operative opioid analgesics are anesthesia-related risk factors for PONV [5]. The mechanism behind these two key risk factors, however, is yet unknown [6]. Female sex, a history of PONV or motion sickness, not smoking, and being younger are non-anaesthesia-related risk factors for PONV [5].

Cholinergic receptor antagonists, histamine receptor antagonists, serotonin antagonists, dopamine antagonists, and NK1 antagonists are among the antiemetic medicines used to treat PONV [6-8]. These medicines, however, may have unwanted side effects such as severe sedation, hypotension, dry mouth, dysphoria, hallucinations, and extrapyramidal signs [8].

Because of their demonstrated efficacy and low side-effect profile, selective serotonin (5 hydroxytryptamine Type 3 [5-HT_3]) receptor antagonists are regarded first-line therapy in the prevention of PONV [9].

The majority of research has focused on ondansetron, and its efficacy is well established. However, current cardiac safety concerns about ondansetron limit its usage in some anesthetic conditions where a high dose is required [10].

Ramosetron, a recently released 5-HT_3 receptor antagonist, is believed to be more selective and potent, but there are few randomised controlled trials or case–control studies on its use. Ramosetron is a highly specific 5-HT_3 antagonist. When compared to previous 5-HT_3 receptor antagonists, it has a stronger affinity for the receptors and a slower dissociation, resulting in a prolonged receptor-antagonising effect [11,12].

Hence, the present study was undertaken to compare the antiemetic effects of intravenous Ondansetron and Ramosetron for prophylaxis of PONV in patients undergoing elective surgeries under general anesthesia.

Aims and objectives

The objectives of the study are as follows:

1. To compare the intravenous Ramosetron 0.3 mg with intravenous Ondansetron 4 mg, to prevent PONV in adults undergoing surgeries under general anaesthesia
2. To study the side effects and to assess the requirement of rescue antiemetics in the post-operative period.

METHODS

Study design

This is a prospective, randomized, single-blinded, and comparative study conducted from July 2016 to June 2017 at PES Institute of Medical Sciences and Research, Kuppam, Chitoor district, A.P. The study was approved by ethical committee of our institution. All the patients were well informed about the study and informed written consent was taken from the patients in both groups.

Inclusion criteria

ASA physical class I and II, age between 18 and 65 years, elective surgeries under general anesthesia, and surgery for which the duration is expected to last for at least 30 min or more were included in the study.

Exclusion criteria

ASA physical class III and above, inability to understand or cooperative with the study, hypersensitivity to drugs, extremes of age, emergency surgeries, patients suffering from motion sickness, severe pulmonary, gastrointestinal (GERD), cardiovascular system, renal, hepatic, endocrinological diseases, and neurological diseases, patients who received antiemetics 24 h before surgery or had emetic episode 24 h before the study, and pregnant and lactating female patients were excluded from the study.

Patients were randomly divided into two groups of 40 each. Group "R": Ramosetron group (n=40), received 0.3 mg IV. Group "O": Ondansetron group (n=40), received 4 mg IV.

Pre-operative assessment

A thorough pre-operative evaluation of the patient was performed, including a history, physical examination, and appropriate investigations. Pre-anesthetic examination was used to determine ASA physical categorization. Patients enrolled in the study as per inclusion and exclusion criteria.

A typical pre-induction monitor was used, which included an electrocardiograph, noninvasive blood pressure, pulse oximetry (SpO_2), and extracorporeal membrane oxygenation ($ETCO_2$). The patients were given an intravenous infusion of crystalloid to keep them hydrated.

Anesthesia was administered after premedication with inj. glycopyrolate 0.2 mg and inj. fentanyl 1.5 ug/kg I.V. All patients were sedated and induced with propofol (2 mg/kg). IV vecuronium (0.1 mg/kg) was administered to aid in tracheal intubation. The anesthesia was kept up by 0.5–2% isoflurane and 33% oxygen in nitrous oxide. Fentanyl (2–3 ug/kg) and diclofenac (2 mg/kg) IV were used for intraoperative analgesia.

The residual neuromuscular block was reversed with neostigmine (0.05 mg/kg) and glycopyrolate (0.01 mg/kg) IV at the end of the surgery. The study medication was supplied intravenously by the attending anesthesiologist 30 min before the completion of the surgery. Paracetamol or diclofenac was used to provide post-operative analgesia.

Over the next 24 h, the incidence of PONV, severity of nausea, and requirement for rescue antiemetic were reported at four intervals: 0–3 h, 3–6 h, 6–12 h, and 12–24 h. Vomiting was characterised as either vomiting (expulsion of stomach contents) or retching (an involuntary attempt to vomit that does not result in the production of stomach contents). The desire to vomit was defined as nausea.

Patients were asked to rate the severity of their nausea on a four-point scale, with 0 indicating no nausea, 1 indicating mild nausea, 2 indicating moderate nausea, and 3 indicating severe nausea. On the patient's request or complaint of established nausea or vomiting, rescue medication for PONV (metoclopramide 10 mg IV) was delivered. Patients were taught how to request treatment if and when PONV occurred in the post-operative phase during the pre-operative time.

Results were compiled and statistical analysis was done using Student's "t" test and Chi-square test. $p<0.05$ was considered as significant.

RESULTS

There were no statistically significant differences between the two groups in terms of demographic characteristics of the patients, namely, age, sex, body weight, and duration of surgery (Table 1).

Maximum number of patients, that is, 22.5% of the patients in the immediate post-operative period had nausea when compared to only 1.25%, 6.25%, and 1.25% in the 3–6 h, 6–12 h, and up to 24 h period, respectively. The incidence of nausea was lower in Group R compared to Group O, especially in the 0–3 h periods. This difference was statistically significant ($p<0.05$) (Table 2).

The incidence of vomiting was lower in Group R compared to Group O which was not statistically significant ($p>0.05$) (Table 3).

The commonly observed adverse side effects were headache and dizziness. The side effects were slightly more in Group O compared to Group R and the difference was not statistically significant ($p>0.05$) (Table 4).

Table 1: Demographic profile of patients

Patient variable	O group (n=40)	R group (n=40)	p-value
Age (years)	37.2±13.53	35.7±11.89	0.806
Gender			
Male	14	12	0.734
Female	26	28	
Weight (kg)	66.9±9.82	64.45±8.14	0. 446
Duration of surgery (minutes)	144.75±47.5	147.75±71.7	0.768

Table 2: Incidence of post-operative nausea

Period in hours	Group O		Group R		Total	p-value
	No.	%	No.	%	No.	
0–3	13	32.5	5	12.5	18	0.032*
3–6	1	2.5	0	0	1	1.000
6–12	4	10	1	2.5	5	0.359
12–24	1	2.5	0	0	1	1.000

*Significant

Table 3: Incidence of post-operative vomiting

Period in hours	Group O		Group R		Total	p-value
	No.	%	No.	%	No.	
0–3	5	12.5	3	7.5	8	0.712
3–6	1	2.5	1	2.5	2	1.000
6–12	3	7.5	0	2.5	3	0.241
12–24	4	10	0	0	4	0.116

Aboout 17.5% of patients in Group O required rescue antiemetics compared to 12.5% of patients in Group R. This difference was not statistically significant (p>0.05) (Table 5).

DISCUSSION

PONV remain among the most prevalent problems following surgery, occurring in more than 30% of cases or as high as 70–80% in select high-risk patients without prophylaxis [13].

PONV are a serious concern in modern esthetic practice, with negative effects such as delayed recovery, unexpected hospital admissions, ambulatory patients' delayed return to work, pulmonary aspiration, wound dehiscence, and dehydration [14]. PONV is also one of the most common causes of post-operative patient dissatisfaction.

The key event in the onset of the vomiting reflex is 5-HT_3 receptor stimulation [15]. These receptors are found on the periphery of the vagus nerve and centrally on the chemoreceptor trigger zone (CTZ) of the region postrema. Anesthetics start the vomiting reflex by engaging the central 5-HT_3 receptors on the CTZ, as well as by releasing serotonin from the enterochromaffin cells of the small intestine and then triggering the 5-HT_3 receptors on vagus nerve afferent fibers [8].

5-HT_3 antagonists are drugs that function as receptor antagonists at the 5-HT_3 receptor, a subtype of serotonin receptor located in the vagus nerve terminals and specific parts of the brain. Ondansetron, the first 5-HT_3 antagonist, was discovered in 1984. It is a selective serotonin (5HT-$_3$) receptor antagonist that inhibits serotonin receptors in the gastrointestinal tract or in the CTZ [16].

Ramosetron (ramosetron hydrochloride), a selective 5-HT_3 receptor antagonist, has been on the market in a number of Asian countries since 1996 as an antiemetic for cancer patients having chemotherapy or anesthesia. Ramosetron has higher receptor occupancy following typical intravenous dosing than ondansetron and granisetron. Ramosetron exhibits longer-lasting antiemetic effects than previous agents [17] because to its increased binding affinity to the receptor and slower dissociation rate.

The antiemetic effects of ondansetron and ramosetron were examined in our study. Eighty patients were randomly assigned (40 in each group) to one of two groups. The two groups were clinically matched in terms of patient demographics, kind of operation, anaesthetics used, and post-operative analgesics.

The doses of ondansetron (4 mg) and ramosetron (0.3 mg) utilized in this investigation were extrapolated from previous clinical trial doses. Ansari *et al.* [18], Hahm *et al*. [19] also compared the doses of Ondansetron 4 mg and Ramosetron 0.3 mg in the prevention of PONV.

Table 4: Comparison of incidence of side effects

Side effects	Group O		Group R		Total	p-vaule
	No.	%	No.	%	No.	
Headache	5	12.5	2	5	7	0.742
Dizziness	2	5	0	0	2	0.452
Drowsiness	0	0	0	0	0	-
Diarrhea	0	0	0	0	0	-
Qtc prolongation	0	0	0	0	0	-

Table 5: Use of rescue anti-emetics in the study groups

Rescue anti-emetics	Group O		Group R		Total	p-value
	No.	%	No.	%	No.	
Given	7	17.5	5	12.5	12	0.463
Not given	33	82.5	35	87.5	68	

In our study, the incidence of nausea was maximum, that is, 22.5% in the immediate post-operative period. When compared to patients receiving Ondansetron, those receiving Ramosetron experienced less nausea, particularly in the first 3 h which was statistically significant. During the 3–6 h, 6–12 h, and 12–24 h periods, Group R experienced a decreased incidence of nausea; however, this difference was not statistically significant. This outcome is consistent with the findings of research on postoperative nausea (PON) done by Joo *et al*. [20], Ryu *et al*. [21] with respect to PON.

In our study, the incidence of vomiting was maximum, that is, 10% in the immediate post-operative period. In the 0–3 h, 3–6 h, 6–12 h, and 12–24 h periods, individuals receiving Ramosetron experienced less vomiting than those receiving Ondansetron, but the difference was not statistically significant. This outcome is consistent with research on post operative vomiting (POV) during a 24-h period done by Ansari *et al*. [18], Kumar *et al*. [22] with respect to POV during 24 h.

Our study found that the overall incidence of nausea and vomiting was 22.5% in Group O and 11.25% in Group R, respectively. As a result, the Ramosetron group has a 10% of reduction in risk. This difference deemed clinically significant.

Headache and dizziness were the most frequently reported adverse effects. The frequency of side effects did not significantly differ between the groups. Thus, both Ondansetron and Ramosetron are devoid of clinically important side effects.

The use of rescue anti-emetics was also similar between the two groups. About 17.5% of patients in Group O and 12.5% of patients in Group R required rescue anti-emetics with no significant difference between the groups.

The results of our study demonstrate that ramosetron was more effective than ondansetron in the prevention of early PON, especially in 0–3 h and was associated with fewer side effects comparatively. However, our study did not find any statistically significant differences in efficacy between ramosetron and ondansetron in the prevention of POV.

CONCLUSION

- Post-operative nausea was significantly less in the Ramosetron group compared to the Ondansetron group in the 0–3 h period
- No statistically significant differences in efficacy between ramosetron and ondansetron in the prevention of PON during 3–6, 6–12, and 12–24 h period
- No statistically significant differences in efficacy between ramosetron and ondansetron in the prevention of POV
- Although there was no statistically significant difference in the efficacy of ramosetron and ondansetron in the prevention of POV, given the US Food and Drug Administration's cautions about the use of ondansetron in patients with a prolonged QT interval, increased safety would be a good reason to switch from ondansetron to ramosetron.

CONFLICTS OF INTEREST

None.

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