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Intravenous Ramosetron Versus Intravenous Ondansetron for Prevention of Post-Operative Nausea and Vomiting in Patients Undergoing Laparoscopic Surgeries - A Randomized Controlled Trial

Aishwarya S. Pingley[1], Ketaki S. Marodkar[2], Rucha P. Patil, Anjali R. Bhure[3], Sumita V. Bhargava[4], Akanksha N. Upase[5], Siddhi R. Rathod[6]

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ABSTRACT:

Background: Post-operative nausea and vomiting (PONV) is a frequent and distressing complication, with serious implications. As Ramosetron is a newer $5HT_3$ antagonist, we wanted to evaluate intravenous Ramosetron versus intravenous Ondansetron for prevention of post-operative nausea and vomiting.

Methods: This was a hospital based randomized double-blind study conducted in the Department of Anaesthesiology in tertiary care centre from January 2021 to December 2022, among 100 patients who underwent elective laparoscopic surgeries, after obtaining clearance from Institutional Ethics Committee and written informed consent from the study participants.

Results: An observation of occurrence of PONV revealed the following : Nausea (PONV score 1) occurred occurred at 0 minutes, 90 minutes, 2 hours in Group R; while vomiting occurred at 4 hours in Group R. In Group O, vomiting (PONV score 2) was observed at 2 hours, 4 hours, 6 hours and 24 hours.

Requirement of rescue antiemetic showed a non-significant difference between the two groups with Group R requiring lesser rescue antiemetic. Comparison of various side effects of treatment in two groups signified that difference in occurrence of dizziness was statistically significant between the two groups with dizziness occurring more in Group O. Equal number of patients showed occurrence of headache in both Group R and Group O, and none of the patients experienced drowsiness.

Conclusions: Post-operative nausea and vomiting was found to be less in patients receiving intravenous Ramosetron, with less rescue antiemetic requirement as compared to intravenous Ondansetron. Dizziness occurred significantly more in patients who received intravenous ondansetron. Thus, we conclude that intravenous Ramosetron and intravenous Ondansetron have comparable findings in terms of post-operative nausea and vomiting, requirement of rescue antiemetic and requirement of rescue analgesics.

1. Introduction

Although anesthesia practice is improving, there are still few obstacles to be overcome, post-operative nausea and vomiting (PONV) being one of them. The prevalence of PONV following general anesthesia is typically around 30% in all post-surgical patients but can reach 80% in high- risk individuals [1]. Furthermore, practically all surgical specialties are now increasingly and regularly using minimally invasive surgery. The patient's satisfaction with their care is a crucial component of the quality of anesthesia service [1]. One of the most frequent perioperative problems that can be avoided from an anesthesia standpoint is PONV. Majority of the patients coming for surgery are unaware of the vast hemodynamic and systemic effects of anesthetic drugs and are more concerned about the distressing effects of pain and PONV in the post- operative period.

PONV consistently tops the list, among the post-operative side effects that patients would want to avoid the most in preoperative questionnaires [2]. So, patients are ready to bear the cost of drugs being used to avoid PONV. PONV can be associated with delayed recovery, unexpected hospital admission, delayed return to work of ambulatory patients, pulmonary aspiration, wound dehiscence, and dehydration [3] and can also increase hospital cost for the patient. In extreme cases, it can also lead to esophageal rupture, as studied by Baric A et al. (2000) [4]. Numerous perioperative triggers, such as young age, preoperative anxiety, intraoperative drugs like opioids and volatile anesthetics, intra-operative negative hydration status, type of surgery like laparoscopic and ear, nose and throat (ENT) surgeries and post-operative opioid usage can cause PONV [5].

Laparoscopic surgeries pose a specific risk for PONV, which can be attributed to many factors [6]. These include mechanical variables, such as pressure brought on by the pneumoperitoneum on the stomach and intestines; neurological factors, such as vagal reflexes brought on by irritation of parasympathetic nerve terminals in the abdomen; and chemical factors, such as potential impact of carbon dioxide on PONV [6]. Ondansetron, a serotonin 5-hydroxytryptamine (5-HT_3) receptor antagonist prevents and treats nausea and vomiting by acting both centrally and peripherally [6]. The area postrema monitors neurotransmitters including serotonin, toxins, and other signals and plays a role in modulating the sensation of nausea and subsequent vomiting, mediates central effects. Ondansetron's antiemetic effects are thought to primarily be caused by its peripheral action [6].

Ramosetron, a tetrahydrobenzimidazole derivative has stronger and longer-lasting effect than ondansetron [6] and is being studied for its antiemetic action in comparison to other $5HT_3$ antagonist congeners. A study conducted by Ryu JH et al. (2014) [7] showed significant difference in efficacy of preventing PONV when compared to ondansetron.
Aside from 5-HT_3 receptor antagonists, there are other classes of drugs that comprise anti-emetics. Few examples are: Dopamine receptor antagonists like metoclopramide but stopped due to side effects like extra pyramidal symptoms [8]; corticosteroids like dexamethasone, not preferred due to sluggish onset of action [9].

The search for a better antiemetic led to the discovery of 5-HT_3 receptor antagonists, Ondansetron being the first congener to be discovered in 1984. Other 5-HT_3 antagonists such as Tropisetron [10], Palonosetron [11] were also approved. Hence this study was undertaken to compare Ramosetron, a newer 5-HT_3 antagonist with Ondansetron, a conventionally used 5-HT_3 antagonist in elective laparoscopic surgeries under general anesthesia in adult population in an effort to reduce PONV and improve perioperative outcomes.

2. Materials & Methods

This was a hospital based randomized double-blinded study conducted among 100 patients who presented with elective laparoscopic surgeries to the Department of Anesthesiology in a tertiary care center from January 2021 to December 2022 after obtaining clearance from the Institutional Ethics Committee and written informed consent from the study participants.
Inclusion criteria for the present study were American Society of Anesthesiologists (ASA) physical status I/II, patients aged between 18 years and 65 years, patients undergoing elective laparoscopic surgeries, patients willing to participate in the study. Exclusion criteria for the present study were patients with history of motion sickness, migraine, muscular dystrophy, or any other neurological problems, patients with history of multiple episodes of vomiting in the post-operative period, patients who are pregnant and lactating, patients on other medications that lead to QT prolongation, gasless laparoscopic procedures. Subject withdrawal criterion was conversion of laparoscopic surgery to open surgery.
After a thorough preanesthetic assessment, standard ASA monitors were attached in the operating room. Patients were induced with standard general anesthesia with endotracheal intubation, and intraoperative monitoring was done. On exsufflation, prior to extubating patients were given either intravenous Ramosetron 0.3 mg or intravenous Ondansetron 4 mg. PONV score was noted at 0 hours (time at which patient was shifted to recovery), 30 minutes, 60 minutes, 90 minutes, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours. Requirement of rescue antiemetic for the two groups was noted, first rescue antiemetic being intravenous Metoclopramide 10 mg, and second rescue antiemetic being intravenous Ondansetron 4 mg. Occurrence of various side effects like headache, dizziness and drowsiness were noted.

Statistical Analysis
Data was coded and analyzed in a statistical software Stata, version 10.1 (2011). Data analysis included both descriptive and inferential statistics. Descriptive statistics were used to summarize quantitative variables with mean and standard deviation and categorical variables with frequency and percentage. Inferential statistics included tests of significance and p-values. Difference in proportions of qualitative parameters in 2 groups were compared with Pearson's Chi square test or Z-test. Difference in means of the two groups was tested with student's t-test for 2 independent samples with equal variances. A p-value of <0.05 was considered statistically significant for all comparisons.
Results
This study was a double-blind, randomized controlled trial consisting of 100 patients between the ages of 18 and 65. Of these, 64 were males and 36 were females. Group R had 34 males and 16 females, while Group O had 30 males and 20 females. The mean height, weight, and body mass index (BMI) for Group R were 164.38 cm, 61.74 kg, and 22.91 kg/square meters, respectively. The mean height, weight, and BMI for Group O were 164.52 cm, 60.86 kg, and 22.7 kg/square meters, respectively. The baseline heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure (MAP) for Group R were 76.24 beats per minute, 120.8 mm Hg, 77.04 mm Hg, and 91.48 mm Hg, respectively. The baseline heart rate, systolic blood pressure, diastolic blood pressure, and MAP for Group O were 76.58 beats per minute, 121.26 mm Hg, 77.3 mm Hg, and 91.81 mm Hg, respectively. Of the 100 patients, 3 were Type 2 diabetic, 7 were hypertensive, 6 had hypothyroidism, and 1 patient was both Type 2 diabetic and hypothyroid.

PONV scores/grades	**Groups**	**0 min.**	**30 min.**	**60 min**	**90 min.**	**2 hours**	**4 hours**	**6 hours**	**12 hours**	**24 hours**

0= no nausea and vomiting	R	49 (98 %)	50 (100 %)	49 (98 %)	49 (98 %)	49 (98 %)	48 (96 %)	50 (100 %)	50 (100 %)	50 (100 %)
	O	50 (100 %)	50 (100 %)	48 (96 %)	50 (100 %)	49 (98 %)	49 (98 %)	48 (96 %)	50 (100 %)	47 (94 %)
1 = nausea	R	1 (2 %)	-	-	1 (2 %)	1 (2 %)	-	-	-	-
	O	0 (0%)	-	-	0 (0%)	0 (0%)	-	-	-	-
2 = vomiting once	R	-	-	1 (2 %)	-	0 (0%)	2 (4%)	0 (0%)	-	0 (0%)
	O	-	-	2 (4%)	-	1 (2 %)	1 (2 %)	2 (4%)	-	3 (6%)
3 = vomiting more than once	R	-	-	-	-	-	-	-	-	-
	O	-	-	-	-	-	-	-	-	-

Table 1: Comparison of PONV grades at interval of time in the two groups

Occurrence of nausea and vomiting along with PONV score. At 0 minutes, 1 patient in Group R showed PONV. At 30 minutes, none of the patients had PONV. At 60 minutes, 1 patient in Group R showed occurrence of vomiting. At 2 hours, 1 patient in each group had PONV. At 4 hours, 2 patients in Group R had PONV as opposed to 1 patient in Group O. After 6 hours, the PONV score for Group R was 0 throughout the study. At 6 hours and 24 hours, 2 patients and 3 patients respectively in Group O had occurrence of vomiting. Overall P value from Chi-square test for linear trend: P = 0.97693, Not Significant.
Note: - represents no observations in above table.

No. of rescue anti-emetics	**Group R**		**Group O**		
	No.	%	No.	%	
First rescue - IV Metoclopramide 10mg	3	6	9	18	p-value = 0.182
Second rescue - IV Ondansetron 4 mg	-	-	-	-	
NIL	47	94	41	82	(NS)
Total	50	100	50	100	

Table 2: Distribution of subjects according to number of rescue anti-emetics needed in two groups

The number of rescue anti-emetics needed in Group R was less as compared to Group O, however the requirement in two groups was comparable. None of our patients required a second rescue antiemetic intravenous Ondansetron 4 mg. Pearson chi2(1) = 1.7778 NS = not significant

Side Effects	**Group R**		**Group O**		**P Value**
	No.	%	No.	%	
Headache	3	6	3	6	1
Dizziness	0	0	5	10	0.022
Drowsiness	0	0	0	0	NA

Table 3: Occurrence of various side effects of treatment in the two groups

The difference in occurrence of dizziness was statistically significant between the two groups, with dizziness occurring more in patients who received intravenous Ondansetron (Group O). Equal number of patients showed occurrence of headache in patients receiving intravenous Ramosetron (Group R) and Group O, and none of the patients experienced drowsiness.

The two drugs, Ramosetron and Ondansetron, were compared using the PONV score, the requirement of rescue antiemetics, and side effects. The PONV score was comparable between the two groups ($p = 0.976$). The requirement of rescue antiemetic was more prevalent in subjects in Group O; however, the difference was insignificant ($p = 0.182$). Dizziness was significantly higher in Group O (0.02), while headaches were reported by the same number of subjects in both groups ($p = 1.0$). None of the subjects reported drowsiness.

3. Discussion

From the outset, mortality rates were rather high in surgery and anesthesia, many a times attributable to aspiration of vomitus, which led to development of the idea of fasting before surgery saving a lot of lives. Vomiting is listed as the most feared side effect of general anesthesia in a study by Smith from 1934, and corroborated by a study by Morton in 1951 [12]. A study of research on previous incidences of PONV revealed various drugs being used; for example anticholinergics like Atropine, benzamides like Metoclopramide, glucocorticoids like Dexamethasone, etc.

In the early 1980s, a new class of drugs called 5-HT_3 receptor antagonists was introduced. Among the FDA-approved uses are the prevention of post-operative nausea and vomiting (PONV) as well as the prevention of chemotherapy-induced nausea and vomiting (CINV), radiation-induced nausea and vomiting [13]. Selective serotonin receptor (5-HT_3) antagonists impede both central and peripheral actions of serotonin in the chemoreceptor trigger zone and on gastrointestinal (GI) vagal nerve terminals respectively. This has potent antiemetic effects. The first 5-HT_3 antagonist was ondansetron, which was manufactured in 1984.

The vagus nerve can detect gastrointestinal (GI) tract stimuli for nausea and vomiting, such as stomach irritants. It creates synapses in the brainstem's nucleus tractus solitarius. Ondansetron acts on the vagus nerve to mediate its peripheral effects. It functions by acting on the 5-HT_3 receptors present in the terminals of the vagus nerve [14].

Following ondansetron, other $5HT_3$ antagonists were approved by FDA including Tropisetron [10] and Palonosetron [11]. The most recent addition to this class of drugs, Ramosetron has received approval in Japan and certain Southeast Asian countries including India. Aside from its antiemetic profile, Ramosetron also proved beneficial in cases of irritable bowel syndrome with diarrhea (IBS- D) [15]. Ramosetron suppresses vomiting more effectively as compared to previously available antagonists such Ondansetron, Granisetron and Tropisetron [6]. Ramosetron has longer elimination half-life (5.8 hours) [16] than that of Ondansetron (3.5 hours) [16], a higher affinity and a slower dissociation rate ($t_{1/2}$ = 560 minutes) for 5-HT_3 receptors when compared with other 5-HT_3 receptor antagonists. This might minimize the need for an additional rescue antiemetic in the first 24 h post-operative period. Because of its greater binding affinity and slower rate of target receptor dissociation than earlier medications, Ramosetron offers stronger and longer- lasting antiemetic effects [6]. According to a systematic review and meta-analysis conducted by Mihara T et al. (2013) [17] Ramosetron showed a statistically significant superiority in preventing PONV when compared to ondansetron. Another meta-analysis by Gao C et al. (2015) [16] also proved superiority of Ramosetron 0.3 mg over Ondansetron 4 mg. Hence, we chose to compare Ramosetron with Ondansetron, a proven antiemetic drug, for its efficacy in

suppressing PONV and to note if Ramosetron had any significant side effects, as compared to Ondansetron.

The present research compared the safety and effectiveness of Ramosetron with Ondansetron. A total of 100 participants undergoing elective laparoscopies were recruited for the study, randomly allocated to either of the two groups - Group R (Ramosetron) or Group O (Ondansetron). Some studies have observed occurrence of PONV for 48 hours. However, in our study we have observed occurrence of PONV for 24 hours.

An observation of occurrence of PONV revealed the following : Nausea (PONV score 1) occurred occurred at 0 minutes, 90 minutes, 2 hours in Group R; while vomiting occurred at 4 hours in Group R. In Group O, vomiting (PONV score 2) was observed at 2 hours, 4 hours, 6 hours and 24 hours. Average PONV score for Group R was 1.2, while that of Group O was 1.8. Rescue antiemetics were required in 3 patients in the Ramosetron group compared to 9 in the Ondansetron group, difference was statistically insignificant ($p = 0.182$).

Pain increases catecholamines which in turn stimulate the release of $5HT_3$ by interacting with vagal terminals. A study conducted by Porreca F et al. (2009) [18] revealed that one of the strongest associations of nausea and vomiting was pain. Incidence of pain was assessed by Numerical Rating Scale (NRS) in our study, and it was found to be comparable between the two groups. In our study, we observed that none of the patients experienced drowsiness; while dizziness in Group O exceeded that in Group R with a statistically significant value ($p = 0.022$).

Limitations

ASA grade lll and IV patients were not included, so study results could not be generalized to these high risk patients. Patients undergoing emergency laparoscopic surgeries were excluded owing to the presence of many confounding factors such as inadequate fasting period, possible history of pain due to trauma. As subjective feelings could vary greatly between groups, the patient satisfaction score could not be used as the final indicator to assess efficacy of the two antiemetic drugs.

4. Conclusions

Post-operative nausea and vomiting (PONV) score calculated at various time intervals of 0 hours (on shifting to recovery room), 30 minutes, 60 minutes, 90 minutes, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours was noted. Occurrence of PONV as well as PONV score was found to be less in patients receiving Intravenous Ramosetron, as compared to Intravenous Ondansetron. Fewer patients in Group R (3 patients) required rescue antiemetic in the form of Intravenous Metoclopramide as compared to Group O (9 patients). Headache occurred equally in both groups. No drowsiness was observed in both groups. Dizziness occurred significantly more in patients who received Intravenous Ondansetron.

Thus, we conclude that Intravenous Ramosetron 0.3 mg and Intravenous Ondansetron 4mg have comparable findings in terms of post-operative nausea and vomiting (PONV) scores, requirement of rescue antiemetic and requirement of rescue analgesic in the first 24-hour post-operative period.

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