



CLINICAL RESEARCH

Effect of palonosetron, ondansetron and dexamethasone in the prevention of postoperative nausea and vomiting in video cholecystectomy with total venous anesthesia with propofol-remifentanyl – randomized clinical trial[☆]



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KEYWORDS

Anesthesia, adverse effects;
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Abstract

Introduction and objectives: The incidence of Postoperative Nausea and Vomiting (PONV) after video cholecystectomy is high. Progress in pharmacological PONV prophylaxis includes a new generation of 5-HT₃ antagonists. This study aims to assess the effect of the 5-HT₃ antagonist in postanesthetic antiemetic management of patients submitted to laparoscopic cholecystectomy with total intravenous anesthesia.

Methods: Sixty individuals who underwent video cholecystectomy were randomized into three groups of 20 individuals according to the treatment administered: 0.125 mg of palonosetron (Group 1); 4 mg of ondansetron associated with 4 mg of dexamethasone (Group 2); 4 mg

[☆] Estudo realizado no Hospital de Clínicas da Faculdade de Medicina da Universidade Federal de Uberlândia.

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PALAVRAS-CHAVE

Anestesia, efeitos adversos;
Antiêméticos, uso terapêutico;
Colecistectomia laparoscópica, efeitos adversos

of dexamethasone (Group 3). General intravenous anesthesia was performed with propofol, remifentanyl and rocuronium. The group to which the participant belonged was concealed from the investigator who assessed drug effect. PONV was assessed using the Rhodes Scale at 12 and 24 hours after surgery. Rescue medication was 0.655 to 1.5 mg of droperidol.

Results: Group 1 presented a lower incidence of PONV and required less rescue medication in the first postoperative hour. There was no significant difference among the three groups regarding PONV incidence in the first 12 postoperative hours. Groups 1 and 2 were superior to Group 3 regarding the control of PONV from 12 to 24 hours, and after rescue medication from 12 to 24 hours. Group 1 showed significantly superior nausea control in the first 12 postoperative hours.

Conclusions: The present study showed evidence that palonosetron is superior to the drugs compared regarding a protracted antiemetic effect and less requirement of rescue drugs, mainly related to its ability to completely inhibit the uncomfortable symptom of nausea.

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Efeito da palonosetrona, ondansetrona e dexametasona na prevenção de náusea e vômito pós-operatório em videolecistectomia com anestesia venosa total com propofol-remifentanil – ensaio clínico randomizado duplo cego**Resumo**

Justificativa e objetivo: Náuseas e Vômitos (NVPO) têm alta incidência após videolecistectomia. Avanços na profilaxia farmacológica de NVPO incluem a nova geração de antagonista 5-HT₃. O objetivo deste estudo foi avaliar o efeito do antagonista 5-HT₃ no controle antiemético pós-anestésico em videolecistectomia com anestesia venosa total.

Método: Estudo realizado no HC-UFU (Hospital terciário). Sessenta indivíduos submetidos a videolecistectomia foram randomizados em três grupos de igual número, sendo administrados 0,125 mg de palonosetrona (Grupo 1); 4 mg de ondansetrona e 4 mg de dexametasona (Grupo 2); ou 4 mg de dexametasona (Grupo 3). A anestesia geral venosa foi realizada com propofol, remifentanil e rocurônio. O avaliador do efeito da droga desconhecia o grupo ao qual o indivíduo pertencia. NVPO foi avaliada aplicando a Escala de Rhodes após 12 e 24 horas do término da cirurgia. Para resgate terapêutico, foi estabelecido 0,655–1,5 mg de droperidol.

Resultado: Observou-se no Grupo 1 menor incidência de NVPO e de resgate terapêutico na primeira hora de PO. Não foi observada diferença significativa entre os três grupos com relação a ocorrência de NVPO nas primeiras 12 horas de pós-operatório. Os grupos 1 e 2 foram superiores ao Grupo 3 no que se refere ao controle de NVPO de 12 a 24 horas e após o resgate de 12–24 horas. Observou-se que o controle de náuseas nas primeiras 12 horas de pós-operatório do Grupo 1 foi significativamente superior.

Conclusão: O presente estudo mostrou evidências da superioridade da palonosetrona às demais drogas empregadas no que se refere ao efeito antiemético prolongado e menor necessidade de resgate, principalmente na capacidade de inibir completamente o desconfortável sintoma de náusea.

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Introduction

Progress of laparoscopic surgery techniques has provided increase in outcome quality and decrease in morbidity and mortality associated with the procedures. However, some postoperative undesirable events that are also related to the anesthesia technique are still relevant,¹ therefore require similar advances to achieve a satisfactory outcome of the technique.

One of the major and most unpleasant complications after laparoscopic cholecystectomy is Postoperative Nausea

and Vomiting (PONV), which is associated with higher risk of pulmonary aspiration of gastric contents. In previously healthy patients, the PONV rate in the initial 24 hours is 30% to 40%, and it reaches 75% to 80% in high-risk procedures^{2,3} such as laparoscopic surgery.⁴

Progress in PONV prophylaxis includes using several strategies, both pharmacological and non-pharmacological; nevertheless, they are considered of limited effectiveness due to the risk of side effects and are expensive.⁴ Thus, new therapeutic options have been proposed to mitigate the incidence of PONV.

The development of palonosetron, a new long-acting 5-HT₃ antagonist, has provided an opportunity to reduce the incidence of PONV in medical practice. Palonosetron is as effective as other antiemetic drugs, but safer because it has a lower rate of side effects, such as extrapyramidal effects and dysphoria.^{5,6} All 5-HT₃ antagonists, such as ondansetron and palonosetron, have a favorable performance as antiemetic drugs. Alone or in combination with other drugs, ondansetron has been routinely used for prophylaxis of PONV, mainly because of its low cost. Palonosetron, on the other hand, has a significantly greater affinity for the receptor and a longer half-life, providing prolonged duration of action that can be beneficial for PONV management.⁷

This study aimed to assess the effect of palonosetron compared to ondansetron and dexamethasone in the control of PONV after laparoscopic cholecystectomy.

Methods

The study was approved by the University Research Ethics Committee (CEP-UFU), under registration number CAAE 55861514.7.0000.5152, and registered on the Brazilian Clinical Trial Registry platform ReBEC/ICT/LIS, number RBR-9b6486 (<http://www.ensaiosclnicos.gov.br/rg/edit/9141/>).

The parallel, randomized, double-blind clinical trial, with 1:1 allocation was performed to evaluate the possible superiority of palonosetron, and was carried out at the Hospital de Clínicas, Universidade Federal de Uberlândia (public tertiary hospital). The recruitment period was from September 2016 to November 2018. Sixty participants were included divided in three equal groups using a random draw without repetition, with random functions among orders. We included participants aged 18 to 70 years, presenting physical status ASA (American Society of Anesthesiologists) I and II, undergoing elective laparoscopic cholecystectomy under total intravenous anesthesia. A virtual tool (available at <https://www.4devs.com.br>) was employed to use sequences of random numbers placed in sealed and opaque envelopes to perform the allocation of study participants. Allocation was performed when the patient was brought to the operating room, according to the sequence of envelopes. The envelopes were kept in a locked cabinet in the anesthesiology department to ensure confidentiality. We established that if a patient presented ECG with electrical conduction abnormalities, particularly prolonged QTc, the patient would be submitted to further investigation. The study excluded individuals with a history of hypersensitivity or contraindication to the 5-HT₃ antagonist, individuals intellectually unable to cooperate with evaluation procedures; pregnant women; individuals who had participated in any drug investigation within less than 30 days; those who had been using any potentially antiemetic medication in less than the past 24 hours, or who had any symptoms of nausea or vomiting in the same period; alcohol abusers and users of illicit drugs.

Participants were fasting for 8 to 10 hours and did not receive preanesthetic medication. Upon arrival to the operating room, they were continuously monitored with continuous ECG tracing, noninvasive arterial blood pressure

monitor, Pulse Oximeter (SpO₂), and Capnograph (ETCO₂) after Orotracheal Intubation (OTI).

Venipuncture was performed with an 18G Teflon cannula in the upper limb for intravenous (IV) medication administration and fluid replacement with Ringer's lactate solution at a rate of 5 to 10 mL.kg⁻¹.h⁻¹.

For control and prophylaxis of PONV, each group received 0.125 mg of palonosetron (Group 1), 4 mg of ondansetron associated with 4 mg of dexamethasone (Group 2), or 4 mg dexamethasone associated with 2 mL of distilled water (Group 3). The drug was administered intravenously before anesthesia induction, diluted in 100 mL of saline. The professional responsible for evaluating the effect of the intervention, and the assistant anesthesiologist were blind to the medication administered or to which group the participant assessed belonged to.

All individuals were submitted to the same anesthetic technique. Anesthesia was induced and maintained with propofol and remifentanyl. Propofol was administered with target-controlled infusion using the dose of 2.5–3.5 µg.mL⁻¹. For propofol infusion the March pharmacokinetic model was adopted for calculation at the plasma target site. Remifentanyl was manually adjusted with doses ranging from 0.1 to 0.3 µg.kg⁻¹.h⁻¹, according to clinical response to anesthesia. The neuromuscular block was performed with 0.6 mg.kg⁻¹ rocuronium at induction of anesthesia in order to facilitate OTI and the surgical procedure. Pulmonary ventilation was performed using a respiratory rate of 8 to 14 bpm, calculated tidal volume from 6 to 9 mL.kg⁻¹ and 5 cm.H₂O PEEP, adjusted to maintain an Expired concentration of Carbon Dioxide (E_TCO₂) from 35 to 40 mmHg and a 1:1 mixture oxygen to air. Arterial blood pressure, heart rate and arterial O₂ Saturation (SpO₂) were recorded during pre-induction and at five-minute intervals, immediately after induction and until tracheal extubation. ECG with ST segment analysis was continuously monitored. For postoperative analgesia, IV 100 mg ketoprofen and 2 g dipyrone were administered at starting anesthesia. At the PACU (Post-Anesthetic Recovery Room), 10 mg of subcutaneous morphine was provided as rescue analgesia.

Using electronic temperature probes, we measured and recorded esophageal and axillary temperatures. Axillary temperature readings were performed at the side contralateral to the venous fluid infusion line. Temperature readings were obtained immediately after anesthesia induction and every 15 minutes after the pneumoperitoneum was established. Pneumoperitoneum was kept adjusting intra-abdominal pressure between 10 and 15 mmHg. Room temperature was set between 23 and 25 degrees Celsius (°C). The fluids administered were warmed to a temperature between 34° and 36 °C. The CO₂ insufflated was not warmed and all patients were positioned with the table tilted to a 15° head-up position after CO₂ insufflation. All laparoscopic cholecystectomies were performed by the same surgeon, with the same type of surgical instruments.

In the PACU, a warming blanket was used for those patients presenting axillary temperature below 36 °C.

Whenever required, PONV rescue treatment would be performed with 0.655 to 1.5 mg of droperidol IV.

To assess PONV symptoms, the Rhodes scale was used (Table 1) in the first 12 and 24 hours.

Table 1 Description of the Rhodes scale.

During the last 12 hours I threw up ---- times.
During the last 12 hours I nearly threw up or I felt sick to my stomach ----
During the last 12 hours after throwing up I felt sick ----
During the last 12 hours I felt sick to my stomach or was nauseated ----
During the last 12 hours the quantity of each vomit was ----
During the last 12 hours I felt nausea or sick to my stomach ---- times.
During the last 12 hours, without eating or drinking, I threw up or felt retching ---- times.

Statistical analysis

For sample determination the population size considered the number of surgeries performed annually by the same surgeon and totaled 240 procedures (n = 240).

A 95% Confidence Interval ($\alpha=0.05$), 80% statistical power and an 11% margin of error ($E=0.11$) were adopted. Since \hat{p} and $+q$ are unknown, they were considered equal to 0.5. Thus, we estimated the sample study as 60 participants (n = 60).

Descriptive analysis was used to outline and summarize data. Statistical inference analysis was used to assess whether there was a significant difference between participant features regarding biological sex, age and surgical factors, such as duration of anesthesia, duration of surgery, duration of pneumoperitoneum, volume of pneumoperitoneum, and intraoperative intra-abdominal pressure during pneumoperitoneum, and to assess whether there was a significant difference between the drugs administered regarding postoperative complication rates.

The ANOVA F-test was used to compare characteristics of the patient regarding biological sex, age and ASA physical status. Non-parametric tests were adopted if the samples did not present normality, homogeneity and independence.⁸⁻¹⁰

To assess age difference among groups the normality of the residues, the homogeneity of the variances and the independence of the residues were checked with the Shapiro-Wilk test, Bartlett test and Durbin-Watson test, respectively, then followed by the ANOVA test. For the other variables, we used the Kruskal-Wallis test.

Postoperative complication variables (PONV, rescue treatment, nausea and vomiting) were measured by multiple asymptotic comparisons of binomial proportions.⁸⁻¹⁰

Statistical significance was set at 5% ($p < 0.05$).

Statistical analysis was performed using free software⁸ for the reproduction of reports, and the statistician analyzing the data was blinded to the group to which each participant of the study was allocated.

Results

Figure 1 shows the distribution of study participants and their allocation.

Anthropometric data showed no significant difference among groups, as seen in Table 2. The hemodynamic

Table 2 Anthropometric data of individuals studied (Group 1, Palonosetron; Group 2, Ondansetron and dexamethasone; Group 3, Dexamethasone).

	Treatment		
	1 (n = 20)	2 (n = 20)	3 (n = 20)
Age (years)	42.25 ± 8.98 (28–59)	43.45 ± 11.01 (21–64)	43.15 ± 8.29 (28–56)
Gender			
Male	5	3	6
Female	15	17	14
ASA			
I	17	5	6
II	3	15	14

Values shown as mean ± standard deviation (minimum – maximum values).

variables used for anesthesia clinical control during the procedure were uniform among groups, and there was no change in the ST segment.

The anesthesia variables monitored during laparoscopic cholecystectomy (blood pressure, heart rate, SpO₂, E_TCO₂, ST interval) were uniform among groups and showed no significant difference.

The variables studied during the surgery are shown in Table 3. There was a significant difference when Group 1 was compared to the other groups.

Table 4 shows the Rhodes Scale data for the groups studied. Group 1 (palonosetron) was observed to have a lower incidence of PONV and required less rescue treatment in the first hour. Group 1 also showed lower incidence of nausea and required less rescue treatment in the initial 12 hours postoperatively. In addition, we observed that Group 3 had a higher incidence of vomiting, PONV and required more rescue treatment during the period of 12 to 24 hours postoperatively.

Detailed data description and statistical analysis can be found on the link: <https://data.mendeley.com/datasets/7tfhyj9hyt/draft?a=44d0389e-ffe8-45f1-832f-7d0447d80713>.

Discussion

At the beginning of the 19th century, when ether was used as the inhalation anesthetic agent, the incidence of PONV was high, approximately 70–80%. Currently, with the progress in anesthetic practice, PONV incidence has dropped by 50%, mainly due to the use of non-opioid drugs for pain relief. There is a strong correlation between the dose of opioid used for postoperative pain control and the incidence of PONV. Thus, the opioid dose administered must be judiciously titrated to trigger minimal effect on antiemetic drug effectiveness.¹¹⁻¹³

Certain surgeries are associated with a high incidence of PONV (e.g. abdominal surgeries), not specifically because of involvement of emetogenic pathways, but possibly due to long exposure to inhaled anesthetics and high doses of opioids. In addition, selected types of surgery themselves are

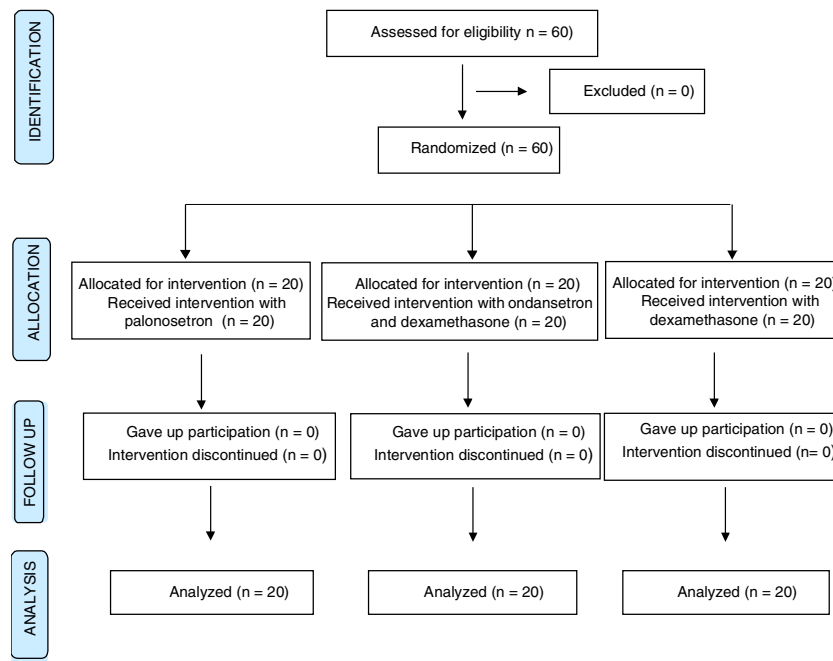


Figure 1 CONSORT 2010 study flow chart.

Table 3 Surgical procedure data of patients in study groups (Group 1, Palonosetron; Group 2, Ondansetron and dexamethasone; Group 3, Dexamethasone).

	Treatment		
	1 (n = 20)	2 (n = 20)	3 (n = 20)
Anesthesia duration (min)	96.9 (50–140) 100 ^a	77.75 (55–100) 76	81.45 (60–100) 80
Surgery duration (min)	66.75 (20–120) 65 ^a	50.9 (35–90) 48.5	52.85 (40–70) 52.5
Pneumoperitoneum duration (min)	44.55 (30–99) 46.5	35.1 (25–69) 34	36.9 (28–52) 35
Pneumoperitoneum volume (L)	87.73 (45–168) 72.5 ^a	56.78 (35–110) 56.5	55.45 (30–118) 51
Transoperative intra-abdominal pressure (mm Hg)	14.6 (12–15) 15	14.9 (13–15) 15	14.7 (10–15) 15

Values shown as mean (minimum – maximum values), median.

^a Difference among groups was statistically significant.

Table 4 Results from the multiple comparisons proportion test for postoperative complication variables.

Time	Event	Treatment		
		1 (n = 20)	2 (n = 20)	3 (n = 20)
0–1 h	PONV	0	2 (10) ^a	6 (30) ^a
	Rescue	0	3 (15) ^a	(30) ^a
1–12 h	Nausea	3 (15)	15 (75) ^a	13 (65) ^a
	Vomiting	2 (10)	9 (45)	7 (35)
12–24 h	PONV	2 (10)	9 (45)	7 (35)
	Rescue	0	11 (55) ^a	11 (55) ^a
	Nausea	1 (5)	2 (10)	6 (30) ^a
	Vomiting	0	0	2 (10) ^{a,b}
	PONV	0	0	2 (10) ^{a,b}
	Rescue	0	0	2 (10) ^{a,b}

PONV, Postoperative Nausea and Vomiting.

Results are shown as absolute numbers and percentage (%).

^a Statistically significant difference versus Group 1.

^b Statistically significant difference versus Group 2.

risk factors that increase PONV, among which, laparoscopy, gynecological surgery, and cholecystectomy.^{14–18}

Our study sample correlates with previous criteria, in the expectation of achieving post-anesthesia benefits in patients undergoing laparoscopic cholecystectomy surgeries.

For surgical populations presenting high risk for PONV, such as those above listed, combined treatments such as general anesthesia with propofol and other drugs are recommended,¹⁹ and were the rationale for the anesthetic technique used in the present study. We aimed to compare the effects of three drugs, administered alone or in combination, as methods of PONV prophylaxis. Studies investigating the dose of ondansetron considered optimal for PONV control, suggested 8 mg as the appropriate dose.¹⁸ However, a recent PONV management consensus published by Gan et al.⁴ described high-level evidence pointing out that 4 mg of ondansetron showed less side effects and effects similar to 8 mg of ondansetron. This was the proposal adopted and carried out by the present study, as well as the indication of the association of 4 mg of dexamethasone to reduce PONV incidence.

Dexamethasone administered alone was used in this study due to its intrinsic antiemetic⁴ and analgesic effects, according to a meta-analysis that demonstrated strong evidence in the first two postoperative hours.²⁰

Palonosetron, another 5-HT₃ receptor agonist, was used in this study. The drug is currently recommended for the prevention of PONV based on scientific evidence, however, there are divergences as to the ideal dose, that ranges from 0.025 to 0.125 mg. In this study we administered the dose of 0.125 mg, as recommended by Gan et al.⁴

Palonosetron is a second generation serotonergic 5HT₃ receptor antagonist, and it differs from other antagonists by its unique structure as well as its clinical and pharmacological features. Serotonin (5HT₃) is a ubiquitous central and peripheral neurotransmitter and it is considered the main mediator of the perception of nausea and vomiting, due to the central and peripheral serotonin pathways of nausea and vomiting. Other antagonists, such as ondansetron, compete with serotonin, but palonosetron has an indirect effect on allosteric inhibition of the 5HT₃ receptor.²¹ Thus, palonosetron inhibits the release of substance P secreted by specific sensory nerves and inflammatory cells, inhibiting the activation of Neurokinin-1 (NK-1R) receptors and consequently promotes antiemetic effect. This explains the strong drug affinity for the receptor and its longer half-life, when palonosetron is compared to other drugs.²²

Because the participants of the study were considered high-risk for PONV, justifying the use of prophylactic measures, for ethical reasons this study did not include a placebo control group.

We observed that Group 1 showed a lower incidence of PONV and less rescue drug requirement in the first postoperative hour. There was no significant difference among the three groups regarding the occurrence of PONV in the first 12 postoperative hours. Groups 1 and 2 showed superior results when compared to Group 3 regarding PONV control from 12 to 24 hours and after rescue from 12 to 24 hours.

This study showed that in the initial 12 postoperative hours, nausea control using palonosetron presented results significantly superior to the other methods used. Therefore, it supports the results of previous studies that compared

the effect of palonosetron to other 5HT₃ receptor antagonists. Among these, Park and Cho²³ compared the use of 8 mg ondansetron versus 0.075 mg palonosetron in laparoscopic gynecological surgery, and in the first 24 postoperative hours there was a significantly lower incidence of PONV in the palonosetron group compared to the ondansetron group, 42.2% versus 66.7%, respectively.²³ Similarly, Moon et al. compared the effects of palonosetron versus ondansetron in the prevention of PONV in patients submitted to thyroidectomy and concluded that palonosetron showed results superior to ondansetron in the period between 2–24 postoperative hours, with PONV incidence of 42% versus 62%, respectively.²⁴ Similar studies in different clinical scenarios corroborate these results.^{25–29}

This study presents limitations. The characteristics of study participants are different, with Group 1 presenting longer surgery and anesthesia durations and larger pneumoperitoneum volume. Nonetheless, this group profited the most by the reduction in the incidence of PONV. Both number of participants and number of outcomes are low. Thus, results from the intervention may be superior to those achieved by this study, and as new studies are added answers may surface.

The present study showed evidence of possible superiority of palonosetron to the drugs compared regarding a protracted antiemetic effect and fewer requirements for rescue drug, mainly related to its ability to completely inhibit the uncomfortable nausea symptom. We believe that additional studies assessing the beneficial impact on the length of hospital stay, as well as cost-effectiveness can provide complementary data on the actual benefit of palonosetron, since both the number of participants and outcomes in this study were low.

Conflicts of interest

The authors declare no conflicts of interest.

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References

1. Kapur PA. The big ‘‘little problem’’. *Anesth Analg.* 1991;73: 243–5.
2. Sniadach MS, Alberts MS. A comparison of the prophylactic antiemetic effect of ondansetron and droperidol on patients undergoing gynaecologic laparoscopy. *Anesth Analg.* 1997;85:797–800.
3. Apfel CC, Laara E, Koivuranta M, et al. A simplified risk scores for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centres. *Anesthesiology.* 1999;91:693–700.
4. Gan TJ, Belani KG, Bergese S, et al. Forth consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg.* 2020;131:411–48.
5. Paxton DL, Mckay CA, Mirakin KR. Prevention of nausea and vomiting after day case gynaecological laparoscopy. A compari-

- son of ondansetron, droperidol, metoclopramide and placebo. *Anaesthesia*. 1995;50:403–6.
6. Loewen PS, Marra CA, Zed PJ. 5-HT₃ receptor antagonists vs. traditional agents for the prophylaxis of postoperative nausea and vomiting. *Can J Anaesth*. 2000;47:1008–18.
 7. Wong EH, Clark R, Leung E, et al. In vitro the interaction of RS 25259-197, a potent and selective antagonist, with 5-HT₃ receptors. *Br J Pharmacol*. 1995;114:851–9.
 8. Core R, Team R. A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2013.
 9. Conover WJ. Practical nonparametric statistics. 3. ed. John Wiley & Sons, Inc; 1999.
 10. Dunn OJ. Multiple comparisons using rank sums. *Technometrics*. 1964;6:241–52.
 11. Rowbotham DJ. Current management of postoperative nausea and vomiting. *Br J Anaesth*. 1992;69:46–59.
 12. Boer HD, Detriche O, Forget P. Opioid-related side effects: postoperative ileus, urinary retention, nausea and vomiting, and shivering. A review of the literature. *Best Pract Res Clin Anaesthesiol*. 2017;31:499–504.
 13. Roberts GW, Bekker TB, Carlsen HH, et al. Postoperative nausea and vomiting are strongly influenced by postoperative opioid use in a dose related manner. *Anesth Analg*. 2005;101:1343–8.
 14. Sinclair DR, Chung F, Mezei G. Can postoperative nausea and vomiting be predicted? *Anesthesiology*. 1999;91:109–18.
 15. Apfel CC, Kranke P, Katz MH, et al. Volatile anaesthetics may be the main cause of early but not delayed postoperative vomiting: a randomized controlled trial of factorial design. *Br J Anaesth*. 2002;88:659–68.
 16. Apfel CC, Kranke P, Eberhart LH. Comparison of surgical site and patient's history with a simplified risk score for the prediction of postoperative nausea and vomiting. *Anaesthesia*. 2004;59:1078–82.
 17. Cohen MM, Duncan PG, DeBoer DP, et al. The postoperative interview: assessing risk factors for nausea and vomiting. *Anesth Analg*. 1994;78:7–16.
 18. Wallenborn J, Gelbrich G, Bulst D, et al. Prevention of postoperative nausea and vomiting by metoclopramide combined with dexamethasone: randomised double-blind multicentre trial. *BMJ*. 2006;333:324.
 19. Habib AS, Gan TJ. Evidence-based management of postoperative nausea and vomiting: a review. *Can J Anaesth*. 2004;51:326–41.
 20. Waldron NH, Jones CA, Gan TJ, et al. Impact of perioperative dexamethasone on postoperative analgesia and side-effects: systematic review and meta-analysis. *BJA*. 2013;110:191–200.
 21. Rojas C, Stathis M, Thomas AG, et al. Palonosetron exhibits unique molecular interactions with the 5-HT₃ receptor. *Anesth Analg*. 2008;107:469–78.
 22. Rojas C, Li Y, Zhang J, et al. Anti-emetic 5-HT₃ receptor antagonist palonosetron inhibits substance P-mediated responses in vitro and in vivo. *J Pharmacol Exp Ther*. 2010;335:362–8.
 23. Park SK, Cho EJ. A randomized, double-blind trial of palonosetron compared with ondansetron in preventing postoperative nausea and vomiting after gynaecological laparoscopic surgery. *J Int Med Res*. 2011;39:399–407.
 24. Moon YE, Joo J, Kim JE, et al. Anti-emetic effect of ondansetron and palonosetron in thyroidectomy: a prospective, randomized, double-blind study. *Br J Anaesth*. 2012;108:417–22.
 25. Braga ELC, Figueiredo NV, Barrucand L, et al. Use of palonosetron and ondansetron in the prophylaxis of postoperative nausea and vomiting in women 60 years of age or older undergoing laparoscopic cholecystectomy: A randomized double-blind study. *Eur J Anaesthesiol*. 2019;36:241–2.
 26. Chatterjee A, Sahu S, Paul M, et al. Comparison of efficacy of palonosetron- dexamethasone combination with palonosetron or dexamethasone alone for prophylaxis against post-operative nausea and vomiting in patients undergoing laparoscopic cholecystectomy. *Indian J Anaesth*. 2017;61:978–84.
 27. Kumar A, Solanki SL, Gangakhedkar GR, et al. Comparison of palonosetron and dexamethasone with ondansetron and dexamethasone for postoperative nausea and vomiting in post-chemotherapy ovarian cancer surgeries requiring opioid-based patient- controlled analgesia: A randomised, double-blind, active controlled study. *Indian J Anaesth*. 2018;62:773–9.
 28. Campos GO, Martins MJ, Jesus GN, et al. Palonosetron versus ondansetron for prevention of nausea and vomiting after total abdominal hysterectomy under spinal anesthesia with intrathecal morphine: a double-blind, randomized controlled trial. *BMC Anesthesiol*. 2019;19:2–6.
 29. Ferreira NGA, Cavalcanti IL, Assad AR, et al. A prospective, randomized, double-blind trial to compare body weight-adjusted and fixed doses of palonosetron for preventing postoperative nausea and vomiting in obese female patients. *PLOS ONE*. 2020;14:1–11.