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Original Research Article

A Comparative Study of Granisetron, Palanosetron and Ondansetron in Post-Operative Nausea and Vomiting After Gynaecological Surgery under General Anaesthesia

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Abstract

Background: Postoperative nausea and Vomiting (PONV), one of the most common and distressing adverse events experienced by patients after an anaesthesia and surgery. It may prolong recovery, delay patient discharge and increase hospital costs. The overall incidence of PONV has been reported to be between 20%-30% but can increase up to 80% in high risk cases. Adult women are two to four times more likely to suffer from PONV than men. Patients undergoing gynecological surgery have been associated with highest risk of PONV, of around 58% after general anaesthesia.

Aims and Objectives: This study was carried out to compare the efficacy of Granisetron, Palanosetron and Ondansetron in preventing PONV after Gynaecological surgery under general anaesthesia.

Setting and Design: It was a prospective randomized cotrolled study.

Methods and Materials: The healthy adult female patients posted for elective gynaecological surgery were randomly allocated in to three equal groups. Group G (n=30) received inj. Granisetron 2.5 mg iv, Group P received inj Palanosetron. 75 mg iv and Group O received inj Ondansetron 8 mg iv immediately before the induction of anaesthesia. All the groups had similar fasting guidelines and received similar premedication**.** Episodoses of PONV were noted at 0.5,1,2, 4, 6, 12 hours postoperatively.

Results: In this study, the number of patients with nausea over the 24 hrs study period was 10% in granisetron group, 3.3% in the palanosetron group and 33.3% in the ondansetron group. The percentage of patients with vomiting was 6.7% in the granisetron group, 3.3% in the palanosetron group and 30% in the ondansetron group.

Conclusion: On the basis of the present study it can be concluded that: Prophylactic granisetron, palonosetron and ondansetron individually are effective and safe antiemetic in prevention of PONV. Palanosetron and Granisetron are superior to Ondansetron in the prevention of postoperative nausea and vomiting. There was no significant difference in the incidence of side effects among the three study groups.

Keywords: Gynaecological Surgery, Granisetron, Palanosetron, Ondansetron, Post-operative nausea and vomiting.

Introduction

Postoperative nausea and vomiting (PONV), one of the most common and distressing adverse events experienced by patients after an anaesthesia and surgery [1,2]. PONV is one of the most distressing complications after anaesthesia and surgery and may lead to serious complications like dehydration, electrolyte imbalance, disruption of surgical repair thereby increasing cost of therapy. Prevention and treatment of PONV help to accelerate post-operative recovery and increase patient satisfaction. [3,4] The overall incidence of PONV has been reported to be between 20%-30% but can increase up to 80% in high risk cases. Adult women are two to four times more likely to suffer from PONV than men [5]. Patients undergoing gynecological surgery have been associated with highest risk of PONV, of around 58% after general anaesthesia [6-7].

A number of pharmacological agents like antihistamine, butyrophenones, dopamine receptor antagonists have been tried for the prevention and treatment of PONV but undesirable side effects like excessive sedation, hypertension, dryness of mouth, dysphoria, hallucinations and extrapyramidal symptoms have been noted. [6] Avoiding PONV while minimizing adverse events still remain a challenge as there is no single drug available for the complete control and treatment of PONV.

The introduction of 5-HT_3 receptor antagonists in 1990 was heralded as a major advance in the treatment of PONV because of the absence of adverse effects that were observed with commonly used traditional antiemetics. [8-9] The $5HT_3$ receptor antagonists produced less adverse effects on vital signs or laboratory tests or drug interaction with other anaesthetic medications. [10]

Ondansetron is the most researched of the 5-HT_3 receptor antagonist and has been well established in chemotherapy induced nausea and vomiting and prevention and treatment of PONV [11-12]. It has been observed that granisetron is a highly selective and potent 5-HT_3 receptor antagonists and may produce long duration of antiemetic effect. [13]

Aims and Objectives

To compare the incidence and severity of PONV between the groups of patients receiving granisetron, palanosetron and ondansetron. To assess the requirement of rescue antiemetics for first 24 hrs postoperatively. To assess the requirement of rescue antiemetics for first 24 hrs postoperatively. The incidence of adverse effects during the study period, if any.

Methods and Materials

After obtaining permission from institutional ethics committee, written consent was taken. The study was done at Murshidabad Medical College and Hospital on and from 1st November 2020 to 31st March 2021. This is a prospective, randomized controlled study among 90 adult female patients, aged 35-60 years, of ASA physical status 1&2 scheduled for elective gynaecological surgery under General anaesthesia. Total 90 adult female patients (with 95% confidence level) were randomly allocated to three equal groups (n=30 in each group) using computer generated random number list. In three equal groups (n=30) either to receive inj granisetron (2.5mg), inj palanosetron (0.75mg) or ondansetron (8mg) IV

respectively before induction of anaesthesia. The total volume of the study material was 3 ml by adding normal saline. The study materials were prepared, labelled and postoperative observation were done by an anaesthesiologist who was not involved in the study.

Patient refusal, any known allergy or contraindication to any of the three drugs, pregnancy, lactation and children, subjects who vomited or received antiemetics within 24 h before surgery, hepatic, renal or cardiopulmonary abnormality, alcoholism, diabetes, significant gastrointestinal disorders and motion sickness were excluded.

In preoperative assessment, patients were enquired about heartburn, belching and abdominal discomfort, h/o motionsickness, any antiemetic received, h/o previous exposure to anaesthesia and h/o PONV, h/o drug allergy or prolonged drug treatment. General and systemic examination and assessment of the airway were done. All patients received premedication of tablet diazepam 5mg orally the night before surgery to allay anxiety, apprehension and for sound sleep. The patients were preoxygenated with 100% oxygen for a period of 5 minutes. Injection fentanyl (2mcg) and glycopyrrolate (0.01mg /kg) were given intravenously 3mins before induction of anaesthesia. All the patients were induced with IV injection of Thiopentone 2.5% (5mg/kg) titrated till the loss of eyelash reflex. Inj.atracurium (0.5mg/kg)) was given to facilate laryngoscopy and intubation. Controlled ventilation was maintained with 33% oxygen and 67% nirous oxide. Muscle relaxation was maintained with intermittent intravenous atracurium (0.2mg/kg) as when required. Intraoperatively, the pulse rate, respiratory rate, Arterial oxygen saturation, ECG, Capography, systolic and diastolic pressure were measured continuously. At the completion of surgery, residual neuromuscular blockade was antagonized with neostigmine 0.05mg/kg and atropine 0.02mg/kg intravenously and patient was extubated in concious condition. Postoperative analgesia was given with Tramadol 2mg/kg IV 20 mins before the end of surgery and inj. Diclofenac 50mg postoperatively. All patients were observed postoperatively by resident doctors who was unaware of the study drug. Patients were transferred to post anesthetic care unit (PACU) for the first six hours after anaesthesia. During the observation period, blood pressure, heart rate, respiratory rate and SpO_2 was monitored except when the patient was sleeping.

The incidence of PONV, severity of nausea and the need for rescue antiemetics was evaluated. Patients were asked to evaluate the maximum degree of nausea during the interval assessments. When the patient had vomiting, rescue antiemetics like metoclopromide 10mg was given intramuscularly.

All patients received moist oxygen supplementation (3l/min) for 2h. All the patients were on intravenous drip and did not have any oral fluid during the study period of 12h. Throughout the 18h of postoperative period, all the parameters were recorded on 0.5,1,2,4,6,12h. All episodes of nausea, retching, vomiting and rescue antiemetic provided were rcorded by using score of Bellville and co-workers, 24 being the primary assessment parameter. Rescue antiemetic was given with IV Metoclopramide (10 mg) slowly.

Statistical analysis

All raw data was entered into a Microsoft excel spreadsheet and analyzed by using standard statistical tests. Numerical variables between groups were analyzed using the student T test or the Mann Whitney U test. Categorical variables were analyzed using the Chi Square Test and the Fisher's exact test as applicable. All tests were two tailed. A P value <0.05 was considered statistically significant.

Results:

Table 1: Age (in years) profile in the three study groups and their statistical analysis.

GROUPS	MEAN	MAXIMUM	MINIMUM	SD
Group G (n=30)	47.31	58	36	6.65
Group P(n=30)	49.07	56	40	5.27
Group O(n=30)	51.12	60	38	7.33

The mean age group in the granisetron group was 47.31 ± 6.65yrs, in palanosetron group was 49.07 ± 5.27 yrs and 51.12 ± 7.33yrs in the ondansetron group
There was no statistically significant difference in age distribution among the study groups as 'p' value was > 0.05 and hence the groups were comparable to each other in terms of age.

Table 2: Body weight (in kilogram) distribution in the three study groups and their statistical analysis.

GROUPS	MEAN	MAXIMUM	MINIMUM	SD
GROUP G (n=30)	50.36	62	39	5.568
GROUP P (n=30)	47.06	59	36	6.680
GROUP O (n=30)	49.43	62	41	5.667

The mean body weight in the granisetron group was 50.36 ± 5.56 kgs, in the palanosetron group it was 47.06 ± 6.68 kgs and in the ondansetron group was 49.43 ± 5.66 kgs.
There was no statistically significant difference in age distribution among the study groups as 'p' value was > 0.05 and hence the groups were comparable to each other in terms of body weight.

Table 3: Comparison of the baseline heart rate in the three study groups and their statistical analysis.

GROUPS	MEAN	MAXIMUM	MINIMUM	STD DEV
GROUP G (n=30)	74.37	90	62	8.512
GROUP P (n=30)	75.33	89	56	9.238
GROUP O (n=30)	74.83	90	62	8.226

P=0.911 (when groups were compared by ANOVA test).

The baseline heart rate in the granisetron group was 74.37 ± 8.51, the palanosetron group was 75.33 ± 9.23 and the ondansetron group was 74.83 ± 8.22.
The difference in the baseline heart rate between the three groups was found insignificant as 'p' value was >0.05 and hence the groups are comparable in terms of heart rate.

Table 4: Comparison of baseline mean arterial pressure in the three study groups and their statistical analysis.

GROUPS	MEAN	MAXIMUM	MINIMUM	STD DEV
GROUP G (n=30)	83.73	89	72	4.143
GROUP P(n=30)	83.20	89	72	4.180
GROUP O(n=30)	83.40	89	72	4.760

P=0.890 (when groups were compared by ANOVA test).

The baseline mean arterial pressure in the granisetron group was 83.73 ± 4.143, the palanosetron group was 83.20 ± 4.18 and the ondansetron group was 83.40 ± 4.76.

The difference in the baseline mean arterial pressure between the three groups was found insignificant as 'p' value was >0.05 and hence the groups are comparable in terms of mean arterial pressure.

Table 5: Shows distribution of patients according to postoperative nausea and vomiting over 0-4 hrs after anaesthesia and their statistical analysis.

	GROUP G (n=30)	GROUP P (n=30)	GROUP O (n=30)	p value
No emetic response	100%(30)	100%(30)	93.3%(28)	0.135
Nausea	0	0	6.7%(2)	0.333
Vomiting	0	0	3.3%(1)	0.368
Rescue antiemetic	0	0	3.3%(1)	0.368

Table 5: shows that 100% of patients in group G had complete response (no incidence of PONV and no requirement of antiemetics) compared to 100% in group P and 93.3% in group O. The incidence of vomiting in group G and group P was nil. Group O had 3.3% incidence of vomiting.

There was no significant difference in the incidence of vomting on comparing group G, group P and group O in the first 4 hrs postoperatively.The incidence of vomiting between group G and group P and group O was comparable so was statistically insignificant.

Table 6: Shows distribution of patients according to postoperative nausea and vomiting over 4-8 hrs after anaesthesia and their statistical analysis.

	GROUP G (n=30)	GROUP P (n=30)	GROUP O (n=30)	P value
No emetic response	96.7%(29)	100%(30)	86.7%(24)	**0.074**
Nausea	0	0	10%(3)	**0.050**
Vomiting	3.3%(1)	0	10%(3)	**0.097**
Rescue antiemetic	3.3%(1)	0	10%(3)	**0.097**

Table 6: shows that 96.7% of patients in group G had complete response (no incidence of PONV and no requirement of antiemetics) compared to 100% in group P and 86.7% in group O.

The incidence of nausea in group O was 10% as compared to no incidence of nausea in group G and group P. There was significant difference in the incidence of nausea on comparing group P and group G with group O.

P value of **0.050** (calculated by Friedman's analysis of variance) was statistically significant

There was no significant difference in terms of vomiting and the need for rescue antiemetics when the three groups were compared

P value for vomiting between the three groups was found to be **0.097** (p>0.05) which is statistically insignificant.

Table 7: Shows distribution of patients according to postoperative nausea and vomiting over 8-16 hrs after anaesthesia and their statistical analysis.

	GROUP G (n=30)	GROUP P (n=30)	GROUP O (n=30)	P value
No emetic response	96.7%(29)	100%(30)	73.3%(22)	**0.002**
Nausea	3.3%(1)	0	16.7%(5)	**0.030**
Vomiting	3.3%(1)	0	13.3%(4)	**0.039**
Rescue antiemetic	3.3%(1)	0	13.3%(4)	**0.039**

Table 7: shows that 96.7% of patients in group G had complete response (no incidence of PONV and no requirement of antiemetics) compared to 100% in group P and 73.3% in group O. The incidence of vomiting in group G was 3.3% as compared to 10% in group O and there was no vomiting in group P.

P value=0.002($p<0.05$) calculated by Friedman's analysis of variance was statistically significant

Incidence of nausea was 3.3% in group G,nil in group P and 16.7% in group O.

P value=0.030 ($p<0.050$) calculated by Friedman's analysis of variance was statistically significant

The incidence of vomiting and the need of rescue antiemetic in group G was 3.3% as compared to 13.3% in group O and there was no vomiting in group P.

P value=0.039 ($p<0.050$) calculated by Friedman's analysis of variance was statistically significant.

Table 8: Shows distribution of patients according to postoperative nausea and vomiting over 16-24 hrs after anaesthesia and their statistical analysis.

	GROUP G (n=30)	GROUP P (n=30)	GROUP O (n=30)	P value
No emetic response	90%(27)	93.3%(28)	70% (21)	0.028
Nausea	6.7%(2)	3.3%(1)	23.3%(7)	0.032
Vomiting	3.3%(1)	3.3%(1)	20%(6)	0.028
Rescue antiemetic	3.3%(1)	3.3%(1)	20%(6)	0.028

Table 8 shows that 90% of patients in group G had complete response (no incidence of PONV and no requirement of antiemetics) compared to 93.3% in group P and 70% in group O. **P=0.028** ($p<0.05$) calculated by Friedman's analysis of variance was statistically significant.

The incidence of nausea in group G was 6.7%, in group P was 3.3% and 23.3% in group O.**P=0.030** ($p<0.05$) calculated by Friedman's analysis of variance was statistically significant.

The incidence of vomiting and the need for rescue antiemetic in group G and group P was 3.3% as compared to 20% in group O. **p=0.028** ($p<0.05$) calculated by Friedman's analysis of variance was statistically significant.

Table 9: Shows distribution of patients according to postoperative nausea and vomiting over 0-24 hrs after anaesthesia and their statistical analysis.

	GROUP G (n=30)	GROUP P (n=30)	GROUP O (n=30)	P value
No emetic response	83.3%(25)	93.3%(28)	66.7%(20)	0.038
Nausea	10%(3)	3.3%(1)	33.3%(10)	0.002
Vomiting	6.7%(2)	3.3% (1)	30%(9)	0.009
Rescue antiemetic	6.7%(2)	3.3%(1)	30%(9)	0.009

Table 9 shows that 83.3% of patients in group G had complete response (no incidence of PONV and no requirement of antiemetics) compared to 93.3% in group P and 66.7% in group O. **P=0.038** ($p<0.05$) calculated by Friedman's analysis of variance was statistically significant.

The incidence of nausea in group G was 10%, in group P was 3.3% and 33.3% in group O.**P=0.002** ($p<0.05$) calculated by

Friedman's analysis of variance was statistically significant

The incidence of vomiting and the need for rescue antiemetic in group G was 6.7, group P was 3.3% as compared to 30% in group O. **p=0.009** ($p<0.05$) calculated by Friedman's analysis of variance was statistically significant.

Table 10: Showing the comparison of the incidences of side effects among the study groups and their statistical analysis.

SIDE EFFECTS	GROUP G (n=30)	GROUP P (n=30)	GROUP O (n=30)
Pruritus	3.3%(1)	0	3.3%(1)
Headache	3.3%(1)	3.3%(1)	6.7%(2)
Hypertension	3.3%(1)	0	0
Bradycardia	3.3%(1)	0	0
Dizziness	3.3%(1)	0	0
ECG changes	0	0	0

Table 10 shows that 1 patient each in group G and O had pruritus. The incidence of headache was 1 in group Gand group P and 2 patients in group 0 had headache.One patient in group G had hypertension, dizziness and bradycardia.

Discussion

PONV is one of the most common distressing side effects after surgery performed under general anaesthesia. Adult women are two to four times more likely to suffer from PONV than men and major gynaecological surgery is known to carry a risk of around 58% of PONV [14]. This incidence may justify the use of prophylactic antiemetics for the control of PONV. Further patients who suffer from PONV require additional health care professional time and material resources leading to higher costs [15].

The incidence of nausea and vomiting after gynaecological surgery performed under general anaesthesia varies considerably. A number of factors including age, operative procedure, anaesthetic technique and postoperative pain are thought to increase the incidence of this symptom [16].

Many drugs have been tried since the recognition of this unpleasant complication and this problem is still considered as an important cause of morbidity in surgical patients. However, avoiding PONV while minimizing adverse effects still remain a challenge. Palanosetron is a unique 5-HT_3 receptor antagonist approved for the prevention of chemotherapy induced nausea and vomiting [16]. The exact mechanism of palanosetron in the prevention of PONV is unknown but palanosetron may act in the area postrema which contain a number of 5-HT_3 receptors [17].

Granisetron is effective for the treatment of emesis in gynaecological patients [18]. It has been suggested that granisetron may act on sites containing for 5-HT_3 receptors with demonstrated antiemetic effects.

The effective dose of granisetron is 40µg/kg for the treatment of postoperative nausea and vomiting. The dose of granisetron 2.5mg (approx. 45 µg/kg) selected for this study was within the effective dose range [19]. Kovac LA and colleagues demonstrated that palanosetron 75µg is the more effective dose for the prevention of PONV after major laparoscopic and gynaecological surgery than 25 µg and 50 µg [20]. Ondansetron, 4 or 8 mg IV has been recommended for preventing PONV, the meta analysis by Tramer and colleagues suggested than an 8 mg dose of ondansetron was optimal for prevention of PONV. Therefore ondansetron 8 mg was chosen for the study [21].

The present study was designed to compare the efficacy of single iv dose of granisetron, palanosetron or ondansetron for the prevention of PONV. In this prospective, randomized double-blind study 90 adult healthy patients of ASA (American Society of Anaesthesiologists) physical status I and II were taken so that other risk factors which may contribute to the increased incidence of PONV could be eliminated. The patients were randomly allocated into three groups Group G (n=30) received inj granisetron 2.5mg, Group P received inj palanosetron 75µg and group O received inj ondansetron 8mg slow iv before the induction of anaesthesia.

In this study, all the operations were elective and performed between 9 AM and 2 PM. Patients were prepared with optimum period of fasting preoperatively.

Andrews et al. 1990, showed in their study that patients having symptoms of delayed gastric emptying increased the risk of PONV. This study also excluded the patients with symptoms of delayed gastric emptying. So this factor could not influence our study result [22]. Hovorka Jet al 1990, showed that patients with history of PONV after previous anaesthesia and motion sickness are more susceptible to PONV than those without a history of postoperative emesis. Purkis etal established that PONV is almost three times more likely in patients who had previous experience of emesis after operation.

In this present study any patient having history of motion sickness and previous history of motion sickness was excluded. So the relation of PONV with motion sickness could not be elicited [23].

The major deficiency in this study design is the failure to include a control group receiving placebo. As PONV is recognised to be a common complication of gynaecological surgery performed under general anaesthesia it was believed to be unethical to include a placebo arm in this study. Further, Aspinall and Goodman have shown that there is a poor quality of clinical information in placebo controlled trials of ondansetron (5-HT_3 receptor blocker) for preventing postoperative emesis [24].

Palazzo MGA et al, observed that movement of patients from one bed to other and from one ward to other increased the incidence of PONV. In this present study the transfer of all the patients from the operative table to the bed, was carried out in a similar fashion. So difference in the incidence of PONV among the groups due to movement was eliminate. [25] As far as the premedication is concerned no opioid was used in the premedication which could have modified the incidence of PONV.

Table 1-2 shows the demographic profile of the patients assigned to the three groups and the statistical tests performed to determine the comparability between the three groups. There was no statistically significant difference among the groups in terms of age and body weight. Hence the groups were comparable with respect to the demographic characteristics.

Table 3-4 shows the baseline hemodynamic parameters of the patient. This included the heart rate and the systolic and diastolic blood pressure. The statistical tests performed to determine the comparability between the three groups showed no significant difference among the groups in terms of heart rate and blood pressure. Hence the groups were comparable with respect to the demographic characteristics.

Visceral or pelvic pain is common cause of postoperative emesis. Anderson and Krogh [26] found that relief of pain was significantly associated with a relief of nausea. This relationship between pain and vomiting is supported by the increased emesis following naloxone reversal of opioid mediated pain relief. So the

incidence of pain was evaluated. As use of opioids is associated with an increased incidence of PONV the routine analgesic was provided with Inj diclofenac sodium 75mg IM.

Table 9: shows the incidence of nausea, vomiting and rescue antiemetic needed in the three groups in the first 4 hrs in the postoperative period. The complete response which is defined as no PONV and no need for rescue antiemetic during the 0-4 hrs postoperative period was seen in 100% in the granisetron and palanosetron group and 93.3% in the ondansetron group.

The percentage of requirement of rescue antiemetic in the granisetron and palanosetron group was nil whereas it was 3.3% in the ondansetron group. The differences between the groups were statistically significant except between granisetron group and palanosetron group where overall incidence was statistically insignificant. SK Park and EJ Cho; 2011 observed that incidence of PONV was significantly lower in the palanosetron group compared with the ondansetron group. Thus it was concluded that palanosetron was more effective than ondansetron in preventing PONV [27].

In the present study the complete response to PONV over the 24 hrs period was 83.3%, in the granisetron group, 93.3% in the palanosetron group and 66.7% in the ondansetron group. (Table 13). The difference between the groups were statistically significant except granisetron group and palanosetron group where overall incidence was statistically insignificant. [28]

In this study the percentage of patients with vomiting was 6.7% in the granisetron group, 3.3% in the palanosetron group and 30% in the ondansetron group. The difference between the groups was statistically significant except between granisetron and palanosetron group where overall incidence was statistically insignificant. In the present study the number of patients needing a rescue antiemetic over the 24 hrs study period was6.7% in granisetron group, 3.3% in the palanosetron group and 30% in the ondansetron group.

Thus the major findings of the present study were that during the 24 hrs recovery from anaesthesia, the frequencies of PONV in the palanosetron group was far less than the ondansetron group and it was comparable with the granisetron group. The most frequently reported side effects were headache. Headache was seen in one patient in the granisetron group and the palanosetron group and in two patients in the ondansetron group. Pruritis was observed in one patient each of the granisetron and ondansetron group. Dizzyness was observed in one patient in the granisetron group.One patient each in the granisetron group had hypertension and bradycardia. The difference was statistically insignificant.

Conclusion

On the basis of the present study it can be concluded that:

1. Prophylactic granisetron, palanosetron and ondansetron individually are effective and safe antiemetic in prevention of PONV.
2. Palanosetron and Granisetron are superior to Ondansetron in the prevention of postoperative nausea and vomiting.
3. There was no significant difference in the incidence of side effects among the three study groups.

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