



Effects of ondansetron, metoclopramide and granisetron on perioperative nausea and vomiting in patients undergone bariatric surgery: a randomized clinical trial

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Abstract

Introduction Post-operative nausea and vomiting (PONV) is a common problem after sleeve gastrectomy. In recent years, following the increase in the number of such operations, special attention has been paid to preventing PONV. Additionally, several prophylaxis methods have been developed, including enhanced recovery after surgery (ERAS) and preventive antiemetics. Nevertheless, PONV has not been completely eliminated, and the clinicians are trying to reduce the incidence of PONV yet.

Methods After successful ERAS implementation, patients were divided into five groups, including control and experimental groups. Metoclopramide (MA), ondansetron (OA), granisetron (GA), and a combination of metoclopramide and ondansetron (MO) were used as antiemetics for each group. The frequency of PONV during the first and second days of admission was recorded using a subjective PONV scale.

Results A total of 130 patients were enrolled in this study. The MO group showed a lower incidence of PONV (46.1%) compared to the control group (53.8%) and other groups. Furthermore, the MO group did not require rescue antiemetics, however, one-third of control cases used rescue antiemetics (0 vs. 34%).

Conclusion Using the combination of metoclopramide and ondansetron is recommended as the antiemetic regimen for the reduction of PONV after sleeve gastrectomy. This combination is more helpful when implemented alongside ERAS protocols.

Keywords Bariatric surgery · Postoperative nausea or vomiting · Sleeve gastrectomy · Ondansetron · Metoclopramide · Granisetron

Postoperative nausea and vomiting (PONV) is one of the leading causes of patient morbidity after laparoscopic bariatric surgeries. A wide variety of complications related to PONV have been described, such as prolonged length of stay (LOS) in hospital, unnecessary readmissions, delay in oral intake, and bad experiences for patients [1]. Although several antiemetic regimens have been tried up to now in different studies, the incidence of PONV is not significantly

decreased, and it seems impossible to totally eliminate it. On the other hand, the implementation of enhanced recovery after surgery (ERAS) has dramatically reduced the incidence of PONV and LOS in different types of surgeries [2]. Therefore, a combination of ERAS and multiple antiemetic regimens is currently used to reduce the incidence of PONV. Nevertheless, the optimal regimen has not been identified yet, and numerous trials are conducting to find out the best antiemetic regimen [1, 2]. Also, there are some evidence suggesting strong antiemetic effects of medications like ondansetron and metoclopramide in laparoscopic surgeries other than bariatric operations [3, 4]. Regarding that these drugs are more available and cheaper we decided to use these medications in our trial.

This randomized clinical trial compares four different combined and single-drug regimens alongside the

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implementation of ERAS to show which regimen is more effective.

Methods

Study design

A single-center, five-group randomized clinical trial (NCT05087615), was performed to compare the effects of antiemetic regimens on PONV among patients who underwent laparoscopic bariatric surgery. This trial compared the incidence of PONV within the first 48 h after the surgery. The incidence of PONV on first and second postoperative days was measured using a subjective PONV scale. In addition, this study was approved by Iran National Committee for Ethics in Biomedical Research (IR.SBMU.MSP.REC.1399.784).

Setting and population

The study was conducted at Loghman Hakim Hospital, an educational hospital affiliated with Shahid Beheshti University of Medical Sciences, Tehran, Iran. As a minimally invasive academic center, approximately 1000 bariatric surgeries were performed before the COVID-19 outbreak, annually. Operative services are available 24 h a day, observed by attending general surgeons. Board-certified advanced

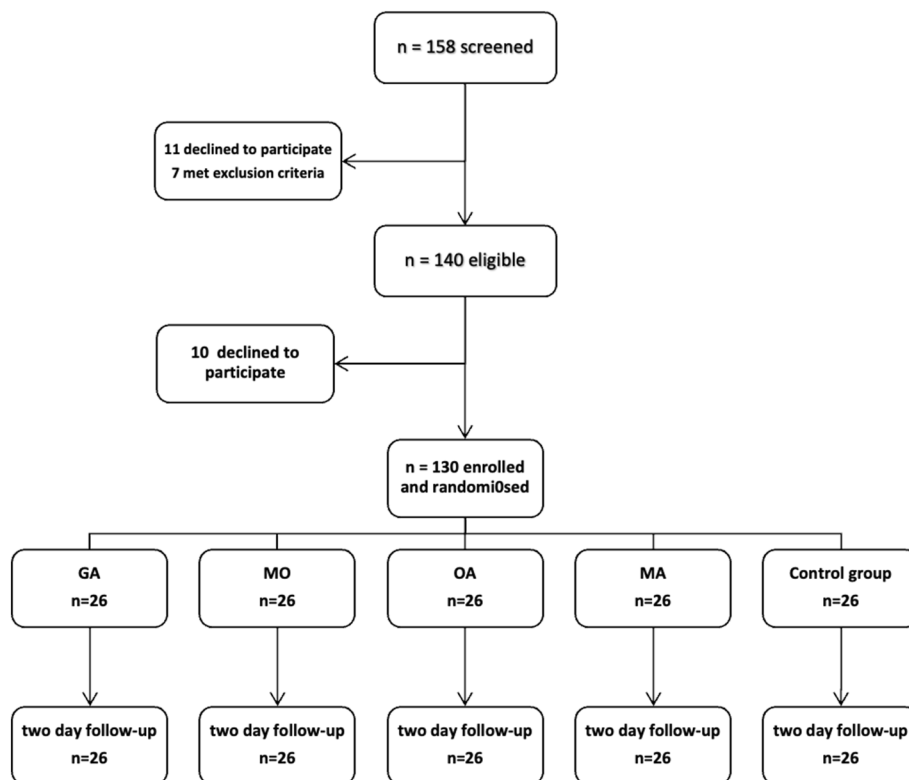
laparoscopic surgeons perform all bariatric surgeries. We use our standardized institutional surgical protocols and preoperative and postoperative care in the management of bariatric patients based on ERAS guidelines for bariatric surgeries [5]. Although our surgical techniques are based on updated international guidelines, we usually use a 44-Fr bougie to calibrate the lumen of the remained stomach [6]. Also, we always perform staple reinforcement by placing the omentum with absorbable continuous sutures alongside the staple line [7].

All the appropriate patients for laparoscopic bariatric surgery were enrolled in the present study based on their Body Mass Index (BMI = weight in kilograms/height in meters squared). Eligible participants were adult patients (age > 18 years) with a BMI of higher than 40 kg/m², or 35 kg/m² with an underlying metabolic disease [8]. Moreover, a structured informed consent was obtained from all the participants.

Study protocols

The CONSORT guidelines were followed in this study [9]. The Enrolled patients were randomized using permuted block randomization technique with software-generated blocks. According to the blocks, the patients were sequentially called for elective surgery (Fig. 1). After performing the operation, we randomly placed the pre-written order sheets in the patients' files. This action was performed by

Fig. 1 The Enrollment Flow Chart of the Patients (CONSORT). GA Granisetron only group, MA Metoclopramide only group, OA Ondansetron only group, MO group received both ondansetron and metoclopramide



a research coordinator who was not involved in the study (usually PGY-1 residents). All the surgery team was unaware of the type of antiemetic used for the PONV. The conventional laparoscopic sleeve gastrectomy (LSG) was performed for all the patients using the above-mentioned guidelines.

Every patient received intravenous (IV) proton-pump inhibitor (pantoprazole 20 mg) and subdermal Enoxaparin (weight-based dosage adjusted [10]) for each day postoperatively.

After the surgery, PONV was measured within the first 2 days in the mornings and evenings using a simplified PONV impact scale questionnaire [11]. The episodes of both nausea and vomiting were recorded. Scores equal to or more than one were considered positive for both nausea and vomiting. Also, If the sum of the two scores was greater than 4, it would be regarded as clinically significant, and the rescue antiemetic was initiated for the patient (Fig. 2).

All the patients underwent ERAS protocols (Fig. 3). Furthermore, In cases where the patient had developed PONV (including Group 1), IV Metoclopramide 0.2 mg (immediately, without delay [STAT], and twice a day [BiD]) was used as a rescue antiemetic (rescue regimen was only used in patients who failed to prevent PONV, and was not a usual part of ERAS).

We only studied the rate of PONV during the admission days, and did not evaluate the incidence of nausea or vomiting after discharge. This is due to the high rate of PONV after the surgery within the first days.

For the reduction of the incidence of bias and confounding factors, all used anesthetics and antiemetics were provided from the same brand for each drug (see Appendix).

Inclusion and exclusion criteria

Patients with severe or moderate gastritis or duodenitis on esophagogastroduodenoscopy were excluded from the study, nevertheless patients with mild gastritis or positive rapid urease test on endoscopy were treated for 2 weeks with three drugs, namely pentazole, amoxicillin, and metronidazole [12]. Following triple therapy, if the respiratory urease test was negative, they were included in the study; however, in refractory cases of *Helicobacter Pylori*, they were excluded and treated with sequential or quadruple therapy [13]. According to the American Society of Anesthesiologists (ASA) classification [14], patients with severe respiratory or cardiovascular problems (ASA III or higher), or a history of gastric or small bowel surgery were also excluded. Patients who underwent simultaneous cholecystectomy with bariatric surgery were also excluded. On the other hand, patients with early mechanical complications, such as leakages, strictures, and peritonitis, were not included. In addition, other exclusion criteria were thromboembolic events (e.g., deep vein thrombosis, myocardial infarction, and pulmonary embolism).

Sample size calculation and group stratification

Analysis of covariance with web-based tools based on G*Power (version 3.1) was used to calculate the sample

Fig. 2 A copy of Simplified PONV impact scale used to measure the incidence of PONV. It should be noted that we used a persian copy of this questionnaire

Q1. Have you vomited or had dry-retching*?

- 0. No
- 1. Once
- 2. Twice
- 3. Three or more times

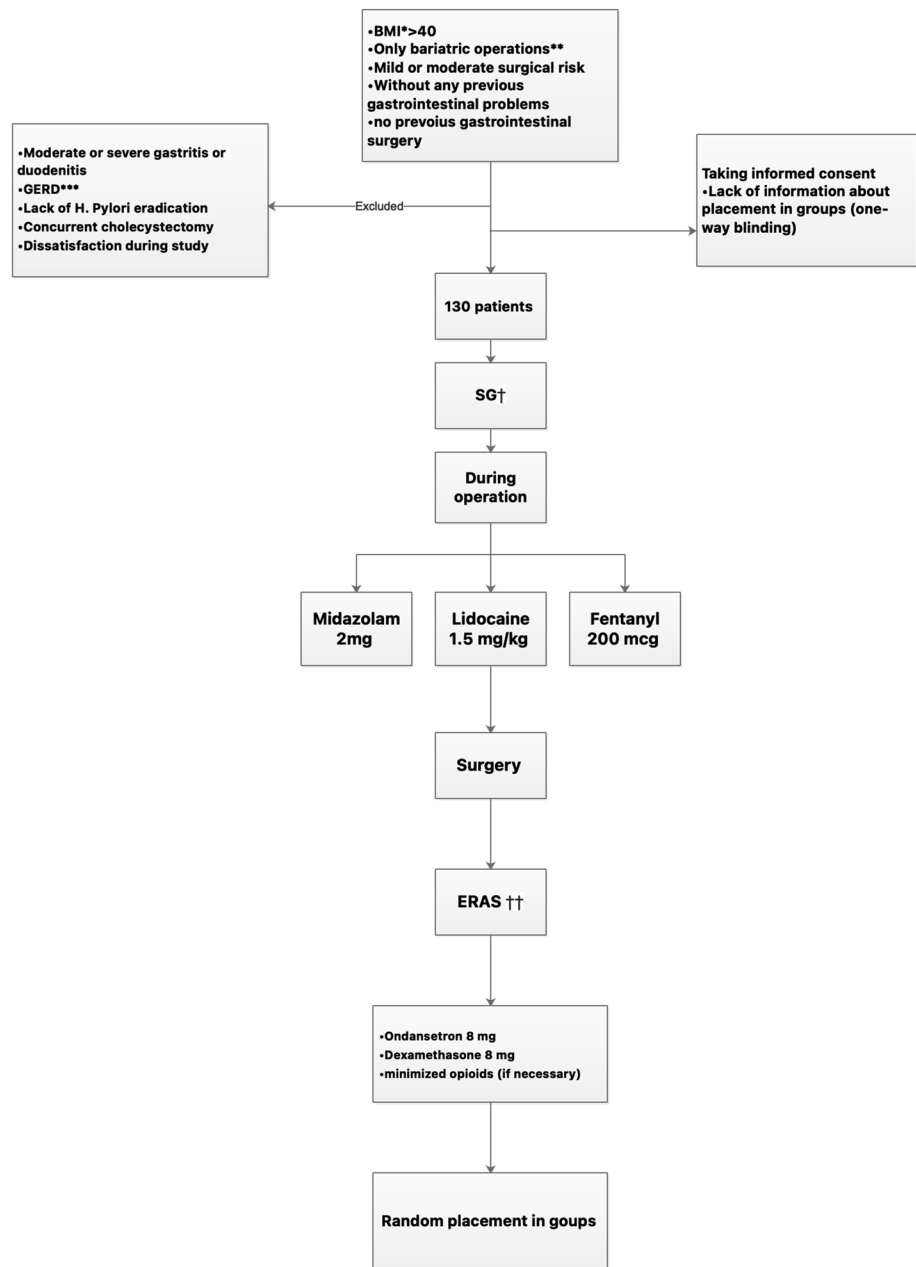
Q2. Have you experienced a feeling of nausea (“an unsettled feeling in the stomach and slight urge to vomit”)? If yes, has your feeling of nausea interfered with activities of daily living, such as being able to get out of bed, being able to move about freely in bed, being able to walk normally, or eating and drinking?

- 0. Not at all
- 1. Sometimes
- 2. Often or most of the time
- 3. All of the time.

To calculate the PONV Impact Scale score, add the numerical responses to questions 1 and 2. A PONV Impact Scale score of ≥ 5 defines clinically important PONV.

*count distinct episodes: several vomits or retching events occurring over a short time frame, say 5 min, should be counted as one vomiting/dry-retching episode; multiple episodes require distinct time periods without vomiting/dry-retching.

Fig. 3 Study stages showed as a flowchart. *Body Mass Index. **Patients who underwent concurrent intrabdominal operations were not included. ***Gastroesophageal Reflux Disease. †Sleeve Gastrectomy. ††Enhanced Recovery After Surgery (has been described in details below the methods section)



size in this clinical trial. With an effect size of 0.47 (large), the priori power analysis estimated a minimum sample size of 120. Twenty-six patients were estimated for each group [15, 16]. Based on this logic, patients were divided into the following five groups:

Group 1: Patients who did not receive any antiemetic during hospitalization (NA).

Group 2: Patients who received metoclopramide (0.2 mg/kg up to 10 mg/IV/three times a day [TDS]) alone (MA).

Group 3: Patients who received ondansetron (0.1 mg/kg of body weight up to 8 mg/IV) only. (OA).

Group 4: Patients who received a combination of metoclopramide and ondansetron (MO).

Group 5: Patients who received granisetron alone (2 mg/IV/BiD) (GA).

Rescue antiemetic was metoclopramide (0.2 mg/kg up to 10 mg/IV/TDS). It should be noted that in MA and MO groups, an extra dose of metoclopramide did not exceed the normal upper limit (60 mg daily). All antiemetics were administered intravenously via an antecubital 18Fr venous line. Additional information about drug doses and manufacturers is available in the [Appendix](#) file.

ERAS protocols

This study followed ERAS guidelines in preoperative, intraoperative, and postoperative care in bariatric surgery. All the patients received preoperative consultation. Prehabilitation measures, including light exercises, were performed two consecutive weeks before the surgery. All the patients were advised on the cessation of smoking and alcohol consumption. In non-diabetic cases, fasting time was within 2 to 6 h before the induction of general anesthesia. The IV fluids were minimized in the preoperative period. Nasogastric tubes were not used in any of the patients. Also, the use of morphine sulfate was limited to perioperative administration if indicated (5 mg/IV as rescue analgesic when other medications weren't effective). We used Non-steroidal anti-inflammatory drugs (NSAIDs) as the primary analgesics. Suppository acetaminophen was added in cases in which extra painkillers were required. In cases where the pain was not controlled with those medications, we inevitably used minimal doses of opioids.

Postoperative adequate oxygenation was provided by placing the patients in a semi-sitting position and face mask oxygen supplementation [5]. Since, almost all patients were at high risk for PONV [17], a preventive antiemetic strategy during the perioperative era was implemented using IV dexamethasone 8 mg and ondansetron 8 mg. In Addition, we did not use a transdermal patch of scopolamine prior to surgeries [18].

Statistical analysis

Information about demographic, clinical, and paraclinical variables and intraoperative data were entered into an electronic dataset. For the measurement of the demographic variables, identification information, digital scales, and meters, as well as obtaining a direct history of the patient, were used. The duration of anesthesia was calculated in minutes from the moment of induction of the anesthetic agent to the moment the patient regained consciousness and was transferred to Post-Anesthesia Care Unit (PACU).

Descriptive and analytical functions were used to analyze the information. Frequency, mean, median, and standard deviation were used for the variables such as age, gender, weight, height, BMI, and the incidence of nausea and vomiting, etc. (Tables 1, 2, 3, 4).

As our aim was to compare two categorical variables (i.e. antiemetic regimens and PONV), we used the Chi-Square test to identify any significant statistical correlation between the two nominal variables. Due to the close frequency of PONV in different groups, the Chi-Square test was insufficient in some situations to show the relationship between the two variables. Therefore, we used Correspondence Analysis to investigate the correlations.

Partial correlation with the Pearson formula was also used to investigate the confounding effect of other variables and their impact on nausea and vomiting.

Results

Demographics

A total of 130 morbidly obese patients were enrolled in this study within March 2021 to August 2021. They were divided into five groups of 26 participants. Table 1 shows all demographic information.

Clinical and paraclinical findings

Information like the presence of underlying diseases, history of previous episodes of anesthesia, esophagogastroduodenoscopy results, Helicobacter Pylori infection, and fatty liver grade has been described in Table 1.

Perioperative variables

Table 2 indicates the average time of general anesthesia, and the mean dosage of anesthetic medications. Also, the findings related to the incidence of nausea and vomiting in the postoperative period on the first and second days are presented in Table 3. It can be quickly realized that the incidence of nausea and vomiting was generally higher on the first day after surgery than on the second day. On the other hand, the highest and the lowest incidence of nausea on the first day (before starting a liquid diet) was in the metoclopramide group ($n=12$) and metoclopramide and ondansetron group ($n=7$), respectively. The incidence of vomiting on the first day had a similar distribution. Therefore, the highest and lowest levels were in the metoclopramide group alone ($n=8$) and the ondansetron group alone ($n=5$), respectively. On the second day, the lowest incidence of nausea and vomiting was in the metoclopramide and ondansetron groups (Table 3).

Analysis of results

Figure 4 shows the final incidence of nausea and vomiting during the whole hospital stay. The lowest incidence of nausea or vomiting was in the group that used metoclopramide and ondansetron together (46.1%). The highest incidence of PONV was related to the ondansetron or granisetron group alone (61.5%). The Chi-Square test for each group did not show any significant statistical correlations ($p=0.783$). However, Correspondence Analysis detected a negative number in MA and MO groups indicating a

Table 1 Demographics, preoperative clinical and paraclinical information

Variable	Numbers (%)	Statistical significance (<i>p</i> value) between groups
Total cases	130 (100%)	
Age	36.3 (19–59)	0.930
Gender		0.837
Men	31 (23.8%)	
Women	99 (76.2%)	
Weight (average, kilograms)	121.36	0.863
Height (average, centimeters)	164.6	0.796
Body mass index (average, $\frac{kg}{m^2}$)	44.6, Std=5.22	0.956
Underlying diseases		0.722
No UD	83 (63.8%)	
Hypothyroidism	19 (14.6%)	
Type-2 Diabetes Mellitus	14 (10.8%)	
Hypertension	14 (10.8%)	
Two concurrent UD	13 (10%)	
Equal or more than three UD	3 (2.3%)	
History of previous surgery (general anesthesia) ^a		0.069
No surgeries	55 (42.3%)	
One	48 (36.9%)	
Two	19 (14.6%)	
Three or more	8 (6.1%)	
Upper endoscopy findings		0.849
Normal	80 (61.5%)	
Antral gastritis	21 (16.2%)	
Erosive gastritis	13 (10%)	
Duodenal erythema	5 (3.8%)	
Duodenal diverticula	2 (1.5%)	
Biliary gastritis	4 (3.1%)	
Esophagitis	4 (3.1%)	
Stomach polyp(s)	1 (0.8%)	
Respiratory urease test		0.601
Negative	100 (76.9%)	
Positive	28 (21.5%)	
Fatty liver (based on abdominal ultrasonography)		0.797
No fatty liver	20 (15.4)	
Grade 1	41 (31.5)	
Grade 2	49 (37.7)	
Grade 3	20 (15.4)	

UD underlying disease(s)

^aSurgeries other than upper gastrointestinal tract included abdominoplasty, rhinoplasty, cesarean section, appendectomy, labioplasty, etc.

negative relationship with the incidence of PONV (Score in dimension = -0.546).

The Apfel Simplified Score system was utilized to estimate the overall risk of PONV in all patients [17], and the average risk was 58.0%. All the patients had more than one risk factor. However, there was no significant statistical relationship between the final outcome (PONV) and risk scores ($p=0.405$). Although using a three-dimensional cross tab

showed a more substantial reduction in PONV in patients with three or four risk factors, the MA regimen in patients with two risk factors seemed to be less effective than those with higher risk scores.

Furthermore, Table 4 shows the relationship between each of the variables that might confuse the results of PONV. In almost all fields, there was no significant relationship between nausea and vomiting with age, gender, BMI,

Table 2 Intra and postoperative information

Variable	Numbers (percent)
Surgery type	
Sleeve gastrectomy	130 (100)
Average time of anesthesia	141.8 (75 to 305)
Average dose of anesthetics	
Fentanyl	195.16
Midazolam	2.28
Lidocaine	91.9
Thiopental	498.3
Atracurium	63.05

Table 3 Incidence of PONV in the perioperative period

Regimen	Before oral intake (day 1)		After oral intake (day 2)		Rescue usage
	Nausea	Vomiting	Nausea	Vomiting	
Control	11	6	7	3	9
MA ^a	12	8	7	2	2
OA ^b	10	5	9	2	6
MO ^c	7	6	2	0	0
GA ^d	9	7	6	3	8

^aMetoclopramide alone

^bOndansetron alone

^cMetoclopramide and ondansetron together

^dGranisetron alone

duration of operation, types of drugs used during anesthesia, underlying diseases and previous surgery, and endoscopic findings. A lower p-value (0.01) in the variables, such as

Table 4 Correlation between other variables in the incidence of PONV

Variable	Before oral intake (day 1)		After oral intake (day 2)		Between groups (<i>p</i> value)
	Nausea (<i>p</i> value)	Vomiting (<i>p</i> value)	Nausea (<i>p</i> value)	Vomiting (<i>p</i> value)	
Age	0.740	0.075	0.785	0.192	0.930
Gender ^a	0.474	0.027	0.501	0.285	0.837
BMI	0.974	0.358	0.162	0.477	0.956
Operation time	0.01 ^b	0.905	0.933	0.137	0.070
Fentanyl	0.065	0.515	0.562	0.324	0.998
Midazolam	0.225	0.427	0.265	0.690	0.636
Lidocaine	0.186	0.099	0.046	0.000	0.293
Thiopental	0.080	0.948	0.187	0.991	0.584
Underlying disease ^a	0.210	0.591	0.298	0.246	0.722
Number of previous surgeries ^a	0.591	0.260	0.602	0.375	0.069
Endoscopy findings ^a	0.029	0.031	0.723	0.540	0.849

^aThis variable is qualitative and Correspondence Analysis was used to examine its correlation

^bNegative correlation with Pearson’s coefficient equal to − 0.247

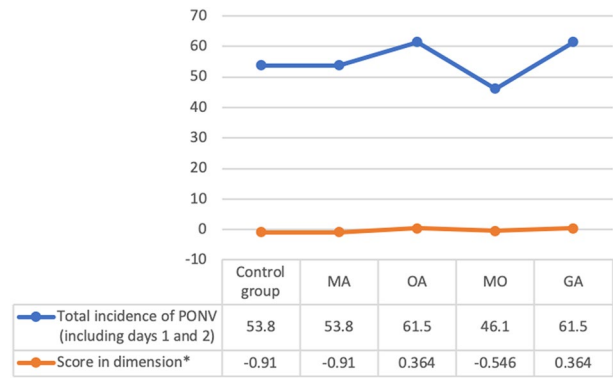


Fig. 4 The linear graph showing the incidence of PONV in each group. *Score in dimension of Corresponding Analysis. Positive numbers correlated with more PONV while negative scores reveal less PONV. Also, the absolute score indicates the power of correlations

duration of operation, usage of fentanyl, and thiopental drugs on the first day, means that these variables might have an effect on the incidence of nausea; however, this change was not significant (see p-values in Table 4).

Finally, it should be noted that different groups of antiemetics did not statistically affect LOS ($p = 0.713$; analysis of variance). Moreover, the average LOS for patients with positive PONV was 2.06; nevertheless, this value was 2.07 in the group that was negative for PONV. The aforementioned values indicated that there was no statistical significance in LOS in patients with less PONV ($p = 0.731$; independent t-test).

Discussion

Currently, LSG is a well-known bariatric procedure. This type of minimally invasive surgery is rapidly replacing complex anastomotic bariatric operations [1, 19]. Similar to any other major abdominal surgery, LSG has its own complications. In addition to technical difficulties, which are well described in the literature, perioperative complications are still addressed. The PONV is a common problem after laparoscopic bariatric surgeries. Researchers have made relentless efforts to reduce the rate of PONV, but due to technical aspects of LSG, the complete elimination of PONV seems far-fetched. Several studies with contradictory results have been conducted to minimize PONV in the postoperative era in bariatric patients. Nevertheless, the common denominator that exists between all studies is one statement: “PONV is unavoidable” [20].

As PONV is not an objective variable, different subjective scales have been developed to measure the entity. This limitation led to inconsistent results in epidemiologic estimations. By definition, PONV is “emesis and queasiness occurring after anesthesia”. This nonnumeric definition might confuse both patients and surgeons. With all this in mind, authors reported numbers between 30 and 65% for the incidence of PONV after bariatric operations [20]. These numbers indicate that PONV is a highly common problem after bariatric surgeries.

Fortunately, with the introduction of ERAS in recent years, PONV has been reduced significantly. But it should be noted that PONV is even common after the implementation of ERAS protocols. To solve this problem, several antiemetic medicines are used worldwide to decrease PONV. Many pharmaceutical families are known as antiemetics, and researchers utilized almost all of them in this context. Dopamine receptor antagonists, 5-HT₃ receptor antagonists, corticosteroids, and anticholinergics are widely used [21]. Also, single or multiple drug regimens have been used.

It seems that there are few trials in this field that are methodologically acceptable. Therefore, the results of the present study are briefly compared to the results of the existing trials in this regard. Our results indicated lower episodes of PONV in the MO group. Furthermore, single-drug regimens showed equal or higher PONV in comparison to the controlled group. Granisetron is a serotonin-receptor antagonist (5HT_{2A}) with an excellent reputation for the treatment of nausea/vomiting after chemotherapy or radiotherapy.

Accordingly, insufficient information is available about the effect of this drug on PONV after bariatric surgery. The only study in this regard showed a 30% incidence of PONV after bariatric surgery. Also, combining granisetron with droperidol reduced this value even more [22]. However, in

the present study, GA could not achieve this reduction, and the incidence of PONV was 61.5%.

Ondansetron is another 5HTA that has been studied many times in practice, unlike granisetron. The overall incidence of OA has been reported to be about 50%, which is slightly lower than the results of the current study [23–26]. On the other hand, there are numerous data from combining ondansetron with other medications, such as Aprepitant [27] and Dexamethasone [28] that could lower PONV more than OA.

The ondansetron combination of the present study was the MO group. Metoclopramide belongs to the group of medications known as dopamine-receptor antagonists and is widely used as an antiemetic. However, metoclopramide alone is used as an antiemetic for PONV prophylaxis [29], but it seems that several clinicians used it as a rescue antiemetic [20]. Interestingly, although these two drugs alone are well known, the combination of the two has been less commonly used in PONV after bariatric surgery (see Appendix). More interestingly, this combination has been less used in other laparoscopic surgeries, such as cholecystectomy [30]. On the other hand, in our study, the MO group showed a significantly lower incidence of PONV than the other groups (46.1%). Given that these two drugs have two different mechanisms of action, it seems that this combination can be a helpful regimen to control PONV.

In addition to the narrow scope of geographic participants and lack of previous randomized trials on this regimen, there are some concerns about the present study. Considering the low sample size, it would be better to conduct this study with paired match groups to reduce the effects of confounding factors like age, gender and the usage of volatile and opioid anaesthetic agents. However, we demonstrated that the distribution of cases in each group follows a similar pattern. We used multidrug regimens (not drug classes), and some groups included drugs with the same class. Although this randomized clinical trial did not compare the effectiveness of drug classes in reducing PONV, it might guide the researchers to use the appropriate anti-PONV regimen. This multidrug regimen (i.e., a combination of metoclopramide and ondansetron) might be provided as a single compound drug and administered once for the patients. However, further studies with larger sample sizes are recommended to identify its effectiveness.

Conclusion

Although there was no statistically significant reduction in the rate of PONV in different groups, it seems that using a combination of metoclopramide and ondansetron could be a proper antiemetic regimen. This combination is more helpful when implemented alongside ERAS protocols.

Consequently, we strongly recommend a larger trial using this combination to reveal its impact on PONV of sleeve gastrectomy.

Appendix

Search strategies conducted to find combination of metoclopramide and ondansetron

Search Engine	Query	Results	Date
PubMed	"Ondansetron"[MeSH Terms] AND "Metoclopramide"[MeSH Terms] AND "Bariatric Surgery"[MeSH Terms]	0 results	August 2021
EMBASE	('ondansetron'/exp OR ondansetron) AND ('metoclopramide'/exp OR metoclopramide) AND ('bariatric surgery'/exp OR 'bariatric surgery')	46 non-relevant results	August 2021
Web of sciences	TOPIC: (ondansetron) Indexes = SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan = All years AND TOPIC: (metoclopramide) Indexes = SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan = All years AND TOPIC: (bariatric surgery) Indexes = SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan = All years	0 results	August 2021

Brand used for each medications and dosage

Drug	Dose	Company
Ondansetron	0.1 mg/kg of BW up to 8 mg	Alborz Darou Pharmaceutical Co
Metoclopramide	0.2 mg/kg up to 10 mg/tds	Alborz Darou Pharmaceutical Co
Granisetron	2 mg/bid	Alborz Darou Pharmaceutical Co
Midazolam	2 mg	Exir Pharmaceutical Co
Lidocaine	1.5 mg/kg	Sinadarou Labs Company

Author contributions S-HM and BO developed the concept and performed the surgery. AZ and RS supervised the correct implementation of protocols. ME reviewed and analyzed the cases and wrote the manuscript. MK and NG reviewed and co-wrote the paper.

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Declarations

Disclosures Drs. Manoochehr Ebrahimian, Seyed-Hadi Mirhashemi, Bahador Oshidari, Amir Zamani, Roozbeh Shadidi-Asil, Mehrnoosh Kialashaki, and Negin Ghayebi have no conflicts of interest or financial ties to disclose.

Ethical approval This topic is approved by Iran National Committee for Ethics in Biomedical Research (IR.SBMU.MSP.REC.1399.784).

Consent for publication An informed consent was taken from the patients.

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