A COMPARATIVE STUDY OF ONDANSETRON AND GRANISETRON IN THE PREVENTION OF POST-OPERATIVE NAUSEA AND VOMITING (PONV) IN DAY-CARE SURGERY

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ABSTRACT

CONTEXT

A major factor behind this Day-Care surgery has been substantial savings in medical costs apart from increasing the convenience to the patient. From an anaesthetic viewpoint, one of the primary goals with respect to outpatient anaesthesia is prompt recovery with minimal side effects and quick discharge.

AIMS

To compare the efficacy and side effects of ondansetron and granisetron in the prevention of Postoperative Nausea and Vomiting (PONV) in female patients of reproductive age group undergoing Day-Care surgery.

SETTINGS AND DESIGN

Randomised double blind.

METHODS AND MATERIAL

150 female patients, ASA I and II, between the age of 18-45 yrs. undergoing Day-Care surgery. The patients were randomly allocated to one of the three groups (50 in each group). Group C (n=50): Control group. Received normal saline 2 mL intravenously. Group G (n=50): Granisetron group received Inj. Granisetron 1 mg IV made to 2 mL with normal saline. Group O (n=50): Ondansetron group. Received Inj. Ondansetron 4 mg IV in 2 mL. Incidence of PONV was studied during two periods after surgery in the PACU (0-2 hrs.) and in the ward (2-6 hrs.). Patients were asked to rate nausea on a four-point scale as 0 - none, 1 - mild, 2 - moderate or 3 - severe. A telephonic interview was held with the patient 24 hours after surgery. This assessed the incidence of retching/vomiting, the incidence and severity of nausea and pain during the 24 hours after discharge.

STATISTICAL ANALYSIS

ANOVA, Chi-square, Fisher's Exact test was done.

RESULTS

9 patients (18%) in the placebo group suffered from vomiting, whereas only 6 (12%) in the ondansetron group and 3 (6%) in the granisetron group were affected. The incidence of PONV without prophylaxis was 20% with Group G (Inj. granisetron) was 10% and Group O (Inj. ondansetron) was 16%. This difference was not statistically significant in the 2-6 hours' period, Group G (Inj. granisetron) was found to be more effective than Group C (placebo) ($p < 0.05$) in preventing vomiting. In the post discharge period (6-24 hrs.), Group G (Inj. granisetron) was more effective than Group C (placebo) ($p < 0.005$) and Group O (Inj. ondansetron) ($p < 0.05$) in the prevention of PONV.

CONCLUSION

We conclude either granisetron and ondansetron is equally effective for the control of PONV in the first 6 hours after Day-Care surgery, granisetron is more effective than ondansetron in the post-discharge period.

KEYWORDS

5-HT₃ Antagonists, Granisetron, Ondansetron, Day-Care Surgery, Post-Operative Nausea and Vomiting.

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INTRODUCTION

It is a well-known fact that the number of surgeries performed on a day-care basis is on the increase. A major factor behind this growth has been substantial savings in medical costs apart from increasing the convenience to the patient.^[1]

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From an anaesthetic viewpoint one of the primary goals with respect to outpatient anaesthesia is prompt recovery with minimal side effects and quick discharge. Subsequently, Postoperative Nausea and Vomiting (PONV), appropriately called "the big little problem^[2]" of ambulatory surgery has become a serious issue in the outpatient setting. This is due to its potential to partially or completely negate the savings in medical costs, increase the expenses for treatment of PONV and decrease patient satisfaction. Thus, a key objective of the providers of day-care anaesthesia has been the prevention of PONV. Similarly, the objective of this investigation was the study of prevention of PONV in female patients, who are at a

higher risk of PONV with a specific focus on the newest class of antiemetics, the serotonin antagonists.

Serotonin antagonists were developed through modifications in the antiemetic metoclopramide, and work by selectively blocking the serotonin receptors both centrally - in the hypothalamus, the chemoreceptor trigger zone and the cerebral cortex and peripherally in the enterochromaffin cells of the intestinal mucosa. Ondansetron was the first drug in this group to be introduced in 1991.^[3,4] Granisetron was introduced in 1993 and was initially used only for prevention of chemotherapy-induced nausea and vomiting.^[5] Its use for PONV was approved by the FDA only in 2002.

While there are a number of studies comparing ondansetron with conventional antiemetics for PONV, there are a smaller number of studies comparing granisetron with other antiemetics and even fewer comparing the two serotonin antagonists (ondansetron and granisetron) to one another.

Hence, this study was designed to differentiate the efficacy of ondansetron and granisetron in the prevention of PONV in female patients undergoing day-care surgery.

AIM

To compare the efficacy and side effects of ondansetron and granisetron in the prevention of Postoperative Nausea and Vomiting (PONV) in female patients of reproductive age group undergoing day-care surgery.

MATERIAL AND METHODS

150 female patients between the age of 18 to 45 yrs., belonging to ASA I and II classes who gave informed consent for undergoing day-care surgery with duration less than 45 mins, general surgery like breast lump excision, sebaceous cyst excision, wound debridement, lymph node biopsy and Gynaecological surgeries like diagnostic hysteroscopy, diagnostic laparoscopy, interval sterilisation, laparoscopic myomectomy, laparoscopic ovarian cyst excision, Medical Termination of Pregnancy (MTP), MTP with sterilisation were included into the study after getting the Institutional Ethical Committee approval. The following patients were excluded from the study, history of reaction to ondansetron, granisetron or metoclopramide, any previous history of PONV, patients with gastro-intestinal disease or pre-existing nausea or vomiting, patients who had taken antiemetics within 24 hours of surgery, pregnant or lactating mothers, patients not willing to take part in the study. No premedication was given to any of these patients. On arrival in the operating room, after starting an intravenous cannula and infusion, routine monitoring devices were attached and baseline blood pressure, heart rate and oxygen saturation were recorded.

The medications were prepared in equivalent volumes (2 mL) by an assistant. Both the patient and the observer were blinded to the nature of the medication administered. The prepared medication was administered intravenously over one minute before induction.

Anaesthesia was induced with fentanyl 1.0-1.5 µg kg⁻¹ IV followed by propofol 2.0-2.5 mg kg⁻¹ IV. The airway was maintained using a facemask or LMA (Laryngeal Mask Airway). The airway was handled by expert anaesthesiologist, spontaneous respiration was maintained and gentle assisted ventilation in case the respiration becomes shallow care was taken not to distend the abdomen during mask ventilation.

Anaesthesia was maintained with isoflurane 1%-1.5% in a mixture of nitrous oxide and oxygen in the ratio of 2:1. The anaesthetic agent was adjusted with the goal of maintaining blood pressure within 20% of pre-induction value. Diclofenac suppository 50 mg was inserted after induction of anaesthesia prior to the start of surgery. All the patients received oxygen 5 litre per minute by face mask for one hour after the procedure was over.

Blood pressure, heart rate and SpO₂ were monitored every minute for the first 10 mins and every 5 mins subsequently till the end of surgery, every 15 mins for 2 hrs. after surgery in the PACU. Thereafter, the blood pressure and heart rate were monitored hourly in the ward till discharge. The nature and duration of surgery was recorded. Recovery time, i.e. the time taken to respond to verbal command was also noted. The patients were monitored in the PACU for 2 hours and shifted to the ward. They were discharged from the hospital when they were able to walk comfortably and take oral fluids.

Incidence of PONV was studied during two periods after surgery in the PACU for 2 hrs. and in the ward 2 to 6 hrs. The assessments were made at the end of each period. Patients were asked to rate nausea on a four-point scale as 0 - none, 1 - mild, 2 - moderate or 3 - severe. Retching and vomiting were assigned together under the common category - emetic episode and assessed as present or absent.

If the patient had a nausea score of ≥ 2 for more than one hour or ≥ 2 emetic episodes they were treated with 10 mg metoclopramide IV. If the initial "rescue" antiemetic was inefficient, promethazine 12.5 mg IV was administered. Pain intensity was also rated on the verbal response score and the presence of other side effects were also noted.

A telephonic interview was held with the patient 24 hours after surgery. This assessed the incidence of retching/vomiting, the incidence and severity of nausea and pain during the 24 hours after discharge.

Statistical Analysis

The age, height, weight and BMI in the three groups are compared and analysed using ANOVA. The distribution of facemask versus laryngeal mask, and the ASA grading in the three groups, was analysed by chi-square test and there was no statistically significant difference between the three groups. The duration of surgery and the time to recovery after cutting off of the anaesthetic agent was also studied and analysed by ANOVA. In the third time frame, there was no incidence of PONV in the Granisetron group. With a value of zero, Chi-square test was not applicable and hence Fisher's exact test was done. Granisetron was found to be more effective than placebo in this period with a P value of < 0.005, and more effective than ondansetron with a P value of < 0.05. A P value of <0.05 was considered statistically significant. SPSS for Windows, Version 11.0. Chicago, SPSS Inc. was used.

RESULTS

The three groups in the study were comparable in terms of age, weight and body mass index (Table 1). The method of induction and maintenance of anaesthesia was uniform. Airway was maintained with either a facemask or a laryngeal mask and there was no significant difference in the distribution of the two among the groups (Table 2). Duration of surgery and recovery time (Table 3). Type of Surgery in each Groups (Table 4). Incidence of PONV (Table 5). In the third

time frame, there was no incidence of PONV in the Granisetron group. With a value of zero, Chi-square test was not applicable and hence Fisher's exact test was done. Granisetron was found to be more effective than placebo in this period with a P value of < 0.005, and more effective than ondansetron with a P value of < 0.05.

(Table 6) The incidence of PONV without prophylaxis was 20% with Group G (Inj. granisetron) was 10% and Group O (Inj. ondansetron) was 16%. This difference was not statistically significant in the immediate postoperative period; there was no statistically significant difference between the three groups. In the 2–6 hours' period Group G (Inj. granisetron) was found to be more effective than Group C (placebo) ($p < 0.05$) in preventing vomiting. In the post discharge period (6–24 hrs.) Group G (Inj. granisetron) was more effective than Group C (placebo) ($p < 0.005$) and Group O (Inj. ondansetron) ($p < 0.05$) in the prevention of PONV. Use of Rescue Antiemetic (Table 9). Headache and giddiness were the main side effects seen during the study. Two patients, both belonging to the placebo group had to stay in the hospital overnight, as they were not able to tolerate oral feeding.

Parameter	Placebo Mean $\pm$ SD	Granisetron Mean $\pm$ SD	Ondansetron Mean $\pm$ SD	F Value†
Age	31.24 $\pm$ 6.67	30.66 $\pm$ 5.88	30.30 $\pm$ 6.21	.296
Weight	58.94 $\pm$ 8.86	59.70 $\pm$ 10.88	58.44 $\pm$ 10.37	.198
Height	1.53 $\pm$ 0.058	1.52 $\pm$ 0.093	1.53 $\pm$ 0.069	.382
BMI	25.02 $\pm$ 3.64	25.82 $\pm$ 4.93	24.80 $\pm$ 4.21	.782

Table 1: Distribution of Age, Height, Weight and BMI

BMI (Body Mass Index), SD Standard deviation, †ANOVA result is reported as an F-value

	Placebo	Granisetron	Ondansetron	χ^2 *
ASA Gr I	42	46	45	1.72
ASA Gr II	8	4	5	1.72
GA/MASK	20	24	27	1.98
GA/LMA	30	26	23	1.98

Table 2: ASA Grade & Type of Anaesthesia

ASA (American Society of Anaesthesiologist), LMA (Laryngeal Mask Airway), GA (General Anaesthesia)

* χ^2 chi-squared test statistic

Parameter	Placebo Mean $\pm$ SD	Granisetron Mean $\pm$ SD	Ondansetron Mean $\pm$ SD	F Value†
Duration of Surgery (min.)	30.40 $\pm$ 11.5	28.60 $\pm$ 13.32	28.90 $\pm$ 13.02	.291
Recovery Time (min.)	5.34 $\pm$ 1.89	5.26 $\pm$ 1.88	5.04 $\pm$ 1.62	.370

Table 3: Duration of Surgery and Recovery Time

SD = Standard Deviation, †ANOVA result is reported as an F-value

Surgery	Prophylactic Placebo	Antiemetic Granisetron	Ondansetron	Total
Breast lump excision	9	11	5	25
Dilatation & Curettage dilatation & Evacuation	8	9	11	28
Diag. hysterolaparoscopy	2	0	0	2
Diag. laparoscopy	5	7	6	18
Ganglion removal	2	1	4	7
Hysteroscopic polypectomy	0	0	1	1
Hysteroscopy	1	0	0	1
Incision & drainage	5	4	6	15
Interval sterilisation	1	1	0	2
Lap. Myomectomy	1	1	1	3
Lap. Ovarian Cystectomy	1	0	1	2
Lap. Sterilisation	1	1	0	2
Lateral Sphincterotomy	2	2	3	7
Lymph node biopsy	2	0	0	2
MTP*	0	2	2	4
MTP*, Lap sterilisation	3	7	6	16
Sebacous cyst excision	5	3	3	11
Wound debridement	1	1	0	2
	1	0	1	2
Total	50	50	50	150

Table 4: Type of Surgery in Each Group

*MTP Medical Termination of Pregnancy

PONV	Placebo	Granisetron	Ondansetron	χ^2 *
0-24 Hrs.	10	5	8	1.72
0-2 Hrs.	7	3	2	2.70
2-6 Hrs.	7	3	3	2.70
6-24 Hrs.	8	0	5	

Table 5: Incidence of PONV

* χ^2 Chi-Squared Test Statistic

Nausea	Placebo (n)	Granisetron (n)	Ondansetron (n)	F Value†
0-24 Hrs.	10	5	7	1.981
0-2 Hrs.	7	3	2	1.691
2-6 Hrs.	7	3	2	2.049
6-24 Hrs.	7	0	5	3.166*

Table 6: Incidence of Nausea in the Three Groups

†ANOVA result is reported as an F-value, * $p < .05$

No. of Patients	Placebo	Granisetron	Ondansetron	F Value†
E.E in 24 Hrs.	9	3	6	1.016
E.E 0 - 2 Hrs.	5	3	2	0.888
E.E 2 - 6 Hrs.	7	0	2	4.855*
E.E 6 - 24 Hrs.	3	0	3	1.499

Table 7: Number of Patients with Emetic Episodes in the Three Groups

E.E – Emetic Episodes, †ANOVA result is reported as an F-value, * $p < 0.05$.

Frequency of E.E	Placebo	Granisetron	Ondansetron
In 24 Hrs.	29	6	11
0-2 Hrs.	12	6	4
2-6 Hrs.	14	0	3
6-24 Hrs.	3	0	4

Table 8: Frequency of Emetic Episodes in the Three Groups

E.E – Emetic Episodes

Rescue Antiemetic	Placebo	Ondansetron	Granisetron	χ^2 *
Metoclopramide	7	5	4	0.98
Promethazine	4	0	0	0.058*

Table 9: Use of Rescue Antiemetic

* χ^2 chi-squared test statistic

*Fisher's test value

DISCUSSION

Post-operative nausea and vomiting continues to be the bane of day-care surgery despite the numerous modalities available for the prophylaxis and treatment of the same. In fact, the controversy whether prophylaxis or treatment is more cost effective in the management of PONV is yet to be settled. The search for an ideal agent for the prophylaxis of PONV is still on.

The three groups in the study were comparable in terms of age, weight and body mass index. The method of induction and maintenance of anaesthesia was uniform. Airway was maintained with either a facemask or a laryngeal mask and there was no significant difference in the distribution of the two among the groups. In addition, there were no significant differences in the duration of surgery or recovery time in the three groups. A relationship between PONV and airway management was demonstrated by L. Doubravská^[6] was highest after orotracheal intubation (18.8%), but lower with face mask (8.9%) or laryngeal mask (6.2%) placement. Kovac AL^[7] and Gan TJ^[8] observed that certain surgical like abdominal, laparoscopic, ophthalmic, gynaecological, neurological, plastic and aesthetic or middle ear surgery and strumectomy and anaesthetic management influencing PONV include premedication, type of anaesthesia, induction agents used, opioids, nasogastric suction, muscle relaxation reversal, anaesthesiologist's experience, etc.

Of the 50 patients who did not receive any prophylaxis for PONV, 10 patients suffered from nausea or vomiting at some point over the study period. Hence, there was a 20% incidence of PONV without prophylaxis in this study group. Watcha MF and White PF^[9] have associated general anaesthesia with volatile agents to be associated with a 20-30% incidence of PONV, which corresponds to the results of our study. But this incidence was found to vary depending on a number of factors. However, let us consider the risk scores developed by Apfel et al^[10] where a score is developed from 4 predictors: female gender, history of motion sickness, non-smoking status and use of postoperative opioids. If none, one, two, three or four predictors were present, the incidences of PONV were 10, 21, 39, 61 and 70% respectively. In this study population, two risk factors namely female gender and non-smoking status were present and so the expected incidence of PONV would be around 39%. But the actual incidence was only 20%. This could probably be due to the use of propofol with known antiemetic effects for induction and Inj. Fentanyl, which causes less emesis than the opioids in use earlier.

A complete response in terms of absence of PONV within 2 hours after surgery was seen in 86% of patients who received placebo as against 96% in the Ondansetron group and 94% in the Granisetron group. This same trend continued in the 2-6 hours' period. The corresponding values in the 6-24 hours' period were 84%, 90% and 100%.

While there is an appreciable reduction in the incidence of PONV when antiemetic prophylaxis is used, the results did not reach statistical significance except in the 6-24 hours' period when granisetron was found to be more effective than placebo and ondansetron in controlling PONV. However, when the entire 24-hour period was considered, the incidence of PONV was 20% in the Placebo group, 10% in the Granisetron group and 18% in the Ondansetron group.

Almost all the studies comparing ondansetron and granisetron for the prophylaxis of PONV like those by Naguib

M et al^[11] Gan TJ et al^[12] and White PF et al^[13] did not find any difference between the two 5-HT₃ receptor antagonists.

This was in contrast to the better efficacy of granisetron in the prevention of chemotherapy-induced nausea and vomiting, which was proven in a number of studies like those by Specter JI et al^[14] Carmichael et al^[15] and De Wit et al.^[16] So also in our study there was no significant advantage of one 5-HT₃ receptor blocker over the other for the prevention of PONV over 24 hours.

It is evident that the severity of nausea was more in the placebo group compared to the other two groups. While three patients in the placebo group continued to experience nausea over 24 hours despite treatment, no such complaints were seen in the groups receiving prophylaxis.

The number of patients who suffered from emetic episodes was 9 in the placebo group as compared to 7 in the ondansetron group and 3 in the granisetron group. While this difference does not seem to be much, when a comparison of the number of emetic episodes in each group is made the gap is wider. There were 29 episodes in the Placebo group, 11 in the Ondansetron group and 6 in the Granisetron group and this difference was significant showing that both the 5-HT₃ receptor blockers reduced the severity of vomiting in the postoperative period.

A finding of possible significance was that 4 patients in the ondansetron group developed PONV only in the post discharge period. One of these patients also resorted to a single dose of oral ondansetron 4 mg, 9 hours after surgery and her symptoms were effectively controlled.

Hartsell T et al^[17] studied the efficacy of oral ondansetron versus placebo given postoperatively in patients who underwent surgery for acoustic neuroma. They found that ondansetron 8 mg b.i.d. for two days postoperatively was better than placebo. This also raises the question whether in our study the use of an oral dose of ondansetron in the postoperative period would have prevented PONV in these 4 patients. Bhattacharya D et al^[18] compared the efficacy of ondansetron and granisetron for prevention of PONV after day care gynaecological laparoscopy in a double-blind randomised placebo controlled trial. They found that incidences of emetic episodes were 20% in ondansetron group and 7% in granisetron group, which is clinically significant ($P < 0.05$).

The difference seen between ondansetron and granisetron in the post-discharge period could be due to the more prolonged action of the latter. Moreover, the difference between the two drugs was statistically significant in the post-discharge period proving that granisetron could be a better drug for control of post-discharge nausea and vomiting in day-care surgery.

While 7 patients in the Placebo group needed treatment with inj. metoclopramide 10 mg, only 4 patients needed rescue antiemetic in each of the other two groups. What was more significant was the fact that while there was complete response in the groups which received prophylaxis, 4 patients needed another antiemetic in the form of inj. promethazine 25 mg. Hence, the use of prophylaxis with granisetron or ondansetron reduced the need for rescue antiemetics and also allowed for better response to the treatment of PONV if it occurred.

The side effects commonly associated with the use of 5-HT₃ receptor antagonists are headache, diarrhoea and constipation. In this study 5 patients in the Ondansetron

group, 2 patients each in the Granisetron group and Placebo group had headache. The pain was mild in most of the patients. Only 2 patients in the Ondansetron group had moderate pain, which necessitated treatment with Tab. Paracetamol 650 mg. There were no complaints of diarrhoea or constipation in any patient.

The other problem which was encountered was giddiness, which occurred in 2 patients in the Placebo group. Since both these patients had also received Inj. promethazine for PONV, the giddiness was probably due to this.

5-HT₃ receptors have also been proven to cause QTC prolongation. However, no significant arrhythmia was noted in any of the patients during the intraoperative period or during the 0-2 hours' recovery period in the PACU.

Two of the patients in the placebo group who were otherwise planned for day-care surgery had to be admitted to the hospital overnight, as they were not able to tolerate oral feeds. While this difference was not statistically significant, no such untoward result was seen in any of the patients who received PONV prophylaxis with either ondansetron or granisetron.

CONCLUSION

We conclude either granisetron and ondansetron is equally effective for the control of PONV in the first 6 hours after day-care surgery, granisetron is more effective than ondansetron in the post-discharge period. Hence, granisetron will be a better choice for prophylaxis of PONV.

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