

QUALITATIVE COMPARISON OF METOCLOPRAMIDE, ONDANSETRON AND GRANISETRON ALONE AND IN COMBINATION WITH DEXAMETHASONE IN THE PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING IN DAY CARE LAPAROSCOPIC GYNAECOLOGICAL SURGERY UNDER GENERAL ANAESTHESIA

USHA DARIA*¹, VINOD KUMAR²

¹Assistant Professor, Department of Anaesthesia, Jhalawar Medical College, Jhalawar (Rajasthan), 326001, ² Assistant Professor, Department of Psychiatry, Jhalawar Medical College, Jhalawar (Rajasthan), 326001, Email: drvinodusha@gmail.com

Received: 15 January 2012 Revised and Accepted: 11 March 2012

ABSTRACT

AIM: To compare qualitatively Metoclopramide, Ondansetron and Granisetron alone and in combination with Dexamethasone in the Prevention of Postoperative Nausea and Vomiting in Day Care Laparoscopic Gynaecological Surgery under General Anaesthesia.

METHOD: 180 adult female patients of ASA Grade I and II, BMI <30, aged 18 to 55 years undergoing laparoscopic gynaecological surgery under general anaesthesia included in the study. Patients with history of motion sickness and past history of PONV were excluded from the study. The study was carried out in six groups consisting of randomly selected 30 patients in each. Before induction of general anaesthesia, the antiemetic drugs under study given intravenously i.e. Metoclopramide (10 mg), Ondansetron (4mg) and Granisetron (3 mg) were given alone in group A, B and C respectively while in group D, E and F these drugs were combined with Dexamethasone (8 mg) respectively. The study drugs were given as intravenous injections.

RESULT: The study found that Metoclopramide is very poor because of higher incidence of side effects and only 36.7% success rate in the prevention of PONV. The success rate in the prevention of PONV is poor in Ondansetron & Granisetron (nearly two-third, 63.3% & 66.7% respectively). The success rate found good (nearly three-fourth, 73.3%) in combination of Metoclopramide with Dexamethasone and very good in combination of Ondansetron & Granisetron with Dexamethasone (90% in both).

Key words: laparoscopic, gynaecological, nausea, vomiting, PONV

INTRODUCTION

Postoperative nausea & vomiting [PONV] are common distressing complications of Anaesthesia. Pain, nausea & vomiting are frequently listed by the patient as their most important perioperative concerns. In one study, patients were more concerned about PONV than about postoperative pains¹; while in another study, patients were willing to spend up to US \$ 100 for an effective antiemetic treatment². PONV results in increased patient's discomfort and dissatisfaction³ and in increased costs related to length of hospital stay. One study revealed that time to discharge was increased by 25% in patients with PONV⁴. Despite continuing advances in anaesthetic & surgical technique, both the incidence and severity of PONV remained relatively unchanged. In general, a number of factors, including age, gender, history of motion sickness and/or previous postoperative emesis, pain, operative procedure, and anesthetic technique, are all considered to affect the occurrence of PONV^{5,6}. Female patients have 3 times greater incidence of emetic symptoms than males, due to increased gonadotropin, estrogen, and plasma progesterone levels during their menstrual cycles⁷.

Woman undergoing Gynaecological surgery are particularly at risk of experiencing these problems. In the absence of any anti-emetic treatment, the incidence of nausea & vomiting in high risk patients can as high as 70-80% after surgery⁸. Obesity appears to increase the risk of PONV. Fat soluble anaesthetic agents may accumulate in adipose tissues which then release and slowly causing postoperative emesis.

In laparoscopic procedure, the peritoneal cavity is inflated with carbon dioxide; vagal afferents on the bowel and peritoneum are triggered which induces emesis by activating the vomiting center⁹. Also the insufflations leads to abdominal discomfort if abdominal cavity is not adequately decompressed after the procedure which further adding to the general level of unpleasant sensations.

Many studies are done on PONV so far, but most of them compared the antiemetic drugs with placebo only and either reported emetic episodes or nausea only. Very less number of studies compared two or three approaches for control of PONV in postoperative period in day care surgery which is increasing nowadays. So we choose six antiemetic approaches for comparison by taking three antiemetics drugs Metoclopramide, Ondansetron, Granisetron alone and their combination with Dexamethasone in another three groups in day

care surgery for prevention of both nausea and vomiting under this study.

MATERIAL AND METHODS

After approval from ethical committee and written informed consent, the study was carried out in 180 adult female patients of ASA Grade I and II, BMI <30, aged 18 to 55 years undergoing laparoscopic gynaecological surgery under general anaesthesia. The duration of procedure was 15-20 minutes. All patients in present study were subjected to detailed pre anaesthetic evaluation, which included their present complaints, any history of nausea, retching/vomiting within past 24 hours, drug history or any past history of operation under general anaesthesia. Patients with gastrointestinal disease i.e. patients with hiatus hernia, acid peptic disease, reflux esophagitis and cirrhosis liver, with history of motion sickness, past history of PONV, patients who were menstruating, taking hormonal therapy and patients who had taken antiemetic within 24 hrs before surgery were excluded from the study. The study was carried out in six groups consisting of randomly selected 30 patients in each. Before induction of general anaesthesia, the antiemetic drugs under study i.e. Metoclopramide (10 mg), Ondansetron (4mg) and Granisetron (3 mg) were given alone in group A, B and C respectively while in group D, E and F these drugs were combined with Dexamethasone (8 mg) respectively. The study drugs were given as intravenous injections.

All patients were premedicated with injection Glycopyrrolate 0.2 mg IV, injection Midazolam 0.04 mg/kg body weight & injection Tramadol 2 mg/kg body weight and preoxygenated with 100% oxygen for three minutes. Before induction of anaesthesia the patients were administered antiemetic drugs either alone or in combination according to the random selection of the patient to one of the six study groups. Induction of anaesthesia was done with freshly prepared 2.5% solutions of injection Thiopentone at a dose of 3-5 mg/kg body weight slowly followed by injection Succinyl Choline 1.5 mg/kg body weight. Patients were ventilated with 100% oxygen with IPPV till the onset of effect of Succinyl Choline and after proper relaxation tracheal intubation was done with proper size endotracheal tube. Anaesthesia was maintained with 60% N₂O in oxygen and if necessary Succinyl Choline was repeated. All patients were observed for vital parameters (Pulse, B.P. & respiration),

emetic episodes (including retching) and nausea for first 6 hours. Nausea was defined as the subjectively unpleasant sensation associated with awareness of the urge to vomit, whereas vomiting was defined as the forceful expulsion of gastric contents from the mouth. Retching was defined as the labored, spasmodic, rhythmic contraction of the respiratory muscles without the expulsion of gastric contents. Rescue anti emetic was given at first episode of emesis in the observation period. The adverse effects like headache

dizziness sedation and other side effects were observed. Statistical analysis was performed with ANOVA test for continuous variables expressed as mean \pm SD (patient's age, weight, BMI and duration of operation). Discrete variables, such as the incidence of complete response, nausea, retching or vomiting and the incidence of adverse effects, were compared by using chi square, Fisher's exact tests. P value of 0.05 was considered significant.

RESULTS

Table No. 1: Data of Age (in years), Body Weight (in Kg), Body Mass Index (BMI) and Duration of Anaesthesia (as GA Time in minutes)

Variables Mean \pm S.D	Group A N=30	Group B N=30	Group C N=30	Group D N=30	Group E N=30	Group F N=30	P value
Age \pm S.D	26.2 \pm 5.33	26.4 \pm 6.18	27.4 \pm 6.21	26.27 \pm 5.13	27.47 \pm 4.88	26.33 \pm 5.66	P = 0.899 *NS
Body Weight \pm S.D	52.63 \pm 6.33	51.33 \pm 7.58	50.1 \pm 9.05	48.9 \pm 7.48	52.3 \pm 8.90	48.13 \pm 7.39	P=0.153 NS
BMI \pm S.D	21.59 \pm 2.88	21.44 \pm 2.83	21.40 \pm 3.55	20.83 \pm 2.77	21.69 \pm 3.65	20.8 \pm 2.56	P = 0.807 NS
GA time \pm S.D	11.06 \pm 2.30	11.26 \pm 1.96	11.56 \pm 1.97	11.1 \pm 1.58	10.5 \pm 1.63	11.17 \pm 1.62	P = 0.389 NS

Group A = Metoclopramide, Group B = Ondansetron, Group C = Granisetron,
Group D = Metoclopramide + Dexamethasone, Group E = Ondansetron + Dexamethasone, Group F = Granisetron + Dexamethasone,
*Non significant

Table No. 2: Incidence of Post Operative Nausea and Vomiting (PONV)

Study Groups	No PONV reported	PONV Reported	Comparison Groups	P value	Significance
Group A	11 (36.7%)	19 (63.3%)	A & B	P < 0.05	Significant
Group B	19 (63.3%)	11 (36.7%)	B & C	P > 0.05	Non Significant
Group C	20 (66.7%)	10 (33.3%)	A & C	P < 0.05	Significant
Group D	22 (73.3%)	8 (26.7%)	A & D	P < 0.01	Significant
Group E	27 (90%)	3 (10%)	B & E	P < 0.05	Significant
Group F	27 (90%)	3 (10%)	C & F	P < 0.05	Significant

Group A=Metoclopramide, Group B=Ondansetron, Group C=Granisetron,
Group D= Metoclopramide + Dexamethasone, Group E=Ondansetron + Dexamethasone, Group F=Granisetron + Dexamethasone

Table No. 3: Incidence of side effects

Study Groups	Headache	Dizziness	Sedation	Any other
Group A	4	8	3	3
Group B	1	2	1	0
Group C	1	2	0	0
Group D	3	2	1	3
Group E	1	5	0	0
Group F	1	3	0	0

Group A=Metoclopramide, Group B=Ondansetron, Group C=Granisetron,
Group D= Metoclopramide + Dexamethasone, Group E=Ondansetron + Dexamethasone, Group F=Granisetron + Dexamethasone

***Metoclopramide (Group A) has significantly higher incidence of Dizziness.**

The sample of all six groups is matched for age, weight, BMI and duration of anaesthesia, as data summarized in table 1. During first 6 hours after anaesthesia the complete response was 36.6% in group A, 63.6% in group B, 67.7% in group C, 73.3% in group D, 90% in both group E and F as shown in table 2. On comparison of individual drug with each other the success rate to prevent PONV of Ondansetron and Granisetron is significantly higher than Metoclopramide while no difference is observed in between Ondansetron and Granisetron. In another comparison of individual drug and their combination with Dexamethasone, the success rate of all 3 combination groups are found significantly higher than individual respective drugs. The most common side effects reported are headache, dizziness and sedation (table 3). On comparison

dizziness is found significantly higher in Metoclopramide. Other side effects are not significant.

DISCUSSION

PONV is one of the most common complications after major gynecological surgery performed under general anesthesia. The etiology of PONV after gynecologic surgery is multifactorial in origin. In this study, gender, type of operation, anaesthetic drugs and analgesia administered are same for all patients. Patients with a previous history of motion sickness or PONV were excluded from the study and all six groups are matched for age, body weight, BMI and duration of operation (table 1). Therefore, the difference in the incidence of PONV among the groups can be attributed to the difference in drugs tested for success in prevention of PONV. Ethical consideration dominated our decision not to use a placebo group, which is in agreement with Olver et al¹⁰. Metoclopramide is chosen as the antiemetic agent for comparison because it is the drug used routinely for this purpose. Intermittent Suxamethonium was used to allow controlled ventilation because the mean time of operation was short (in between 10 to 12 minutes in all the study groups). Although this technique is uncommon in day-care surgery, it may result in less emesis than is associated with the use of non-depolarizing neuromuscular blocking drugs, by avoiding the requirement for the antagonism of neuromuscular block with Neostigmine.

For qualitative inter group comparison, all the study groups are compared for prophylaxis of PONV in two ways. First Metoclopramide, Ondansetron & Granisetron are compared individually with each other. Then each drug was compared with its combination with Dexamethasone. So far individual drug

comparison is considered, it can be concluded that both Ondansetron & Granisetron were found to be nearly equally effective though both the drugs had significantly better control over PONV when compared with Metoclopramide. Our findings are in agreement with Raphael and Norton¹¹, Alon E. and Himmelseher¹², DeSilva et al¹³, and Paxton L.D. et al¹⁴ who found Ondansetron superior to Metoclopramide. Our results were also supported by Naguib M. et al¹⁵ who had compared Ondansetron 4 mg, Granisetron 3 mg with Metoclopramide 10 and Fuji Y. et al¹⁶ compared Granisetron with Metoclopramide.

In direct comparison of Metoclopramide alone and its combination with Dexamethasone in our study, combination of Metoclopramide and Dexamethasone is found superior to Metoclopramide (free from PONV are 73.3% vs 36.7%). This finding is contrary to Fujii et al¹⁷ who did not found such significant difference. Combination of Ondansetron & Dexamethasone found superior to Ondansetron alone (no PONV is 90% vs 63.7%) as studied by Rajeev et al¹⁸ and Lopez-Olando L. et al¹⁹ while McKeinze R. et al²⁰ found very low success rate in combination group as 52% only. Similarly combination of Granisetron & Dexamethasone is also found superior to Granisetron alone (success rate is 90% vs 67.7%) but efficacy reported by Fujii et al¹⁷ is very high in patients receiving Granisetron alone as 80%.

The improvement of success rate in the combination groups can be explained by the fact that Dexamethasone is itself a potent antiemetic drug and act via different mechanism in controlling PONV. So the two different mechanisms operating simultaneously in the combination group in controlling PONV may be responsible for better results. Mechanism of antiemetic action of Dexamethasone is not exactly known till yet but it may involve central inhibition of prostaglandin and it also reduces the level of 5- hydroxytryptophan in neural tissue by depleting its precursor tryptophan. Fujii Y et al¹⁷ proved that Dexamethasone was effective in prevention of PONV in doses of 8-10 mg. Splinter and Roberts²¹ evaluated the effect of Dexamethasone on vomiting after elective tonsillectomy and found that Dexamethasone reduced the overall incidence of vomiting from 72% (placebo) to 40% (P < 0.001). Biswas et al²² reported only 20% incidence of PONV with Dexamethasone alone. Comparison of incidence of side effects between Ondansetron and Granisetron is insignificant but both of the drugs produced much less side effects as compared to Metoclopramide. Dizziness is significantly higher in Metoclopramide. The statistical difference for headache, sedation and other side effects is insignificant among the study groups.

In conclusions, this study found that Metoclopramide is very poor because of higher incidence of side effects and only 36.7% success rate in the prevention of PONV. The success rate in the prevention of PONV is poor in Ondansetron & Granisetron (nearly two-third, 63.3% & 66.7% respectively). The success rate found good (nearly three-fourth, 73.3%) in combination of Metoclopramide with Dexamethasone and very good in combination of Ondansetron & Granisetron with Dexamethasone (90% in both).

REFERENCES

- Macario A, Weinger M, Carney S, Kim A. Which clinical anesthesia outcomes are important to avoid? *Anesth Analg* 1999;89:652-8.
- Gan T, Sloan F, Dear Gde L, El-Moalem HE, Lubarsky DA. How much are patients willing to pay to avoid postoperative nausea and vomiting? *Anesth Analg* 2001;92:393-400
- Palazzo MG, Strunin L. Anaesthesia and emesis: Etiology. *Can Anaesth Soc J* 1984;31:178-87.
- Chung F, Mezei F. Factors contributing to a prolonged stay after ambulatory surgery. *Anesth Analg* 1999;89:1352-9.
- Watcha MF, White PF. Postoperative nausea and vomiting: its etiology, treatment, and prevention. *Anesthesiology* 1992; 77: 162- 84.
- Kovac AL. Prevention and treatment of postoperative nausea and vomiting. *Drugs* 2000;59:213-43.
- Beattie WS, Lindblad T, Buckley DN, et al. The incidence of postoperative nausea and vomiting undergoing laparoscopy is influenced by the day of menstrual cycle. *Can J Anaesth* 1991; 38: 298- 302
- Camu F, Lauwers MH, Verbessem D. Incidence and aetiology of postoperative nausea and vomiting. *Eur J Anaesthesiol* 1992; 9(Suppl 6);25-31
- Alahuhta S, Kangas-Saarela T, Hollmen AI, et al. Visceral pain during caesarean delivery under spinal and epidural anaesthesia with bupivacaine. *Acta Anaesthesiology Scand* 1990; 34: 95-8.
- Olver IN, Simon RM, Aisner J. Antiemetic studies: a methodological discussion. *Cancer Treat Rep* 1986; 73: 250-54.
- Raphael JH and Norton AC: Antiemetic efficacy of prophylactic Ondansetron in laparoscopic surgery: Randomized, double blind comparison with Metoclopramide. *British Journal of Anaesthesia* 1993; 71: 845-48.
- Alon E and Himmelseher S: Ondansetron in treatment of postoperative vomiting a double blind comparison with Droperidol and Metoclopramide. *Anaesthesia and Analgesia* 1992; 75(4): 567-75.
- Desilva PH, Darvish AH, Mc Donald SM Cronin MK and Clark K: The efficacy of prophylactic Ondansetron, Droperidol, Periphanazine and Metoclopramide in prevention of nausea and vomiting after major gynaecological surgery. *Anaesthesia and Analgesia* 1995; 81: 139-43.
- Paxton LD, McKay AC and Mirakhur RK: Prevention of nausea and vomiting after day case gynaecological laparoscopy. A comparison of Ondansetron, Droperidol, Metoclopramide and placebo. *Anaesthesia* 1995; 50: 403-06.
- Naguib M, el Bakry AK, Khoshim MH, Channa AB, el Gammal M, el Gammal K, et al: Prophylactic antiemetic therapy with Ondansetron, Tropisetron, Granisetron and Metoclopramide in patients undergoing laparoscopic cholecystectomy: a randomized, double-blind comparison with placebo. *Canadian Journal of Anaesthesia* 1996; 43: 226-31.
- Fujii Y, Tanaka H and Toyooka H: Reduction of postoperative nausea and vomiting with Granisetron. *Canadian Journal of Anaesthesia* 1994; 41(4): 291-94.
- Fujii Y, Tanaka H and Toyooka H: The Effects of Dexamethasone on Antiemetics in Female Patients Undergoing Gynecologic Surgery. *Anesth Analg* 1997;85:913-7
- Rajeev V, Bhardwaj N, Batra YK and Dhaliwal LK: Comparison of Ondansetron with Ondansetron and Dexamethasone in prevention of PONV in diagnostic laparoscopy. *Canadian Journal of Anaesthesia* 1999; 46: 40-44.
- Lopez-Olaondo L, Carrascosa F, Pueyo FJ, Mondero P, Busto N and Saez A: Combination of Ondansetron and Dexamethasone in the prophylaxis of postoperative nausea and vomiting. *British Journal of Anaesthesia* 1996; 76: 835-40.
- McKenzie R, Tantisira B, Karambelkar DJ, Riley TJ and Abdelhady H: Comparison of Ondansetron with Ondansetron plus Dexamethasone in the prevention of postoperative nausea and vomiting. *Anaesthesia and Analgesia* 1994; 79: 961-64.
- Splinter W and Roberts DJ: Dexamethasone decreases vomiting in children after tonsillectomy. *Anaesthesia and Analgesia* 1996; 83: 913-16.
- Biswas BN, Rudra A, Das K, Nath S and Biswas SC: A comparative study of Glycopyrolate, Dexamethasone and Metoclopramide in control of post-operative nausea and vomiting after spinal anaesthesia for caesarian delivery. *Indian Journal of Anaesthesia* 2003; 47(3): 198-200.