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Comparison of Granisetron, Palonosetron and Ondansetron for Prevention of Postoperative Nausea and Vomiting in Gynaecological Surgery under General Anaesthesia.

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ABSTRACT

Background: 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. As the aetiology of PONV is multifocal, avoiding it still remains a challenge. In this study efficacy of single dose granisetron, palonosetron and ondansetron for prevention of PONV in patients undergoing elective gynaecological surgery under general anaesthesia were compared.. **Methods**: 90 healthy adult females of ASA physical grade I and II scheduled for elective gynaecological surgery under general anaesthesia were randomly allocated in to three equal groups. Group G (n=30) received inj. Granisetron 2.5 mg iv, Group P received inj Palonosetron 75µg iv and Group O received inj Ondansetron 8 mg iv immediately before the induction of anaesthesia. All the groups had similar fasting guidelines and underwent similar premedication and anaesthetic protocol. The incidence of PONV and the need for rescue antiemetics was evaluated. Statistical evaluation: All raw data was entered into a Microsoft excel spreadsheet and analyzed by using standard statistical tests. A p value <0.05 was considered statistically significant. **Results:** 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 palonosetron group and 66.7% in the ondansetron group. **Conclusion**: In conclusion Prophylactic granisetron, palonosetron and ondansetron individually are effective and safe antiemetic in prevention of PONV. However Palonosetron is more effective in the prevention of postoperative nausea and vomiting.

Keywords: Postoperative nausea and vomiting, granisetron, ondansetron, palonosetron.

INTRODUCTION

Postoperative nausea and vomiting (PONV) has been variously described as the "big little problem" and the "final therapeutic challenge" for the anaesthesiologists.[1] Surveys have confirmed that PONV is feared considerably by patients undergoing surgery. Indeed it is often rated above postoperative pain when patients are asked to rank their concerns. It may lead to serious complications like dehydration, electrolyte imbalance, disruption of surgical repair thereby increasing cost of therapy.[2,3]

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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.[4] Patients undergoing gynecological surgery have been associated with highest risk of PONV, of around 58% after general anaesthesia.[5,6]

A number of pharmacological agents like antihistamine, butyrophenones, and dopamine receptor antagonists have been tried for the prevention and treatment of PONV but undesirable side effects like excessive sedation, hypertension, and dryness of mouth, dysphoria, hallucinations and extrapyramidal symptoms have been noted.[5] 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-HT3 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.[7] The 5HT3 receptor antagonists produced less adverse effects on vital signs or laboratory tests or drug interaction with other anaesthetic medications.[8]

Ondansetron is the most researched of the 5-HT3 receptor antagonist and has been well established in prevention and treatment of chemotherapy induced PONV.[9,12] Granisetron is a highly selective and potent 5-HT3 receptor antagonists and may produce long duration of antiemetic effect.[13] Palonosetron is a recently developed 5HT3 receptor antagonist used for treatment of chemotherapy induced nausea and vomiting with minimum side effects.[14]

In this prospective, randomized, double-blinded study an attempt has been made to assess the efficacy of single dose granisetron, palonosetron, and ondansetron for prevention of PONV in patients undergoing elective gynaecological surgery under general anaesthesia.

MATERIALS AND METHODS

After obtaining the clearance of the institutional ethics committee the present prospective, randomized, double-blind Study was carried out in the Department of Anaesthesiology of Nilratan Sircar Medical College & Hospital, Kolkata, for a period of one and half years. 90 healthy female patients, ASA physical status: I and II, aged between 35 to 60 yrs posted for elective gynaecological surgery like abdominal/vaginal hysterectomy, ovarian cystectomy and salpingo-oopherectomy were included into our study. Patients having hypersensitivity to study drugs, GI disease, H/o motion sickness, body wt more than 30% of ideal wt and smokers were excluded from the study. Patients with history of vomiting or retching within 24 hrs of surgery and those are with administration of antiemetics or steroids or psycho-active medications within 24hrs of surgery were also excluded. Patients with respiratory, cardiovascular, renal, hepatic, endocrinal and neurological disease were also excluded from the study.

Every patient selected for the study was explained details of the procedure in her native language and written informed consent was taken from each of them before the day of operation. Ninety patients were randomly allocated by a computerized randomized table in three equal groups (n=30) either to receive inj granisetron (2.5mg), inj palonosetron (0.75mg) or inj ondansetron (8mg) IV respectively before induction of anaesthesia. The total volume of the study material was 4 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.

All the patients were instructed not to consume solid food after midnight on the day of operation but clear fluids were permitted till four hours prior to the scheduled time of operation and received premedication of tablet diazepam 10mg the night before the operation and tablet ranitidine 150mg in the previous night and the morning.

A standardized anaesthesia regime was followed. After preoxygenation for 3 minutes the study drug was intravenously administered according to the protocol. Anaesthesia was induced with 4-5mg/kg of thiopentone sodium and 2µg/kg of fentanyl intravenously. Vecuronium 0.2mg/kg intravenously was used to facilitate tracheal intubation. Anaesthesia was maintained with 33% oxygen with 67% of nitrous oxide. Ventilation was mechanically controlled and was adjusted to maintain EtCO2 between 35-40 mmHg. At the end of the operation neuromuscular block was decurarized by using neostigmine and glycopyrolate and subsequent extubation was done.

All patients were observed postoperatively by resident doctors who were unaware of the study drug. Patients were transferred to post anesthetic care unit (PACU) for the first six hours after anaesthesia. During the 6-24 hrs period patient was observed in the ward. During the observation period, blood pressure, heart rate, respiratory rate and SpO2 was monitored except when the patient was sleeping. If the patient experienced brief instances of nausea and vomiting within an interval of one minute, it was classified as a single emetic episode. Conversely, when the interval between bouts of emesis exceeded one minute, those were deemed separate events. The number of patients who required rescue antiemetic was recorded. The complete response was defined as no vomiting and no administration of antiemetic rescue medication during the 24 hr observation period. This was also the primary efficacy end point of the study. The details of any side effects were also recorded throughout the study following either general questioning of the patients or spontaneous comment of the patient.

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. Postoperative analgesia was taken care of by giving inj diclofenac sodium i.m 75mg 8 hourly.

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 was 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

The study was conducted with 90 individuals of ASA physical status I & II, posted for elective gynaecological surgery. They were randomly divided into three groups (n=30). All three groups were comparable for their demographic profiles with

respect to age and body weight. The baseline parameters like heart rate and blood pressure before start of operation and duration of operation were also comparable [Table 1]. p value (calculated by One-Way Analysis of Variance ANOVA) was found to be >0.05 for all the variable mentioned above.

Table 1: Distribution of Age, Body weight, Baseline Heart rate, Baseline Mean Arterial Blood pressure, Duration of Surgery (in minutes) among the groups (mean and standard deviation) and their stastical significance.

	Group G (n=30)	Group P (n=30)	Group O (n=30)	Significance (ANOVA)
Age(yrs)	47.33 ±6	49.07 ± 5.28	51.33 ± 7	P=0.081
Body wt(kgs)	50.37 ± 5.56	47.07 ± 6.68	49.43 ± 5.66	P=0.095
Baseline Heart Rate	74.37 ± 8.51	75.33 ± 9.23	74.83 ± 8.22	P=0.911
Baseline MAP	83.73 ± 4.143	83.20 ± 4.18	83.40 ± 4.76	P=0.890
Duration of surgery	104.83±11.02	100.50±15.39	102.67±10.06	P=0.224

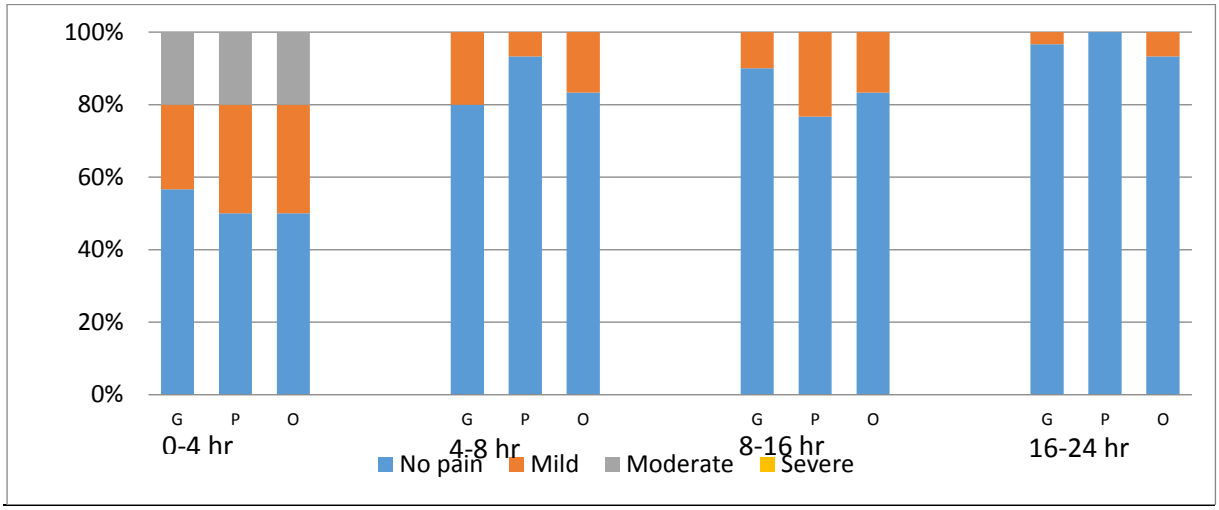

Figure 1: Shows the distribution of patients with intensity of wound pain observed between 0-4 hrs, 4-8 hrs, 8-16 hrs and 16-24 hrs postoperatively among three study groups. Data expressed in the form of percentage.

Patients of all the group (Group G, P and O) were compared in terms of postoperative pain scores between 0-4 hrs, 4-8 hrs, 8-16 hrs and 16-24 hrs interval [Figure 1]. The scores when compared in different interval of time between the groups found to be statistically insignificant. p value(calculated by Friedman's analysis of variance) was found to be >0.05.

Table 2: 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 3: 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	0	0	0
Headache	3.3%(1)	3.3%(1)	6.7%(2)
Hypertension	3.3%(1)	0	0
Bradycardia	3.3%(1)	0	0
Dizzyness	3.3%(1)	0	0
ECG changes	0	0	0

During 24hrs observation it was found 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; Friedman's analysis of variance). The incidence of nausea in group G was 10%, in group P was 3.3% and 33.3% in group O. (P=0.002 Friedman's analysis of variance). 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 calculated by Friedman's analysis of variance was statistically significant). Incidence of side effects like headache, hypertension, bradycardia, dizzyness found to occur in some of the patients, but were not significant statistically. There was no incidence of pruritus and abnormal ECG changes.

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.[15] 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.[16] 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.[17] Many drugs have been tried since the recognition of this unpleasant complication in surgical patients. However, avoiding PONV while minimizing adverse effects still remain a challenge. Palonosetron is a unique 5-HT3 receptor antagonist approved for the prevention of chemotherapy induced nausea and vomiting.[14] The exact mechanism of palonosetron in the prevention of PONV is unknown but palonosetron may act in the area postrema which contain a number of 5-HT3 receptors.[18]

Granisetron is effective for the treatment of emesis in gynaecological patients. It has been suggested that granisetron may act on sites containing sites for 5-HT3 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]

Candiotti A.K and colleagues demonstrated that palonosetron 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 mg or 8 mg IV has been recommended for preventing PONV, the meta-analysis by Tramer and colleagues suggested that 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, palonosetron or ondansetron for the prevention of PONV. In this study patients in Group G (n=30) received inj granisetron 2.5mg, Group P received inj palonosetron 75µg and Group O received inj ondansetron 8mg slow iv before the induction of anaesthesia. All the operations were elective and performed between 9 AM and 2 PM. Patients were prepared with optimum period of fasting preoperatively.

Hovorka J et al 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.[22] Purkis et al 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 PONV was excluded.[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. 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.[24] 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 eliminated. As far as the premedication is concerned no opioid was used in the premedication which could have modified the incidence of PONV.

[Table 1] shows the demographic profile and baseline hemodynamic parameters 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, body weight baseline heart rate and base line mean arterial 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 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.[25] Pain intensity was controlled in our study with the use of Inj diclofenac sodium 75mg IM. Intensity of pain was evaluated during 24 hr period [Figure 1]. The statistical analysis showed no significant difference regarding intensity of pain among the groups during the period of observation.

In the present study only 3.3% of study population in the ondansetron group had a complaint of vomiting and required of rescue antiemetic whereas in the granisetron and palonosetron group nobody complaint of nausea and vomiting during first four hour of observation. The complete response to PONV over the 24 hrs period was 83.3% in the granisetron group, 93.3% in the palonosetron group and 66.7% in the ondansetron group [Table 2]. The differences between the groups were statistically significant except granisetron group and palonosetron group where overall incidence was statistically insignificant. Patients those had vomiting needing a rescue antiemetic over the 24 hrs study period was 6.7% in the granisetron group, 3.3% in the palonosetron group and 30% in the ondansetron group. The difference between the groups was statistically significant except between granisetron and palonosetron group where overall

incidence was statistically insignificant. Park SK and Cho EJ also observed that palonosetron was more effective than ondansetron in preventing PONV.[26]
Thus the major findings of the present study were that during the 24 hrs recovery from anaesthesia, the frequencies of PONV in the palonosetron 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 palonosetron 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 [Table 3]. The difference was statistically insignificant.

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. Palonosetron 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.

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