Original Article

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Anaesthesia Section

Comparison of Intravenous Ondansetron, Ramosetron and Palonosetron for Prevention of Postoperative Nausea and Vomiting in Patients Undergoing Total Abdominal Hysterectomy: A RCT

SUMANTH TARIGONDA[1], ABHINAYA MANEM[2], KAILASANATH UDUPI SHENOY[3], ARUN KUMAR HANDIGODU DUGGAPPA[4], ROHITH KRISHNA[5]

ABSTRACT

Introduction: Postoperative Nausea and Vomiting (PONV) poses a major problem in anaesthetic practice and is associated with various untoward consequences. The 5-hydroxytryptamine Type 3 (5-HT3) receptor antagonists such as ondansetron, ramosetron have been studied and found effective in prevention of PONV. Palonosetron is a newer antiemetic extensively used in chemotherapy patients for prevention of nausea and vomiting.

Aim: To compare the incidence and severity of PONV, when ondansetron, ramosetron and palonosetron were administered as prophylactic antiemetics in gynaecological surgeries.

Materials and Methods: This was a randomised double blind study conducted on 90 women undergoing total abdominal hysterectomy under general anaesthesia. Patients were randomly assigned to three groups to receive intravenously, either ondansetron 8 mg (Group O) or ramosetron 0.3 mg (Group R) or palonosetron 75 µg (Group P), 30 minutes prior to extubation. Incidence and severity of PONV was measured on a Visual Analogue Scale (VAS). A one-way Analysis of Variance (ANOVA) was used to compare continuous variables between the groups.

Results: Incidence of nausea was similar in all the three groups and though not statistically significant, only 2 patients (6.6%) in group P had incidence of nausea at 6 hours after surgery (T6) when compared to 8 (26.6%) in group O. The incidence of vomiting was 9 (30%) in group O compared to 3 (10%) in group P, which was statistically insignificant.

Conclusion: Incidence and severity of PONV is similar in patients who received prophylactic doses of ondansetron, ramosetron and palonosetron, while undergoing abdominal hysterectomy under general anaesthesia.

Keywords: 5-hydroxytryptamine type 3 receptor antagonists, General anaesthesia, Gynaecological surgeries

INTRODUCTION

Postoperative nausea and vomiting, one of the routinely encountered distressing complication in the perioperative period has an overall incidence of 20% to 30%. Though various risk factors have been proposed that are associated with increased incidence, gynaecological surgeries especially abdominal hysterectomies have higher risk of PONV [1]. 5-hydroxytryptamine type 3 (5-HT3) receptor blockers are considered the first-line medications, because of their superior efficacy and lesser side-effects, when compared to others [2]. Ondansetron is the 5-HT3 Receptor Antagonist (5-HT3RA) which has been extensively studied with an established efficacy in chemotherapy induced nausea and emesis [3,4].

Ramosetron, a selective 5-HT3RA, exhibits greater binding affinity and slower rate of dissociation. Hence it is more potent and longer acting compared to older 5-HT3RAs [5]. Palonosetron is the first of "second-generation" 5-HT3RAs and is superior to the "first generation" 5-HT3RAs with respect to high receptor binding affinity. In a study conducted on receptor binding affinity of 5-HT3RAs, palonosetron interacted with 5-HT3 receptors positively and allosterically, but at different sites compared to other 5-HT3RAs [6].

Ondansetron is one of the most commonly used 5-HT3 receptor antagonist used as prophylactic as well as rescue antiemetic in surgeries associated with increased risk of PONV. Lower abdominal surgeries especially abdominal hysterectomy is associated with increased risk of PONV. A meta-analysis on use of ramosetron for PONV suggested a dose of 0.3 mg in adults and 6 µg/kg in children to be effective and safe, when administered either before induction or at the end of surgery [7]. Palonosetron was effective in preventing chemotherapy induced nausea and vomiting when compared to ondansetron and it was also cost effective [4]. But its efficacy in preventing or reducing the incidence and severity of PONV in gynaecological surgeries has not been studied.

The primary objective of the study was to compare the efficacy of ondansetron, ramosetron and palonosetron in reducing the incidence and severity of PONV in the postoperative period. Secondary objectives included comparison of patient satisfaction scores and incidence of drug related side effects.

MATERIALS AND METHODS

This was a randomised double blinded study conducted at Manipal Academy of Higher Education, Manipal, Karnataka, India, between December 2012 to May 2014. The study was commenced after approval of Institutional Ethics Committee (No.MAHE/IEC/591/2012).

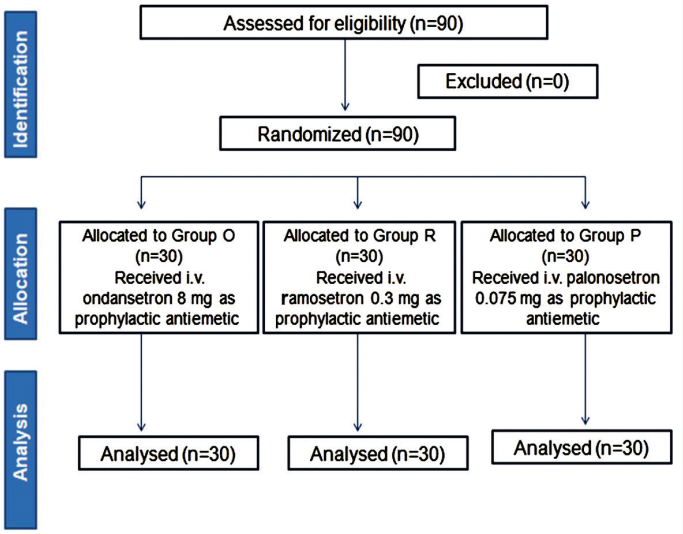
Inclusion criteria: Female patients belonging to American Society of Anaesthesiologists (ASA) physical status I and II, aged 35 to 70 years, with a Body Mass Index (BMI) between 19.5 to 34.9 kg/m^2, undergoing abdominal hysterectomy were included in the study.

Exclusion criteria: Patients with history of gastro-oesophageal reflux, motion sickness, allergy to any of the study drugs, severe cardiovascular, respiratory, renal or hepatic impairment were excluded from the study.

Sample size calculation: Using a power analysis based on primary objective, sample size was calculated as 90 patients with 30 patients in each group to observe a 30% reduction in PONV from baseline 70% considering a power of 80% and α=5%.

Randomisation and Blinding

Patients were randomly allocated to one of the three groups using a computer generated randomisation table. The randomisation sequence was concealed using sealed, opaque, sequentially numbered envelopes and provided to the operator in each case. In group O, patients received i.v. ondansetron 8 mg, in group R, patients received i.v. ramosetron 0.3 mg and in group P, patients received i.v. palonosetron 0.075 mg [Table/Fig-1]. The total volume of the injectate was made up to 2 mL for the purpose of blinding.



[Table/Fig-1]: CONSORT flowchart.

Observer 1 administered the antiemetic drug intraoperatively as per the allocated group and Observer 2 who was blinded to the antiemetic given, was responsible for evaluating the patient the day prior to surgery, explaining the procedure and obtaining written informed consent from the patient and recording the study measurements postoperatively.

After adequate preoxygenation for three minutes, general anesthesia was induced within i.v. fentanyl 2 mcg/kg, i.v. propofol 2 mg/kg. After checking the adequacy of mask ventilation, neuromuscular blockade was achieved with i.v. vecuronium 0.1 mg/kg. After ensuring complete neuromuscular blockade, laryngoscopy and intubation was done. Adequate plane of anaesthesia was maintained with isoflurane and 33% oxygen in nitrous oxide to achieve a Minimum Alveolar Concentration (MAC) of 1. Supplemental analgesia was provided with i.v. boluses of fentanyl 1 µg/kg and i.v. paracetamol 1 gm. Thirty minutes prior to the end of the procedure, the study drug was administered by observer 1, as per the allocated group. Surgeons were asked to infiltrate the surgical site with 0.25% bupivacaine. After the completion of surgery, residual neuromuscular blockade was reversed using i.v. neostigmine (0.05 mg/kg) and i.v. glycopyrrolate (0.01 mg/kg) and subsequently extubated. Patients were then transferred to Postanaesthesia Care Unit (PACU) for further monitoring.

Parameters Observed

1. Nausea is defined as unpleasant sensation associated with awareness of the urge to vomit.
2. Vomiting is defined as the forceful expulsion of gastric contents from the mouth.
3. Complete response (free from emesis) is defined as no PONV and no need for any rescue medication.

All episodes of PONV (nausea, vomiting and retching) were recorded at the following intervals: T1-One hour after surgery, T6-Six hours after surgery, T12–12 hours after surgery and T24–24 hours after surgery. A 100 mm Visual Analogue Scale (VAS) was used to measure the intensity of nausea (0: none; 100: maximum). Patients were asked to evaluate their maximal degree of nausea during the interval assessments. Rescue medication for PONV (ondansetron 4 mg i.v. as an initial rescue drug, metoclopromide 10 mg i.v. as a second rescue drug) was administered upon patient request or complaint of established nausea (VAS score >50) or vomiting. Adverse events such as dizziness, drowsiness, headache, dyspepsia were evaluated and recorded. Patients' overall satisfaction with the anaesthetic experience was ranked on a 3-point scale (satisfied, neutral, and dissatisfied).

STATISTICAL ANALYSIS

Data was entered and analysed using Statistical Package for the Social Sciences (SPSS) version 16.0 (IBM SPSS Statistics, Somers NY, USA). Categorical data was represented as frequencies and proportions. Chi-square test was used as test of significance for qualitative data. A one-way analysis of variance (ANOVA) was used to compare the continuous variables among the groups. If a significant difference was noted, a Bonferroni multiple comparison test was used to determine intergroup differences. A p-value of <0.05 was considered statistically significant. Data were presented as mean (Standard Deviation {SD}), numbers, and percentages.

RESULTS

Patients in all the three groups were comparable with respect to age, weight, BMI, duration of surgery and total intraoperative requirement of fentanyl [Table/Fig-2]. The type of surgery was standardised by including only patients undergoing abdominal hysterectomy with lower abdominal incision. Postoperative incidence of nausea was similar at T1 in all the three groups and though not statistically significant, only 2 patients (6.6%) in group P had incidence of nausea at T6 when compared to 8 (26.6%) in group O [Table/Fig-3]. Similarly the incidence of vomiting was 3 (10%) in group P compared to 9 (30%) in group O, which again was not statistically insignificant [Table/Fig-4]. Though the number of complete responders was more in group P compared to the other two groups, it was not statistically significant (p-value=0.42) [Table/Fig-5]. The requirement for rescue medication was comparable amongst three groups [Table/Fig-6]. Incidence of adverse events were similar (p-value=0.979) in all the three groups [Table/Fig-7]. None of the patients in the study were dissatisfied regarding management of PONV. Also, the overall patient satisfaction scores were comparable between the three groups [Table/Fig-8].

Variables	Group O Mean (SD)	Group R Mean (SD)	Group P Mean (SD)	p-value (One-way ANOVA)
Age in years	45.17 (9.93)	44.60 (10.04)	45.10 (10.87)	0.97
Weight in Kg	61.53 (8.77)	58.00 (9.94)	60.33 (11.23)	0.386
BMI in Kg/m²	25.12 (3.15)	23.65 (3.22)	24.92 (3.90)	0.206
Duration of surgery (Minutes)	142.17 (21.48)	145 (19.47)	140 (18.47)	0.621
Intraoperative fentanyl in µg/kg	149.17 (33.142)	149.17 (33.131)	145.83 (36.603)	0.907

[Table/Fig-2]: Comparison of patient characteristics among three groups, n=30 in each group.
SD: Standard deviation; BMI: Body mass index

Postoperative time period	Group O n (%)	Group R n (%)	Group P n (%)	p-value (ANOVA)
T1	16 (53.3)	13 (43.3)	16 (53.3)	0.774
T6	8 (26.6)	6 (20)	2 (6.6)	0.156
T12	1 (3.3)	0	0	1.00
T24	0	1 (3.3)	0	1.00

[Table/Fig-3]: Incidence of postoperative nausea.

Postoperative time period	Group O n (%)	Group R n (%)	Group P n (%)	p-value
T1	9 (30%)	5 (16.6%)	3 (10%)	0.167
T6	0	1 (3.3%)	2 (6.7%)	0.774

[Table/Fig-4]: Incidence of postoperative vomiting.

Complete response	Group O n (%)	Group R n (%)	Group P n (%)	p-value
Yes (%)	14 (46.6%)	13 (40%)	14 (46.6%)	0.420
No (%)	16 (53.4%)	17 (60%)	16 (53.4%)	0.561

[Table/Fig-5]: Complete response from the subjects.

Postoperative time period	Group O n (%)	Group R n (%)	Group P n (%)	p-value
T1 (0-1 hour)	9 (30%)	5 (16.6%)	7 (23.3%)	0.525
T6 (1-6 hours)	0	2 (6.7%)	1 (3.3%)	0.770

[Table/Fig-6]: Requirement for rescue antiemetic medication.

Adverse events	Group O n (%)	Group R n (%)	Group P n (%)	p-value
Dizziness	6 (20%)	4 (13.3%)	4 (13.3%)	0.979
Drowsiness	6 (20%)	5 (16.7%)	7 (23.3%)	0.842
Headache	0	1 (3.3%)	1 (3.3%)	0.779
Dyspepsia	2 (6.7%)	2 (6.7%)	3 (10%)	0.912

[Table/Fig-7]: Incidence of adverse events.

Patient satisfaction	Group O (n=30)	Group R (n=30)	Group P (n=30)	p-value
Satisfied	24 (80%)	21 (70%)	23 (76%)	0.749
Neutral	6 (20%)	9 (30%)	7 (24%)	0.656

[Table/Fig-8]: Patient satisfaction scores.

DISCUSSION

Postoperative nausea and vomiting is a significant problem in day to day anaesthetic practice. A number of factors such as age, obesity, gender, previous history of motion sickness, anaesthetic techniques, surgical procedure as well as intraoperative opioids were all associated with an increased incidence of PONV [8]. In this study, patient characteristics and surgical factors were common amongst the study groups, thereby allowing the differences observed between the groups possibly due to the treatment involved.

Aspinall RL and Goodman NW suggested that it is unethical to use placebo for control in gynaecological surgeries, as they are associated with increased risk of PONV [9]. In this study, three 5-HT3RAs viz., ondansetron, ramosetron and palonosetron are used as prophylactic antiemetics. Although ondansetron 4 and 8 mg i.v. have been recommended as prophylactic doses for PONV, the meta-analysis by Tramer MR et al. suggested that an 8 mg dose of ondansetron was optimal for the prevention of PONV [10]. Ryu J et al., in their study identified that ondansetron in a dose of 8 mg is more effective in reducing PONV than 4 mg [11]. Therefore, ondansetron 8 mg i.v. was selected for this study.

Ramosetron at a dose of 0.3 mg i.v. is proven to be effective for PONV in gynaecological surgeries [12]. The manufacturer's recommended dose is 0.3 mg i.v. once a day. Therefore, ramosetron 0.3 mg i.v. dose was chosen for this study.

Candiotti KA et al., found that 75 µg palonosetron i.v. is a better dose for preventing PONV in gynaecological laparoscopic surgeries, than either 25 µg or 50 µg doses [13]. Therefore, palonosetron 0.075 mg was used. In this study, the type of surgery was standardised by including only patients undergoing abdominal hysterectomy with lower abdominal incision. By this study design, type of surgery and incision were eliminated as confounding factors, as type of surgery is a possible confounding factor affecting PONV.

The results of this study showed that efficacy of the ramosetron and palonosetron in prevention of PONV is the same as that of ondansetron. Kim SI et al., compared ramosetron and ondansetron for alleviating PONV in patients undergoing gynaecological surgery. They observed that, when compared to control group (44%), there was lesser incidence of vomiting in both ondansetron (20%) and ramosetron (17%) groups. Therefore, they concluded that ondansetron 8 mg and ramosetron 0.3 mg were equally effective in reducing the incidence of PONV [14].

In a randomised control trial, done on 140 women undergoing abdominal hysterectomy under spinal anaesthesia with intrathecal morphine, the incidence of PONV was 42.9% amongst those who received palonosetron as compared to 52.9% amongst those that received ondansetron (p>0.05). There were no significant differences observed in the incidence of early onset as well as late onset nausea between the two groups. Late onset vomiting was found to be significantly lower in the palonosetron group [15].

In this study, the severity of nausea as given by VAS score was comparable between all the three groups. Also, the severity of nausea in all the three groups reduced over a period of time in the first 24 hours after surgery. In a dose ranging study done comparing three different doses of ramosetron (0.3 mg, 0.45 mg and 0.6 mg) the incidence and severity of PONV reduced significantly in the first 24 hours and it was similar across all the three groups [16]. The requirement for rescue medication also was more or less the same in all the three groups. Nausea and vomiting in those patients who required a rescue medication subsided with i.v. ondansetron 4 mg when given as rescue medication. None of the patients in this study required i.v. metoclopramide as second rescue drug. This suggests that a single 4 mg dose of i.v. ondansetron is good enough to treat PONV in those patients in which prophylactic antiemetic medications failed to prevent PONV. In a study comparing granisetron, ramosetron and palonosetron, in patients undergoing laparoscopic gynaecological surgery, the number of complete responders were similar in all the three groups [17]. In this study, the percentage of complete responders was much less compared to study done by Lee WS et al. [17]. The most common adverse events reported with 5-HT3 receptor antagonists were dizziness, drowsiness, headache and dyspepsia. The findings were similar to study done by Cho JS et al, who reported similar side effects [16]. None of the patients in this study were dissatisfied with the antiemetic prophylaxis given to them.

Limitation(s)

Firstly, a control group was not included as deemed it unethical to withhold prophylactic antiemeics in patients who are at risk of PONV. Secondly, we did not measure serum biochemistry parameters associated with nausea and vomiting such as C-Reactive protein, aldehydes and ketones. Also, nitrous oxide was used that further would have exacerbated PONV.

CONCLUSION(S)

The efficacy of palonosetron and ramosetron was comparable to that of ondansetron in reducing the overall incidence of postoperative nausea and vomiting in patients undergoing abdominal hysterectomy under general anaesthesia.

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PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Anaesthesiology, Sri Devaraj Urs Medical College, Tamaka, Kolar, Karnataka, India.
2. Senior Resident, Department of Anaesthesiology, Sri Devaraj Urs Medical College, Tamaka, Kolar, Karnataka, India.
3. Professor, Department of Anaesthesiology, Kasturba Medical College, Manipal, Karnataka, India.
4. Associate Professor, Department of Anaesthesiology, Kasturba Medical College, Manipal, Karnataka, India.
5. Associate Professor, Department of Anaesthesiology, Kasturba Medical College, Manipal, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Abhinaya Manem,
G5, J-Block, Doctors Quarters, Sduaher, Tamaka, Kolar, Karnataka, India.
E-mail: abhimanem12@gmail.com

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