ISSN: 2515-8260 Volume 08, Issue 04, 2021

A CONTROLLED, RANDOMIZED, DOUBLE BLIND, FIXED DOSE COMPARATIVE STUDY TO EVALUATE THE EFFICACY OF GRANISETRON, ONDANSETRON AND METOCLOPRAMIDE IN PREVENTION OF POST-OPERATIVE NAUSEA AND VOMITING IN GYNECOLOGICAL ONCOSURGERIES

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Abstract
The etiology of PONV is not fully understood. PONV is multifactorial in etiology and depends on a variety of factors like, age, gender, previous history of PONV, type and duration of operation, anaesthesia technique and postoperative care.[10]So as an anesthesiologist it is essential to understand the mechanism involved in nausea and vomiting and the available peri-operative treatment options. After Institutional Ethical Committee approval, one hundred and twenty females aged 18-60yr of ASA I and II who satisfied the inclusion criteria were randomly allocated into four groups of 30 each by a computer generated random number table. There is statistically significant difference in incidence of vomiting among the groups over the study period in total (p value is 0.010), but no significance in the case of nausea among the groups (p value is 0.103).

Keywords: Oncosurgeries, PONV, granisetron, ondansetron and metoclopramide

Introduction

Post-operative Nausea and Vomiting (PONV) are among the most common unpleasant experiences after the surgery and recovery from anesthesia. In spite of many advancements for treating PONV, this problem still continues to occur with unacceptable frequency in association with surgery and anaesthesia· PONV is very distressing to the patient and increases clinical workload for nursing staff. In ambulatory surgery, it may lead to delayed discharge andhospital readmission. Thus PONV creates considerable extra cost for health care delivery systems[3].

PONV is an unpleasant experience to the patients and potentially detrimental to post-operative recovery. Complications like aspiration of vomit, dehydration, oozing from operative site, muscular pain, fatigue, alkalemia and wound dehiscence may occur[4Recently,most of the surgeries are performed on day care basis; for example, tonsillectomy,strabismus surgery, breast surgery, and obstetric surgery which are associated with a high incidence of PONV[5].The incidence of PONV ranges from 20% to 30% during the first 24 hours following anaesthesia and surgery[6].Its incidence is higher in females[7]and more so with gynaecological surgeries[8].The incidence of PONV with gynaecological surgeries is 20-40%[9].Thus prophylactic antiemetic therapy is indicated in this high risk group.

The etiology of PONV is not fully understood. PONV is multifactorial in etiology and depends on a variety of factors like, age, gender, previous history of PONV, type and duration of operation, anaesthesia technique, and postoperative care[10].So as an anesthesiologist it is essential to understand the mechanism involved in nausea and vomiting and the available peri-operative treatment options.

Many of the traditional antiemetics have been proved disappointing, either because of low efficacy or unacceptable side effects such as sedation, extrapyramidal symptoms[11].Several 5HT3 receptor antagonists like

ondansetron, granisetron and tropisetron have been used successfully in preventing chemotherapy (cisplatinum) induced nausea and vomiting. Both ondansetron and granisetron have similar antiemetic efficacy for prophylaxis against chemotherapy induced nausea and vomiting[12].

Ondansetron is an effective drug in preventing chemotherapy induced nausea and vomiting. Though ondansetron is safe and effective with few side effects, it has to be administered intravenously three times a day for an optimal result[13, 14].Frequency of dizziness and blurred vision is more in patients treated with this drug[15].Even though ondansetron is commonly used to prevent PONV because of its potent antiemetic effect and lack of sedative and extra pyramidal effect, significant portion of patients continue to suffer from PONV[16].

Granisetron, is another 5HT3 receptor antagonist, exhibits different receptor binding affinity, dose response and duration of effect with almost complete absence of nausea and vomiting. It has extended period of action for up to 24 hours when compared to ondansetron in prevention of cisplatin induced nausea and vomiting[17].In patients undergoing chemotherapy, there was complete response i.e. absence of nausea and vomiting with granisetron. It is safe and effective for a duration of up to 24 hours, with no need of additional supplemental antiemetics[17, 18].Granisetron is more effective in preventing emetic symptoms during and after spinal anaesthesia for caesarean section[19].Metoclopramide has been used for decades to prevent PONV. Its antiemetic properties are primarily mediated through its antidopaminergic action and it also has prokinetic properties[20].

In the present study we compared the antiemetic efficacy of intravenous ondansetron, granisetron and metoclopramide for prevention of PONV following gynecological oncosurgeries.

Materials and methods

Inclusion and exclusion criteria

Inclusion Criteria:

- ASA Grade I & II
- Age 18-60yr
- Female patients scheduled to undergo non-laparoscopic lower abdominal surgery under general anesthesia
- Exclusion Criteria:
- Patient with history of motion sickness
- Pregnancy
- Those who have taken antiemetic drugs within 24hrs of surgery
- ASA III & IV
- Laparoscopic surgeries
- Emergency cases

After Institutional Ethical Committee approval, one hundred and twenty females aged 18-60yr of ASA I and II who satisfied the inclusion criteria were randomly allocated into four groups of 30 each by a computer generated random number table.

- **Group I:**The patients received0.9%isotonic saline as control [3mL].
- **Group II:** The patients received Granisetron 3 mg [3mL].
- **Group III:** The patients received Ondansetron 4 mg [2mL diluted to 3mL with normal saline].
- **Group IV:** The patients received Metoclopramide 10mg [2mLdiluted to 3ml with normal saline].

Dose of drugs used in our study were based on previous reports in literature-Bhatia N, Katyal. S.[21]

A common standard anesthetic regimen was followed for all patients which included overnight fasting and premedication in the form of Tab Diazepam 5 mg the night before surgery. All patients received the study drug 10min prior to induction. The study drug was prepared by an anesthesiologist not involved in the study and was handed over to the attending anesthesiologist just before the induction of anaesthesia. Neither the attending anesthesiologist who collected the data nor the patients were aware of the group allocation.

After pre-oxygenation with 100% oxygen for 3minutes, anaesthesia induced with fentanyl 1.5mcg/kg iv, thiopentone 5mg/kg iv and succinylcholine 2mg/kg to facilitate tracheal intubation. Anaesthesia was maintained with N_2O: O_2 = 66%:33% and halothane 1% and muscle relaxation maintained with vecuronium. Perioperative monitoring consisted of continuous ECG, blood pressure, heart rate, respiratory rate and pulse oximetry.An orogastric tube was also introduced. At the end of surgery all patients received paracetamol 1gm iv infusion and residual neuromuscular blockade was reversed with iv glycopyrrolate (0.01mg/kg) and iv neostigmine (0.05mg/kg). Patients were extubated after establishment of spontaneous respiration and transferred to recovery room. All patients received paracetamol infusion 1gm every 8^{th} hourly and ketorolac 30mg iv 12^{th} hourly for postoperative pain relief as per institutional practice.

Parameters noted were-

- Heart Rate, Systolic blood pressure, Diastolic blood pressure & Mean blood pressure at baseline, 1 hour, 2 hour and 3 hour interval.

- Post operatively, patients were observed for nausea, vomiting or retching every hour for the first 24 hours (0hr-immediate post-operative time, 1hr, 2hr, 3hr, 4hr, 5hr, 6hr and at 24hr).

Number of nausea and vomiting episodes were counted.Patients with nausea for as long as 10 min oremetic episode were given a rescue antiemetic in the form of injection ondansetron 4 mg iv and inj dexamethasone 8mg iv.

Sample size: Bhatia N *et al*.,in their study noted the incidences of PONV with granisetron, ondansetron, metoclopramide and placebo as 6.6%, 13.3%, 33.3% and 43.3% respectively. In the present study expecting similar results with 95% confidence and 80% power and considering a 30% minimum detectable difference, the study required a minimum of 30 subjects in each group.

Statistical methods: Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD.
(Min-Max) and results on categorical measurements are presented in Number (%).
Significance is assessed at 5% level of significance.Analysis of variance (ANOVA) has been used to Chi-square/2x4 3x4 Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

Results

Study design: A Comparative evaluation randomized controlled study of 120 patients with 30 in Group I (Normal Saline), 30 in Group II (Granisetron), 30 in Group III (Ondansetron) and 30 in Group IV (Metoclopramide) was undertaken to study the incidence of nausea and vomiting.

Table 1: Age distribution

Age in years	Group I		Group II		Group III		Group IV	
	No	%	No	%	No	%	No	%
18-40	9	30.0	12	40.0	12	40.0	11	36.7
41-50	13	43.3	11	36.7	13	43.3	8	26.7
51-60	8	26.7	7	23.3	5	16.7	11	36.7
Total	30	100.0	30	100.0	30	100.0	30	100.0
Mean ± SD	43.43±7.52		43.53±8.59		42.17±8.12		45.00±10.02	

Samples are age matched with p=0.624, the average age of subjects in Group I is 43.43, Group II is 43, Group III is 42, Group IV is 45.

Table 2: Incidence of episodes of Nausea: A Comparative Evaluation

Incidence of Nausea	Group I (n=30)		Group II (n=30)		Group III (n=30)		Group IV (n=30)	
	No	%	No	%	No	%	No	%
0 hours	2	6.7	0	0.0	0	0.0	2	6.7
1 hours	4	13.3	1	3.3	2	6.7	1	3.3
2 hours	2	6.7	0	0.0	0	0.0	0	0.0
3 hours	0	0.0	0	0.0	0	0.0	1	3.3
4 hours	1	3.3	1	3.3	2	6.7	0	0.0
5 hours	1	3.3	0	0.0	0	0.0	0	0.0
6 hours	0	0.0	0	0.0	0	0.0	1	3.3
24 hours	1	3.3	0	0.0	0	0.0	1	3.3

The number episodes of nausea at different time intervals during the first 24 hours postoperatively have been depicted in the table above.

Table 3: Incidence of episodes of Vomiting: A Comparative Evaluation

Incidence of Vomiting	Group I (n=30)		Group II (n=30)		Group III (n=30)		Group IV (n=30)	
	No	%	No	%	No	%	No	%
0 hours	4	13.3	0	0.0	2	6.7	3	10.0
1 hours	2	6.7	0	0.0	0	0.0	2	6.7
2 hours	0	0.0	0	0.0	1	3.3	2	6.7
3 hours	1	3.3	0	0.0	0	0.0	0	0.0
4 hours	3	10.0	0	0.0	0	0.0	0	0.0

5 hours	0	0.0	0	0.0	0	0.0	1	3.3
6 hours	2	6.7	1	3.3	0	0.0	0	0.0
24 hours	2	6.7	0	0.0	1	3.3	2	6.7

The number episodes of vomiting at different time intervals during the first 24 hours postoperatively have been depicted in table the above.

Table 4: Incidence of episodes of "Nausea and Vomiting": A Comparative Evaluation

Incidence of NV	**Group I (n=30)**		**Group II (n=30)**		**Group III (n=30)**		**Group IV (n=30)**	
	No	**%**	**No**	**%**	**No**	**%**	**No**	**%**
0 hours	6	20.0	0	0.0	2	6.7	5	16.7
1 hours	6	20.0	1	3.3	2	6.7	3	10.0
2 hours	2	6.7	0	0.0	1	3.3	2	6.7
3 hours	1	3.3	0	0.0	0	0.0	1	3.3
4 hours	4	13.3	1	3.3	2	6.7	0	0.0
5 hours	1	3.3	0	0.0	0	0.0	1	3.3
6 hours	2	6.7	1	3.3	0	0.0	1	3.3
24 hours	3	10.0	0	0.0	1	3.3	3	10.0

The number episodes of nausea and vomiting (PONV) at different time intervals during the first 24 hours postoperatively have been depicted in the table above.

Table 5: Over all incidences of episodes Nausea and Vomiting during the study period (24hrs)

Incidence in 24 hours of time	**Group I (n=30)**		**Group II (n=30)**		**Group III (n=30)**		**Group IV (n=30)**		**P value**
	No	**%**	**No**	**%**	**No**	**%**	**No**	**%**	
Nausea	11	36.7	2	6.7	4	13.3	6	20.0	0.103
Vomiting	14	46.7	1	3.3	4	13.3	10	33.3	0.010**

There is statistically significant difference in incidence of vomiting among the groups over the study period in total (p value is 0.010), but no significance in the case of nausea among the groups (p value is 0.103).

Table 6: Incidence of episodes of PONV

Incidence of nausea& vomiting together over 24 hrs	**Group I**		**Group II**		**Group III**		**Group IV**	
Nausea and vomiting	No	%	No	%	No	%	No	%
	25	83.3	3	10	8	26.7	16	53.3

Table 7: Pair wise comparison of Incidence of Nausea

	Group I vs Group II	**Group I vs Group III**	**Group I vs Group IV**	**Group II vs Group III**	**Group II vs Group IV**	**Group III vs Group IV**
Nausea	0.020*	0.029*	0.552	0.024*	0.044*	0.048*
Vomiting	0.003**	0.028*	0.390	0.032*	0.042*	0.046*

The difference in incidence of nausea and vomiting is very significant among Groups I&II; I & III; II & III; II & IV; III & IV (p value < 0.05) and not significant in case of comparison between I&IV.

Table 8: Side effects seen in different groups

Side effects	**Group I**	**Group II**	**Group III**	**Group IV**
Headache	1	2	3	3
Dizziness	0	2	1	1
Sedation	0	1	0	1

Discussion

Post-operative nausea and vomiting is one of the distressing side effects following general

anaesthesia and surgery, and has been characterized as big little problem[2].The etiology ofPONV is multifactorial and depends upon factors like age, gender, previous history of PONV, type and duration of surgery, anaesthetic technique and postoperative care[10].The incidence of PONV in females is up to three times higher than in males[7]and more so with those undergoing gynaecological surgeries[8].PONV is a troublesome problem following anaesthesia that has proved difficult to prevent. Despite advances in anaesthesia the incidence and severity of PONV still remains relatively unchanged and elusive to complete prevention. PONV is not only a leading cause of patient discomfort and dissatisfaction, but also increases the health care costs by lengthening the hospital stay[22].

A wide variety of prophylactic antiemetic regimens have been employed perioperatively. There are four main classes of drugs commonly used in the prevention and treatment of PONV; which includes anticholinergics, antihistamines, D2 antagonist and 5 HT3 antagonists. As vomiting center can be triggered by many ways, hence no single class of drug is completely effective in controlling post-operative nausea and vomiting[23].The introduction of 5 HT3 receptor antagonist was a major advancement in the management ofpostoperative nausea and vomiting because there was less adverse effects that were observed than commonly used traditional antiemetic[24].

Ondansetron is a selective 5 hydroxy tryptamine receptor antagonist possessing property of superior antiemetic prophylaxis compared to the traditional agents. This drug has been widely used for treatment of postoperative nausea and vomiting. Granisetron is another, 5 HT3 receptor antagonist with stronger 5 HT3 binding.Metoclopramide blocks dopamine receptors in the CTZ and vomiting center and has prokinetic action.

In the present study we randomly administered granisetron 3mg, ondansetron 4mg and metoclopramide 10mg to groups of 30 female patients who underwent lower abdominal gynaecological surgery under general anaesthesia.All the groups were well matched for known risk factors for PONV such as age, weight, type and duration of anaesthesia and type of surgery.

Fujii Y *et al*.,[19]in their study used granisetron 20microgram/kg, 40 microgram/kg and 80 microgram/kg for the prevention of nausea and vomiting following breast surgeries. They concluded that 40 microgram/kg is the minimum effective dose. In the present study we used granisetron in dose of 3mg which amounts to a dose between 40microgram/kg and 80 microgram/kg. In study conducted by Pearman MH*et al*.,[25]in patients undergoing laparoscopic surgery, ondansetron 4mg was compared with placebo and the authors recommended 4mg iv as the effective and safe dose. Dose of 10 mg for metoclopramide was used based on previous reports in literature[21].

PONV is known to be a common problem following gynaecological surgery performed under general anaesthesia[6].The use of placebo arm in studies of PONV is contentious as it raises ethical issues of balancing patient's interest with that of scientific benefit. It is clear that scientific requirements should never over-ride ethical ones. Tramer MR *et al*.,[26]have argued in favor of using placebo in trials investigating postoperative nausea and vomiting, as it is a condition which lacks a gold standard treatment and the likelihood of an outcome is expected to vary widely. They opine that the trial designs without placebo control are unlikely to yield sensible results. They contend that the ethics of recruiting patients into trials that cannot yield sensible results as dubious. Hence in the present study we included a placebo group.

Olando*et al*.,[27]Rajeeva*et al*.,[28]and Thomas *et al*.,[5]administered ondansetron and granisetron for prevention of post-operative nausea and vomiting, at the time of induction. Since literature support the efficacy of 5HT3 receptor antagonist in preventing postoperative nausea and vomiting while administered at the time of induction of anesthesia, hence all agents were chosen to be given at the time of induction.

The most likely causes of PONV under general anaesthesia are volatile anesthetics, nitrous oxide.The effects of volatile anesthetics on postoperative nausea and vomiting are dose dependent and particularly prominent in the first 6 hrs after surgery[29].Similarly, we observed episodes of nausea and vomiting for hourly for the first 6 hrs post operatively.Theincidenceof nausea and vomiting in the present was found to be significant at zero hour(p=0.039),theincidence was found to be 20% in placebo group, 0 % in Granisetron group, 6.7% in Ondansetron group and 16.7% in Metoclopramide group. However the incidence reduced with passage of time in the postoperative period. The incidence of post-operative nausea (N) and vomiting (V) was maximum in placebo group (N= 36.7%, V= 46.7%), followed by Metoclopramide (N = 20%, V= 33.3%), Ondansetron group (N= 13.3%, V= 13.3%) and Granisetron group (N= 6.7%, V= 3.3%). This is comparable with study done by Bhatia *et al*.[21]

Overall incidence of post-operative nausea and vomiting during study period was found to be 10% with granisetron, 26.7% with ondansetron, 53.3% with metoclopramide and 83.3% with placebo over the first 24

hours postoperatively.

Table 9: Comparison of incidence of PONV with other studies

Study	Granisetron	Ondansetron	Metoclopramide	Placebo
Present study	10%	26.7%	53.3%	83.3%
Bhatia N *et al*.[21]	6.67%	13.33%	33.33%	43.33%
Bestas A *et al*.[30]	23%	30%	-	70%
Savant K *et al*.[31]	13.3%	40%	-	-
Ommid M *et al*.[32]	20%	52%	-	-
Jalali A *et al*.[33]	9.9%	-	42%	-
Farhat K *et al*.[34]	-	11.4%	42.4%	-

The overall incidences of PONV reported in literature in various studies with prophylactic administration of the drugs have been depicted in the table above. The incidence of PONV ranges from 6%-48% with granisetron, 11%-52% with ondansetron, 33%-70% with metoclopramide and 43%-72% with placebo. The wide variation observed in the studies is mainly due to the differences in the surgical procedures and patient population. Also, there is a lot of heterogeneity in the way data for PONV is collected. This heterogeneity in the patient population and data collection makes comparison of different studies difficult. However, the incidence of PONV noted in the present study in various groups falls well within these values. The incidence of PONV with placebo in the present is very high (83.3%). The reason for this may be female patients undergoing gynecological surgery, which is a population with a very high incidence of PONV[6-8].

The study done by Bhatia N *et al*.,[21] compared the three drugs (granisetron, ondansetron and metoclopramide), similar to the present study. The incidence of PONV with metoclopramide was higher than granisetron and ondansetron; in addition the incidence of PONV with granisetron was lower when compared to ondansetron, which was similar to that noted in the present study.

Studies done by Bestas A *et al*., [30] Savant K *et al*., [31] and Ommid M *et al*.,[32] comparing granisetron and ondansetron for prevention PONV have similarly noted the superiority of granisetron over ondansetron when administered prophylactically. The results of the present study are thus in agreement with the above studies reported in literature.

Though both ondansetron and granisetron belong to the same group of 5HT3 receptor antagonist and they act on the same receptor, granisetron is seen to be clinically more efficacious than ondansetron. The high affinity of granisetron, coupled with the insurmountable antagonism displayed at 5HT3 receptors, and a longer duration of action is thought to underlie its good clinical efficacy[35].

In the present study, patients in various study groups were administered ondansetron and dexamethasone as the rescue antiemetic. It may be criticized that ondansetron being on the study drugs should not have been used as the rescue antiemetic. Though we do agree that such criticism is valid, it was beyond the financial resource of our institution to have any other injectable antiemetic other than that used in the present study. Hence, ondansetron (one of the study drug) and dexamethasone combination was employed as the rescue antiemetic. It may also, be noted there are studies where they have used one of the study drugs as the rescue antiemetic [21,32,36].

The requirement for rescue antiemetic was higher in placebo group (22 patients) and metoclopramide group (16 patients) compared to granisetron (2 patients) and ondansetron (5 patients). The results of the present study was similar to other studies[21]where rescue antiemetic was required in more patients with placebo and metoclopramide compared to ondansetron and granisetron.

The side effects noted with the various drugs was minimal. Headache, dizziness and sedation were the side effects noted and it was comparable between the groups. Statistical inference with respect of side effects cannot be drawn as the present study was not powered to study the same. Similar side effects have been noted in literature and have not caused any major untoward patient incidents.

It was observed that there was no statistical significant difference observed among four groups at basal, 1hr, 2 hour and 3 hour. The administration of Granisetron had no significant effect on vital signs or clinical laboratory test profiles. The hemodynamic effects were similar to the findings in our study.Gan.TJ *et al*.,[4] showed no significant intraoperative hemodynamic and respiratory changes among study groups. Our study correlated with their results.

Conclusion

This study was performed to compare the effectiveness of Granisetron, Ondansetron, Metoclopramide for the prevention of postoperative nausea and vomiting. The results of the study revealed that in the prevention of postoperative nausea and vomiting, Granisetron was more effective than Ondansetron and Metoclopramide.

Limitation for the study

1. Limited sample size.
2. Not surgery specific as all gynecological surgeries were included.

Recommendations for future work

In future the studies can be performed on larger patient population with surgery specific indications. However this study and its results are showing below mentioned recommendation to work on in future.

Study with combination of these drugs: A combination drug study can be performed on the PONV with different surgery indication as combination therapy.

Multi centric: Study can be conducted at different sites on larger sample size with different indications of surgery in order to prove more potent drug.

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