Impact of combining dexmedetomidine to ondansetron and dexamethasone for prophylaxis against postoperative nausea and vomiting after laparoscopic bariatric surgery

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Background Postoperative nausea and vomiting (PONV) are common and highly distressing following laparoscopic bariatric surgery. However, there is inadequate evidence regarding the impact of combining dexmedetomidine to dexamethasone and ondansetron. We aimed to study the impact of combining dexmedetomidine to dexamethasone and ondansetron in the prevention of PONV.

Patients and methods Seventy-two adult patients scheduled for laparoscopic bariatric surgery were randomized in this double-blind study to receive either single dose of dexmedetomidine 1 μg/kg; ondansetron 4 mg; dexamethasone 8 mg (group D, *n*=36) or ondansetron 4 mg and dexamethasone 8 mg (group B, *n*=36), after induction of anaesthesia. Anaesthesia administration was performed similarly for both groups using a standard protocol. During the first 24 h postoperatively, the primary outcomes were the incidence of PONV. The severity of PONV and use of rescue antiemetic were the secondary outcomes. χ^2-Test and Student's *t*-test were utilized to evaluate significant differences in categorical and continuous variables.

Results The incidence of PONV was significantly reduced in group D (13.9 vs. 52.8%, $P<0.001$). The severity of PONV was significantly lower in group D (34.22±10.48 vs. 62.50 ±13.34, $P=0.03$). Ondansetron consumption was reduced significantly during 24 h in group D (2.33±2.93 vs. 3.58±2.68, $P=0.03$).

Conclusion Addition of dexmedetomidine to ondansetron and dexamethasone was efficacious in decreasing incidence, severity of PONV, and the total analgesic consumption during the first 24 h after laparoscopic bariatric surgery.

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Introduction

Bariatric surgery is an effective technique for weight reduction in morbidly obese individuals; however, it is not without potential complications [1]. PONV is the second common complaint in the postoperative period after pain [2]. The incidence of PONV according to the procedure of laparoscopic bariatric surgery and the size of gastric lumen that stay after surgery are different which may reach 50–65% in 24 post-operative hours, and 80% in high-risk patients [3–5].

No single antiemetic pharmaceutical has been provided to be a universal solution to PONV. In general, multimodal combination treatment has superior viability for PONV prophylaxis compared with monotherapy [6,7].

This study aimed to know the impact of combining dexmedetomidine to dexamethasone and ondansetron in the prevention of PONV. The primary outcome was the incidence of PONV and the secondary outcome was the severity of PONV and the use of rescue antiemetic.

Patients and methods

This double-blind, randomized, single-dose study was approved by our local ethics and research committee, over a period of 20 months (between March 2016 and October 2017) at Al-Hussein Hospital. Seventy-two adult patients scheduled for laparoscopic bariatric surgery consented to participate in the study and written informed consents were obtained. The inclusion criteria were morbidly obese patients, aged 18–66 years of age and patients with American Society of Anesthesiologists (ASA) physical status I–II experiencing laparoscopic bariatric surgery (either gastric banding or gastric bypass). The exclusion criteria were hypersensitivity to study medications, a history of alcohol or drug abuse, conditions associated with delayed gastric emptying (such as chronic cholecystitis, neuromuscular disorders, diabetes mellitus), got an opioid analgesic prescription within a 24 h period before the operation, and getting antiemetic during the last 48 h before surgery.

Patients were randomly distributed into two groups: group D (*n*=36) to receive intravenous single dose of

1 μg/kg of dexmedetomidine plus 8 mg dexamethasone plus 4 mg ondansetron and group B (n=36) to receive intravenous single dose of 8 mg dexamethasone plus 4 mg ondansetron, after induction of anaesthesia and just before skin incision for port introduction. Randomization depended on computer-generated codes maintained in successive random numbered envelopes.

Preanaesthetic visit included general examination and airway assessment. All patients were familiarized during the preoperative visit with a visual analogue scale (VAS) of 0–100 mm for PONV [6]. On this scale, a score of 0 meant no nausea, while a score of 100 meant the worst imaginable nausea. Event of vomiting or retching was scored as 100. VAS was also applied to score pain: a score of 0 meant no pain, while a score of 100 meant the worst imaginable pain.

Anaesthesia administration was performed similarly for both groups using a standard protocol. Patients were presedated with intravenous midazolam (1–3 mg) in the preoperative holding area. Patients were then transferred to the operating room. Standard monitoring included a five-lead ECG, heart rate (HR), arterial oxygen saturation, measured by pulse oximeter, noninvasive blood pressure, and end-tidal CO_2. Baseline vital signs were then obtained.

After preoxygenation with 100% O_2 for 3 min, anaesthesia was induced with intravenous fentanyl 2 μg/kg and propofol 2–2.5 mg/kg. Endotracheal intubation was facilitated using rocuronium bromide 6 mg/kg.

After the endotracheal tube is fixed, volume-controlled ventilation was started with 0.5 fraction of inspired oxygen, using a mixture of air and oxygen, with a tidal volume of 6–8 ml/kg, respiratory rate of 10–12 breaths/min, and inspiratory-to-expiratory ratio of 1 : 2. Ventilatory adjustments were done to keep end-tidal CO_2 tension around 35 mmHg.

Anaesthesia was kept up with 1.0–2.5% end-tidal concentration sevoflurane in 50% oxygen and 50% air. Boluses of rocuronium were given to look after 1/4 to 2/4 twitches of train-of-four. After induction of anesthesia, Bougie was inserted oesophageally to deflate the stomach and was suctioned and removed just before extubation.

Group D patients received a single dose of 1 μg/kg of dexmedetomidine (Precedex; Ho-Spira Inc., Lake Forest, Illinois, USA), plus 8 mg dexamethasone (dexamethasone; Amriya Pharmaceutical Industries, Egypt), plus 4 mg ondansetron (Zofran; GlaxoSmithKline, Alexandria, USA). All drugs were delivered in identical syringes with a total volume of 4 ml (dilution was with 0.9% saline). Group B received intravenous single dose of 8 mg dexamethasone (dexamethasone; Amriya Pharmaceutical Industries), plus 4 mg ondansetron (Zofran; GlaxoSmithKline, USA). All drugs were delivered in identical syringes with a total volume of 4 ml (dilution was with 0.9% saline) plus syringe filled with 4 ml saline to ensure blindness of the groups. Data were collected by anesthesiologists who were blinded to the study drug.

Drugs were prepared in identical 5 ml syringes labelled as the 'study drug' outside the operation theatre by an independent anaesthesiologist not involved further in the study. The anaesthesiologist administrating the study drug and monitoring the patients were unaware of the group allocation.

During anesthesia, all patients got intravenous lactated Ringer's solution at a rate of 10 ml/kg. They were kept on 2 ml/kg/h during recovery until the point that they could tolerate oral fluids.

All patients were placed in a standard reverse Trendelenburg position with head up 30° and the right side of the OR table was raised 15°. Intra-abdominal pressure was noted to be kept up at 10–12 mmHg, with established pneumoperitoneum with CO_2.

Under video guidance with four punctures of the abdomen, laparoscopic gastric bypass or gastric sleeve was performed. Paracetamol infusion (1 g) over 15 min was given to all patients, after gas deflation.

Furthermore, 10 ml of bupivacaine (0.5%) was injected locally at the four punctures of the abdomen for postoperative pain. Atropine and neostigmine (1/2.5 mg) were given slowly intravenously, upon completion of surgery to reverse residual neuromuscular block, which was trailed by tracheal extubation.

Intravenous ephedrine (5 mg), boluses was given when hypotension (defined as a decrease in mean arterial pressure (MAP) value 25% of the baseline value on two consecutive readings within 2 min), not responding to a 0.5% (volume%) decrease in the inspired sevoflurane concentration and a 200-ml fluid bolus. Intravenous propranolol (5 mg) boluses were given when hypertension (defined as an increase in MAP value

25% of the baseline value on two consecutive readings within 2 min) and/or tachycardia (defined as an increase in HR value 25% of the baseline value 2 min) in spite of 0.5% increase in the inspired sevoflurane concentration (volume %). Intravenous atropine (0.2 mg) boluses were given when bradycardia (HR<45) persisted for 2 min and the patients were moved to intensive care unit and oxygen was managed at 3 l/min.

Anaesthesia time (from the start of induction to cessation of sevoflurane) and the time of surgery (from the surgical incision to the placement of surgical dressings) were recorded.

The total number of patients who had nausea and/or vomiting was calculated, during the initial 24 h postoperatively. Ondansetron 4 mg was given slowly intravenously when the patients experienced nausea more than 60 on a 100 mm VAS, and/or retching or vomiting, or requested an antiemetic. At 24 h postoperatively, the patients were requested to rate their nausea throughout the study period on a 100 mm VAS. Nausea is defined as the subjectively unpalatable sensation associated with awareness of the desire to vomit. Retching is defined as the worked, spastic, rhythmic contraction of the respiratory muscles without the expulsion of the gastric contents. Vomiting is defined as the forceful expulsion of gastric contents from the mouth.

Additionally, pain severity was assessed utilizing a 100 mm VAS. Pain score was estimated at the following intervals: on arrival in the ICU, and hourly for the following 10 h (T1–T10). If the pain score was more than 40 mm on a 100 mm VAS, intravenous tramadol 50–100 mg was given, during the 24 h after surgery. For both study groups, the total amounts of tramadol and ondansetron, during the 24 h after surgery were calculated. After arrival in the ICU, sedation was assessed hourly using Ramsay sedation score [8].

MAP and HR were recorded at the following time points: baseline (before induction), at induction, every 5 min at the first 30 min, then every 10 min till the end of the operation. None of the patients were excluded from the study.

Study variables and data were coded utilizing the statistical package for the social sciences, version 22.0 (SPSS Inc., Chicago, Illinois, USA). Descriptive data analysis was performed, and the results were compared between the two study groups and presented in the form of mean and SD or number and percent. The continuous data such as patient's age and weight are expressed as mean±SD, whereas the categorical data, such as sex, ASA physical status, type of surgery, and the incidence of PONV, which were expressed as frequencies (percentages). The data were analyzed using one-way analysis of variance and Pearson's χ^2-test for continuous and categorical variables, respectively. A P value of less than 0.05 was considered as statistically significant.

Results

A total of 115 patients were screened for eligibility to participate in the study and 72 patients were selected in this study (n=36/group). Concealment was due to the exclusion criteria. No patient from any of the study groups were excluded.

There were no statistically significant differences among the two groups with respect to age, gender, weight, height, smoking, ASA physical status, the type of surgery, and duration of surgery and anaesthesia (Table 1).

There was no statistically significant differences (P>0.05) between study groups with respect to postoperative nausea, retching, or vomiting. The incidence of overall PONV was 13.9% (five patients) in group D compared with 52.8% (19 patients) in group B, showing statistically significant differences (P=0.0003) (Table 2).

The severity of PONV evaluated by VAS was less in group D compared with group B (34.22±10.48 vs. 62.50±13.340, with statistical significance (P=0.03). Also, fewer patients in group D required an antiemetic compared with the group B (44.4 vs. 72.2%, respectively). Similarly there was significant difference in the mean total amount of ondansetron utilization during the first 24 h (2.33±2.93in group D vs. 3.58±2.68 in group B, P=0.003). The mean total amount of intraoperative fentanyl was significantly lower in group D, P=0.04). Within the initial 24 h postoperatively, the mean total amount of tramadol utilization was significantly lower in group D (74.44 ±12.29 vs. 89.89±15.08, P=0.002). The first analgesic request was significantly delayed in group D compared with group B (136.58±9.34 vs. 95.92±19.10, P=0.01) (Table 3).

When the VAS was used to assess pain, the severity of pain was significantly lower in group D during the 5 h assessment after arrival in the ICU compared with group B (Fig. 1). During the postoperative 6 h, the

Table 1 Demographic characteristics, the type of laparoscopic surgical procedures, and duration of surgery and anaesthesia

Variables	Group D (*n*=36)	Group B (*n*=36)	*P*-value
Age (years)	32.2±8.3	24.1±6.7	0.68
Sex (male/female) (*n*)	17/19	15/21	0.72
Weight (kg)	137.9±8.4	143.2±8.5	0.2
Height (cm)	1.76±0.33	1.7±0.05	0.08
ASA (I/II) (*n*)	13/19	11/21	0.6
Smokers (yes/no)	7 (19)/29 (81)	10(28)/26 (72)	0.41
History of previous PONV (yes/no)	3 (8.33)/33 (91.67)	4 (11.11)/32 (88.89)	0.65
Type of laparoscopic surgery (*n*)			
Gastric banding	20	19	0.8
Gastric bypass	16	17	
Duration of surgery (min)	121.58±33.7	138.2±22.23	0.46
Duration of anaesthesia (min)	174.47±36.2	153.92±33.0	0.15

Values are expressed as mean±SD. Sex, ASA and type of laparoscopic surgery are expressed in number of patients. History of previous PONV are expressed in *n* (%). ASA, American Society of Anesthesiologists; PONV, postoperative nausea and vomiting.

Table 2 Number of patients who experienced postoperative nausea and vomiting within 24-h postoperatively

Variables	Group D (*N*=36)	Group B (*N*=36)	RR	95% CI	*P*- value
Nausea					
Yes	2 (5.6)	8 (22.2)	0.25	0.57–1.10	0.066
No	34 (94.4)	28 (77.8)			
Retching					
Yes	2 (5.6)	5 (13.9)	0.40	0.08–1.93	0.254
No	34 (94.4)	31 (86.1)			
Vomiting					
Yes	1 (2.8)	6 (16.7)	0.17	0.17–0.02	0.089
No	35 (97.2)	30 (83.3)			
Overall PONV					
Yes	5 (13.9)	19 (52.8)	0.26	0.26–0.11	0.0003
No	31(86.1)	17 (47.2)			

Values are expressed as *n* (%). CI, confidence interval; PONV, postoperative nausea and vomiting; RR, relative risk.

Table 3 Comparison of severity of postoperative nausea and vomiting within 24-h postoperatively and intraoperative and postoperative medications

Variables	Group D (*N*=36)	Group B (*N*=36)	Mean of difference	95% CI	*P*-value
Severity of PONV (VAS)	34.22±10.48	62.50±13.34	–28.28	–29.84 to 26.72	0.03
Ondansetron dose during 24 h (mg)	2.33±2.93	3.58±2.68	–1.25	–1.59 to 0.91	0.03
Intraoperative fentanyl	50.42±13.96	88.89±25.83	–38.47	–41.30 to –35.65	0.04
Tramadol dose during 24 h (mg)	74.44±12.29	89.89±15.08	–24.44	–26.04 to –22.85	0.002
First analgesic request	136.58±9.34	95.92±19.10	40.67	38.65–42.68	0.01

Values are expressed as mean±SD. CI, confidence interval; PONV, postoperative nausea and vomiting; VAS, visual analogue scale.

mean Ramsey sedation score was significantly higher in group D (4.2±0.8) compared with group B (2.7±0.9), with a *P* value of less than 0.0001. However, all patients in both groups were aroused and they responded to oral commands.

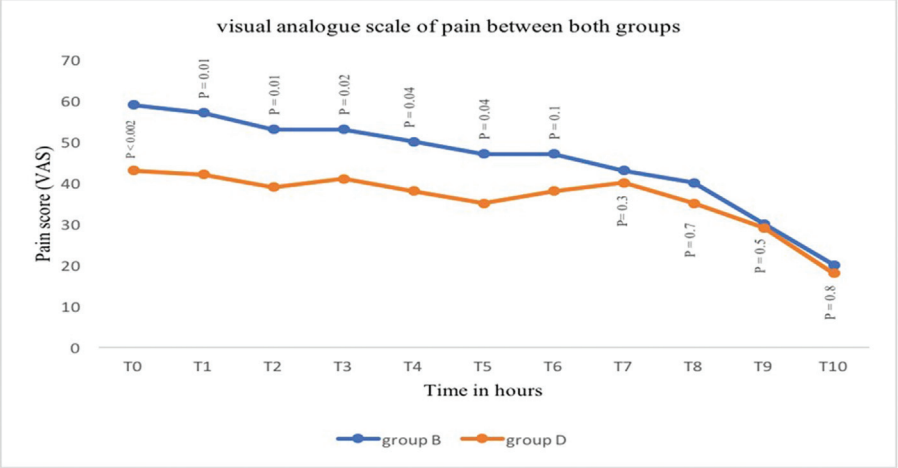
Intraoperative MAP was significantly statistically lower in group D after administration of dexmedetomidine, in 5, 10, 15, 20 min, but no significant changes occurred after that ($P>0.05$) (Fig. 2).

However, after administration of study medication during anaesthesia, ephedrine (10 mg) was required to treat hypotension in one patient in group D compared with none in the group B; otherwise, the differences were not clinically significant.

Intraoperative HR values show a decrease in values in group D, with significant decrease in 10 and 15 min, no significant changes occurred after that ($P>0.05$) (Fig. 3). None of the patients in either group were given atropine to treat bradycardia during anaesthesia.

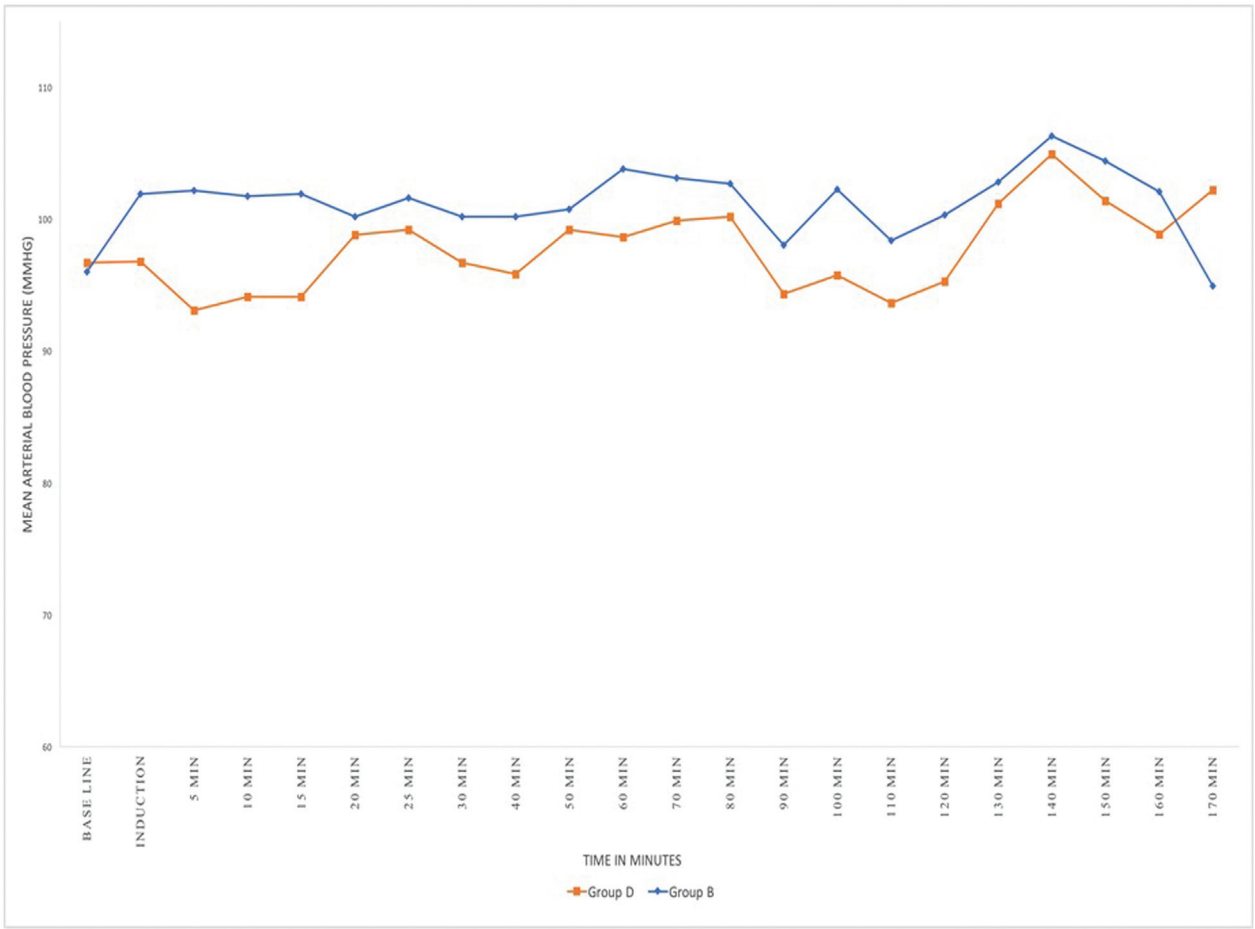
In the postoperative period, none of the patients needed ephedrine or atropine.

Figure 1



Comparison of postoperative visual analogue scale (VAS) of pain between both groups.

Figure 2



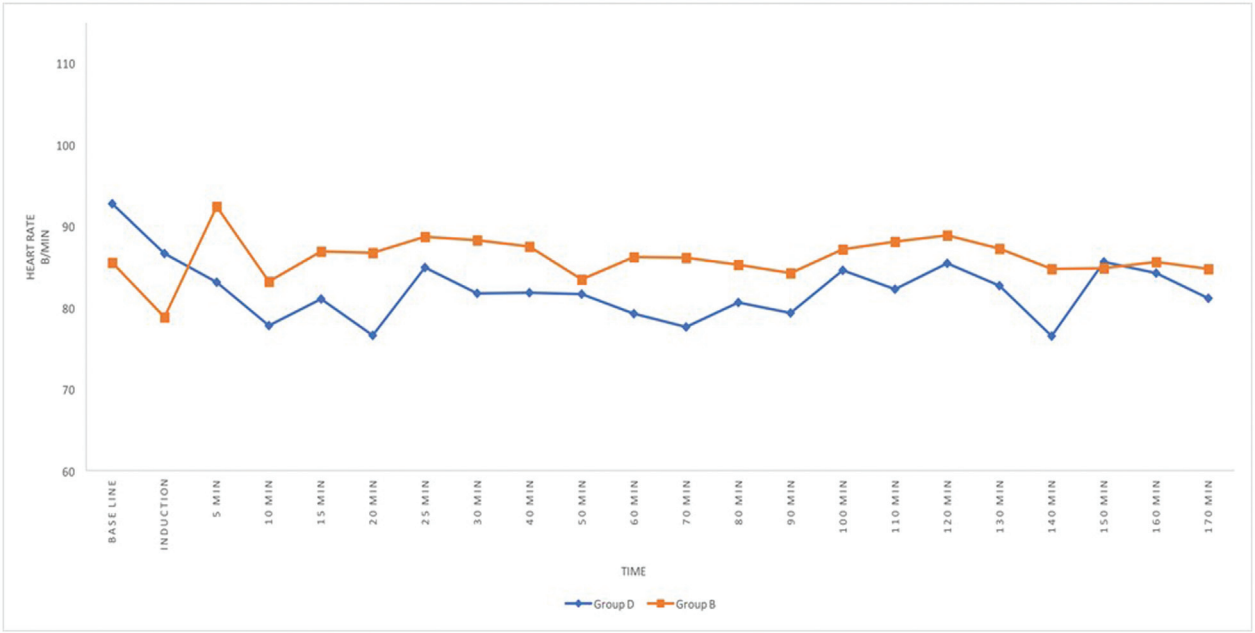
Perioperative changes in mean arterial blood pressure in both groups.

Discussion

PONV is not a new concept in anaesthesiology; it is a long-standing problem. Regardless of a lot of studies over the recent decades, PONV remains an extremely problematic challenge, because it results in serious consequences. In this way, a successful method to prevent or counteract PONV is critically required as ever.

In this study, we compare the antiemetic efficacy of dexmedetomidine–ondansetron–dexamethasone with ondansetron–dexamethasone in 72 patients undergoing

Figure 3



Perioperative changes in heart rate in both groups.

laparoscopic bariatric surgery. It was unethical to incorporate a placebo control group, as there is risk of development of PONV.

According to the findings of the present single-dose study, a combination of dexmedetomidine–ondansetron–dexamethasone is more effective than ondansetron–dexamethasone in abolishing the incidence of PONV in a higher percentage of obese adult patients during the first 24 h after laparoscopic bariatric surgery. Moreover, dexmedetomidine–ondansetron–dexamethasone combination reduces both analgesic consumption and ondansetron as a rescue antiemetic drug.

Our finding is steady with Massad *et al.* [9], who found that combining dexmedetomidine to other anesthetic agents results in more balanced anaesthesia and a significant drop in the incidence of postoperative nausea and vomiting after laparoscopic gynaecological surgeries with a significant drop in overall consumption of fentanyl.

Similar incidence of Wang *et al.* [10] indicated that perioperative dexmedetomidine decreased postoperative nausea in laparoscopic surgical patients (risk ratio 0.43;95% confidence interval, 0.28–0.66; $P < 0.0001$).The antiemetic effect may be induced by direct antiemetic properties of α_2 agonists through the inhibition of catecholamine by parasympathetic tone [11]. Also, administration of dexmedetomidine reduced the perioperative fentanyl consumption in this study which may explain the decreased incidence of PONV. It can prevent surgical stress response by decreasing blood pressure and HR [12].

The decrease of postoperative pain by dexmedetomidine could be clarified by inhabitation of the release of substance P through the activation of the α_2-adrenoreceptor in the dorsal horn of the spinal cord, which modulates the transmission of nociceptive signals in the central nervous system, prompting lessening of nociceptive contributions amid the intense postoperative period [13].

Contrary to our results, Bakri *et al.* [14] announced that dexmedetomidine reduces the incidence and severity of PONV, similar to dexamethasone when he compared the effects of a single dose of dexmedetomidine with dexamethasone for reducing PONV after laparoscopic cholecystectomy.

Also, Geng *et al.* [15] found that the supplemental use of dexmedetomidine during general anaesthesia reduced the incidence of early postoperative nausea but not vomiting within the 24 h after surgery.

Our study limitations were the study population, that is, ASA I/II patients do not represent the entire population undergoing laparoscopic bariatric surgery. In the duration of this study 30 patients were excluded because of ASA III.

Conclusion

On the basis of this study finding, addition of dexmedetomidine to ondansetron and dexamethasone has an effect superior to that of dexamethasone plus ondansetron in reducing the incidence and severity of PONV. In addition, dexmedetomidine is superior in reducing postoperative pain and total analgesic consumption during the first 24 h after laparoscopic bariatric surgery, without any major adverse effects.

We therefore conclude that a single dose of dexmedetomidine plus ondansetron and dexamethasone is appropriate for preventing PONV in patients undergoing laparoscopic bariatric surgery.

Further studies are needed to determine the optimum dose and timing of administration of dexmedetomidine to prevent PONV without any effects on patient haemodynamics or sedation.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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