Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Prophylaxis for Post-operative Nausea and Vomiting: A Randomized Comparative Study between Granisetron versus Granistreon and Dexamethasone among Patients Undergoing Modified Radical Mastectomy

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Abstract

Introduction: The patients undergoing modified radical mastectomy under general anesthesia has been associated with higher incidence of post-operative Nausea and Vomiting (PONV). The present study compares efficacy of Granisetron versus Granistreon and Dexamethasone for the incidence and severity of PONV in early (<6 h) and late (6–24 h) post-operative period in two groups and also to estimate the number of patients who required actual rescue antiemetics and showed complete response after 24 h.

Materials and Methods: This study was carried out on 110 female patients aged 25–60 years undergoing modified radical mastectomy under general anesthesia. They were randomly divided into Group G (Granisetron) and Group G+D (Granisetron + Dexamethasone). Tests drugs were given preoperatively and all followed up in post-operative period.

Results: Both the groups were comparable in terms of demographic variables, physical attributes, duration of surgery, and baseline vital parameters. It was observed that Granisetron+ Dexamethasone combination is better at controlling incidence and severity of PONV in both early and late post-operative period which is statistically significant. There was no need of rescue antiemetic in Group D patients. There is statistically significant difference noted between both groups regarding complete response, that is, after 24 h.

Conclusions: Granisetron + Dexamethasone combination is far more effective in controlling PONV among patients undergoing Modified radical mastectomy.

Key words: Antiemetics, Dexamehasone, Granisetron, Post-operative nausea and vomiting, Prophylaxis

INTRODUCTION

Post-operative nausea and vomiting (PONV) is defined as nausea and/or vomiting experienced by patient within 24 h of a surgical procedure requiring anesthesia.[1] In the recent years, its incidence is ranging from 20% to 30% in general population to 30–40% among population who undergoing surgery under general anesthesia.[2] The female patients undergoing breast surgery with axillary dissection suffer a higher incidence of PONV (60%–80%),[3] due to risk factors associated such as obesity, female gender, and simultaneous chemotherapy. The etiology of PONV is complex and probably multifactorial. The causes can be attributed to various factors such as patient related, surgery related, and anesthetic factors. The impact of PONV and effectiveness of antiemetic therapy play an important role in the recovery of patients from anesthesia and surgery. Post-operative vomiting is frequently accompanied by rise in arterial blood pressure, intracranial pressure, and

Access this article online

www.ijss-sn.com

Month of Submission : 07-2020
Month of Peer Review : 08-2020
Month of Acceptance : 08-2020
Month of Publishing : 09-2020

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intraocular pressure. Persistence of PONV in a patient especially who is kept overnight fasting for general anesthesia can also result in dehydration, electrolyte imbalance. Persistent retching and vomiting can cause tension in suture lines, venous hypertension, bleeding under skin flaps, and increased risk of pulmonary aspiration of gastric contents, if airway reflexes are depressed from the residual effects of anesthetic and analgesic drugs. Over the years, there are various advances in PONV prophylaxis which include use of non-pharmacological measures that reduce baseline risk, a change to less emetogenic anesthetic techniques, or the use of new antiemetic drugs. However, the use of anti-emetics, either alone or in combination, remains the mainstay in PONV management.[4]

Most of the published trials and guidelines indicate that an improved antiemetic response when combinations of drugs acting which acts through different receptor sites are used as compared with monotherapy.

Receptors involved in PONV include dopamine, opioid, 5-HT_3 enkephalin, histaminic, muscarinic, and cholinergic receptors and the various drugs which act through these receptors were studied previously. It has been postulated that antiemetic and antinauseant effect of ondansetron is exerted by blockade of serotonin induced depolarization of vagal afferent nerves. It may also involve 5-HT_3 binding sites in the chemoreceptor trigger zone and nucleus tractus solitaire in the brain stem. Emetogenic action of chemotherapeutic agents and radiotherapy as well as PONV may involve activation of 5-HT_3 receptors in vagal afferents in the small intestine as well as central neurons in the area postrema near the fourth ventricles. These actions are effectively blocked by ondansetron which has a half-life of 3 h. Granisetron, new 5-HT_3 receptor antagonist more selective than ondansetron which has been shown to have a greater specificity and potency and longer duration of action. The half-life of Granisetron is 8-9 h which is longer duration of action than ondansetron. It is effective orally as well as intravenous (i.v.). It blocks the 5-HT_3 receptors at both the central and the peripheral sites. It acts on the vagal efferent nerves of the gut and produces blockade of 5-HT_3 receptors. The half-life of Granisetron is 8–9 h which is longer duration of action than ondansetron. Its role has been justified accurately and proven in preventing chemotherapy induced nausea and vomiting.[3] The role of dexamethasone in preventing PONV, decreasing pain and edema, enhance healing, and fasten overall post-operative recovery is very well known. It is also considered to be safe which does not affect patients hemodynamics and neurocognition.[5]

The present study was conducted to study the efficacy of Granisetron versus Granistreon and dexamethasone for PONV prophylaxis for reduction of incidence and severity of PONV in early (0–6 h) and late (6–24 h) post-operative periods. This study also aims to estimate the number of patients requiring rescue antiemetics and their complete response.

MATERIALS AND METHODS

The present study was a prospective, randomized, open-label, and double-blind study. Prior approval of the Institutional Ethics Committee and scientific committee was taken. A total of 110 female patients, aged 25–60 years were included in to this study. All 110 patients were undergoing elective modified radical mastectomy under general anesthesia. Any patients who refusing to give consent, patients taken previous chemotherapy, history of PONV, pregnant and lactating women, morbidly obese patients, patients having any history of motion sickness, migraine, gastroesophageal reflux disease or allergy to the any drugs, or major systemic comorbidity were excluded from the study. Written informed consent was taken from all the patients.

All patients were assessed for preoperative fitness as per protocol. Preoperatively, all patients were kept nil by mouth by 8–10 h. All routine investigations, routine drugs of anesthesia on table and instruments were checked in the morning before general anesthesia.

The patients were, then, randomly divided into two groups into Group G and Group D. The study drug was prepared by a senior qualified anesthesiologist who was not a part of the study team and the same person administered the drug to patient. The study drug was administered just before the induction of anesthesia. Each of the test drugs was diluted to 10 ml of distilled water and administered intravenously slowly over 2 min preoperatively. The anesthesiologist who anesthetized the patient and all involved nurses were unaware of the content of the syringe. Hence, Group G received Inj. Granisetron 20 mcg/kg IV.[1,6] and Group D: received Inj. Granisetron 20 mcg/kg Inj. Dexamethasone 0.1 mg/ kg IV.[6,7]

All the patients were given general anesthesia as per routine standard protocol and their intraoperative course with vital hemodynamic parameters was monitored throughout the surgical procedure. The duration of surgery was noted. All the patients were extubated after surgery carefully and then patients were shifted to post anesthetic care units for monitoring.

The incidence and severity of PONV were assessed at early (less 6 h) and late (6–24 h) post-operative period in all patients. For severity of PONV was assessed, according to four-point verbal descriptive score (VDS).[8]

VDS

- Severity of Nausea: No nausea, mild nausea, moderate nausea, and severe nausea.
- Severity of Vomiting: None = No episode of vomiting, mild = 1 episode of vomiting, Moderate = 2–3 episode of vomiting and Severe = more than 3 episode of vomiting.

Patients who experienced mild severity of nausea and vomiting were reassured and its underlying cause for PONV if any, such as pain, blood loss, hypotension, vasovagal response, hypoxia, dehydration, and hypoglycemia were addressed and treated accordingly.

For rescue treatment in the early post-operative period (0–6 h) the Inj. Metoclopramide 10 mg IV.[2] diluted until 10 ml with distilled water was given slowly over 5 min to those patients who had moderate degree of nausea and vomiting even after the contributing causative factor has been treated and metabolic, hemodynamic derangements if any have been corrected.

Statistical Analysis

The analysis was performed by SPSS. Quantitative data were analyzed using Student's *t*-test, and qualitative data were analyzed using Fischer's test and Chi-square test. $P < 0.05$ was considered statistically significant.

RESULTS

Both the groups were comparable in terms of their physical attributes such as age, weight, height, and BMI. Furthermore, as depicted in Table 1, they were comparable in terms of their American Anesthesia Society (ASA) grading, duration of surgery, and anesthesia. The difference between the both groups for their physical attributes, ASA grading, duration of surgery, and anesthesia was not found out to be significant ($P > 0.05$).

The incidence rate of nausea (5.5%, and 1.8%) and vomiting (3.6%, and 1.8%) was found out to be in Group D while in Group G the incidence of nausea (27.3%, and 20%) and vomiting was found out to be (21.8% and 14.5%) in both early and late post-operative period, respectively, and the difference between groups was also found out to be statistically significant ($P < 0.05$) [Table 2].

The comparison for the severity of nausea and vomiting in early and late period as per four-point verbal response indicated in Table 3. Very few (5.8% and 3.6%) of Group D patients has mild and moderate degree of nausea and vomiting in early period and this difference in both groups was found out to be statistically significant ($P < 0.05$). Similarly as shown in Table 4, in late post-operative period, only 1.8% of patients has complained of mild and moderate degree of both nausea and vomiting and this difference in both groups was also found out to be statistically significant ($P < 0.05$).

As far as, the rescue Antiemetic medication, that is, inj. Metoclopramide is concerned, only in 3.6% patient in early period and it was not required in late period in Group D while it was required in about 30.9% of patients belonging to Group G. This difference is found out to be statistically significant ($P < 0.05$) [Table 5].

Table 1: Characteristics features of patients in Group G and Group D

Characteristics of patients	Group G	Group D	*P* value	Significance
	Mean±SD	Mean±SD		
Age (years)	46.09±6.42	45.84±7.04	0.8	Not significant
Weight (kg)	58.75±6.89	58.73±6.91	0.9	Not significant
Height (cm)	161.49±6.91	161.51±6.87	0.9	Not significant
BMI (kg/m^2)	22.52±2.08	22.51±2.08	0.9	Not significant
Duration of Surgery (in minutes)	73.91±16.82	73.45±17.90	0.9	Not Significant
Duration of Anaesthesia (in minutes)	84.91±16.43	86.00±18.27	0.7	Not Significant
ASA I	41 (74.5%)	43 (78.2%)	0.2	Not significant
ASA II	14 (25.5%)	12 (21.8%)		

Table 2: Comparison of incidence of Nausea and Vomiting in early and late period in Group G and Group D

Time period	Event	Status	Group G (*n*=55) (%)	Group D (*n*=55) (%)	*P* value	Significance
Early period	Nausea	Present	15 (27.3)	3 (5.5)	0.0036	Significant
		Absent	40 (72.7)	52 (94.5)		
	Vomiting	Present	12 (21.8)	2 (3.6)	0.008	Significant
		Absent	43 (78.2)	53 (96.4)		
Late Period	Nausea	Present	11 (20.0)	1 (1.8)	0.004	Significant
		Absent	44 (80.0)	54 (98.2)		
	Vomiting	Present	8 (14.5)	1 (1.8)	0.03	Significant
		Absent	47 (85.5)	54 (98.2)		

Table 3: Comparison of severity of nausea and vomiting in early period in Group G and Group D

Event	4 point verbal descriptive score	Group G (%)	Group D (%)	Total (%)	*P* value	Significance
Nausea	None	40 (72.7)	52 (94.5)	92 (83.6)	0.02	Significant
	Mild	10 (18.1)	2 (3.6)	12 (10.9)		
	Moderate	5 (9.1)	1 (1.8)	6 (5.5)		
	Severe	0 (0.0)	0 (0.0)	0 (0.0)		
Vomiting	None	43 (78.1)	53 (96.4)	96 (87.3)	0.04	Significant
	Mild	7 (12.7)	1 (1.8)	8 (2.7)		
	Moderate	5 (9.1)	1 (1.8)	6 (5.5)		
	Severe	0 (0.0)	0 (0.0)	0 (0.0)		

Table 4: Comparison of Severity of Nausea and Vomiting in late period in Group G and Group D

Event	4 point verbal descriptive score	Group G (%)	Group D (%)	Total (%)	*P* value	Significance
Nausea	None	44 (80.0)	54 (98.2)	98 (89.1)	0.006	Significant
	Mild	7 (12.7)	1 (1.8)	8 (7.3)		
	Moderate	4 (7.3)	0 (0.0)	4 (3.6)		
	Severe	0 (0.0)	0 (0.0)	0 (0.0)		
Vomiting	None	44 (80.0)	54 (98.2)	98 (89.1)	0.02	Significant
	Mild	8 (14.5)	1 (1.8)	9 (8.2)		
	Moderate	3 (5.5)	0 (0.0)	3 (2.7)		
	Severe	0 (0.0)	0 (0.0)	0 (0.0)		

Table 5: Comparison of requirement of rescue anti-emetics (Inj. Metoclopramide) in group G and Group D

Rescue Anti Emetic		Group G (%)	Group D (%)	Total (%)	*P* value	Significance
Early period	No	45 (81.8)	53 (96.4)	98 (89.1)	0.03	Significant
	Yes	10 (18.2)	2 (3.6)	12 (10.9)		
Late period	No	48 (87.3)	55 (100.0)	110 (93.6)	0.01	Significant
	Yes	7 (12.7)	0 (0.0)	7 (6.4)		

Table 6: Comparison of total response (24 h) in Group G and Group D

Complete response	Group G (%)	Group D (%)	Total (%)	*P* value	Significance
No	26 (47.3)	4 (7.3)	30 (27.3)	<0.0001	Significant
Yes	29 (52.7)	51 (92.7)	80 (72.7)		

In our study, 92.7% patients belonging to Group D while only 52.7% in Group G shown complete response and this difference between both groups also found out to be statistically significant ($P < 0.05$) [Table 6].

DISCUSSION

The PONV is frequently the cause of great distress to patients and it is often the worst memory of their hospital stay.[2] The consequences of prolonged PONV (PONV) range from longer duration of stay in hospital for patients with its economic implications to physical, metabolic, and psychological effect[9] and on severe cases many the patients can landed up in aspiration of gastric contents and death.[1] Before 1990, various pharmacological agents belonging to antiemetic class such as phenothiazines, antihistamines, butyrophenones, prokinetics, and anticholinergics have been used alone but study done by Henzi had shown that combination antiemetic therapy was far more superior benefit than monotherapy.[9,10] Since then several studies have been conducted with combination of antiemetics for prophylaxis for PONV like Gan in 2002[11], Apfelbaum *et al.* in 2013[12] in which the anti-emetic efficacy of one drug is at the most a 50% only but when combination of serotonin antagonists with dexamethasone used then it has not only shown better efficacy of controlling PONV but also shown very good response with minimal adverse effects in patients with various risk factors.

The incidence of PONV in female patients undergoing modified radical mastectomy reported to be in range of 60–80% when they have not given any prophylaxis.[2] In our study, the overall incidence of nausea and vomiting found out to be 47.3% and 23.3%, respectively, among patients who received only Inj. Granisetron.

The study conducted by Fuji *et al.*[13] in Japan to evaluate the efficacy of Granisetron-dexamethasone combination for prevention of PONV among 135 female patients aged between 40 and 65 years under general anesthesia for breast carcinoma who received placebo (saline), Granisetron 40 mcg/kg i.v. or Granisetron 40 mcg/kg + dexamethasone 8 mg i.v. immediately before the induction of anesthesia. The corresponding incidence during 3–24 h after anesthesia was 56%, 84% and 96%, respectively. Similar incidences of PONV have been reported to be 40% by Gupta, Jain,[3] and 30% in a study conducted by Moussa *et al.*[14] among patients who received Inj. Granisetron for post-exposure prophylaxis.

In this study, the overall incidence of PONV in the patients who have received prophylaxis of Inj. Granisetron and inj. Dexamethasone has reported to be 6.3% and 5.4% for nausea and vomiting, respectively. This finding of patient receiving both Inj. Granisetron and Inj. Dexamethasone correlate well with study conducted by Islam *et al.*[15] and Gupta *et al.*[16] with 4% and 8%, respectively.

In this study, only 3.6% of patients in Group D had to receive Inj. Metoclopramide in the early post-operative period whereas there was not need of rescue antiemetic in the delayed post-operative in Group D.

Thomas and Jones[17] conducted a prospective randomized comparative study of dexamethasone, ondansetron, and ondansetron + dexamethasone as prophylactic antiemetic therapy in patients undergoing day case gynecological surgery. They found that failure of prophylaxis during 1st 3 h after surgery was recorded in 22%, 28.3%, and 8.6%. The overall incidences for the 24 h post-surgery were 42.4%, 48.3%, and 34.5%, respectively.

The over 24 h period complete response was noted in about 92.7% patients among patients who have received inj. Granisetron and inj. Dexamethasone for PONV. This finding has been coincident with the both studies conducted by Fuji *et al.*[13] and Gupta and Jain[2] in which the complete response was found out to be same, that is, 96% among patients who had received ini. Granisetron with Inj. Dexamethasone, respectively.

Bhattacharya and Banerjee[18] conducted a double-blind randomized placebo controlled trial to compare the efficacy of ondansetron and Granisetron for prevention of PONV after day care gynecological laparoscopy. They found that incidences of emetic episodes were 20% in ondansetron group and 7% in Granisetron group which is clinically significant ($P < 0.05$).

Hence, the results of our study are in concordance with the previous studies by different authors, with few differences, which are insignificant. Hence, it has been seen that combination prophylaxis of Inj. Granisetron and Inj. Dexamethasone has not only reduce the incidence of PONV in modified radical mastectomy among female patients but also reduced its severity in both early and late period.

CONCLUSION

The combination prophylaxis of Granisetron and Dexamethasone is clearly more efficacious in preventing PONV than Granisetron alone in female patients undergoing modified radical mastectomy under general anesthesia.

Limitation of Study

This study did not consider adverse effect of the concerned drugs; hence, we have not drawn any conclusion in this regard. There are some chances that even after thorough pre-operative assessment; certain unidentified or unreported pre-morbid conditions in breast carcinoma patents can affect the nausea and vomiting postoperatively. Furthermore, the present study has been restricted to only female patients undergoing modified radical mastectomy and, hence, the findings cannot be generalized to other variety of surgeries.

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How to cite this article: Darshan U, Chhallani VP, Jaiswal AV. Prophylaxis for Post-operative Nausea and Vomiting: A Randomized Comparative Study between Granisetron versus Granistreon and Dexamethasone among Patients Undergoing Modified Radical Mastectomy. Int J Sci Stud 2020;8(6):27-32.

Source of Support: Nil, **Conflicts of Interest:** None declared.