Rev Bras Anestesiol. 2013;63(5):404-409

REVISTA BRASILEIRA DE ANESTESIOLOGIA

Official Publication of the Brazilian Society of Anesthesiology
www.sba.com.br

SCIENTIFIC ARTICLE

# Combination of Haloperidol, Dexamethasone, and Ondansetron Reduces Nausea and Pain Intensity and Morphine Consumption after Laparoscopic Sleeve Gastrectomy

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Submitted on April 15, 2012; accepted on July 30, 2012

**KEYWORDS**
Antiemetics; Haloperidol; Dexamethasone; Ondansetron; Bariatric Surgery; Postoperative Nausea and Vomiting.

**Abstract**
*Background and objective*: Postoperative nausea and vomiting (PONV) occur frequently after laparoscopic bariatric surgery. The combination of haloperidol, dexamethasone, and ondansetron may reduce these undesirable events. The aim of this study was to evaluate the intensity of nausea and pain, the number of vomiting episodes, and morphine consumption in postoperative (PO) obese patients undergoing laparoscopic sleeve gastrectomy (LSG).
*Method*: A clinical, randomized, controlled, double-blind study conducted with 90 patients with body mass index ≥ 35 $kg.cm^{-2}$. Patients were divided into three groups of 30 individuals to receive ondansetron 8 mg (Group O); ondansetron 8 mg and dexamethasone 8 mg (Group OD); and ondansetron 8 mg, dexamethasone 8 mg, and haloperidol 2 mg (Group HDO). We evaluated the intensity of nausea and pain using the verbal numeric scale, cumulative number of vomiting episodes, and morphine consumption in the period of 0-2, 2-12, 12-24, and 24-36 hours postoperatively.
*Results*: Nausea intensity was lower in Group HDO compared to Group O ($p = 0.001$), pain intensity was lower in Group HDO compared to Group O ($p = 0.046$), and morphine consumption was lower in Group HDO compared to Group O ($p = 0.037$). There was no difference between groups regarding the number of vomiting episodes ($p = 0.052$).
*Conclusion*: The combination of haloperidol, ondansetron, and dexamethasone reduced nausea and pain intensity and morphine consumption in postoperative obese patients undergoing LSG.


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http://dx.doi.org/10.1016/j.bjane.2012.07.012

## Introduction

Postoperative nausea and vomiting (PONV) usually occur after laparoscopic bariatric surgery. In previous studies, the incidence of PONV in patients who did not receive antiemetic prophylaxis was as high as 70-80%.[1,2] The combination of antiemetic drugs has been used as a strategy for reducing PONV. Thus, the combination of three antiemetic drugs with different mechanisms of action may be an option to prevent these undesirable events.

Haloperidol, a prolonged action butyrophenone (18 hours) with high affinity for dopamine $D_2$-receptors, has been used to control agitation and delirium in medical and surgical patients and in palliative care of cancer patients for nausea and vomiting management.[3] It is used in much lower doses (1.2 mg) than drugs used for treating psychiatric disorders, administered by intravenous (IV) route for prevention and treatment of PONV with minimal toxicity. Extrapyramidal symptoms are rare and cardiac arrhythmias have not been reported.[4,5]

Intravenous dexamethasone (8-10 mg) reduces the incidence of PONV by a central mechanism that reduces the production of prostaglandin and controls the release of endorphins.[6,7] Moreover, it may decrease postoperative pain by modulating the systemic physiological response of anti-inflammatory mediators.[6] Despite the various potential side effects, such as infection and delayed wound healing or adrenal gland suppression, Henzi and colleagues did not observe these effects after a single bolus injection of dexamethasone in their systematic review.[7]

Ondansetron, one of the 5-$HT_3$ receptor antagonists, is the most studied drug. Used intravenously at doses of 4-8 mg, it has few side effects and appears to be particularly useful for PONV in patients undergoing gastrointestinal surgery with stimulation of enterochromaffin cells.[8]

Headaches may occur after its IV administration, and transient elevation of liver enzymes occurred in a small numbers of patients.[9]

Among the various types of surgical approaches to obesity, laparoscopic sleeve gastrectomy (LSG) is emerging.[10]

The aim of this study was to evaluate the intensity of nausea, cumulative number of vomiting episodes, pain severity, and morphine consumption in postoperative obese patients undergoing LSG who received one of the three antiemetic prophylactic regimens.

## Method

We conducted this study according to the Declaration of Helsinki Ethical principles and had it approved by the Medical Ethics Committee of the Universidade Federal de Mato Grosso (Protocol 932/CEP-HUJM/2010). We obtained written informed consent from all patients. Between January and October 2011, patients with age ≥ 18 years, physical status ASA I-III, body mass index (BMI) ≥ 35 $kg.cm^{-2}$, and candidates for LSG were invited to participate in this randomized, controlled, double-blind, clinical trial. Exclusion criteria were patients with known hypersensitivity or contraindication to the study drugs; who had experienced serious complications during perioperative period; who have psychiatric disorder; history of migraine; and those who had used opioids, anti-inflammatory hormone, and antiemetic drugs 24 hours before surgery.

Patients, anesthesiologists, and investigators who collected the postoperative data were blinded to the randomization process and types of drugs used.

We used a list of random numbers generated by computer (www.graphpad.com) and the sealed envelope technique. Independent personnel not associated with the study prepared the randomization. Thus, patients were assigned to receive one of three IV treatments. Group O (control): ondansetron (8 mg); Group DO: dexamethasone (8 mg) and ondansetron (8 mg); Group HDO: haloperidol (2 mg), dexamethasone (8 mg) and ondansetron (8 mg). The nurse unit prepared the drugs in volumes of 10 mL with the same color (colorless) and delivered them to the assistant anesthesiologist who administered the volumes. Therefore, two syringes containing 0.9% saline solution (SS) or one containing SS and the other dexamethasone or one containing dexamethasone and the other haloperidol were administered immediately after induction of anesthesia. All patients received ondansetron 20-30 minutes before the end of procedure.

### Anesthetic technique

Anesthetic technique was standardized: we calculated the doses of anesthetic drugs for induction and maintenance of anesthesia based on the ideal weight (IW) and corrected weight (CW) of patients, in which IW = height in cm (-100 for men and -105 for women) and CW = IW + [0.4 x (current weight - ideal weight)]. Thus, anesthesia was induced with IV propofol (2 $mg.kg^{-1}$ CW), fentanyl (3 $\mu g.kg^{-1}$ CW), and cisatracurium (0.1 $mg.kg^{-1}$ IW) for tracheal intubation. Remifentanil (0.1-0.3 $\mu g.kg^{-1}.min^{-1}$ IW), isoflurane (1%) in a mixture of 1:1 oxygen and air, and additional dose of cisatracurium were given for maintenance if required. Neuromuscular block was reversed with IV neostigmine up to 0.04 $mg.kg^{-1}$ and atropine up to 0.015 $mg.kg^{-1}$.

### Surgical technique

LSG was standardized. We insterted five or six trocars after establishing the pneumoperitoneum. Initially, partial release of the stomach's greater curvature was done using the ultrasonic device Ligasure®, preserving the antral region. Then, we positioned an orogastric tube (Fouchet 32 French) into the lesser curvature to delimit gastric resection, which we performed with linear staplers 2 to 5 cm from the pylorus, advancing it to the angle of Hiss. After gastric tube insertion, we did a staple line reinforcement using non-absorbable monofilament sutures with continuous invaginating seromuscular stitches. At the end of surgery, Fouchet tube was aspirated and removed after a leak test using methylene blue.

### Postoperative diet

We introduced fractionated oral liquid diet, initially with water and later with broth without residue, on the first postoperative (PO) day, according to patient's acceptance.

### Verbal numeric scale of nausea (VNSN) and verbal numeric scale of pain (VNSP)

We evaluated nausea intensity by VNSN, ranging from 0 (no nausea) to 10 (worst possible nausea) and pain intensity by VNSP, ranging from 0 (no pain) to 10 (worst possible pain).

### Analgesia

We administered intravenous ketorolac (30 mg) and dipyrone (20-30 mg.kg$^{-1}$ IW) immediately after induction of anesthesia and maintained it every 8 and 4 hours, respectively. We used intravenous bolus doses of morphine (2-3 mg) in post-anesthesia care unit (PACU), if VNSP > 3. If VNSP > 3, we administered subcutaneous morphine (5 mg) after discharge to ward.

### Data collection

We recorded nausea and pain intensity at the end of 0-2, 2-12, 12-24, and 24-36 hours postoperatively, in addition to the cumulative number of vomiting episodes and morphine consumption at 36 hours postoperatively. We also recorded the demographic variables: ASA physical status, non-smoker status, history of PONV, history of kinetosis, preoperative fasting time, duration of anesthesia, amount of fluids administered during operation, and length of PACU stay.

### Statistical analysis

We determined that the sample size of 28 patients per group was adequate to meet the decrease in mean nausea intensity from five to three in VNSN and standard deviation of three (pilot study showed a mean nausea intensity of three with the use of a prophylactic antiemetic drug), assuming a 20% ß-error and 5% α-error.

We assessed continuous data with normal distribution using the analysis of variance test (ANOVA) followed by Tukey's test for post-hoc analysis when necessary.

We assessed continuous or discrete data without normal distribution and ordinal data using Kruskal-Wallis test, followed by Mann-Whitney test for post-hoc analysis, if necessary.

We used a Chi-square test for categorical data. We used repeated measures ANOVA test for comparative analysis of the evolution of variables: VNSN, VNSP, and morphine consumption over time between groups. In this analysis, we considered two factors of interest (time and group), in addition to the possible interaction between them.

To reject the null hypothesis, we established a level of significance at 5% (p value < 0.05). We performed analyses using the Statistical Package for Social Sciences for Windows 17.0.

## Results

Of the 96 randomized patients, six were excluded (one underwent laparotomy, one had surgery postponed, two had surgical complications, one had angioneurotic edema, and one received rescue antiemetic outside the protocol). Thus, 90 patients were included (30 per group). Demographic variables, physical status, non-smoker status, history of PONV, history of kinetosis, preoperative fasting time, duration of anesthesia, amount of fluid administered during operation, and time of PACU stay had homogeneous distribution between the groups (Table l).

### Nausea intensity

Nausea intensity was lower in Group HDO than in Group O (p = 0.001). Nausea intensity remained constant over time in all three groups (time variable, p = 0.17). There was no interaction between group and time (time variable x group, p = 0.96) (Fig. 1).

### Number of vomiting episodes

Kruskal-Wallis test showed a trend towards a statistical difference between groups (p = 0.052). The number of vomiting episodes tended to be lower in Group HDO, followed by DO and O groups (Table 2).

### Pain intensity

Pain intensity was lower in Group HDO than in Group O (p = 0.046). There was also a decrease in pain intensity over time (p = 0.000). There was no interaction between group and time (time variable x group, p = 0.52) (Fig. 2).

**Table 1** Demographic and Other Clinical Variables.

| | Group O n = 30 | Group DO n = 30 | Group HDO n = 30 |
|---|---|---|---|
| Weight (kg)[a] | 118.7 ± 23.1 | 116.5 ± 25.1 | 111.9 ± 15.4 |
| Height (metros)[a] | 1.64 ± 0.1 | 1.65 ± 0.0 | 1.64 ± 0.0 |
| BMI (Kg.cm$^{-2}$)[a] | 43.3 ± 7.4 | 41.9 ± 5.6 | 41.3 ± 3.8 |
| Age[a] | 34 ± 8 | 38 ± 11 | 37 ± 10 |
| Female (n, %) | 21 (70) | 19 (63.3) | 21 (70) |
| ASA I/II/III | 1/26/3 | 0/27/3 | 0/30/0 |
| Non-smoker (n, %) | 26 (86) | 24 (80) | 27 (90) |
| History of PONV (n, %) | 8 (26.6) | 10 (33.3) | 7 (23.3) |
| History of kinetosis (n, %) | 3 (10) | 3 (10) | 2 (6.6) |
| Fasting time (h)[a] | 10.7 ± 1.9 | 11.4 ± 2.1 | 11.1 ± 1.4 |
| Duration of anesthesia (min)[a] | 154 ± 42 | 142 ± 24 | 146 ± 30 |
| IV Fluid IV (L)[b] | 2.74 (2-3.5) | 2.71 (2-3.5) | 2.65 (2-3.5) |
| PACU stay (min)[b] | 175 (90-270) | 177 (120-270) | 140 (80-415) |

DO, dexamethasone and ondansetron; HDO, haloperidol, dexamethasone, and ondansetron; PONV,postoperative nausea and vomiting; O, ondansetron.

[a]Mean ± standard deviation.

[b]Median and variations (minimum-maximum).

**Table 2** Number of Vomiting Episodes 36 Hours after Surgery, According to Group.

| | Group O n = 30 | Group DO n = 30 | Group HDO n=30 | p |
|---|---|---|---|---|
| Number of episodes | 1.10 ± 1.2 | 0.83 ± 2 | 0.63 ± 1.2 | 0.052 |

DO, dexamethasone and ondansetron; HDO, haloperidol, dexamethasone, and ondansetron; O, ondansetron.
Data are expressed as mean and standard deviation.

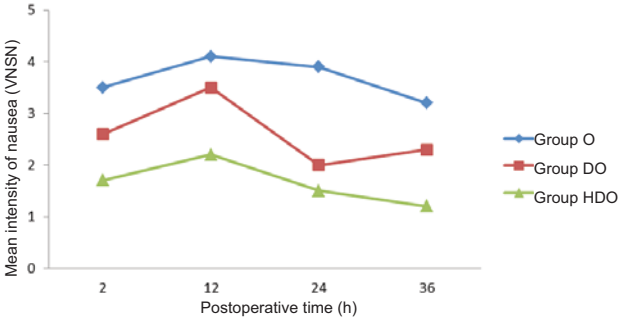


**Figure 1** Nausea intensity variation in verbal numerical scale of nausea (VNSN), according to group and time (hour).

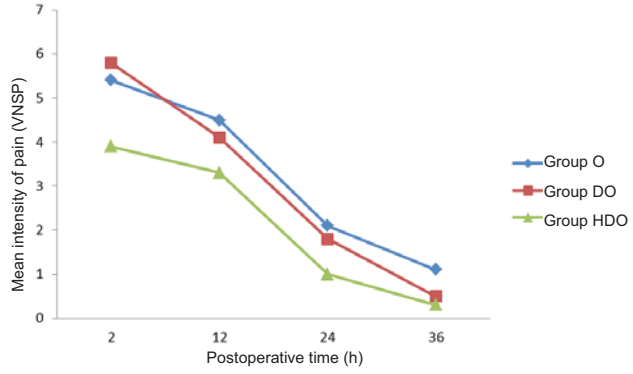


**Figura 2** Variación de la intensidad del dolor por la escala numérica verbal de dolor (ENVD), segundo grupo y tiempo, en horas.

## Morphine consumption

Morphine consumption was lower in Group HDO than in Group O (p = 0.037). There was also a decrease in morphine consumption over time (p = 0.000). There was no interaction between group and time (time variable x group, p = 0.74) (Fig. 3).

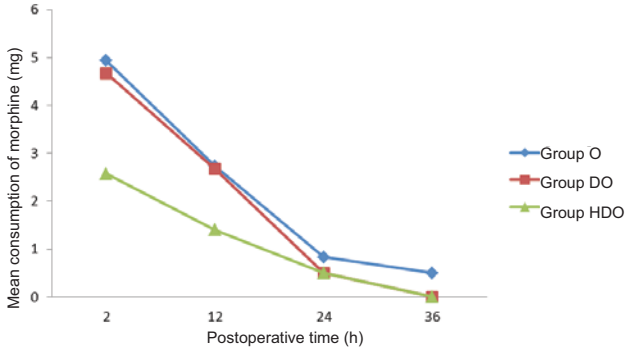


**Figura 3** Variación del consumo de morfina, segundo grupo y tiempo, en horas.

## Discussion

We chose haloperidol, dexamethasone, and ondansetron because they have different mechanisms of antiemetic activity, are inexpensive and have proven efficacy when used alone or in combination.[11-14] We used haloperidol, in particular, because it is an interesting option to droperidol, as it provides less sedation.[15]

The selection of doses was based on previous studies reporting they were safe and effective.[2,16] The study design did not include a control group without prophylactic medication. In fact, there is a higher incidence of PONV after laparoscopic surgeries and the use of balanced anesthesia.[16] which in itself may justify the use of at least one prophylactic antiemetic drug; thus, we believe that it was not ethical to include a placebo group in this study.

In this study, patients received the same type of anesthesia and underwent the same type of surgery. Moreover, the variables age, gender, weight, height, physical status, BMI, non-smoker status, history of PONV and kinetosis, preoperative fasting time, duration of anesthesia, amount of fluid infused during surgery, and time of PACU stay (possible confounding biases) had homogeneous distribution between groups. This is important because the differences between groups could be attributed to the different antiemetic combinations administered.

The study showed that the combination of antiemetics reduced the intensity of nausea, proportionally to the number of drugs used. However, nausea intensity remained constant over time in all three groups. This may be explained by the additive effect of the antiemetic combination,

as suggested by Apfel.[17] and the fact that haloperidol and dexamethasone elimination half-lives are greater than that of ondansetron.

The number of vomiting episodes was not different between groups (p = 0.052), possibly because of the greater anti-vomiting than anti-nausea effect in antiemetics studied or the need for a larger sample size in order to find a statistically significant difference.

Pain is a frequent cause of discomfort during the postoperative period. Pain intensity was lower in groups receiving dexamethasone, but statistically different in Group HDO compared to Group O. Pain relief effect may be attributed to the use of dexamethasone (decrease in proinflammatory cytokines release, such as tumor necrosis factor, interleukin-1 and interleukin-6), similar to results of other studies.[18-20]

Morphine (IV and SC bolus) used as rescue analgesic was adequate, safe, and a good option compared to the use of IV morphine via patient-controlled analgesia. We found increased morphine consumption in the first 2 hours in all groups, with significant decline in subsequent periods. The use of dipyrone [21] and ketorolac [22] at fixed times may have contributed decisively to this result. There was less morphine consumption in Group HDO than in Group O, which may be attributed to the anti-inflammatory and analgesic opioid-sparing action of dexamethasone, as seen in other studies.[23-26]

The combination of haloperidol, dexamethasone, and ondansetron decreased nausea and pain intensity and morphine consumption in obese patients undergoing LSG.

## Conflicts of interest

The authors declare no conflicts of interest.

## References


1. Moussa AA, Oregan PJ - Prevetion of postoperative nausea and vomiting in patients undergoing laparoscopic bariatric surgery - Granisetron alone vs granisetron combined with dexamethasone/droperidol. M.E.J. Anesth. 2007;19(2):367-368.
2. Mendes MN, Monteiro RS, Cruz Martins FAN - Profilaxia de náuseas e vômitos pós-operatórios em obesos mórbidos submetidos a gastroplastias por laparoscopias. Estudo comparativo entre três métodos. Rev Bras Anestesiol. 2009;59(5):570-576.
3. Perkins P, Dorman S - Haloperidol for the treatment of nausea and vomiting in palliative care patient. Cochrane Database of Systematic Reviews. 2009;(2):CD006271.
4. Chu CC, Shieh JP, Tzeng JI et al. - The prophylactic effect of haloperidol plus dexamethasone on postoperative nausea and vomiting in patients undergoing laparoscopically assisted vaginal hysterectomy. Anesth Analg. 2008;106:1402-1406.
5. Wang TF, Liu YH, Chu CC et al. - Low-dose haloperidol prevents post-operative nausea and vomiting after ambulatory laparoscopic surgery. Acta Anaesthesiol Scand. 2008;52:280-284.
6. Karanicolas PJ, Smith SE, Kanbur B et al. - The impact of prophylactic dexamethasone on nausea and vomiting after laparoscopic cholecystectomy: a systematic review and meta-analysis. Ann Surg. 2008;248:751-762.
7. Henzi I, Walder B, Tramer MR - Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systematic review. Anesth Analg. 2000;90:186-194.
8. Laer S, Scholz J, Ritterbach C et al. – Association between increased 5-HIAA plasma concentrations and postoperative nausea and vomiting in patients undergoing general anaesthesia for surgery. Eur J Anaesth. 2001;18(12):833-835.
9. Tramer MR, Reynolds DJ, Moore RA et al. - Efficacy, dose-response, and safety of ondansetron in prevention of postoperative nausea and vomiting: a qualitative systematic review of randomized placebo-controlled trials. Anesthesiology. 1997;87:1277-1289.
10. O'Brein PE - Bariatric surgery: mechanisms, indications, and outcomes. J Gastroenterol Hepatol. 2010;25:1358-1365.
11. Chu CC, Shieh JP, Tzeng JI et al. - The prophylactic effect of haloperidol plus dexamethasone on postoperative nausea and vomiting in patients undergoing laparoscopically assisted vaginal hysterectomy. Anesth Analg. 2008;106:1402-1406.
12. Rosow CE, Haspel KL, Smith SE et al. - Haloperidol versus ondansetron for prophylaxis of postoperative nausea and vomiting. Anesth Analg. 2008;106:1407-1409.
13. White PF, O'Hara JF, Roberson CR - The impact of current antiemetic practices on patient outcomes: a prospective study on high-risk patients. Anesth Analg. 2008;107:452-458.
14. Voigt M, Fröhlich CW, Waschke KF - Prophylaxis of postoperative nausea and vomiting in elective breast surgery. Journal of Clinical Anesthesia. 2011;23:461-468.
15. Carlise JB, Stevenson CA - Drugs for preventing postoperative nausea and vomiting. Cochrane Database Syst Rev. 2006;(3):CD004125.
16. Le TP, Gan TJ - Update on the management of postoperative nausea and vomiting and postdischarge nausea and vomiting in ambulatory surgery. Anesthesiology Clin. 2010;28:225-249.
17. Apfel CC, Laara E, Koivuranta M et al. - A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. Anesthesiology. 1999;91:693-700.
18. Sánchez-Rodríguez PE, Fuentes-Orozco C, González-Ojeda A - Effect of dexamethasone on postoperative symptoms in patients undergoing elective laparoscopic cholecystectomy: randomized clinical trial. World J Surg. 2010;34:895-900.
19. Zhou H, Xu H, Zhang J et al. - Combination of dexamethasone and tropisetron before thyroidectomy to alleviate postoperative nausea, vomiting, and pain: randomized controlled trial. World J Surg. 2012;7:1217-1224.
20. Feroci F, Rettori M, Borrelli A et al. - Dexamethasone prophylaxis before thyroidectomy to reduce postoperative nausea, pain, and vocal dysfunction: a randomized clinical controlled trial. Head Neck. 2011;33(6):840-846.
21. Edwards J, Meseguer F, Faura C et al. - Single dose dipyrone for acute postoperative pain. Cochrane Database Syst Rev. 2010;(9):CD003227.
22. De Oliveira Jr GS, Agarwal D, Benzon HT - Perioperative single dose ketorolac to prevent postoperative pain: a meta-analysis of randomized trials. Anesth Analg. 2012;114(2):424-433.

23. De Oliveira Jr GS, Almeida MD, Benzon HT - Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of randomized controlled trials. Anesthesiology. 2011;115:575-588.
24. Fujii Y, Itakura M - Reduction of postoperative nausea, vomiting, and analgesic requirement with dexamethasone for patients undergoing laparoscopic cholecystectomy. Surg Endosc. 2010;24:692-696.
25. Jokela RM, Ahonen JV, Tallgren M - The effective analgesic dose of dexamethasone after laparoscopic hysterectomy. Anesth Analg. 2009;109:607-615.
26. Murphy GS, Szokol JW, Greenberg SB et al. - Preoperative dexamethasone enhances quality of recovery after laparoscopic cholecystectomy *effect on in-hospital and postdischarge recovery outcomes*. Anesthesiology. 2011;114:882-890.