Evaluation and Comparison of Two Different Combined Regimens for Prophylaxis of Nausea and Vomiting After Laparoscopic Bariatric Surgery: A Double-Blinded Randomized Clinical Trial

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Abstract- Postoperative Nausea and vomiting (PONV) are the most complications after laparoscopic surgeries, especially laparoscopic bariatric surgeries. The incidence of PONV has been estimated in over two-thirds of patients undergoing laparoscopic bariatric surgeries. Prophylactic combined antiemetic therapy is recommended for patients undergoing these surgeries. This is a double-blinded randomized clinical trial. Eighty-three patients of ASA physical status I and II undergoing elective bariatric laparoscopic surgery were enrolled in this clinical trial and divided into two equal groups through simple randomization using a random number table. One group (group A) received a combination of ondansetron, dexamethasone, and haloperidol (ODH); and the other group (group B) received a combination of ondansetron, dexamethasone, and promethazine (ODP). The ODP group received promethazine 25 mg IM 30 minutes before extubation and ODH group received haloperidol 2 mg IM at the beginning of the surgery. Nausea and vomiting were assessed in terms of severity and frequency in the recovery room, 6, and 24 hours postoperatively in both groups using the Numeric Verbal Rating Scale (NVRS). The frequency of PONV was significantly lower in the ODH group compared to the ODP group in the recovery room (20% versus 40%). PONV severity was lower in the ODH group compared to the ODP group. The time to first rescue antiemetic prescription in the ODP group was more than in the ODH group (7.2 h versus 2.6 h). In morbidly obese patients undergoing laparoscopic bariatric surgery, both antiemetic combinations decreased the incidence of PONV, but the combination of haloperidol, dexamethasone, and ondansetron was more effective than promethazine, dexamethasone, and ondansetron.

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Keywords: Postoperative nausea and vomiting (PONV); Dexamethasone; Promethazine; Haloperidol; Laparoscopy

Introduction

The disease of obesity is one of the most important public health issues in our century (1). Bariatric surgery has been demonstrated as an effective treatment (2). Laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux-en-Y gastric bypass (LRYGB) are the 2 most performed bariatric procedures. Nowadays the most effective therapy for morbid obesity and its comorbidities is bariatric surgery because of the increased prevalence of morbid obesity and advances in surgical procedures and instruments (3,4). Postoperative nausea and vomiting (PONV) are the most common complications of bariatric surgeries, and their incidence is up to 70-80% in these patients (5). PONV is mostly self-limited however it may lead to potentially serious complications such as retinal detachment, suture dehiscence, esophageal rupture, aspiration, dehydration,

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pneumothorax, pneumomediastinum, electrolytes imbalance, and raised intracranial pressure. Also, dehydration due to PONV is the most common reason for readmission after bariatric surgery (6-10). We aimed to block Some of the receptors associated with the vomiting reflex including receptors of dopamine, histamine, and serotonin to prevent PONV after bariatric surgery (11). Some side effects for each drug blocking these receptors have been reported especially at high doses. For example, Droperidol blocks dopamine receptors; can cause prolonged QTc (Corrected QT) interval, and can cause life-threatening arrhythmias and received United States Food and Drug Administration (FDA) 'black box' warning (12,13). One of the drugs we used is Haloperidol which also blocks dopamine receptors but has less effect on QTc interval than Droperidol (14). Promethazine is an antihistamine but frequently causes sedation and dry mouth. (15).

The anti-inflammatory agent dexamethasone, used prophylactically before the induction of anesthesia appears to be an effective antiemetic but can cause a temporary rise in blood glucose. Adrenal insufficiency and immunosuppression have not been associated with a single dose (12,16,17). Several studies show that combination therapy of antiemetic drugs with different types of receptors is more efficient than single therapy and it is recommended especially for high-risk populations (18-20). In many studies, the efficacy of ondansetron and haloperidol in the management of PONV has been proven, whether as a single therapy or in combination with other antiemetic drugs. Also, the antiemetic effects of haloperidol and ondansetron have been reported to be similar in previous studies (21,22). In this study, we are going to compare two combined drug regimens ondansetron, dexamethasone, haloperidol (ODH) or group A versus ondansetron, dexamethasone, promethazine (ODP) or group B in patients undergoing laparoscopic bariatric surgery in order to make a better choice for prevention of PONV and improve patients' satisfaction.

Materials and Methods

This is a randomized two-arm parallel double-blinded clinical trial performed in Sina Hospital, 2018-2019. This study was approved by the Ethics Committee and followed the Helsinki Declaration principles. The ethical committee approval number is IR.TUMS.MEDICINE.REC.1395.1085. We obtained Informed consent from all patients before surgery. The trial was registered at the IRCT website before patient enrollment (June 22, 2018). This study has been registered at the IRCT website (https://www.irct.ir): IRCT ID is IRCT20170805035510N3.

The participants were selected from patients aged 18-65 years who did not receive antiemetics before surgery and were candidates for laparoscopic bariatric surgery and had the inclusion criteria: Body mass index (BMI) >35, American Society of Anesthesiologists (ASA) class 1 or 2, and having at least 2 risk factors for PONV according to Apfel criteria (23). Exclusion criteria were: 1) Severe medical diseases such as uncontrolled diabetes mellitus and hypertension. 2) Use of illegal drugs and antiemetics within 24 hours before surgery. 3) A serious medical condition like shock, cardiac arrhythmia, and hemorrhage requiring blood transfusion. 4) Pregnancy and lactation. 5) Psychiatric diseases treated with antipsychotics. 6) History of migraines. 7) Having a cardiac pacemaker. 8) Presence of prolonged QTc (>430 msec for males, >450 msec for females) on electrocardiography.

Eighty-three patients (Sixty-two females and twenty-one males) were enrolled in this randomized clinical trial. Patients were divided into two groups (A and B) through simple randomization using a random number table. Patients and researchers were not informed of each patient's intervention group. A questionnaire was designed on three pages. Page 1 including patients' names, and groups (A or B selected by randomization) was recorded in the operation room by the Anesthetic technician. Only patients' names were recorded on the next pages, including demographic and postoperative data. Pages 2 and 3 would be filled in by the researcher who didn't know the patients' group. Page 1 was kept in a separate folder and pages 2 and 3 were kept together in another folder. Finally, we opened the two folders and sorted the pages according to pharmacological groups. All 83 patients were followed up after the operation. Two females declined to participate and were excluded. We performed close monitoring after surgery for all the patients.

Premedication for anesthesia was induced with midazolam (60 µg kg-1) and fentanyl (2 µg kg-1) for all patients. Anesthesia was induced with propofol (1.5-2 mg kg-1) and muscle relaxation was achieved with atracurium (0.5 mg kg-1). Then, tracheal intubation was performed. Anesthesia was maintained with Isoflurane and 50% oxygen. At the end of the surgery, residual neuromuscular paralysis was antagonized with neostigmine (0.04 mg kg-1) IV and by atropine (0.02 mg kg-1) IV. Group A received a combination of ondansetron 4 mg, dexamethasone 8 mg, and

haloperidol 2 mg (ODH), and group B received a combination of ondansetron 4 mg, dexamethasone 8 mg, and promethazine 25 mg (ODP). Patients in both groups received dexamethasone 8 mg before induction and at the beginning of surgery and ondansetron 4 mg IV at the end of the operation. The ODP group received promethazine 25 mg IM 30 minutes before extubation and ODH group received haloperidol 2 mg IM at the beginning of the surgery.

Postoperative follow-up was done by the researcher who knew the patients' names but not their groups. Nausea and vomiting were assessed in terms of severity and frequency in the recovery room, 6, and 24 hours postoperatively in both groups using the Nausea Verbal Rating Scale (NVRS). It is a self-administered scale in which the patient scores his/her nausea on a range of 0-10 (0= for lack of nausea, 10= for most severe nausea with vomiting). We performed close monitoring during and after surgery to detect any probable adverse events after anesthesia and surgery or side effects of prophylaxis combination therapy of PONV until patients were discharged. An electrocardiogram (ECG) and blood analysis were performed twice per day.

The primary outcome was the comparison of frequency and severity of PONV between two groups.

Secondary outcomes were Time to first rescue antiemetic and antiemetic accumulative dose at 24h. Postoperative Pain was also determined in patients.

Analysis of data was performed by SPSS® Statistics version 18. Descriptive statistics were performed by frequency and percentage (for qualitative variables); mean and standard deviation (for quantitative variables). Analytic statistics were performed by T-tests (for quantitative variables) and Chi-square tests (for qualitative variables). A $P \leq 0.05$ was considered significant and all tests were performed with a 95% confidence interval.

Results

We performed this study during 2018-2019. We found no statistically significant differences in age, gender, BMI, risk factors of PONV, history of smoking, and history of PONV between the two groups (Table 1).

Table 1. Demographic characteristics

		Group A (ODH)	Group B (ODP)	*P*
Age (yr); mean±SD		40.6 ± 2.39	38.3 ± 2.62	0.11
Gender; % (n)	Male Female	22.5% (9) 77.5% (31)	27.5% (11) 72.5% (29)	0. 6
Smoking; % (n)		20% (8)	7.5% (3)	0.10
BMI (Kg/m²); mean±SD		45.9 ± 2.39	44.5 ± 2.62	0.01
History of PONV; % (n)		7.5% (3)	5% (2)	0.66
ASA score; % (n)	1 2	43.5% (27) 72.2% (13)	56.5% (35) 27.8% (5)	0.03
Type of surgery; % (n)	Sleeve Gastric bypass	17.5% (7) 82.5% (33)	10% (4) 90% (36)	0.03
Risk factors of nausea/vomiting; % (n)	Risk score= 1 or 2 (low) Risk score= 3 or 4 (moderate to high)	35% (14) 65% (26)	20% (8) 80% (32)	0.13

ODH: Ondansetron, Dexamethasone, Haloperidol; ODP: Ondansetron, Dexamethasone, Promethazine; BMI: Body Mass Index; PONV: Postoperative Nausea and Vomiting; ASA: American Society of Anesthesiologists. Significance: $P \leq 0.0$.

There was a significant difference in the type of surgery between groups (P=0.03); because "Gastric bypass" is the preferred method of surgery; and because of block randomization for choosing the type of surgery, this difference was expected and inevitable. All patients had a negative history of motion sickness.

In our study, the frequency and severity of PONV were evaluated at recovery, 6, and 24 hours postoperatively; the frequency and severity of PONV were lower in the ODH group (group A) at recovery (P=0.05). The mean NVRS at recovery (P=0.006) and 6 hours postoperatively (P=0.003). The time to first rescue antiemetic prescription was higher in the ODP group (P=0.01) (Table 2). Also, after controlling probable confounding factors by logistic regression, the meantime to receive rescue antiemetic was higher in the ODP group (P=0.01) (Table 3). The accumulative dose of narcotics 6 hours postoperatively was lower in the ODH group (P<0.01) (Table 2). In total, 7.5% of the ODH group and 5% of the ODP group received rescue antiemetic.

To avoid probable confounding factors effects, we used logistic regression to define the effects of the intervention on postoperative nausea and vomiting, the

first time of rescue antiemetic prescription, the cumulative dose of narcotics 24 hours after surgery, and recovery time (Table 3).

Table 2. Outcome variables

		Group A (ODH)	Group B (ODP)	*P*
Incidence of PONV at recovery; % (n)		20% (8)	40% (16)	0.05
NVRS at recovery (0-10); mean ± SD		0.45 ± 0.95	1.52 ± 2.2	0.006
Incidence of PONV at 6h; % (n)		50% (20)	60% (24)	0.36
NVRS at 6h (0-10); mean ± SD		2.08 ± 2.48	4.48 ± 4.37	0.003
Incidence of PONV at 24h; % (n)		50% (20)	65% (26)	0.34
NVRS at 24h (0-10); mean ± SD		2.32 ± 3.03	3 ± 3.06	0.32
NVRS at recovery by Gender (0-10); mean ± SD	Female	0.67	1.26	0.18
	Male	0	3	<0.001
NVRS at recovery by Smoking (0-10); mean ± SD	Non-smoker	0.35	1.45	0.05
	Smoker	1.67	3	0.63
NVRS at recovery by history of PONV (0-10); mean ± SD	Negative	0.56	1.54	0.028
	Positive	0	1.3	0.104
Total rescue antiemetic prescription at recovery; % (n)		7.5% (3)	-	
		-	5% (2)	
Time to first rescue antiemetic (hour); mean ± SD		2.6 ± 1.72	7.2 ± 6.73	0.01
Antiemetic accumulative dose at 24h (mg); mean ± SD		19.2 ± 13.4	22.7 ± 13	0.24
Recovery time (min); mean ± SD		55.12 ± 26.3	56 ± 28	0.88
Pain at recovery (0-10); mean ± SD		1.75 ± 1.8	1.52 ± 1.8	0.59
Pain at 6h (0-10); mean ± SD		4.52 ± 2.8	5.4 ± 3.7	0.24
Pain at 24h (0-10); mean ± SD		4.02 ± 2.9	4.7 ± 3.7	0.27
The accumulative dose of narcotics at 6h (mg); mean ± SD		44.7 ± 15.3	35.6 ± 23.9	<0.01
The accumulative dose of narcotics at 24h (mg); mean ± SD		103.6 ± 57.8	97 ± 70.4	0.1

ODH: Ondansetron, Dexamethasone, Haloperidol; ODP: Ondansetron, Dexamethasone, Promethazine; PONV: Postoperative Nausea and Vomiting; NVRS: Nausea Verbal Rating Score; Significance: $P \leq 0.05$

Table 3. Logistic regression

Intervention effects on:			***P***
	PONV at recovery	1.28	0.002
	First time of rescue	4.5	0.01
	The accumulative dose of antiemetics at 24h	4.87	0.13
	Recovery time	4.5	0.49

PONV: Postoperative Nausea and Vomiting, Significance: $P \leq 0.05$.

Discussion

In general, PONV has different risk factors, some of them are related to surgery such as laparoscopic surgery, or ophthalmic surgery. And some are related to patients such as female gender, History of PONV, Non-smoking, and BMI>35 (23). None of these risk factors were significantly different between the two groups.

Over 66% of patients develop PONV after bariatric surgery (24). In general, combination therapy has superior efficacy, and also because there will not be necessary to administer high doses of drugs compared with single therapy for PONV prophylaxis combination therapy is a better choice in high-risk patients (25,26).

According to the results of this study in patients who received combination therapy of ondansetron, dexamethasone, and haloperidol (group A), incidence and severity of PONV were lower than group B who received a combination of ondansetron, dexamethasone, and promethazine (ODP). This treatment will decrease the incidence and severity of PONV and enhance the overall comfort and satisfaction of patients in the immediate postoperative period. According to previous studies, the incidence of PONV after general anesthesia varies from 20-30% in the general population to 70-80% in the high-risk population (5). In a study of 96 candidates for sleeve surgery, the frequency of PONV in the ODH (ondansetron, dexamethasone, and

haloperidol) group was 23.7% two hours postoperatively. Patients in the ODH group received 0-1 dose of rescue antiemetic in the first 36 hours after surgery (27). In another study of 149 candidates for gynecologic laparoscopic surgeries, the frequency of PONV, two hours postoperatively was 20% in patients who received haloperidol and dexamethasone (28). In a study of 95 patients undergoing craniotomy, the frequency of PONV at 2 hours postoperatively was 36.2% in the group that received promethazine, dexamethasone, and ondansetron (29). In our study, the frequency of PONV was 30% at recovery, 55% at 6 hours, and 57.5% at 24 hours postoperatively. The frequency of PONV at recovery was 20% in the ODH group and 40% in the ODP group (P=0.05). These results are close to previous studies that are mentioned above. The severity of PONV at recovery was lower in the ODH group (P=0.006). Jin Joo, *et al*., demonstrated that the combination of dexamethasone and haloperidol is more effective in patients with a high risk of PONV. Patients who received a combination of haloperidol and dexamethasone had a 12% rate of rescue antiemetic prescription in the first 2 hours postoperatively (28). In the study of Bergese, *et al*., The frequency of PONV at 24 hours postoperatively was 23-46% in patients with a moderate or high risk of PONV. The rate of rescue antiemetic prescription during 2 hours after surgery was 10% in patients who received palonosetron, dexamethasone, and promethazine (30). In another study, the rate of rescue antiemetic prescription in the first two hours after surgery was 19% in the group ondansetron, dexamethasone, promethazine (29). In this study, we showed that ODH combination controlled PONV more efficiently in the high-risk patients (P=0.01). In the ODP group, the frequency of PONV in high-risk patients was 34%; which is close to Bergese study (30). The rate of rescue antiemetic prescription was 6.25% in total, 5% in ODP and 7.5% in ODH group at recovery; the differences with previous studies can be justified with respect to the type of surgeries and sample sizes. In the ODP group, the time to first rescue antiemetic prescription was significantly higher (7.2 h versus 2.6 h; P=0.01) because of promethazine's longer duration of action compared to haloperidol.

One limitation of our study is that there was a significant difference in patient distribution by type of surgery (P=0.03) because gastric bypass is the preferred method of surgery. To avoid such a problem, in further studies like this, we recommend choosing patients undergoing a similar type of surgery.

In conclusion, in morbidly obese patients undergoing laparoscopic bariatric surgery, both antiemetic combinations decreased the incidence of PONV, but the combination of haloperidol, dexamethasone, and ondansetron was more effective than promethazine, dexamethasone, and ondansetron.

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