PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING IN PATIENTS UNDERGOING LAPAROSCOPIC BARIATRIC SURGERY

- Granisetron Alone vs Granisetron Combined with Dexamethasone/Droperidol -

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Summary

Background and Objectives: Laparoscopic bariatric surgeries are associated with an appreciably high rate of postoperative nausea and vomiting. This study was designed to compare the effectiveness of granisetron either alone or in combination with droperidol or dexamethasone, for the prevention of post operative nausea and vomiting (PONV) in patients undergoing laparoscopic bariatric surgeries.

Methods: In a randomized, double-blind, placebo-controlled trial, 120 patients received either Granisetron 1 mg, Granisetron 1 mg plus Droperidol 1.25 mg, Granisetron 1 mg plus Dexamethasone 8 mg or Placebo (saline), intravenously immediately before induction of anesthesia. Perioperative anesthetic care was standardized in all patients. Patients were then observed for 24 hours after administration of the study drugs.

Results: The incidence of PONV was 30% with granisetron alone, 30% with granisetron plus droperidol, 20%, with granisetron plus dexamethanone, and 67% with placebo. ($P < 0.05$; overall Fisher's exact

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probability test). The incidence of adverse events was not different among the 4 groups.

Conclusion: Graniserton is effective and safe drug for reducing the incidence of PONV in patients undergoing bariatric surgeries, and becomes highly effective when combined with dexamethasone.

Key words: Postoperative nausea and vomiting, granisetron, bariatric surgery.

Introduction

Bariatric operations are either restrictive, limiting the amount of food ingested (e.g.; adjustable gastric banding), malabsorptive, limiting the amount of nutrients absorbed (e.g.; Rou-en-Y gastric bypass), or a combination of both (e.g.; sleeve gastrectomy). Bariatric surgery had tremendous growth since its initial sporadic introduction in 1954 with a more than 20-fold increase in the number of procedures performed over the last decade[1].

Postoperative nausea and vomiting (PONV) are distressing and frequent adverse events after general anesthesia and surgery[2]. Institutional incidences varies considerably but on average of 30-50%[3]. The main risk factors to increase PONV are; female gender, non-smoking, history of motion sickness, and using postoperative opioids[4], together with laparoscopic approach and induced pneumoperitoneum, make the prevention of PONV in bariatric surgery a major anesthetic challenge.

When therapeutic intervention to prevent PONV is warranted, selective serotonin type 3 (5-HT_3) receptor antagonists (e.g; Granisetron) are considered a first-line therapy because of their efficacy and safety compaed with other drugs[5]. For patients with high risk of PONV, use of a 5-HT_3 receptor antagonist in combination with other antiemetic drug may be justified to further reduce the likelihood of PONV[6].

Droperidol is an antidopaminergic, neuroleptic drug that may be associated with torsade de points, so, the Food and Drug Administration added a “black box” warning to the drug’s labeling, however, there is

little evidence that antiemetic doses trigger this condition[7].

Dexamethasone has been found to have a prophylactic antiemetic effect in patients for surgery under general anesthesia[8].

The combination of granisetron and dexamethasone is already known to reduce PONV in an anesthetic setting[9]. So far, there is no study that compares the effects of granisetron and its combinations for the prevention of PONV in patients undergoing laparoscopic bariatric surgery. Therefore, we performed this prospective, randomized, double blind and placebo controlled study to compare the antiemetic effect of the prophylactic administration of either granisetron alone, and in combination with droperidol or dexamethasone for preventing PONV in patients undergoing laparoscopic bariatric surgery.

Methods & Materials

This study was prospective, randomized, placebo-controlled and double-blinded. One hundred and twenty patients (ASA II or III; aged between 18-44 years) of both sexes, were enrolled in this study. All patients received general anesthesia for laparoscopic bariatric surgery after obtaining Hospital Ethics Committee approval and written informed consent. Exclusion criteria included 1) known hypersensitivity or contraindication to study medications 2) chronic nausea, vomiting, motion sickness or retching experience in the 24 hours before anesthesia, 3) received an antiemetic drug or drug with antiemetic properties during the 24 hours before anesthesia, 4) breast feeding, or menstruating 5) conditions that required chronic opioid administration, or 6) gastrointestinal disease, diabetes mellitus, neuromuscular diseases and smokers.

Patients were randomly allocated into one of four equal groups, 30 patients each, using a random number table, to receive one of four treatment regimens;

Group I: Granisetron 1 mg.

Group II: Granisetron 1 mg plus Droperidol 1.25 mg.

Group III: Granisetron 1 mg plus Dexamethasone 8 mg.

Group IV: Placebo (saline).

These drugs were given intravenously (I.V) over one minute immediately before induction of anaesthesia.

Randomized numbers generated by a random number function in a computer spread sheet, resulted in a list of 30 assigned to patients receiving one of each four groups. According to this list, personnel not involved in the study prepared identical 5 ml syringes containing each regimen. The same surgeon performed all surgeries. No premedication were administered and a standardized anesthetic regimen was performed.

General anesthesia was induced with IV Propofol up to 2.5 mg/kg and Atracurium 0.6 mg/kg I.V was used to facilitate tracheal intubations. Anesthesia was then maintained with 40-50% oxygen in air and 1.0-3.0% (inspired concentration) Sevoflurane. The sevoflurane concentration was adjusted to maintain blood pressure and heart rate within 15% of preinduction values. No patient received opioids before tracheal intubation or during maintenance of anesthesia. Ventilation was mechanically controlled and was adjusted to maintain $P_{ET}CO_2$ between 4.6-5.2 Kpa using an anesthetic/respiratory analyzer (Capnomac Ultima, Datex, Finland). A nasogastric tube (14-16 Fr, Salem sump tube) was inserted and suction applied to empty the stomach of air and other content. Before tracheal extubation, the nasogastric tube was suctioned and then removed. Muscle relaxation for pneumoperitoneum and surgical procedure was provided with additional doses of atracurium.

During laparoscopy, intra-abdominal pressure was maintained at 1.3-1.8 Kpa by carbon dioxide insufflator and the patients were placed in 20-30° head up position. Patients were monitored by continuous ECG, NIBP, Pulse Oximetry and Capnometry (Solar 8000M, GE, Freiburg, Germany).

At the cessation of surgical procedure, the surgeon was requested to inject Bupivacaine 100 mg in 50 ml 0.9% NaCl through the laparoscopic port into the peritoneal cavity. Sevflurane administration was stopped. Residual neuromuscular blockade was reversed with I.V neostigmine 0.05 mg/kg and glycopyrrolate 5 μg/kg, and then trachea was extubated (defined as end of surgery) when the patient was awake. Rectal

temperature was monitored and maintained at 37 ± 1°C, using hot water warming mattress and forced air warming device (Bair Hugger, Augustine Medical, USA).

If two or more episodes of PONV occurred during the first 24 h after anesthesia, another rescue antiemetic, (Metoclopramide 0.2 mg/kg I.V) was given. Postoperative analgesia was provided with indomethacin 100 mg p.r. for moderate pain and buprenorphine 0.3 mg i.m for severe pain.

During the postoperative period, all episodes of PONV were recorded within the first 24 hours after anesthesia (0-4 h in post anesthesia care unit (PACU), and 4-24 hours in the ward) by direct questioning by trained BSc students unaware about the patient antiemetic regimen or by spontaneous complaint by the patient.

Nausea was defined as a 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[10]. Retching was defined as the labored, spasmodic, rhythmic contraction of the respiratory muscles including the diaphragm, chest wall and abdominal wall muscles without the expulsion of gastric contents[10] and was classified as PONV. The details of any other adverse effects throughout the study was recorded by the follow-up nurses who interviewed the patients and also record spontaneous complaints.

Statistical Power

To show that reducing PONV from 60% to 25%, a treatment of 29 patients in each group would be necessary using type I error of 5% and a type II error of 20%, according to calculation of sample size with Win Episcope 2.0.

Statistical Analysis

Analysis of data among the groups was performed by one-way

analysis of variance (ANOVA) with Banferroni correction. For multiple comparison, Chi-square test, or Fisher's exact test as appropriate. A p value < 0.05 was considered significant. All values are expressed as mean ± standard deviation (SD) and number (%).

Results

There were no significant differences among the four treatment groups as regards patients' demographic data, risk factors for PONV, duration of surgery and anesthesia, type of operation performed and the amount of postoperative analgesia used (Table 1).

Table 1

Patients' demographic data and surgical procedures

Group	Group I (n = 30)	Group II (n = 30)	Group III (n = 30)	Group IV (n = 30)	P value
Age (years)*	29.50±5.29	29.42±5.39	28.62±5.66	30.29±5.09	*NS*
Sex ratio (F/M)	22/8	21/9	22/8	20/10	*NS*
Weight (kg)*	109.45±7.34	105.14±14.25	107.32±11.35	106.15±11.33	*NS*
Height (cm)*	154±4	153±5	156±5	154±5	*NS*
History of motion sickness**	4 (13.3)	4 (13.3)	4 (13.3)	4 (13.3)	*NS*
Non smoking**	24 (80)	25 (83.3)	24 (80)	27 (90)	*NS*
Previous PONV**	3 (10)	3 (10)	2 (6.7)	2 (6.7)	*NS*
Duration of operation (min)*	99±33	101±34	103±32	102±33	*NS*
Duration of anesthesia (min)*	124±33	125±35	126±34	126±32	*NS*
Postoperative analgesic used (n)					
- Indomethacin	16	14	15	14	*NS*
- Buprenorphine	4	6	5	6	*NS*
Type of operation performed (n)					
- Gastric Banding	21	20	20	21	*NS*

- Gastric Bypas	4	5	5	5	*NS*
- Sleeve	5	5	5	4	*NS*
Gastrectomy					

* Values are expressed as mean ± SD.
** Values indicated the number of patients; values in parentheses indicate percentage.
NS: no significant differences among the groups.

During the first 24 h after anesthesia, the incidence of PONV was 30% with granisetron, 30% with ganisetron plus droperidol, 20% with granisetron plus dexamethasone and 76% with placebo, respectively (Table 2).

Table 2
Incidence of PONV during the first 24 hours after anesthesia

	Group I Granisetron	Group II Granisetron + Droperidol	Group III Granisetron + Dexamethasone	Group IV Placebo
	(n = 30)	(n = 30)	(n = 30)	(n = 30)
PONV				
0-4 h	6 (20%)	3 (10%)	4 (13%)	15 (50%)
4-24 h	3 (10%)	6 (20%)	2 (7%)	5 (16.7%)
Overall	9 (30%)	9 (30%)	6 (20%)	20 (67%)
P value	0.031*	0.01*	0.009*	
Nausea				
0-4 h	2 (7%)	1 (3%)	2 (7%)	9 (30%)
4-24 h	1 (3%)	2 (7%)	1 (3%)	2 (7%)
Overall	3 (10%)	3 (10%)	3 (10%)	11 (37%)
P value	0.043*	0.038*	0.043*	
Retching				
0-4 h	1 (3%)	1 (3%)	0 (0%)	2 (7%)
4-24 h	0 (0%)	1 (3%)	0 (0%)	1 (3%)
Overall	1 (3%)	2 (7%)	0 (0%)	3 (10%)
P value	0.13	0.22	-	
Vomiting				
0-4 h	3 (10%)	1 (3%)	2 (7%)	4 (13%)
4-24 h	2 (7%)	3 (10%)	1 (3%)	2 (7%)
Overall	5 (17%)	4 (13%)	3 (10%)	6 (20%)
P value	0.87	0.33	0.42	

All values are expressed as number (%).
P values versus group IV (Placebo).

In comparison between groups, group III (Granisetron and Dexamethasone), showed significantly lower incidence of PONV than other groups. There was no significant difference between group I (Ganisetron only) and group II (Granisetron and Droperidol), but both were significantly lower than group IV (Placebo). p value < 0.05.

Fourteen patients who had received placebo, 2 of those who had received granisetron alone and 2 of those who had granisetron and droperidol, required another rescue antiemetic (Metoclopramide), for the treatment of 2 or more episodes of PONV, whereas non who had received granisetron plus dexamethasone needed it. There were no differences in the incidence of other adverse effects observed among the four treatment groups (p < 0.05) (Table 3).

Table 3
Adverse effects

Group	Group I (n = 30)	Group II (n = 30)	Group III (n = 30)	Group IV (n = 30)	P value
Headache	3	3	3	3	*NS*
Dizziness	1	1	1	1	*NS*
Drowsiness	2	1	1	2	*NS*
Others	1	0	1	1	*NS*
Total no. of adverse effects	7	5	6	7	*NS*

NS: No significance among the groups.

Discussion

Although the laparoscopic approach for bariatric surgery has decreased surgical morbidity and has become a popular procedure, the incidence of PONV is appreciably high when no prophylactic antiemetic is given[11]. The etiology behind the PONV following laparoscopic bariatric surgery is complex and multifactorial. A number of factors including anesthetic technique, sex, pain, postoperative care and patients

demographic data, are considered to influence the incidence of emesis[10]. Previous studies found the incidence of PONV to be as high as 50-60% in patients undergoing general anesthesia[3]. The incidence of PONV in this study even exceeded 60%, (67%) in patients who had received placebo, and that may be due to the unique demographic parameters and surgical techniques used in bariatric surgery[1,2]. Apfel et al[12] also expressed that the different incidences of PONV after most operations are mainly caused by the associated risk factors and less by the operation itself.

Droperidol is a buterophenone that has been extensively used in anesthesia. In a dose of 1.25 mg, it was more cost-effective than 5-HT_3 receptor antagonists. Although it has a long duration of action as long as 24 hours[12], yet it has relatively short half life of 3 hours only[13].

Although Apfel et al[6] asserted that a 26% reduction in the relative risk of nausea and vomiting for each additional antemetic used, the present study showed no difference between granisetron alone and when droperidol was added. This was an expected result because droperidol in a dose of 1.25 mg does not have as long duration of action as granisetron[12]. Another reason for our results may be due to low number of patients, i.e., a lack of power to detect that effect. However, a meta-analysis did also question whether the combinations of droperidol and 5-HT_3 receptor antagonists could be recommended for routine use[12]. In accordance with our results, this large meta-analysis showed that there was no statistically significant improvement by applying the drug combination of droperidol and 5-HT_3 receptor antagonists compared with the single drug given alone could be detected.

The present study showed the significantly lowest incidence of PONV among the other groups with patients who had received granisetron and dexamethasone. The dose of dexamethasone used (8 mg) was based on previous reports shown to decrease PONV when added to an antiemetic regimen[2,6,8,9,16]. Mataruski et al[17], in a retrospective study showed that patients who received intraoperative steroids were less likely to experience postoperative nausea and vomiting than those who did not. Therefore, in the present study, the same dose of dexamethasone was added to granisetron.

The precise mechanism by which dexamethasone increase the effectiveness of granisetron is not known[14]. Granisetron produces antiemesis by blocking 5-HT_3 receptors[4,5]. Dexamethasone may inhibit stimulation of 5-HT_3 receptors[14] and may also potentiate the other pharmacological receptors[18]. In this study, the results suggest that a complete response is more likely to be achieved in patients who receive granisetron plus dexamethasone prophylactic regimen and also corroborate with the findings of Fujii et al[9,16].

The adverse effects observed in this study were relatively mild, and there were no difference in the incidences of headache, dizziness and drowsiness. Excessive sedation and extra pyramidal symptoms were also not observed in any of the patients. Thus granisetron did not affect mental status, which is in agreement with the previous studies[16,19].

In conclusion, granisetron in combination with dexamethasone is superior to granisetron alone or in combination with droperidol for reducing the incidence of PONV in patients undergoing laparoscopic bariatric surgery.

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