Addition of haloperidol to ondansetron and dexamethasone to prevent postoperative nausea and vomiting in female smoking patients following laparoscopic surgery: A prospective, randomized, double-blind study

CURRENT STATUS: POSTED

Xin-qi Zhuang
Department of Anesthesiology, Second Hospital of Tianjin Medical University

Ji Yang
Department of Anesthesiology, Xqing Hospital

Sen Zhao
Department of Anesthesiology, Second Hospital of Tianjin Medical University

Yue-chun Lu
Department of Anesthesiology, Second Hospital of Tianjin Medical University

Ke-liang Xie
Department of Anesthesiology, Tianjin Medical University General Hospital

Yong-hao Yu yyu@tmu.edu.cn
Department of Anesthesiology, Tianjin Medical University General Hospital

Corresponding Author
ORCiD: 0000-0002-7289-7748

DOI: 10.21203/rs.2.11216/v1

SUBJECT AREAS
Anesthesiology & Pain Medicine

KEYWORDS
Postoperative nausea and vomiting, Ondansetron, Dexamethasone, Haloperidol, Female, Smoking, General anesthesia, Laparoscopy
Abstract

Background

Postoperative nausea and vomiting (PONV) is an unpleasant experience that impacts on patient comfort and satisfaction and may lead to other complications. Some risk factors such as female gender and non-smoking status were used to predict the risk of PONV. Regarding its prevention, the combination of two different types of prophylaxis has been demonstrated to exert an additive effect. The present study aimed to evaluate the efficacy of a triple combination of haloperidol, ondansetron and dexamethasone for the prevention of PONV following laparoscopic gynecological surgery in female smoking patients.

Methods

A total of 210 eligible consecutive female patients ranked as American Society of Anesthesiology physical status I-II and aged 18-60 years who were undergoing selective laparoscopic gynecological surgery were included in the current study and allocated into three groups: Patients in group O received 4 mg ondansetron, group OD received 4 mg ondansetron and 8 mg dexamethasone, group ODH received 4 mg ondansetron, 8 mg dexamethasone and 2 mg haloperidol intravenously prior to anesthesia induction. The incidence of PONV, the need for rescue antiemetics, pain score, patient-controlled analgesia (PCA) consumption, rescue analgesics and adverse events were recorded 48 h after operation.

Results

The final analysis consisted of 193 patients who completed the study. Results indicated that the incidence of PONV was significantly decreased in groups OD (20.00%) and ODH (15.63%) compared with in group O (42.19%; P = 0.005). Furthermore, the need for rescue antiemetics was significantly lower in groups OD (13.85%) and ODH (12.50%) than in
group O (32.81%; P = 0.005). There was no significant difference in the incidence of PONV or the need for rescue antiemetics between groups OD and ODH (P = 0.516 and 0.821 respectively). No statistically significant differences were detected in pain score, PCA consumption, rescue analgesics or adverse events among the groups (all P > 0.05).

Conclusion

The addition of haloperidol to a combination of ondansetron and dexamethasone did not decrease PONV frequency below that obtained with the two-drug combination. As for female smokers, prophylaxis comprising ondansetron and dexamethasone, with or without haloperidol, could effectively reduce PONV following laparoscopic surgery.

Background

Postoperative nausea and vomiting (PONV) remains one of the most common adverse effects to occur following surgery and anesthesia, and may contribute to patient anxiety, higher medical costs, metabolic abnormalities, wound disruption and increased hospital stay, among other issues [1, 2]. The main risk factors including female gender, nonsmoker status, use of postoperative opioids, a history of PONV, and motion sickness may lead to PONV [3]. PONV incidence may also be affected by the type of anesthesia used, and the type and duration of surgery [4, 5]; for instance with laparoscopic surgery, the incidence of PONV is markedly higher [6, 7]. Different types of antiemetic drugs can be used to prevent PONV [8]. As they affect different targets, their combination may exert greater function. A two-drug combination, such as a double prophylaxis with ondansetron and dexamethasone, has been demonstrated to be more effective than use of only one drug in preventing PONV [9-11]. However, limited studies have focused on triple prophylaxis for PONV [12, 13], and to our knowledge, whether addition of haloperidol to ondansetron and dexamethasone may improve therapeutic efficacy has thus far remained unclear. On one hand, the cost-benefit should be considered in the application of multiple drugs [14]. On the other hand, the potential differing response between specific patient subpopulations should be identified so as to provide individualized treatment [15, 16]. The present report is of a prospective, randomized, double-blinded study, conducted to compare the antiemetic efficacy of single prophylaxis (4 mg ondansetron), double prophylaxis (4 mg ondansetron and 8 mg dexamethasone) and triple prophylaxis (4 mg ondansetron, 8 mg dexamethasone and 2 mg haloperidol) in preventing PONV following laparoscopic gynecological surgery in female smoking patients.

Methods

Study design

This prospective, double blinded randomized control trial was conducted at the Second Hospital of Tianjin Medical University after being approved by the Ethical Committee of the Second Hospital of Tianjin Medical University, Tianjin, China (Ref. KY2018K080). The study was registered at Chictr.org.cn registry system on Nov 24th 2018 and received the registration number ChiCTR1800019713. Each patient read and signed a formal, written consent form before enrolment in the study.
Participants
A total of 210 adult smoking female patients aged 18 to 60 years, American Society of Anesthesiologists (ASA) physical status I and II, who were scheduled for laparoscopic myomectomy and laparoscopic adnexectomy at the Second Hospital of Tianjin Medical University between January and April, 2019 were enrolled in the study. Active smoking was defined as having smoked at least one cigarette per day in the week prior to surgery [17]. Patients were informed about the study, and enrolled after written consent was acquired. The exclusion criteria were as follows: Known allergy or intolerance to the study drug; vomiting within the 24 h before surgery; a history of PONV or motion sickness; body mass index (BMI) ≥ 35 or ≤ 18.5; gastrointestinal, renal or hepatic disease; cardiac arrhythmia; insulin-dependent diabetes; psychiatric illness; use of opioids or corticosteroids within 1 week of surgery; use of anti-emetics in the 24 h prior to surgery; currently pregnant or lactating; requiring a > 3 h operation or anesthesia time and preservation of the gastric tube following operation.

Randomized grouping and blinding
A total of 210 patients were randomly allocated into 3 groups (n = 70). Prior to induction of anesthesia, the researcher responsible for patient allocation randomized the patients using a computer generated random number system. Allocation was concealed with numbered, opaque, sealed envelopes until after consent was obtained. Patients were allocated randomly to receive 4 mg ondansetron (group O), 4 mg ondansetron and 8 mg dexamethasone (group OD) or 4 mg ondansetron, 8 mg dexamethasone and 2 mg haloperidol (group ODH) intravenously. The doses used in the present trial have been designated as safe and effective in PONV management guidelines 2014 [5].

A nurse not involved in the treatment opened the envelopes and prepared the corresponding study drugs in identical syringes in a total volume of 10 ml (diluted with saline). The drugs were administered prior to anesthesia induction by another nurse blinded to the group allocation. The patients and attending anesthesiologists involved in the perioperative patient management were blind to the group assignment and intervention. The outcomes were measured and recorded by anesthesiologists and nurses who were not involved in the direct treatment of the patients and also blind to the grouping assignment and intervention.

Anesthetic management
All the patients fasted in the 8 h prior to surgery. No premedication was administered to the patients. Upon arrival in the operation theater, the patients were monitored for multiple vital parameters such as electrocardiogram, pulse oxygen saturation, non-invasive blood pressure and bispectral index. General anesthesia was induced with midazolam (0.04 mg/kg), remifentanil (1.00 µg/kg) and propofol (2.00 mg/kg). Rocuronium (0.60 mg/kg) was used for neuromuscular blockade and to facilitate tracheal intubation. The intraoperative pressure of carbon dioxide pneumoperitoneum was maintained at 13-16 mmHg. Tidal volume and respiratory rate were adjusted in accordance with the partial pressure of end tidal carbon dioxide (P_{ET}CO_2) and airway pressure so that the P_{ET}CO_2 was maintained between 35-45 mmHg. Total intravenous anesthesia was performed using propofol (5.0–15.0 µg/kg/min) and remifentanil (0.1–0.3 µg/kg/min) to attain a bispectral index value ranging from 40 to 60. Rocuronium (0.3 mg/kg) was added intravenously to maintain a single twitch on train-of-four stimulation. Perioperative fluid management was performed by using Ringer’s lactate solution, administered at 6–8 ml/kg/h during surgery according to blood and urine volumes. Temperature was monitored using an esophageal stethoscope with a thermistor and maintained at 36 ± 1ºC with a warm pad throughout surgery. Antagonism of residual neuromuscular blockade was performed by 10.0 mg pyridostigmine and 0.4 mg glycopyrrolate administered intravenously. When the patient awoke, the trachea was extubated.

Postoperative analgesia management
Patients were sent into the post-anesthesia case unit (PACU) for monitoring and given oxygen at 5 L/min. All patients were administered 50 mg flurbiprofen for postoperative pain control. The patients were given intravenous patient-controlled anesthesia (PCA) when discharged from the PACU after 2 h. The PCA regimen consisted of 20 µg/kg fentanyl and 100 mg flurbiprofen diluted in normal saline to a total volume of 100 ml, and was programmed to deliver 1 ml/h as a background infusion and 1 ml bolus per demand with a 15 min lockout interval.

Outcomes and data collection.
The primary outcome was the incidence rate of PONV during the study period. Every episode of nausea or vomiting was recorded under three assessment time frames: 0–2 h, 2–24 h and 24–48 h post-surgery. Nausea was defined as a subjectively feeling which was unpleasant and associated with the urge to vomit; retching was defined as the contraction of respiratory muscles which was labored, spasmodic and rhythmic, but no gastric contents was ejected; and vomiting was defined as the powerful ejection of gastric contents out of the mouth [18, 19]. All the syndromes above were incorporated into total PONV. Cases of retching and vomiting were merged for statistics and calculations. If a patient experienced vomiting or intolerable nausea or requested rescue anti-emetics, 30 mg dimenhydrinate and/or 10 mg metoclopramide was administered as a rescue antiemetic [13].

The secondary outcome was postoperative pain intensity. It was measured by a 10-cm visual analogue scale (VAS) ranking from 0 (no pain) to 10 (the most severe pain imaginable). If a patient complained of severe pain (VAS > 7) or requested analgesia, 1 µg/kg fentanyl was administered.

The presence of nausea, retching and vomiting, VAS score, PCA consumption, use of rescue anti-emetics and rescue analgesics, and the presence of adverse effects, including headache, dizziness, cardiac arrhythmias such as QTc prolongation on electrocardiography and extrapyramidal syndrome such as twitching, dystonia and akathisia were recorded by a nurse in the PACU within the 2 h prior to discharging and then by another nurse every 6 h in wards. Patients’ age, height, weight, ASA physical status and surgery type were recorded prior to operation. The duration of operation and anesthesia was recorded and remifentanil consumption was calculated.

Sample size and statistical analysis
To estimate the required sample size, a power analysis was conducted. The primary endpoint of the study was the incidence of PONV during the study period. A preliminary study of 20 patients who received 4 mg ondansetron indicated that 43% of the patients suffered from PONV for up to 48 h after laparoscopic surgery. The present study aimed for an 80% probability (β = 0.2) of detecting a 25% reduction of PONV incidence with a significance level (α) of 0.05 (two-sided), for which a minimum of 60 patients were required for each group. Considering a < 10% potential dropout rate of patients in preliminary study, 70 patients were enrolled in each group.

Continuous variables (age, height, weight, BMI, duration of surgery and anesthesia, VAS score, remifentanil consumption and PCA consumption) were analyzed by one-way analysis of variance, and categorical variables (ASA physical status, type of surgery, presence of PONV, use of rescue anti-emetics and rescue analgesics and presence of adverse events) were compared using the Chi Square test. Data are expressed as the mean ± standard deviation or count. Post-hoc Bonferroni correction was used for multiple comparisons. PASW Statistics version 18.0 (SPSS Inc., Chicago, IL, USA) was used for the analyses, and P < 0.05 was deemed to indicate statistical significance.

Results
Enrollment
Initially a total of 210 patients were enrolled in the present study, 17 of whom were excluded during the hospitalization or follow-up period. Thus, a total of 193 patients completed the study (Fig. 1). Of the
excluded patients, 4 underwent laparoscopy or anesthesia for > 3 h, 5 changed to open surgery because of laparoscopic failure, 1 was transferred to the intensive care unit for further treatment, 1 underwent a secondary surgery within 48 h of the primary surgery, 2 were administered with incorrect rescue antiemetics and 4 refused further investigation or visitation following surgery.

Demographic data and surgery/anesthesia related information
The demographic information and characteristics of surgery and anesthesia for the final cohort are presented in Table I; no statistically significant differences were detected among the groups (all P > 0.05; Table I).

Postoperative PONV evaluation.
The results for the 0–48 h study period suggested that the incidence of PONV was significantly decreased in groups OD and ODH compared with in group O (P = 0.005; Table II). Furthermore, the need for rescue antiemetics was significantly lower in groups OD and ODH than in group O (P = 0.005; Table II). Although the incidence of PONV in group ODH was lower by ~ 4.37% compared with in group OD, there was no significant difference in the incidence of PONV or the need for rescue antiemetics between groups OD and ODH (P = 0.516 and 0.821 respectively; Table II).

Of note, the incident of PONV and the requirement for rescue antiemetics were significantly lower in groups OD and ODH compared with in group O within 0–2 h after surgery (P = 0.010 and 0.008 respectively; Table II). The incidence of PONV and the requirement for rescue antiemetics were significantly reduced in groups OD and ODH compared with in group O within 2–24 h (P = 0.011 and 0.007 respectively; Table II). Additionally, no statistically significant difference was detected in the occurrence of PONV or requirement for rescue antiemetics between groups OD and ODH within 0–2 h (P = 0.975 and 0.773 respectively; Table II) or 2–24 h (P = 0.668 and 0.616 respectively; Table II) post-surgery. No significant differences in PONV occurrence or rescue antiemetics requirement was detected among the groups within 24–48 h of surgery (all P > 0.05; Table II).

Postoperative pain management and adverse effects.
No significant differences were observed in postoperative VAS pain score, PCA consumption or rescue analgesics use among the groups (all P > 0.05; Table III). Additionally, rates of adverse events including headache and dizziness did not differ to statistically significant extent among the groups (all P > 0.05; Table III). Arrhythmias including QTc prolongation in electrocardiography and extrapyramidal syndrome including twitching, dystonia and akathisia were not detected in group ODH (Table III).

Discussion
In the current perspective, randomized, double-blind study, the antiemetic efficacy of single prophylaxis (4 mg ondansetron) was compared with that of double prophylaxis (4 mg ondansetron and 8 mg dexamethasone) and triple prophylaxis (4 mg ondansetron, 8 mg dexamethasone and 2 mg haloperidol) in preventing PONV following laparoscopic surgery in female smoking patients. The demographics of the patients were homogeneously distributed among the treatment groups, and therefore the differences in PONV incidence could be regarded as being due to the different administrations of antiemetics. The results demonstrated that double prophylaxis (group OD) and triple prophylaxis (group ODH) exhibited improved preventive effects against PONV compared with single prophylaxis (group O), without changing analgesic management or increasing adverse events. However, ODH treatment did not exhibit increased antiemetic efficacy compared with OD treatment on statistical analysis.

During the assessment time frames of 0–2 and 2–24 h, the incidences of nausea and retching, vomiting and need for rescue antiemetics were higher than those at 24–48 h post-surgery in each group, which is similar to the previously reported findings of Ryu et al [20]. In addition to the general risk factors that
give rise to PONV, stretching of the peritoneum, elevated blood pressure of the peritoneal cavity and the effect of carbon dioxide on central system during laparoscopic surgery can lead to intracranial blood flow increment[21], intestinal blood flow reduction[22] and emetogenic substances releasing such as serotonin [23] and have been considered to provoke PONV. Possibly as a result of rescue antiemetics usage within 0–24 h of surgery, particularly in group O, lower incidences of nausea, retching, vomiting and rescue antiemetic requirement were observed 24–48 h postoperatively.

A simplified risk score proposed by Apfel et al [3, 24] has been commonly used to predict the risk of PONV in adults. It corresponds to the number of risk factors present out of the following: Female gender, non-smoking status, a history of PONV and use of postoperative opioids. When 0, 1, 2, 3 or 4 risk factors are present, the corresponding probability for PONV is approximately 10, 20, 40, 60 and 80%, respectively. The patients enrolled in the current study each had an Apfel’s risk score of greater than 2, corresponding to a risk of PONV incidence of over 40%. As laparoscopic gynecological surgery is recognized as an additional risk factor [4, 6], the incidence of PONV without prophylactic antiemetics was expected to be even higher. The highest incidence of PONV observed in the present study was 42% in group O with the single prophylaxis of ondansetron. This rate is similar to that reported by Lee et al [25], but lower than that documented by Gan et al [26] on ondansetron use for prevention of PONV in females undergoing similar surgeries. This may be explained by different anesthesia management regimens between the studies. Gan used inhaled anesthetics including nitrous oxide, isoflurane, sevoflurane and desflurane for anesthesia maintenance; while Lee’s and the current study used midazolam and propofol. The latter drugs have been reported to have lower incident of PONV [12, 27].

There were a few cases of minor adverse events with the drugs used, mainly headache and dizziness, which have been associated with use of 5-hydroxytryptamine 3 receptor antagonists [28]. As an alternative to droperidol, haloperidol has antiemetic properties when used in low doses and with less sedation [29]. However, it is associated with risk of QTc prolongation, and it is advised to use haloperidol with caution for the prevention of PONV [30]. In the current research, haloperidol was administered at a dosage of 2 mg, and no cases of QTc prolongation or neurological syndrome were detected in group ODH, which is in accordance with previous studies [9, 31] and suggests that the drugs used and their combinations were well tolerated and can be considered safe.

Postoperative opioids may increase the risk of PONV in a dose-dependent manner [32]. Additionally, pain is also an established risk factor of PONV, where nausea rather than vomiting presents as the predominant symptom [33, 34]. As the surgeries assessed here were relatively less-traumatic and used small incisions, most patients experienced satisfied perioperative and postoperative analgesia with fentanyl and flurbiprofen and had a VAS score < 3. In fact, VAS scoring and PCA consumption were similar among groups. Therefore, it appeared that in this research pain had less of an effect on PONV following surgery.

As PONV is an important postoperative burden, varieties of antiemetic drugs are used to prevent PONV. Major classes of antiemetic agents include histamine type 1 receptor antagonists, dopamine receptor antagonists, serotonin type 3 receptor antagonists, tachykinin 1 receptor antagonists and corticosteroids. These drugs appear to be similar in efficacy when used as single agents, and to exert an additive effect when in combination [8, 35]. Notably, it has been identified that a combination of two types of the drugs may exert additive effect [9–11], such as double prophylaxis with ondansetron and dexamethasone. Whether adding a third drug could exert greater benefit has remained uncertain. Apfel et al [12] reported that addition of droperidol to ondansetron and dexamethasone resulted in a 6% decrease in the incidence of PONV in a prospective study. Benevides et al [13] identified that adding haloperidol to dexamethasone and ondansetron was superior to double prophylaxis in the prevention of PONV in obese patients undergoing laparoscopic sleeve gastrectomy. However, in a recent report, Bourdaud et al [36] did not observe greater efficacy when adding droperidol to ondansetron and
dexamethasone for prevention of postoperative vomiting in children. The antiemetics used in the current study act on PONV via different mechanisms and targets. Adding sequential prophylactics could exert additional benefit and decrease the relative risk of PONV by a certain percentage each time [8, 35]. Horn et al [35] proposed that the absolute PONV risk may reduce by smaller and smaller amounts with each additional drug but will never be zero; when the decreased percentage becomes less obvious, no additional benefit will be observed. Therefore, it is reasonable to consider risk factors in detail when using more than two prophylactics. For instance, female smoking patients exhibit a relatively lower risk of PONV than female non-smoking patients, the decreased percentage risk may become less obvious when a third prophylaxis is added. In the present study, the incidence rates of PONV were 42.19, 20.00 and 15.63% respectively in groups O, OD and ODH. Adding haloperidol only provided a 4.37% risk reduction, which confirmed our speculation. Other previous studies on triple prophylaxis did not classify patients on risk factors in detail, which may account for the discrepancy among results.

The present study had several limitations. Firstly, there was no absolute control group due to ethical consideration. All patients, including in group O, were administered 4 mg ondansetron during induction. According to the present results, the incidence of PONV may be even higher without any antiemetic (>43%). Therefore, a group without prophylactic antiemetic medication was not included as it would be unethical [37]. Secondly, the patients observed in the study were aged between 18–60 years old; however patients were not classified on their age in detail. Apfel et al [6] suggested younger age (<50 years) to be a significant risk factor for PONV compared with older age. Further investigation will require a more detailed stratification of age groups. Thirdly, our study had a relatively small sample size. So it should be considered as exploratory results, a research on large samples may be necessary for a confirmatory conclusion.

Conclusions

In conclusion, the current study demonstrated that the addition of haloperidol to a combination of ondansetron and dexamethasone did not significantly decrease PONV frequency compared with the combination of ondansetron and dexamethasone, although a combination of two or three prophylactics appeared to exert improved preventive effect against PONV than ondansetron alone. As for female smokers, prophylaxis comprising ondansetron and dexamethasone, with or without haloperidol, could effectively reduce PONV following laparoscopic surgery.

Abbreviations

PONV: Postoperative nausea and vomiting; PCA: Patient-controlled analgesia; ASA: American Society of Anesthesiologists; BMI: Body mass index; \( P\text{ET}_{\text{CO}_2}\): Partial pressure of end tidal carbon dioxide; PACU: Post-anesthesia case unit; VAS: Visual analogue scale;

Declarations

- Ethics approval and consent to participate
This study and its protocol were approved by the Institutional Medical Ethics Committee of the Second Hospital of Tianjin Medical University, Tianjin, China (Ref. KY2018K080). Formal, written informed consents have been obtained from all patients. This research was registered with the Chinese Clinical Trial Registry (URL: http://www.chictr.org.cn. Registry number: ChiCTR1800019713).
- Consent to publish
The patients have provided written informed consent for the publication of any associated data.
- **Availability of data and materials**
The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

- **Competing interests**
The authors declare that they have no competing interests.

- **Funding**
None.

- **Authors’ Contributions**
XQZ helped in conducting the study, collecting the data and writing the manuscript. JY helped in analyzing the data. SZ and YCL helped in conducting the study and collecting the data. KLX helped in designing the study. YHY helped in designing the study, reviewing and revising the manuscript. All authors read and approved the final manuscript.

- **Acknowledgements**
Our gratitude goes to all of the staff of the Department of Anesthesiology and Operating Room, the Second Hospital of Tianjin Medical University. We wish to thank all the doctors and nurses of the Department of Gynaecology at the Second Hospital of Tianjin Medical University who has put trust in our work and allowed us to recruit their patients for this study.

**References**

1. Apfel CC, Heidrich FM, Jukar-Rao S, Jalota L, Hornuss C, Whelan RP, Zhang K, Cakmakkaya OS (2012) Evidence-based analysis of risk factors for postoperative nausea and vomiting. Br J Anaesth 109(5):742–753
2. Moreno C, Veiga D, Pereira H, Martinho C, Abelha F (2013) Postoperative nausea and vomiting: incidence, characteristics and risk factors-a prospective cohort study. Rev Esp Anestesiol Reanim 60(5):249–256
3. Apfel CC, Lääärä E, Koivuranta M, Greim CA, Roewer N (1999) A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. Anesthesiology 91(3):693–700
4. Le TP, Gan TJ (2010) Update on the management of postoperative nausea and vomiting and postdischarge nausea and vomiting in ambulatory surgery. Anesthesiol Clin 28(2):225-249
5. Gan TJ, Diemunsch P, Habib AS, Kovac A, Kranke P, Meyer TA, Watcha M, Chung F, Angus S, Apfel CC, Bergese SD, Candiotti KA, Chan MT, Davis PJ, Hooper VD, Lagoo-Deenadayalan S, Myles P, Nezat G (2014) Philip BK and Tramèr MR. Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg 118(1):85–113
6. Apfel CC, Philip BK, Cakmakkaya OS, Shilling A, Shi YY, Leslie JB, Allard M, Turan A, Windle P, Odom-Foren J, Hooper VD, Radke OC, Ruiz J, Kovac A (2012) Who is at risk for postdischarge nausea and vomiting after ambulatory surgery? Anesthesiology 117(3):475–486
7. Gan TJ (2006) Risk factors for postoperative nausea and vomiting. Anesth Analg 102(6):1884–1898
8. Wiesmann T, Kranke P, Eberhart L (2015) Postoperative nausea and vomiting - a narrative review of pathophysiology, pharmacotherapy and clinical management strategies. Expert Opin Pharmacother 16(7):1069–1077
9. Joo J, Park YG, Baek J, Moon YE (2015) Haloperidol dose combined with dexamethasone for PONV prophylaxis in high-risk patients undergoing gynecological laparoscopic surgery: a prospective, randomized, double-blind, dose-response and placebo-controlled study. BMC Anesthesiol 15:99
10. Song JW, Park EY, Lee JG, Park YS, Kang BC, Shim YH (2011) The effect of combining dexamethasone with ondansetron for nausea and vomiting associated with fentanyl-based intravenous
10. Grecu L, Bittner EA, Kher J, Smith SE, Rosow CE (2008) Haloperidol plus ondansetron versus ondansetron alone for prophylaxis of postoperative nausea and vomiting. Anesth Analg 106(5):1410-1413
11. Apfel CC, Korttila K, Abdalla M, Kerger H, Turan A, Vedder I, Zernak C, Danner K, Jokela R, Pocock SJ, Trenkler S, Kredel M, Biedler A, Sessler DI (2004) and Roewer N. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. N Engl J Med 350(24):2441-2451
12. Benevides ML, Oliveira SS, De Aguilar-Nascimento JE (2013) The combination of haloperidol, dexamethasone, and ondansetron for prevention of postoperative nausea and vomiting in laparoscopic sleeve gastrectomy: a randomized double-blind trial. Obes Surg 23(9):1389-1396
13. Dzwonczyk R, Weaver TE, Puente EG, Bergese SD (2012) Postoperative nausea and vomiting prophylaxis from an economic point of view. Am J Ther 19(1):11-15
14. Van den Bosch JE, Kalkman CJ, Vergouwe Y, Van Klei WA, Bonsel GJ, Grobbee DE, Moons KG (2005) Assessing the applicability of scoring systems for predicting postoperative nausea and vomiting. Anaesthesia 60(4):323-331
15. Pierre S (2011) Risk scores for predicting postoperative nausea and vomiting are clinically useful tools and should be used in every patient: pro-‘don’t throw the baby out with the bathwater’. Eur J Anaesthesiol 28(3):160-163
16. Wu F, Sprung J, Burkle CM, Schroeder DR, Warner DO (2006) Recent smoking behavior and postoperative nausea and vomiting. Anesth Analg 103(1):70-75
17. Madenoglu H, Yildiz K, Dogru K, Kurtsoy A, Guler G, Boyaci A (2003) Randomized, double-blinded comparison of tropisetron and placebo for prevention of postoperative nausea and vomiting after supratentorial craniotomy. J Neurosurg Anesthesiol 15(2):82-86
18. Watcha MF, White PF (1992) Postoperative nausea and vomiting. Its etiology, treatment, and prevention. Anesthesiology 77(1):162-184
19. Ryu J, So YM, Hwang J, Do SH (2010) Ramosetron versus ondansetron for the prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy. Surg Endosc 24(4):812-817
20. Fuji Y, Tanaka H, Tsuruoka S, Toyooka H, Amaha K (1994) Middle cerebral arterial blood flow velocity increases during laparoscopic cholecystectomy. Anesth Analg 78(1):80-83
21. Caldwell CB, Ricotta JJ (1987) Changes in visceral blood flow with elevated intraabdominal pressure. J Surg Res 43(1):14-20
22. Diebel LN, Dulchavsky SA, Wilson RF (1992) Effect of increased intra-abdominal pressure on mesenteric arterial and intestinal mucosal blood flow. J Trauma 33(1):45-48
23. Apfel CC, Kranke P, Eberhart LHJ, Roos A, Roewer N (2002) Comparison of predictive models for postoperative nausea and vomiting. Br J Anaesth 88(2):234-240
24. Lee WS, Lee KB, Lim S, Chang YG (2015) Comparison of palonosetron, granisetron, and ramosetron for the prevention of postoperative nausea and vomiting after laparoscopic gynecologic surgery: a prospective randomized trial. BMC Anesthesiol 15:121
25. Gan TJ, Sinha AC, Kovac AL, Jones RK, Cohen SA, Battikha JP, Deutsch JS, Pergolizzi JV Jr (2009) A randomized, double-blind, multicenter trial comparing transdermal scopolamine plus ondansetron to ondansetron alone for the prevention of postoperative nausea and vomiting in the outpatient setting. Anesth Analg 108(5):1498-1504
26. Lee Y, Wang JJ, Yang YL, Chen A, Lai HY (2007) Midazolam vs ondansetron for preventing postoperative nausea and vomiting: a randomised controlled trial. Anaesthesia 62(1):18-22
27. Markham A, Sorkin EM. Ondansetron (1993) An update of its therapeutic use in chemotherapy-induced and postoperative nausea and vomiting. Drugs 45(6):931-952
28. Smith JC 2nd and Wright EL (2005) Haloperidol: an alternative butyrophenone for nausea and
vomiting prophylaxis in anesthesia. AANA J 73(4):273–275
30. Buttner M, Walder B, von Elm E, Tramer MR (2004) Is low-dose haloperidol a useful antiemetic? A meta-analysis of published and unpublished randomized trials. Anesthesiology 101(6):1454–1463
31. Chu CC, Shieh JP, Tzeng JI, Chen JY, Lee Y, Ho ST, Wang JJ (2008) The prophylactic effect of haloperidol plus dexamethasone on postoperative nausea and vomiting in patients undergoing laparoscopically assisted vaginal hysterectomy. Anesth Analg 106(5):1402–1406
32. Roberts GW, Bekker TB, Carlsen HH, Moffatt CH, Slattery PJ, McClure AF (2005) Postoperative nausea and vomiting are strongly influenced by postoperative opioid use in a dose-related manner. Anesth Analg 101(5):1343–1348
33. Kenny GN (1994) Risk factors for postoperative nausea and vomiting. Anaesthesia 49:6–10
34. Lerman J (1992) Surgical and patient factors involved in postoperative nausea and vomiting. Br J Anaesth 69:245–251
35. Horn CC, Wallisch WJ, Homanics GE, Williams JP (2014) Pathophysiological and neurochemical mechanisms of postoperative nausea and vomiting. Eur J Pharmacol 722:55–66
36. Bourdaud N, François C, Jacqmarq O, Guye ML, Jean J, Studer C, Engrand-Donal C, Devys JM, Boutin F, Guyot E, Bouazza N, Treluyer JM, Orliaguet GA (2017) Addition of droperidol to prophylactic ondansetron and dexamethasone in children at high risk for postoperative vomiting. A randomized, controlled, double-blind study. Br J Anaesth 118(6):918–923
37. Aspinall RL, Goodman NW (1995) Denial of effective treatment and poor quality of clinical information in placebo controlled trials of ondansetron for postoperative nausea and vomiting: a review of published trials. BMJ 311(7009):844–846

Tables

Table I. Demographic data and surgical characteristics of the patients in the three groups.

|                        | Group O (n = 64) | Group OD (n = 65) | Group ODH (n = 64) | P-value |
|------------------------|-----------------|------------------|-------------------|---------|
| Age, years, years      | 46.67 ± 8.61    | 46.44 ± 8.35     | 43.96 ± 9.33      | 0.154   |
| Height, cm             | 160.31 ± 7.12   | 160.66 ± 6.82    | 160.47 ± 6.63     | 0.959   |
| Weight, kg             | 65.91 ± 11.75   | 66.68 ± 11.14    | 68.02 ± 8.64      | 0.524   |
| BMI, kg/m²             | 25.55 ± 3.54    | 25.63 ± 3.96     | 26.46 ± 3.36      | 0.297   |
| ASA I/II, n (%)        | 35 (54.69)/29   | 27 (41.54)/38    | 31 (48.44)/33     | 0.327   |
| Surgery type, n (%)    | 0.394           |                  |                   |         |
| Myomectomy             | 29 (45.31)      | 24 (39.62)       | 31 (48.44)        |         |
| Adnexectomy            | 35 (54.69)      | 41 (63.08)       | 33 (51.56)        |         |
| Duration of surgery, min | 89.56 ± 28.14 | 88.51 ± 26.81    | 91.08 ± 29.93     | 0.875   |
| Duration of anesthesia, min | 130.58 ± 27.91 | 129.06 ± 29.23 | 129.03 ± 29.56 | 0.942   |
| Remifentanil consumption, µg | 1217.47 ± 481.41 | 1184.09 ± 464.61 | 1233.31 ± 514.73 | 0.842 |

Data are expressed as mean ± standard deviation (SD) (One-way ANOVA test) or number of patients n (%) (Chi Square test). None showed any statistical significance among groups (all P > 0.05). BMI, body mass index; ASA, American Society of Anesthesiologists physical status.

Table II. Incidence of PONV and rescue antiemetics use.
|                                | Group O (n = 64) | Group OD (n = 65) | Group ODH (n = 64) | P-value |
|--------------------------------|------------------|-------------------|--------------------|---------|
| Postoperative 0–48 h Nausea    | 27 (42.19)       | 13 (20.00)*       | 10 (15.63)**#      | 0.001   |
| Retching and vomiting         | 15 (23.44)       | 5 (7.69)*         | 4 (6.25)**#        | 0.005   |
| Total PONV                    | 27 (42.19)       | 13 (20.00)*       | 10 (15.63)**#      | 0.001   |
| Rescue antiemetic use         | 21 (32.81)       | 9 (13.85)*        | 8 (12.50)**#       | 0.005   |
| Postoperative 0–2 h Nausea    | 18 (28.13)       | 7 (10.77)*        | 7 (10.94)**#       | 0.010   |
| Retching and vomiting         | 13 (20.31)       | 4 (6.15)*         | 3 (7.81)**#        | 0.006   |
| Total PONV                    | 18 (28.13)       | 7 (10.77)*        | 7 (10.94)**#       | 0.010   |
| Rescue antiemetic use         | 16 (25.00)       | 6 (9.23)*         | 5 (7.81)**#        | 0.008   |
| Postoperative 2–24 h Nausea   | 24 (37.50)       | 12 (18.46)*       | 10 (15.63)**#      | 0.007   |
| Retching and vomiting         | 14 (21.88)       | 5 (7.69)          | 4 (6.25)**#        | 0.011   |
| Total PONV                    | 24 (37.50)       | 12 (18.46)*       | 10 (15.63)**#      | 0.011   |
| Rescue antiemetic use         | 19 (29.69)       | 9 (13.85)         | 7 (10.94)**#       | 0.007   |
| Postoperative 24–48 h Nausea  | 10 (15.63)       | 6 (9.23)          | 5 (7.81)#          | 0.318   |
| Retching and vomiting         | 4 (6.25)         | 1 (1.54)          | 2 (3.13)#          | 0.347   |
| Total PONV                    | 10 (15.63)       | 6 (9.23)          | 5 (7.81)#          | 0.318   |
| Rescue antiemetic use         | 2 (3.13)         | 0                 | 0 N/A              |         |

Data are expressed as number of patients n (%) (Chi Square test). N/A, not applicable due to small number of samples. *P < 0.017, compared with Group O; #P > 0.017, compared with Group OD. PONV, postoperative nausea and vomiting.

Table III. Postoperative pain, PCA consumption, rescue analgesics use and postoperative adverse effects.
|                              | Group O (n = 64) | Group OD (n = 65) | Group ODH (n = 64) | P-value |
|------------------------------|-----------------|------------------|-------------------|---------|
| Postoperative 0–2 h          |                 |                  |                   |         |
| VAS score                    | 4.39 ± 1.70     | 4.13 ± 1.76      | 4.47 ± 1.79       | 0.515   |
| PCA consumption, ml          | 4.59 ± 1.73     | 4.31 ± 1.65      | 4.52 ± 1.60       | 0.614   |
| Rescue analgesics use, n (%) | 6 (9.38)        | 8 (12.31)        | 6 (9.38)          | 0.819   |
| Postoperative 2–24 h         |                 |                  |                   |         |
| VAS score                    | 2.13 ± 1.62     | 2.23 ± 1.44      | 1.96 ± 1.43       | 0.469   |
| PCA consumption, ml          | 25.41 ± 4.88    | 27.18 ± 8.02     | 26.22 ± 5.38      | 0.273   |
| Rescue analgesics use, n (%) | 16 (25.00)      | 17 (26.15)       | 14 (21.88)        | 0.843   |
| Postoperative 24–48 h        |                 |                  |                   |         |
| VAS score                    | 1.06 ± 1.20     | 1.05 ± 1.18      | 0.91 ± 1.14       | 0.703   |
| PCA consumption, ml          | 25.78 ± 2.62    | 26.28 ± 3.54     | 25.94 ± 2.78      | 0.633   |
| Rescue analgesics use, n (%) | 2 (3.13)        | 4 (6.15)         | 2 (3.13)          | 0.608   |
| Adverse effect 0–48 h        |                 |                  |                   |         |
| Headache                     | 1               | 0                | 0                 | N/A     |
| Dizziness                    | 0               | 0                | 1                 | N/A     |
| Cardiac arrhythmias          | 0               | 0                | 0                 | N/A     |
| Extrapyramidal syndrome      | 0               | 0                | 0                 | N/A     |
| Others                       | 0               | 0                | 0                 | N/A     |

Data are expressed as mean ± standard deviation (SD) (One-way ANOVA test) or number of patients n (%) (Chi Square test). None showed any statistical significance among groups (all P > 0.05). N/A, not applicable due to small number of samples. VAS, visual analogue scale; PCA, patient-controlled analgesia.

Figures
Supplementary Files

This is a list of supplementary files associated with the primary manuscript. Click to download.

Data.xls