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Antiemetic Prophylaxis in Major Gynaecological Surgery With Intravenous Granisetron Versus Metoclopramid0e – A Randomized Double Blind Comparitive Study

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SUMMARY: *In a prospective double blind randomized study we evaluated the prophylactic anti emetic efficacy of granisetron, a 5HT3 receptor antagonist and metoclopramide, a benzamide anti emetic on postoperative nausea and vomiting after major gynaecological surgery under general anaesthesia. The patients received a single dose of granisetron, 40mcg/kg (Group A, n = 25) or metoclopramide, 0.15mg/kg (Group B, n = 25) before induction of anaesthesia in a coded syringe.*
The response was assessed during 0-4 hrs, 4-8 hrs, 8-16hrs and 16-24 hrs time intervals after recovery from anaesthesia by means of presence or absence of nausea, retching or vomiting. The overall control of PONV during early postoperative period (0-4 hrs) did not show statistically significant differences after administration of either drug. The incidence of PONV during the next 20 hours was 12% and 48% with Group A (Granisetron) and Group B (Metoclopramide) respectively.
Nausea scores are significantly lower in-group A (Granisetron) than in Group B (Metoclopramide) in all the four assessment periods. Although there were no emetic episodes in the granisetron group, 32% of patients in metoclopramide group were observed to have such episodes during the assessment periods. (P value< 0.05). No clinically important adverse events due to drugs were observed in any of the groups. In conclusion, the prophylactic use of granisetron is more effective and superior to metoclopramide in preventing postoperative nausea and vomiting in patients under going major gynaecological surgery under general anaesthesia.

Keywords: *PONV, Nausea, Vomiting, Retching, Anti emetics, 5HT3 receptor antagonist, Granisetron, Metoclopramide.*

I. INTRODUCTION

Post operative nausea and vomiting (PONV) are distressing and frequent adverse events after general anaesthesia and surgery; with a relatively high incidence in women undergoing major gynaecological surgeries. A variety of pharmacological modalities, including dopamine receptor antagonists (eg. Metoclopramide); Butyrophenones (eg. Droperidol; [1]Antihistaminics and many others have been advocated for the prevention and treatment of PONV [1, 2]. Metoclopramide was evaluated in some studies and was found to be effective in decreasing post operative vomiting following gynaecological surgery. [2,3,4] How ever these antiemetics have undesirable side effects like sedation, hypotension, dry mouth, dysphoria, hallucinations and extra pyramidal symptoms. Recently it has-been reported that on dansetron; a selective 5 HT3 receptor antagonist has antiemetic effects against chemo therapy induced emesis[5]. Another 5HT3 receptor antagonist, Granisetron has more potent and longer acting anti emetic property against cisplatin induced emesis than ondansetron.[6,7,8]The effective anti emetic dose for preventing PONV was 40mcg/kg body weight.Recent studies demonstrated that Granisetron reduces the incidence of severity of vomiting following strabismus repair, tonsillectomy and day care laparoscopic surgery . However, prophylactic ant emetic efficacy of Granisetron in postoperative patients have been studied in a randomized double blind comparison with Metoclopramide in patients who were scheduled to under go major gynaecological surgery.[9]

II. METHODS

After approval of our institutional ethical committee, fifty female patients of ASA physical status I & II, aged 20-55 years were scheduled for major gynaecological surgery under general anaesthesia. An informed written consent was obtained from every patient. Patients were excluded from the study; if there had been recent (with in 24 hrs) or chronic ingestion of any other medicine with potential anti emetic properties, hyper sensitivity to study drugs, those with history of motion sickness and patients with significant cardiovascular, pulmonary, renal, hepatic, neurological or endocrine abnormalities. Every effort was made to standardize the

anaesthetic technique. Patients were allocated to one of the two groups before induction of anaesthesia. Each study drug, Granisetron, 40 mcg/kg or Metoclopramide, 0.15mg/kg is diluted and administered in a 10 ml coded syringe. Patient's pulse rate and blood pressure were recorded 5min before and 5min after the administration of the drug. Patients and the investigator who collected the postoperative data were blinded to randomization. Patients received no other preanaesthetic medication. Anaesthesia was induced with Thiopentone sodium (5mg/kg) after the administration of glycopyrrolate, 0.2mg; Buprinorphine, 4ug/kg and Midazolam 0.03mg/kg body weight; all through intravenous route. Tracheal intubation was fecilitated with Vecuronium bromide (0.1mg/kg). Anaesthesia was maintained with N2O & O2 (5:3) and muscle relaxation with vecuronum bromide by one fifth of loading dose. Ventilation was controlled manually. At the end of surgery,Inj Neostigmine 0.05 mg/kg and atropine 0.02mg/kg were administered for the reversal of neuro muscular blockade and the patients were extubated.

After surgery, patients were observed for 24 hrs for nausea, retching and vomiting. We made no distinction between retching and vomiting (i.e. retching event is considered as an emetic episode). Nausea and vomiting were evaluated on three-point ordinate scale (0 = none, 1 = nausea, 2 = retching/vomiting). Events of nausea and vomiting occurring postoperatively during first four hours are considered as early nausea and vomiting and those occurring after this period are considered as late emetic episodes. Incidence of postoperative nausea and vomiting was also recorded during time intervals of 0-4 hrs, 4-8 hrs, 8-16 hrs & 16-24 hrs.

The incidence of PONV in two different groups was analyzed using Chi square test and student 't' test value. Probability value was estimated using 't' test of statistical tables and P value < 0.05 is considered significant.

III. RESULTS

A total number of 50 cases were taken into study. 25 of them received Granisetron (40ug/kg) and the other 25 received Metoclopramide (0.15 mg/kg) for preventing postoperative nausea and vomiting through a period of 24 hours. Demographic and anaesthetic data in two groups were not different. (Table-1).

Both the groups were observed for differences in pulse rate and blood pressure (systolic & diastolic) 5 minutes after giving the anti emetic medication. There was statistically significant increase in pulse rate and systolic blood pressure in metoclopramide group while the diastolic blood pressure remained relatively constant (Table-2). The patients in graniseton group did not show any significant variation in either pulse rate or blood pressure.

Incidence of nausea during first 4 hrs after surgery in Granisetron (Group A) and Metoclopramide (Group B) groups were 4% and 30% respectively (P value> 0.05); where as nausea from 4-24 hours after surgery were 12% and 48% in group A and Group B respectively. (P value<0.05). There are no statistically significant differences noted between the two groups with reference to emetic episodes in early postoperative period (0-4hrs). During 4-24 hours of postoperative period 32% of patients who received metoclopramide developed emesis (P value<0.05) while there were no emetic episodes in granisetron group,

In Granisetron group 4% had nausea during first three assessment periods and8% complained of nausea in the last assessment period. Incidence of nausea with Metoclopramide group during four successive assessment periods: 0-4hrs, 4-8hrs, 8-16hrs&16-24hrs postoperatively, were20%, 20%, 32% and38% respectively.Although there were no episodes of vomiting in the group of granisetron, the patients in metoclopramide group were observed to have 8%, 16%, 16%& 4% in 0-4 hrs, 4-8hrs, 8-16 hrs and 16-24 hrs assessment periods respectively.

IV. DISCUSSION

The incidence of postoperative nausea and vomiting in female patients under going major gynaecological surgeries varies from 24% to 75%.[1] Although various anti emetics (E.g.: Anti cholinergics, Anti histaminics, Dopamine receptor antagonists) are available to treat PONV, their use is limited by untoward side effects.[1,2] Granisetron is a potent anti emetic with high selectivity for 5HT3 receptor, resulting in fewer adverse side effects than other anti emetics.[7] It was primarily used against chemotherapy induced vomiting and was proved to have promising role in the field of oncology.[6,7,8]Current 5HT3 receptor antagonists include ondansetron, granisetron, dolasetron and tropisetron.

In the present study the anti emetic efficacy of metoclopromide, a dopamine receptor antagonist and granisetron, a 5HT3 receptor antagonist was assessed in prevention of postoperative nausea and vomiting for a period of 24hours.[9, 10, 11]

The complex act of vomiting involves coordination of respiratory, gastrointestinal and abdominal musculature and is controlled by emetic center.[15,16]The area situated in the lateral reticular formation close to the tractus solitarius in the brain stem is thought to be the emetic center.[15,16]Stimuli from several areas with in the central nervous system can affect the emetic center.These includes afferents from the pharynx and the gastrointestinal tract and mediastinum as well as afferents from higher cortical centers (visual center &

vestibular portion of eighth cranial nerve) and the chemoreceptor trigger zone(CTZ) in the area Postrema.The area Postrema of brain is rich in Dopamine, Opioid and Serotonin (5-Hydroxy tryptamine) receptors.[8]

Four major neuro transmitter systems appear to play important role in mediating the emetic response viz. dopaminergic, histaminic (H1), cholinergic (muscarinic) and 5HT3 (serotinergic).[8] As there are four different types of receptors, there are at least four sites of actions of the antiemetic drugs. Antiemetic agents may have actions at more than one receptor, but they tend to have more prominent actions at one or two recptors.[15,16] 5HT3 antagonists have the same basic double nitrogen ring that acts on serotonin (It has 6 & 5 ring nitrogen based structure). Metoclopramide is a dopamine receptor antagonist which acts upon dopamine receptors present in CTZ in medulla as well as solitary tract nucleus (Emetic center). Granisetron was more effective than Ondansetron which showed better results than Metoclopramide[17.]

PONV is multi factorial in cause and possibly more complex to understand when compared to nausea and vomiting after chemotherapy. A number of factors including age, obesity, operative procedure, anaesthetic technique and post operative pain are thought to increase the incidence of this post operative symptoms.[12]
The 5HT3 receptor antagonists produced no sedation, extra pyramidal reactions or adverse effects on vital signs.Elimination half life of Granisetron is 8-9 hours.The other study drug Metoclopramide is known for its extrapyramidal reactions and other CNS side effects.The elimination half life is 5-6 hrs. No clinically important adverse events due to drugs were observed in either the metoclopramide or the granisetron groups in the present study.This was not in accordance with Scheller's report which described toxic neurological reactions in patients who received metoclopramide.[13] This difference may have been caused by the relatively small number of patients in the present study.

In this study however the treatment groups were similar for patient characteristics, surgical procedures and anaesthetics administered. Analgesic used for postoperative pain was standardized. Buprenorphine, a long acting, potent, synthetic narcotic analgesic with a high emetic tendency was used to have better control of pain during postoperative period so that pain does not contribute to PONV. There fore, the differences in the scores among the groups can be attributed to the differences in the study drugs. Unlike in other studies, we have not included the 'placebo' group for want of approval from Hospital Ethical Committee, as the incidence of PONV is very high in our set up with out prophylactic anti emetics.

While both the study drugs are effective in preventing PONV during first 4 hours of assessment period, granisetron was found to be very effective in preventing postoperative nausea and vomiting during 4-24 hrs assessment period. The postoperative period was again subdivided into four groups of assessment periods (0-4 hrs, 4-8hrs, 8-16hrs & 16-24hrs) to assess the efficacy of both the drugs during different time intervals. Nausea scores are significantly lower in-group A (Granisetron) than in Group B (Metoclopramide) in all the four assessment periods. Although there were no emetic episodes in the granisetron group, 32% of patients in metoclopramide group were observed to have such episodes during the assessment periods. (P value < 0.05).

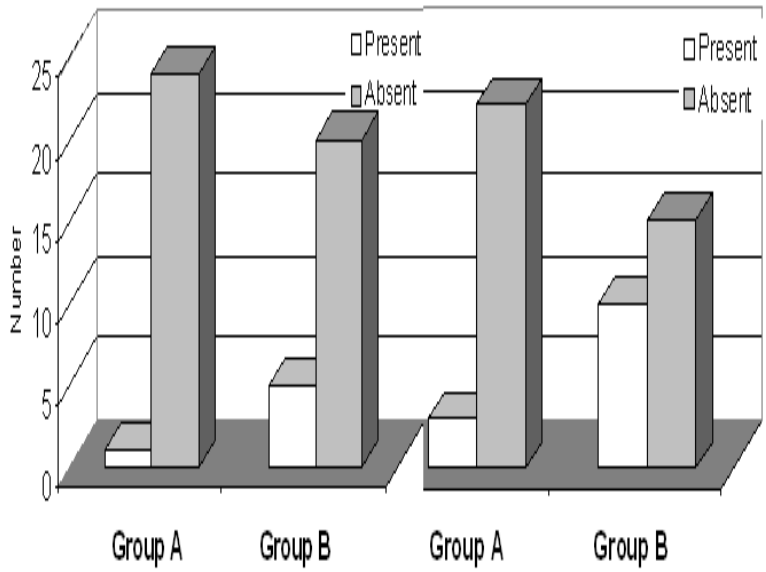
V. CONCLUSION

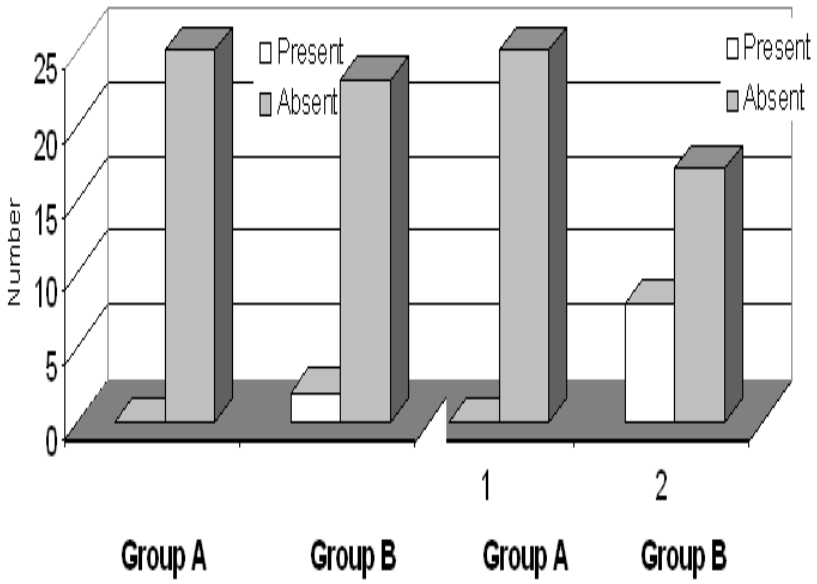
In conclusion, the administration of graniseton before induction of anaesthesia is superior to metoclopramide in long term prevention of postoperative nausea and vomiting following major gynecological surgery under general anaesthesia.[14]

REFERENCES

[1]. Cohen SE, Woods WA, Syner J. Antiemetic efficacy of droperidol and metoclopramide. Anaesthesiology 1984: 60:67-9.
[2]. Dundee J. W. and Clarke, R.S.J (1973) The premedicant and antiemetic action of metoclopramide Post grad. Med J., 4. 34.
[3]. Shah, Z. P., and Wilson, J (1972).An evaluation of metoclopramide as an anti emetic in minor gynaecological surgery. Br. J. Anaesth.,44,865.
[4]. Madej.T.Simpson K. Comparison of the use of domperidone, droperidol and metoclopramide in the prevention of nausea and vomiting following gynaecological surgery in day cases. Br. J. Anaesth 1986: 58: 879-83.
[5]. VittorioGebbia, M.D; PhD., Giuseppa Cannata, M.D., Antonio Tesla, M.D.Ondansetron versus granisetron in the prevention of chemotherapy-induced nausea and vomiting- A prospective randomized trial, CANCER october1, 1994,volume 74 No. 71, 945-52.
[6]. Ray McKenzie,Boonrak Tantisira,Deepa J Karambelkar,Theodore J.Riley, Abdelhady. Comparison of ondansetron with ondansetron plus dexamethasone in the prevention of postoperative nausea and vomiting. Anesth Analg 1994; 79: 961-4.
[7]. Andrews PLR, Bhandari P, Davey PT, Bingham S, Marr HE, Blower PR. Are all 5HT3 receptor antagonists the same? Eur J Cancer 1992; 28: S2-S6.
[8]. Soukop. M. A Comparison of two dose levels of granisetron in patients receiving high dose cisplatin. Eur. J. Cancer 1990; 26 (suppl.): S15-S19. 7.
[9]. Yoshitaka Fujii MD, Hiroyoshi Tanaka MD, Hidenori Toyooka MD. Optimal anti emetic dose of granisetron for preventing postoperative nausea and vomiting. Can J Anaesth 1994:41:9:794-7.
[10]. Kortilla K, Kauste A, Auvinen J.Comparison of domperidone, droperidol and metoclopramide in the prevention and treatment of nausea and vomiting after balanced general anaesthesia. Anesth Analg 1979; 58: 396-400.s
[11]. Mikawa K, Takao Y, Nishina K, et al. The antiemetic efficacy of granisetron in gynaecological surgery.Anesth Analg 1995; 80:970-4.
[12]. .Lerman J Surgical and patient factors involved in postoperative nausea and vomiting.
[13]. Br J Anaesth 1992:69(Suppl 1):24S-32S.

[14]. 14.Scheller MS, Sears KL. Postoperative neurologic dysfunction associated with preoperative administration of metoclopramide. Anesth Analg 1987; 66:274-6.
[15]. Fujii Y, Tanaka H, Toyooka H. Reduction of postoperative nausea and vomiting with granisetron. Can J Anaesth 1994:41:291-4.
[16]. TM Craft,PM Upton.Anaesthesia clinical aspects .3rd edition 2001;279-281.
[17]. Matti Aapro, M.D Granisetron: An Update on its Clinical Use in the Management of Nausea and Vomiting. The Oncologist journal,July 7, 2004**.**
[18]. Ashutosh Sayana,Yogesh Barshiliya, Comparative Study of Metoclopramide, Ondansetron, and Granisetron in Prophylaxis of PONV in Patient Undergoing Laparoscopic Cholecystectomy Under General Anaesthesia. Asian Journal of Pharmacy and Life Science ISSN 2231 – 4423 Vol.2 (1), Jan-March, 2012





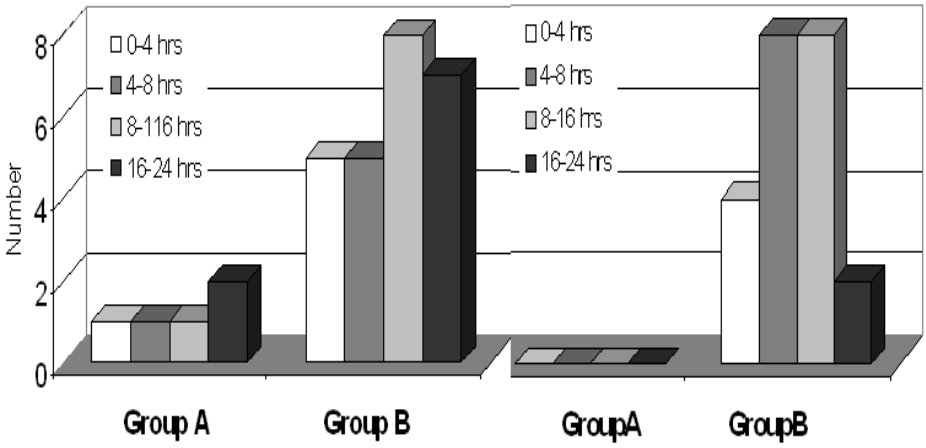


Table-1
Demographic And Anaesthetic Data

Patient Characteristics	Mean Group A	Mean Group B	SD Group A	SD Group B	T value
Age	40.5200	39.8400	8.7088	7.4424	0.2968 NS
Weight	50.3600	48.1600	5.8158	6.7186	1.2379 NS
Duration of Anaesthesia (min)	100.0000	89.0000	26.6145	23.6291	1.5454 NS
Duration of Surgery (min)	91.2000	99.2000	17.3973	25.1529	1.3079 NS

- Group A- Granisetron
- Group B- Metoclopramide

Change In Haemodynamic Parameters

GROUP A	Mean (Before)	SD (Before)	Mean (After)	SD (After)	Paired T
Pulse rate	86.96	8.15	86.24	6.99	1.3407 NS
Systolic Blood Pressure	126.64	14.09	126.32	13.73	0.6094 NS
Diastolic Blood Pressure	83.84	7.07	82.88	7.73	1.7677 NS
GROUP B					
Pulse rate	92.28	10.22	104.40	14.36	8.4974 **
Systolic Blood Pressure	127.28	15.61	130.32	16.01	5.2528 **
Diastolic Blood Pressure	81.76	4.74	82.00	5.89	0.4856 NS
GROUP A & GROUP B					
Pulse rate	89.62	9.53	95.32	14.46	4.8003 **
Systolic Blood Pressure	126.96	14.72	128.32	14.90	2.9881 **
Diastolic Blood Pressure	82.80	6.05	82.44	6.81	0.9642 NS