Original Research Article

Indian Journal of Anesthesia and Analgesia
2018; 5(12): 2107-15
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.51218.22

Comparative Study of Granisetron, Metoclopramide and Droperidol in Prevention of Post Operative Nausea and Vomiting

Mohammed Abdul Moiz[1], Sunil Bablu Pulla[2]

[1,2]Assistant Professor, Department of Anaesthesia, Bhaskar Medical College, Yenkapally, Moinabad, Ranga Reddy Dist, Telangana 500075, India.

Abstract

Objective: The aim of the present study is to compare the effectiveness of intravenously administered Granisetron Metoclopramide and Droperidol in the prevention of postoperative nausea and vomiting in patients undergoing gynaecological Diagnostic laparoscopy under general anaesthesia. *Design:* The antiemetic efficacy of granisetron, and metoclopramide was assessed in postoperative nausea and vomiting for a period of 24 hours. *Duration:* December 2016 to November 2017. *Setting:* Department of Anesthesia, Bhaskar Medical College, Ranga Reddy, Telangana. *Participants:* A total number of 75 female cases between the age group of 18–35 years belonging to ASA grade I and ASA grade II with primary infertility coming for gynecological diagnostic laparoscopy. *Methods:* Patients were divided into 3 groups of 25 each. Group A received intravenous granisetron (40mcg/kg), Group B received Metoclopramide (0.2mg/kg) and Group C received droperidol (25mcg/kg) prophylactically for prevention of postoperative nausea and vomiting. The primary end point was the occurrence of PONV. The main outcomes were monitored for study period of 24hours postoperatively. Postoperatively the patients were observed in postoperative ward for 24hours for postoperative nausea, retching and vomiting, headache, sedation, dizziness, allergic reactions, extra pyramidal symptoms. Nausea and vomiting were evaluated on three point ordinal scale (0 = none, 1= nausea, 2 = vomiting/retching), with no distinction between vomiting and retching (i.e. retching was considered a vomiting event). *Results:* In the early postoperative period (0-4hrs), the incidence of nausea & vomiting was effectively controlled with use of granisetron & droperidol, it was significantly higher in metoclopramide group. In the late postoperative period (4-24hrs), PONV was significantly lower with granisetron and droperidol when compared to metoclopromide (p value <= 0.001). *Conclusion:* Administration of granisetron preoperatively is superior to metoclopramide and droperidol in long term prevention of PONV following gynecological diagnostic laparoscopy.

Keywords: PONV; Post Operative Nausea; Post Operative Vomiting; Granisetron; Metoclopramide and Droperidol.

How to cite this article:

Mohammed Abdul Moiz & Sunil Bablu Pulla. Comparative Study of Granisetron, Metoclopramide and Droperidol in Prevention of Post Operative Nausea and Vomiting. Indian J Anesth Analg. 2018;5(12):2107-15.

Introduction

Despite the rapid progress in the field of modern anaesthesia, the incidence of postoperative nausea and vomiting (PONV) still remains 25–30% (Lerman 1992) which is consistently lower when compared to 75 to 80% (Blumfield 1899) incidence reported during the " Ether Era". The increase of day surgery in the 1990's has been challenged by the high incidence of PONV. One of the major limiting factors in the early discharge of day surgery patients is the presence of PONV (Gold et al. 1989) implying that economic consequences are involved. In the present scenario, it is estimated that 25 to 30% of adult patients will develop postoperative nausea and vomiting [1]. As

Corresponding Author: Sunil Bablu Pulla, Assistant Professor, Department of Anaesthesia, Bhaskar Medical College, Yenkapally, Moinabad, Ranga Reddy Dist, Telangana 500075, India.
E-mail: drabbdulmoiz@gmail.com

Received on 26.08.2018, **Accepted on** 01.10.2018

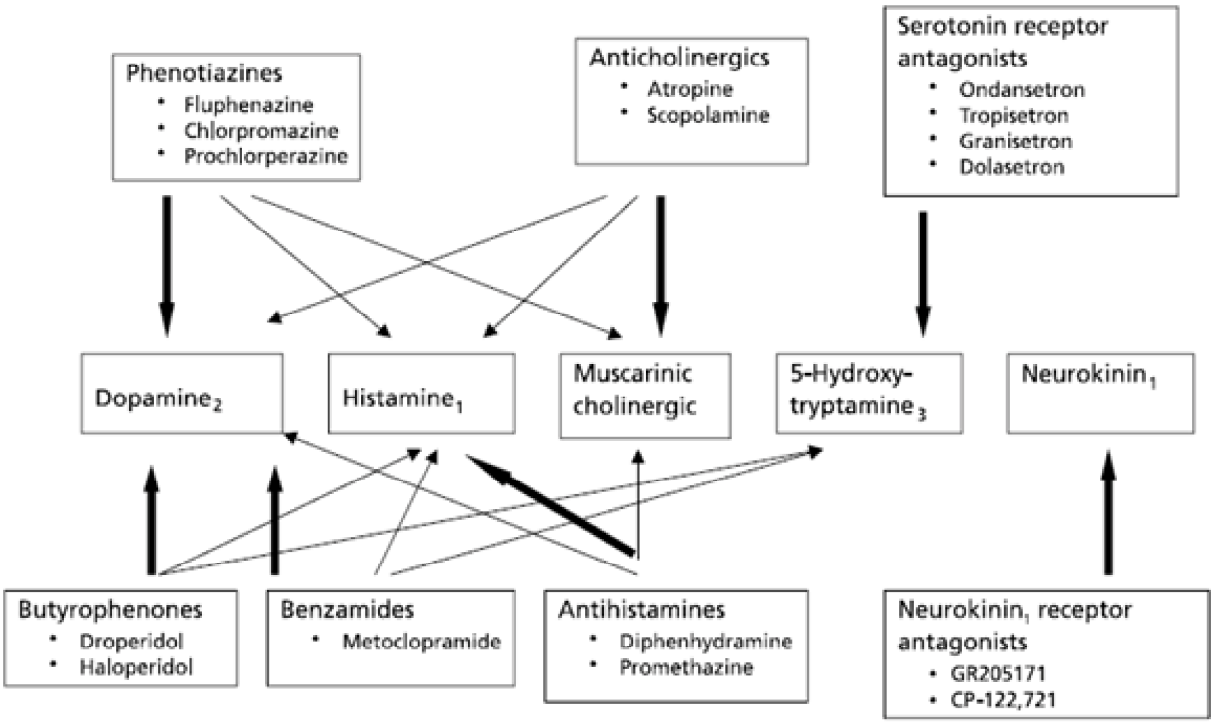
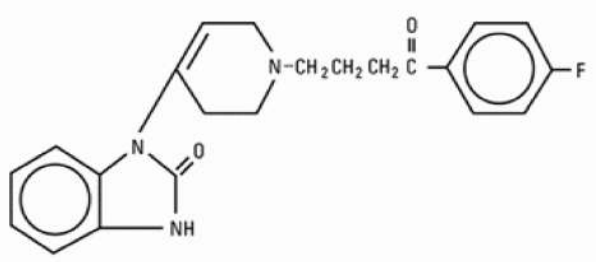


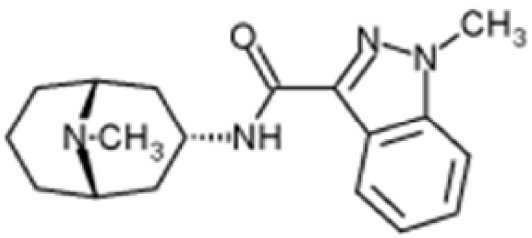
Fig. 1: Agonists and antagonists associated with nausea and vomiting

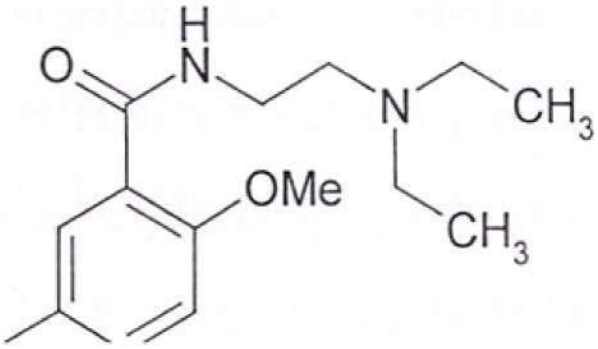
per the literature, incidence of postoperative nausea and vomiting ranges from 25 to 55% following inpatient surgery and 8 to 47% for outpatient surgery. Postoperative nausea and vomiting is a major contributor to burgeoning health care costs for both the hospital and the patient. These costs may result from longer recovery, extended stay in the hospital, added attention required from nurse and physicians, additional drug supplies as well as unanticipated admissions following outpatient procedures [2]. Most of the currently used antiemetic drugs like antihistamines, anticholinergics and dopamine receptor antagonists possess clinically significant side effects. No single drug or class of drug is fully effective in controlling PONV, presumably because none block all pathways to the Vomiting Centre. However, because of the multi-receptor origin of PONV, combination therapy is being more widely employed [3,4,5]. A recent British Journal of Anaesthesia editorial suggests this approach may be appropriate (Heffernan AM, Rowbotham-2000). Using a decision-analysis treatment model, it has been suggested that prophylactic anti-emetic therapy can be more cost-effective compared with treatment of established symptoms where operations are associated with a high risk of emesis (Watcha MF and Smith-1994). Adequate pain relief, hydration and maintenance of blood pressure will contribute to the control of PONV, as will prior patient education and information. In many cases protocols will involve either prophylactic drug treatment for all patients or pre-operative risk assessment with appropriate treatment for at risk groups [6,7].



is a butyrophenone. Butyrophenones produce central nervous system (CNS) depression, and they are potent anti-emetics. Droperidol produces its action centrally at sites where dopamine, norepinephrine, and serotonin act [8]. As a principal mechanism it has been suggested that droperidol may occupy GABA receptors at the postsynaptic membrane; this may reduce synaptic transmission and result in a build-up of dopamine in the intersynaptic cleft. A subsequent imbalance in dopamine and acetylcholine is thought to occur, which results in an alteration of normal transmission of signals in the CNS, as, for instance, in the emetic centre in the chemoreceptor trigger zone [9]. This is thought to be the mechanism by which droperidol exerts its anti-emetic effect. Droperidol is a butyrophenone derivative structurally

similar to haloperidol. It is a sedative hypnotic. Droperidol is indicated as an inducing agent and an adjunct to general anaesthesia. When combined with an opiate analgesic, it provides neuroleptanalgesia. Droperidol has powerful antiemetic effects making it very effective for nausea and vomiting induced by anaesthetics or antineoplastic medications such as ciplatin.





Metoclopramide is a dopamine antagonist that is structurally similar to procainamide (methoxychloroprocainamide) but lacks local anaesthetic activity. Metoclopramide hydrochloride is a white crystalline, odourless substance, freely soluble in water. Chemically it is 4-amino-5-chloro-N-[2-(diethylamino) ethylj-2-methoxy benzamide monohydrochloride monohydrate. Molecular weight: 354.3. Metoclopramide stimulates motility of the upper gastrointestinal tract without stimulating gastric, biliary or pancreatic secretions. Its mode of action is unclear. It seems to sensitize tissues to the action of acetylcholine. The effect of metoclopramide on motility is not dependent on intact vagal innervation, but it can be abolished by anticholinergic drugs. Metoclopramide increases the tone and amplitude of gastric (especially antral) contractions, relaxes the pyloric sphincter and the duodenal bulb, and increases peristalsis of the duodenum and jejunum resulting in accelerated gastric emptying and intestinal transit. It increases the resting tone of the lower esophageal sphincter [10,11,12]. It has little, if any effect on the motility of the colon or gallbladder.

Granisetron hydrochloride is an antinauseant and antiemetic agent. Granisetron hydrochloride is a white to off-white solid that is readily soluble in water and normal saline at 20°C. Granisetron HCl injection is a clear, colorless, sterile, nonpyrogenic, aqueous solution for intravenous administration. Each 1 ml of preservative-free aqueous solution contains 1.12 mg granisetron hydrochloride equivalent to granisetron, 1.0 mg an d sodium chloride, 9.0 mg. The solution's pH ranges from 4.7 to 7.3. Granisetron is a selective 5-hydroxytryptamine (5-HT3) receptor antagonist with little or no affinity for other serotonin receptors, including 5-HTI; 5-HTIA; 5-HTIB1C; 5¬HT2; for alpha-, alpha2-, or beta- adrenoreceptors; for dopamine-D2; or for histamine-HI; benzodiazepine; picrotoxin, or opioid receptors. Serotonin receptors of the 5-HT3 type are located peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. During chemotherapy that induces vomiting, mucosal enterochromaffin cells release serotonin, which stimulates 5-HT3 receptors [13,14]. This evokes vagal afferent discharge, inducing vomiting. Animal studies demonstrate that, in binding to 5-HT3 receptors, granisetron blocks serotonin stimulation and subsequent vomiting after emetogenic stimuli such as cisplatin [15].

The present study compared antiemetic efficacy of granisetron, a selective 5HT3 receptor antagonist, metoclopramide which prevents vomiting by increasing the resting tone of gastroesophageal sphincter and blocking central dopaminergic receptors with Droperidol, a strong D2 receptor antagonist acting at CTZ and area postrema.

Materials and Methods

A total number of 75 female cases between the age group of 18 – 35 years belonging to ASA grade I and ASA grade II with primary infertility coming for gynecological diagnostic laparoscopy selected for the study. Patients were divided into 3 groups of 25 each. Group A received intravenous granisetron (40mcg/kg), Group B received Metoclopramide (0.2mg/kg) and Group C received droperidol (25mcg/kg) prophylactically for prevention of postoperative nausea and vomiting. The primary end point was the occurrence of PONV. The main outcomes were monitored for study period of 24 hours postoperatively. Postoperatively the patients were observed in postoperative ward for 24 hours for postoperative nausea, retching and vomiting, headache, sedation, dizziness, allergic reactions, extra pyramidal symptoms. Nausea and vomiting were

evaluated on three point ordinal scale (0 = none, 1= nausea, 2 = vomiting/retching), with no distinction between vomiting and retching (i.e. retching was considered a vomiting event). Preoperative data included age, weight, basal pulse rate, blood pressure, respiratory rate, SpO_2, history of migraine, motion sickness, previous surgery, postoperative nausea and vomiting or use of an antiemetic in the last 24 hours. All the patients were premedicated before induction with slow intravenous inj. Glycopyrolate 0.2mg, inj.midazolam 1mg and inj. Fentanyl 1mcg/kg body weight along with a study drug (i.e. Group A- Inj.Granisetron 40mcg/kg, Group B- Inj.Metoclopramide 0.2mg/kg, Group C- Inj.Droperidol 20mcg/kg).Monitoring included heart rate, non invasive blood pressure, pulse oximetry (SpO_2), ECG and end tidal carbon dioxide ($ET\text{-}CO_2$). Patients were induced with Inj.thiopentne sodium (5mg/kg). Tracheal intubation was facilitated with Inj. Vecuronium bromide (0.8mg/kg). After intubation, normocapnic mechanical ventilation was maintained with N_2O and O_2 (5:3) and muscle relaxation if needed with inj. Vecuronium bromide (0.1mg/kg) and volatile anaesthetic (Halothane 0.2-0.4 vol%) according to stratification. Intraoperative hydration with solute was set at 10ml/kg and monitoring at regular intervals till the end of procedure. At the end of surgery Inj. Neostigmine 0.05mg/kg and atropine 0.02mg/kg was administered for reversal of neuromuscular blockade and after complete recovery the patients were extubated. Postoperatively the patients were observed in postoperative ward for 24 hours for postoperative nausea, retching and vomiting, headache, sedation, dizziness, allergic reactions, extra pyramidal symptoms. At the end of surgery pulse rate, blood pressure, respiratory rate were recorded every 15min for first 2hours, 2nd hourly up to 8hours then 4th hourly till the end of 24hours. All patients received inj. diclofenac sodium 75mg IM 12th hourly as postoperative analgesia.

Observations and Results

Demographic & Anaesthetic Data of the Patients

Table 1: Demographic & Anaesthetic Data of the Patients

PT Characteristics	Mean (Group-A)	Mean (Group-B)	Mean (Group-C)	SD (Group-A)	SD (Group-B)	SD (Group-C)	F-Ratio
Age (yrs)	26.000 (21-35)	25.720 (21-35)	25.720 (20-35)	4.021	3.714	3.035	0.05 N S
Weight (Kgs)	49.760 (36-60)	52.280 (35-65)	50.480 (38-60)	8.521	6.943	6.850	0.75 N S
Duration of Surgery (mins)	25.960 (18-35)	25.000 (18-32)	25.440 (18-32)	4.178	4.082	4.104	0.34 N S

*NS denotes Not Significant.

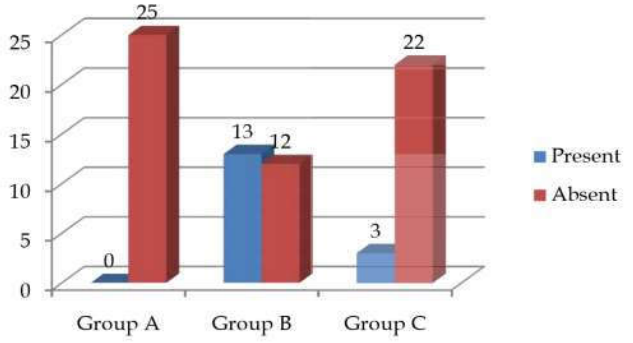
There was no statistical difference between the 3 groups with respect to demographic and anaesthetic characteristics.

Incidence of Nausea in First 24 Hrs of Post-Operative Period

Table 2: Incidence of Nausea in First 24 Hrs of Post-Operative Period

Nausea	Group A	Group B	Group C
Present	0	13	3
Absent	25	12	22
Total	25	25	25

Incidence of Nausea in First 24 hours of Post Operative period was significantly high in group B (52%) then group C (12%).



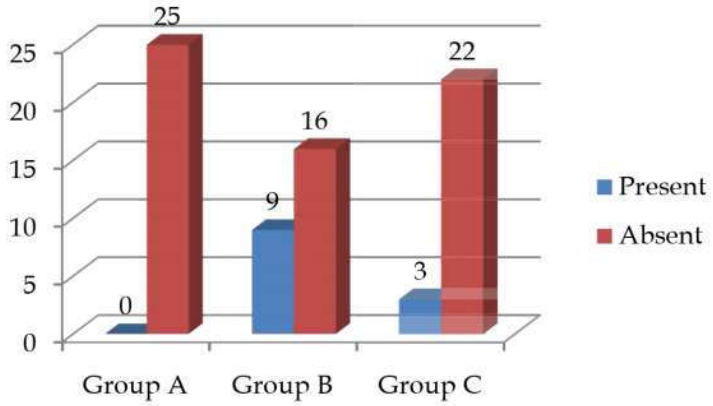
Graph 1: Incidence of Nausea in First 24 Hrs Of Post-Operative Period

Incidence of Vomiting in First 24 Hrs of Post-Operative Period

Table 3: Incidence of Vomiting in First 24 Hrs of Post-Operative Period

Vomiting	Group A	Group B	Group C
Present	0	9	3
Absent	25	16	22
Total	25	25	25

No emetic events observed in group A. Emetic events in group B is 36% and group C is 12%. Significantly high incidence of vomiting I in group B compared to group A and C (P<0.01).



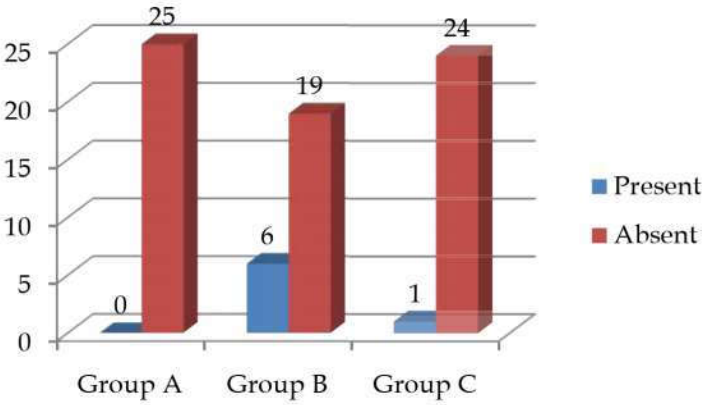
Graph 2: Incidence of Vomiting in First 24 Hrs of Post-Operative Period

Incidence of Early Nausea (0-4 Hrs)

Table 4: Incidence of Early Nausea (0-4 Hrs)

Early Nausea	Group A	Group B	Group C
Present	0	6	1
Absent	25	19	24
Total	25	25	25

Incidence of early nausea (0-4hrs) in gransetron and droperidol did not show any statistically significant difference while with metoclopramide showed significant difference. Chi square = 9.769, Degree of freedom = 2, p= 0.01.



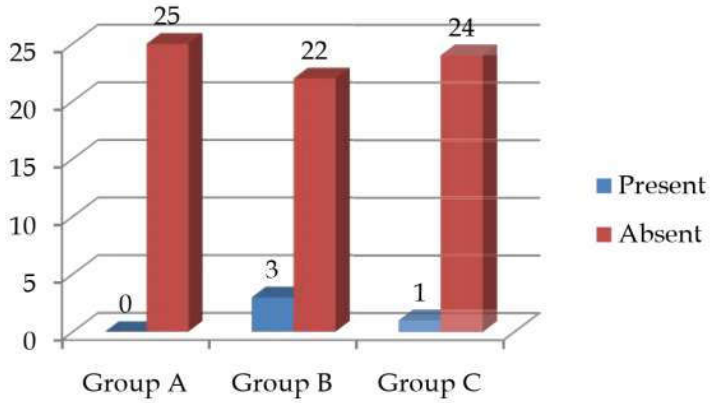
Graph 3: Incidence of Early Nausea (0-4 Hrs)

Incidence of Early Vomiting (0-4 Hrs)

Table 5: Incidence of Early Vomiting (0-4 Hrs)

Early Nausea	Group A	Group B	Group C
Present	0	3	1
Absent	25	22	24
Total	25	25	25

Granisetron, Metoclopramide and droperidol were equally efficient in preventing vomiting in early postoperative period, (p > 0.05).



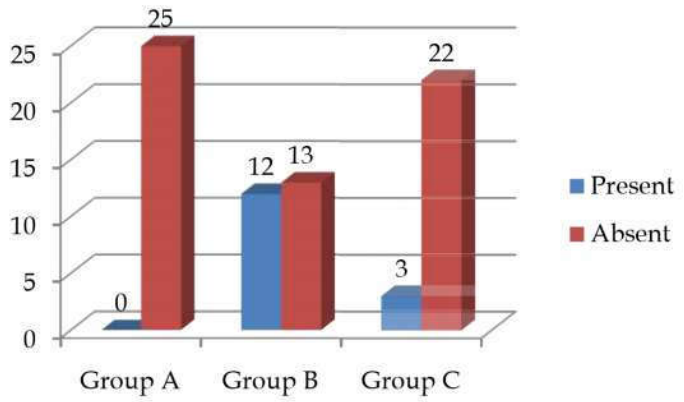
Graph 4: Incidence of Early Vomiting (0-4 Hrs)

Incidence of Late Nausea (4-24 Hrs)

Table 6: Incidence of Late Nausea (4-24 Hrs)

Early Nausea	Group A	Group B	Group C
Present	0	12	3
Absent	25	13	22
Total	25	25	25

Incidence of late nausea was 12% and 48% in droperidal and metoclopramide which shows high significance.



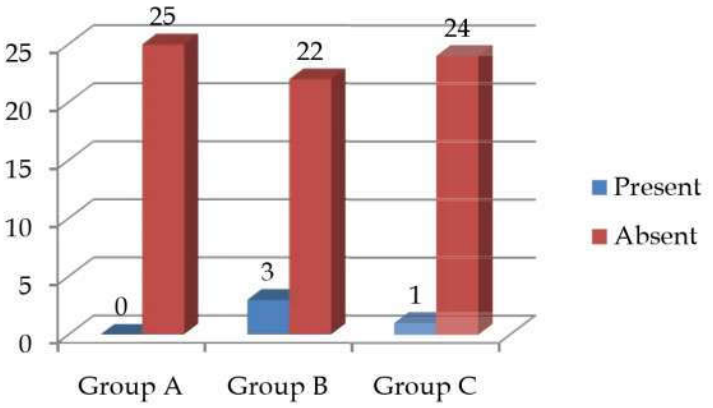
Graph 5: Incidence of Late Nausea (4-24 Hrs)

Incidence of Late Vomiting (4-24 Hrs)

Table 7: Incidence of Late Vomiting (4-24 Hrs)

Early Nausea	Group A	Group B	Group C
Present	0	3	1
Absent	25	22	24
Total	25	25	25

There was no emetic episode during 4-24hrs. post operative period in granisetron group where as 8% of patients with droperidol, 32% in metoclopramide developed emesis during late post operative period, which showed statistically significant difference



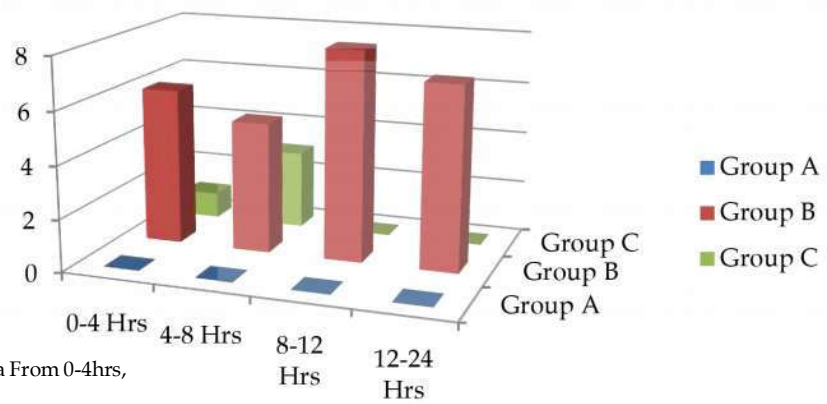
Graph 6: Incidence of Late Vomiting (4-24 Hrs)

Incidence of Nausea FROM 0-4Hrs, 4-8Hrs, 8-16Hrs, 16-24Hrs

Table 8: Incidence of Nausea From 0-4hrs, 4-8hrs, 8-16hrs, 16-24hrs

Assessment Period	Granisetron	Metoclopramide	Droperidol
0-4Hrs	0	6*	1
4-8Hrs	0	5*	3*
8-16Hrs	0	8*	0
16-24Hrs	0	7*	0

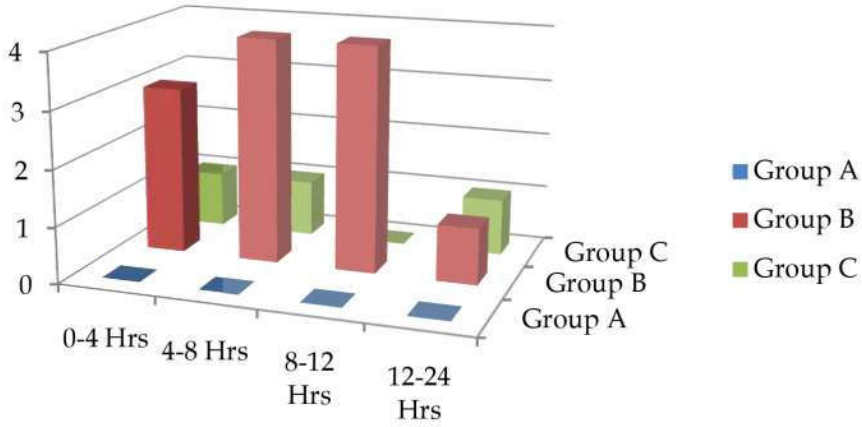
Incidence of nausea from 0-4, 4-8, 8-16, 16-24 hrs assessment periods-24%, 20%, 32%, 28% respectively for metoclopramide, while 4% had nausea during the 1st assessment period and 12% during 2nd (ie, 4-8 hrs). No incidence of nausea was observed in granisetron group.



Graph 7: Incidence of Nausea From 0-4hrs, 4-8hrs, 8-16hrs, 16-24hrs

Table 9: Incidence of Vomiting From 0-4hrs, 4-8hrs, 8-16hrs, 16-24hrs

Assessment Period	Granisetron	Metoclopramide	Droperidol
0-4Hrs	0	3*	1
4-8Hrs	0	4*	1
8-16Hrs	0	4*	0
16-24Hrs	0	1	1



Graph 8: Incidence of Vomiting From 0-4hrs, 4-8hrs, 8-16hrs, 16-24hrs

No incidence of emesis was seen with the granisetron group during entire assessment period. Patient had vomiting in 1st assessment period whereas another had emesis during 2nd and 4th assessment period. A total of 3 patients experienced emesis during a period of 24 hrs following anaesthesia in droperidol group. Total of 8 patients experienced vomiting during the 24 hrs period following anaesthesia with metoclopramide group, 3 during 1st assessment period, 4 each during the 2nd and 3rd assessment period and 1 during the 4th assessment period.

Discussion

Nausea and vomiting following general anaesthesia has been a distressing problem for the patients and is frequently listed among the most important preoperative concerns apart from pain [14,5,16]. With the change in emphasis from inpatient to outpatient office based medical/surgical environment, there has been increasing interest in the "the big little problem" of postoperative nausea and vomiting following general anaesthesia. lnspite of so much advancement in the management of postoperative nausea and vomiting with the invention of new drugs, multimodal approaches of management like administering multiple different antiemetic medications, less emetogenic anaesthetic techniques, adequate intravenous hydration, adequate pain control etc., the incidence of postoperative nausea and vomiting remains still high ranging from 25%-55% following inpatient surgery and 8%-47% following outpatient surgery [17,18]. An effective antiemetic that could be used to treat nausea and vomiting without extending recovery time and that remain effective for 24 hours following treatment would be significant asset to the anaesthesiologist's armamentarium, especially in settings like office- based anaesthesia where the patient is admitted for day care surgery and discharged on the same day [19]. vomiting. published data in Indian literature. In the present study the antiemetic efficacy of granisetron, and metoclopramide was assessed in postoperative nausea and vomiting for a period of 24 hours. The postoperativc period was again subdivided into four groups of assessment periods (0-4hrs, 4-8hrs, 8-16hrs and 16-24 hrs) to assess the efficacy of both the drugs during different time intervals. We have selected similar group of patients in respect of age, weight, duration of surgery, type of surgery and duration of anaesthesia technique and drugs ware standardized to compare the efficacy of the drugs. Analgesia for postoperative pain was standardized and patients of all three v groups were observed for a period of 24 hours postoperatively. Hence we believe that difference in the incidence of postoperative nausea

and vomiting is attributed exclusively to the study drugs. In the present study 25 patients with granisetron did not have emetic symptoms while 9 patients (significant) receiving metoclopramide had emetic symptoms compared to Fujii study in which only one patient who received granisetron had emetic symptom compared to 12 patients of 20 had emetic symptoms [20,21]. Both observations agree that granisetron is superior to metoclopramide in the long term prevention of PONV. Schellers (1987) reported toxic neurological reactions in patients who received metoclopramide. Bilajham (1992) noted headache (6.6%) and constipation (3.5%) in patients with cytotoxic therapy over multiple cycles of granisetron. Delas Ramirez et al. (2001) In their study using fixed doses of metoclopramide (10mg), droperidol (1.25mg) and placebo (saline) every 8hrs. for prevention of PONV in patients undergoing intra-abdominal gynaecological surgery under general anaesthesia using standardized technique [22,23,24]. They concluded that droperidol at dose of 1.25mg is effective in prevention of PONV and has minimal side effects then placebo or metoclopramide. In our study we have not observed any adverse effects as above studies, whereas the amount of sedation, dizziness following droperidol use was significant. In the study conducted by Fujii et al. (2000) in 120 female patients undergoing gynaecological surgery in established PONV within first 3hrs of anaesthesia with granisetron (40mcg) metoclopramide (0.2mg) droperidol (20mcg/kg) [25,26,27]. Patients were then observed for 24hrs postoperatively and concluded that granisetron was most effective (88%) then droperidol (55%) and metoclopromide (50%) in treatment of PONV with droperidol there has been some amount of sedation and drowsiness noted in immediate post-operative period [28,29]. We found that granisetron has better advantage over metoclopramide and droperidol in treatment of PONV in female patients undergoing major gynaecological surgery under general anaesthesia. Hence our study agrees with and confirms that granisetron has definite superior efficacy than the other drugs compared (Metoclopramide, Droperidol) [30,31].

Conclusions

Although droperidol was equally efficient in the prevention of PONV, but due to its sedation, dizziness, hypotension and other adverse effects associated with it can cause delayed recovery, risk of pulmonary aspiration, economic burden, anxiety etc. Hence administration of granisetron preoperatively is superior to metoclopramide and droperidol in long term prevention of PONV following gynaecological diagnostic laparoscopy.

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