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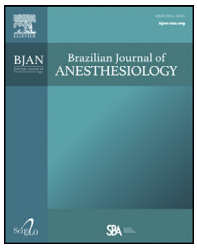

ORIGINAL INVESTIGATION

Palonosetron versus ondansetron for prophylaxis of postoperative nausea and vomiting in laparoscopic cholecystectomy: a non-inferiority randomized controlled trial☆

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Abstract

Background: We tested the hypothesis that, within the margin of 15% of risk difference, palonosetron is not inferior to ondansetron in reducing the incidence of postoperative nausea and vomiting (PONV) in laparoscopic cholecystectomy.

Methods: We conducted a double-blind, non-inferiority, randomized, controlled trial of 212 patients aged 18 to 65 years undergoing laparoscopic cholecystectomy under general anesthesia in two secondary care hospitals. Patients were randomly assigned to receive either palonosetron (0.075 mg) or ondansetron (8 mg) intravenously at induction of anesthesia. Ondansetron (8 mg) was also administered 8 and 16 hours postoperatively. All anesthetic and surgical procedures were standardized. Patients were evaluated for 24 hours postoperatively for the occurrence of PONV.

Results: A high incidence of PONV was observed at 2–6 hours postoperatively, with a rate of 36.8% (95% confidence interval [CI] 28.2–46.3) in the palonosetron group, as compared to 43.4% (95% CI 34.4–52.9) in the ondansetron group. The risk difference (95% CI) between palonosetron and ondansetron for PONV was 0 (-10.9 to 10.9) at 0–2 hours, -6.6 (-19.4 to 6.5) at 2–6 hours, -0.9 (-11.0 to 9.2) at 6–12 hours, and -2.8 (-9.6 to 3.6) at 12–24 hours. There was no statistically significant difference between the palonosetron and ondansetron groups in the use of rescue medication (dimenhydrinate). There were no adverse events associated with the medications under study.

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Conclusion: Palonosetron is not inferior to ondansetron in patients at risk of PONV undergoing laparoscopic cholecystectomy, providing a good option for PONV prophylaxis, as it can be administered in a single dose.
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Introduction

Nausea and vomiting are undesirable events commonly experienced by patients postoperatively, which are frequently cited as a major cause of patient dissatisfaction with anesthesia.[1] After general anesthesia, the occurrence of nausea and vomiting may lead to prolonged stay of patients in the recovery room and, consequently, to delayed discharge from hospital.[2] These symptoms occur more frequently in the first 24 hours after general anesthesia, with an incidence of up to 80% in patients with associated risk factors and without the use of any prophylactic medication.[3]

Ondansetron was one of the first 5-hydroxytryptamine-3 ($5\text{-}HT_3$) receptor antagonists to be used in the prophylaxis of postoperative nausea and vomiting (PONV) and, currently, it is still widely used. In the same pharmacological class, palonosetron has a receptor binding affinity 100 times that of other antiemetics.[4] Its use has been reported in the control of PONV with a prolonged half-life of 40 hours and therapeutic effect lasting up to 72 hours when administered intravenously. Palonosetron is the only $5\text{-}HT_3$ receptor antagonist not associated with prolonged QT interval.[5]

Several studies have compared palonosetron and ondansetron in laparoscopic surgery,[6–9] but none has evaluated palonosetron versus three intravenous doses of ondansetron, 8 mg, a dose considered to be optimal in the prophylaxis of PONV.[10] Considering this strategy to be fairer than those comparing palonosetron with a single dose or with lower doses of ondansetron, as these two drugs have a very different pharmacokinetic profile, we planned a non-inferiority trial to compare the efficacy of palonosetron versus ondansetron in reducing the incidence of PONV in adults undergoing elective laparoscopic cholecystectomy. The non-inferiority hypothesis is that palonosetron, compared with ondansetron (control), does not have an inferior effect in reducing PONV due to a risk difference less than or equal to the non-inferiority margin of 15%.

Methods

After approval by the institution's research ethics committee, a double-blind, non-inferiority, randomized, controlled trial was conducted in adult patients undergoing elective laparoscopic cholecystectomy in two secondary care hospitals. The trial was designed and reported according to the CONSORT Statement and is registered at the Brazilian Clinical Trials Registry platform (ReBEC, www.ensaiosclinicos.gov.br), number RBR-4mjv6r. We prospectively included patients in the study from February 2017 to October 2018. Eligible participants were aged 18 to 65 years, of both sexes, with physical status classified as American Society of Anesthesiologists (ASA) I and II. Exclusion criteria were allergy to the medications under study, use of antiemetics within 48 hours prior to surgery, and presence of hiatal hernia. During preanesthetic evaluation, patients were informed of the study purpose and procedures, and those interested in participating provided written informed consent for enrolment in the study.

Interventions

After an 8- to 10-hour fast and 30 minutes before surgery, a single dose of midazolam was administered orally as a 15-mg tablet. A peripheral intravenous line was placed in the upper limb and lactated Ringer's solution was infused ($20\ mL.kg^{-1}.h^{-1}$) throughout the surgery.

A staff member with no active involvement in the anesthetic-surgical procedures prepared the syringes with the medications to be administered according to previously sealed envelopes, which had been prepared and sequentially numbered from 1 to 212, as follows: ondansetron group, three identical syringes containing 4 mL of solution, with 8 mg of ondansetron (4 mL), were prepared and numbered 1, 2, and 3; palonosetron group, one syringe containing 0.075 mg of palonosetron (1.5 mL) and 2.5 mL of 0.9% saline was prepared and numbered 1, while two identical syringes containing 4 mL of 0.9% saline were prepared and numbered 2 and 3. The solutions were prepared following the numerical order of the envelopes. Before induction of anesthesia, the anesthesiologist, blinded to group allocation, administered solution number 1 intravenously. Eight hours after intravenous injection of solution number 1, solution number 2 was administered intravenously by a healthcare professional blinded to group allocation; after 16 hours, solution number 3 was also administered intravenously. Patients with recurrent PONV were given an intravenous injection of a solution containing dimenhydrinate, 30 mg, repeated every 6 hours, if necessary.

Induction of anesthesia was standardized for all patients, who received fentanyl ($3\ \mu g.kg^{-1}$), propofol ($2\ mg.kg^{-1}$), and atracurium ($0.4\ mg.kg^{-1}$). Anesthesia was maintained with remifentanil (0.1 to $0.3\ \mu g.kg^{-1}.min^{-1}$) and sevoflurane at an alveolar concentration of 2 to 3%, fresh gas flow of $2\ L.min^{-1}$, and inspired oxygen fraction of 60%. We did not plan to reverse neuromuscular blockade, but, if necessary and according to our clinical judgement, neostigmine ($0.03\ mg.kg^{-1}$), preceded by atropine (1 mg), would be administered. For postoperative analgesia, patients received ketoprofen (100 mg) intravenously every 12 hours, metamizole (2 g) intravenously every 8 hours,

and methadone (0.1 mg.kg^{-1}) intravenously 15 minutes before the end of surgery, repeated every 12 hours if necessary. With return of adequate ventilatory function and after awakening, patients were extubated and taken to the postanesthesia care unit, where they stayed for at least 90 minutes. Patients were discharged to the ward after achieving a score of 9 or 10 on the Aldrete-Kroulik scale.

Outcomes

A dichotomous assessment was performed of whether nausea, vomiting, or nausea and vomiting were present or absent. Patients were evaluated for 24 hours postoperatively, and the outcomes were analyzed according to the period of symptom occurrence: a) first 2 hours after surgery; b) from 2 to 6 hours after surgery; c) from 6 to 12 hours after surgery; and d) from 12 to 24 hours after surgery. An anesthesiologist blinded to group allocation evaluated the patients. The absolute number of doses of dimenhydrinate used in each group was evaluated as a secondary outcome. All adverse effects observed and possibly related to the medications under study were recorded.

Statistical analysis

The non-inferiority margin for this study was defined based on the lowest risk difference calculated between intravenous ondansetron and placebo in the incidence of PONV in patients undergoing laparoscopic surgery.[11–15] The combined analysis of these studies showed a 30% risk reduction for ondansetron, with a minimum effect of 19% (risk difference: -0.3; 95% confidence interval [95% CI] -0.41 to -0.19). Because 19% was the lowest difference, as calculated in these studies, the non-inferiority margin was set at 15%, considering this value to be reasonable from a clinical point of view, in addition to reducing patient exposure to undesirable effects, since the sample size is inversely proportional to the square of the non-inferiority margin. Based on the rate of patients without PONV in these studies (74%) and considering α = 5% and a power of 80%, a sample size of 212 patients was necessary for the upper limit of the 95% CI of the risk difference between palonosetron and ondansetron to exclude the difference favoring the control group (ondansetron) by more than 15%, with this value being used as the non-inferiority margin.

A computer-generated list of random numbers was used for allocation of the participants. The total number of patients was divided into two groups of 106 patients each with a 1:1 allocation ratio by electronic randomization using blocks of eight patients, with an equal distribution of groups in each block. The allocation sequence was concealed by placing the results in opaque envelopes sequentially numbered from 1 to 212, and the study followed the numerical order of the envelopes.

The risk difference used to determine the non-inferiority margin was calculated using Review Manager (RevMan), version 5.2 (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2012). The sample size to test the non-inferiority hypothesis was calculated using a virtual platform (Sealed Envelope Ltd. Power calculator for binary outcome non-inferiority trial, https://www.sealedenvelope.com/power/binary-noninferior). Demographic variables and risk factors were compared between groups using Student's *t* test or the chi-square test, as appropriate, on GraphPad Prism, version 7.00.

Results

All 212 patients were evaluated and discharged home 24 hours after the end of anesthesia (Fig. 1). Using the risk score for the incidence of PONV proposed by Apfel et al.,[3] in both groups, most patients had two or three risk factors, accounting for 86 patients (81.2%) in the palonosetron group and 93 patients (87.7%) in the ondansetron group. Demographic characteristics and risk factors for PONV are listed in Table 1. There was no statistically significant difference between groups in duration of anesthesia, surgery, or pneumoperitoneum (Table 2). Only one patient in the palonosetron group had neuromuscular blockade reversed with neostigmine. Only one patient in the ondansetron group received a single dose of methadone 12 hours after surgery.

The overall incidence of nausea and/or vomiting during the 24-hour postoperative period was 47.1% and 51.8% in palonosetron and ondansetron groups, respectively ($p > 0.05$). The highest incidence of PONV, in both groups, occurred between 2 and 6 hours after surgery, with no significant difference between groups. In all periods of the study, the upper bound of the risk difference was inferior to the non-inferiority margin of 15%, thereby characterizing non-inferiority of palonosetron compared with ondansetron (Table 3).

No patient had adverse events attributable to the medications under study, such as headache, arterial hypotension, and extrapyramidal symptoms.

As for the use of rescue medication, the 2- to 6-hour postoperative period had the highest values of all four periods assessed (Table 4). Nonetheless, for this specific period, the value of the upper limit of the 95% CI of the risk difference was above the non-inferiority margin used in the present study, i.e., 15% (risk difference: 3.8, 95% CI -8.2 to 15.6). According to the non-inferiority method, this yields inconclusive results regarding the non-inferiority hypothesis (for the use of rescue medication at 2 to 6 hours postoperatively). In all other postoperative periods, non-inferiority results were found, as the upper limit of the 95% CI of the risk difference was below the non-inferiority margin of 15%.

The patients' raw data file is available at https://data.mendeley.com/datasets/gn2pzvgj82/1.

Discussion

The present study confirmed the hypothesis that palonosetron is non-inferior to ondansetron in the prophylaxis of PONV in laparoscopic cholecystectomy, within the non-inferiority margin of 15%, since the 95% CIs of the risk difference found in the postoperative periods assessed were below the non-inferiority margin.

Considering that palonosetron has been identified as the only 5-HT$_3$ receptor antagonist that does not promote QT interval prolongation,[16,17] that there are no other significant differences between the side effects of ondansetron and palonosetron,[18] and that palonosetron is administered

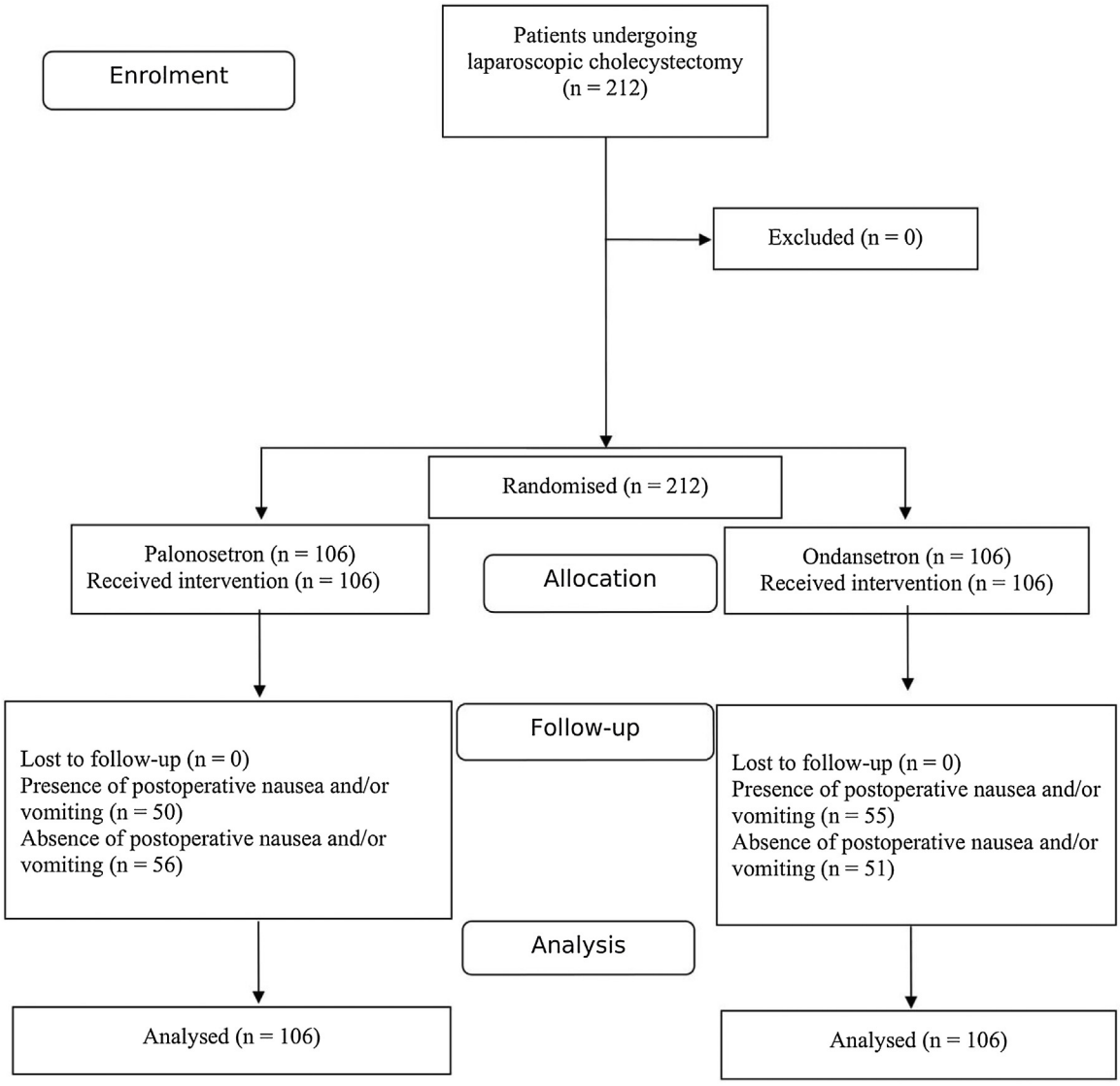

Figure 1 Flow diagram of the study.

Table 1 Demographic data and risk factors in patients receiving palonosetron or ondansetron for the treatment of postoperative nausea and vomiting in laparoscopic cholecystectomy.

Variables	Palonosetron n = 106	Ondansetron n = 106	*p*-value
Female sex	76 (71.7)	87 (82.1)	0.102
Age (years)	45.5 (13.1)	47.1 (13.8)	0.382
Weight (kg)	75.9 (19.0)	75.7 (16.8)	0.924
Body mass index (kg.m-2)	27.5 (5.5)	28.2 (5.7)	0.366
Non-smoker	95 (89.6)	96 (90.6)	0.999
Motion sickness	16 (15.1)	13 (12.3)	0.689
Patients with risk factors			
0	0 (0)	0 (0)	0.416
1	5 (4.7)	2 (1.9)	
2	29 (27.4)	23 (21.7)	
3	57 (53.8)	70 (66.0)	
4	15 (14.2)	11 (10.4)	

Values are presented as absolute number (percentage) or mean (standard deviation).

Table 2 Duration of anesthesia, surgery, and pneumoperitoneum in patients receiving palonosetron or ondansetron for the treatment of postoperative nausea and vomiting in laparoscopic cholecystectomy.

Variables	Palonosetron n = 106	Ondansetron n = 106	*p*-value
Duration of anesthesia (min)	88.7 (23.8)	88.8 (25.8)	0.967
Operative time (min)	60.0 (22.1)	60.0 (20.3)	0.999
Duration of pneumoperitoneum (min)	51.9 (20.0)	51.0 (18.3)	0.747

Values are presented as mean (standard deviation).

Table 3 Incidence of postoperative nausea and vomiting in patients receiving palonosetron or ondansetron for the treatment of postoperative nausea and vomiting in laparoscopic cholecystectomy.

Variables	Palonosetron n = 106	Ondansetron n = 106	Risk difference (Palonosetron - Ondansetron)
0 to 2 h after surgery			
Nausea	17.0 (11.0–25.3)	13.2 (8.0–21.0)	3.8 (-6.0 to 13.5)
Vomiting	3.8 (1.5–9.3)	7.5 (3.9–14.2)	-3.8 (-10.8 to 3.9)
Nausea and/or vomiting	20.8 (14.1–29.4)	20.8 (14.1–29.4)	0 (-10.9 to 10.9)
2 to 6 h after surgery			
Nausea	13.2 (8.0–21.0)	19.8 (13.3–28.4)	-6.6 (-16.6 to 3.5)
Vomiting	23.6 (16.5–32.5)	23.6 (16.5–32.5)	0 (-11.4 to 11.4)
Nausea and/or vomiting	36.8 (28.2–46.3)	43.4 (34.4–52.9)	-6.6 (-19.4 to 6.5)
6 to 12 h after surgery			
Nausea	5.7 (2.6–11.8)	5.7 (2.6–11.8)	0 (-6.9 to 6.9)
Vomiting	10.4 (5.9–17.6)	11.3 (6.6–18.8)	-0.9 (-9.6 to 7.7)
Nausea and/or vomiting	16.0 (10.3–24.2)	17.0 (11.0–25.3)	-0.9 (-11.0 to 9.2)
12 to 24 h after surgery			
Nausea	3.8 (1.5–9.3)	6.6 (3.2–13.0)	-2.8 (-9.6 to 3.6)
Vomiting	0 (0–3.5)	0 (0–3.5)	0 (-3.5 to 3.5)
Nausea and/or vomiting	3.8 (1.5–9.3)	6.6 (3.2–13.0)	-2.8 (-9.6 to 3.6)

Values are presented as percentage (95% confidence interval).

Table 4 Use of rescue medication (dimenhydrinate) in patients receiving palonosetron or ondansetron for the treatment of postoperative nausea and vomiting in laparoscopic cholecystectomy.

Variables	Palonosetron n = 106	Ondansetron n = 106	Risk difference (Palonosetron - Ondansetron)
0 to 2 h after surgery	3.8 (1.5–9.3)	7.5 (3.9–14.2)	-3.8 (-10.8 to 2.9)
2 to 6 h after surgery	29.2 (21.4–38.5)	25.5 (18.1–34.5)	3.8 (-8.2 to 15.6)
6 to 12 h after surgery	9.4 (5.2–16.5)	12.3 (7.3–19.9)	-2.8 (-11.5 to 5.8)
12 to 24 h after surgery	1.9 (0.5–6.6)	2.8 (1.0–8.0)	-0.9 (-6.3 to 4.1)

Values are presented as percentage (95% confidence interval).

in a single dose, we can state, based on the results of the present study, that palonosetron provides a good option for the control of PONV in patients with associated risk factors.

Despite obtaining the necessary values to demonstrate non-inferiority in the pre-specified margin, the present study was not planned to investigate a possible superiority of palonosetron over ondansetron.[19] Nonetheless, according to the risk difference and its 95% CI (always crossing the zero-risk difference), our study, besides showing non-inferiority, also shows equivalence between palonosetron and ondansetron.

Finding the right balance in the prevention or treatment of PONV is critical. In recent years, there has been an increased interest in research that focuses on non-pharmacological or alternative treatments for these symptoms, such as acupuncture, use of ginger, vitamin C, and even chewing gum, among others. However, finding the best setting that might demonstrate the efficacy of each antiemetic drug associated with its side effects, duration of action, patients' level of satisfaction with postoperative recovery, and mainly the best cost-benefit ratio to reduce hospital expenses is not an easy task. As for minimizing hospital expenses, it is worth noting the marked reduction observed in the present study in the incidence of nausea and vomiting between 12 and 24 hours postoperatively, which could allow these patients to be discharged within

12 hours of surgery with respect to PONV, since the presence of these symptoms is one of the most common causes of delayed discharge from hospital.[20] In these cases, patients would receive only a single dose of palonosetron, with post-hospital continuity of care. This should reduce the length of stay in wards and, consequently, health care expenses, in addition to possibly increasing the level of satisfaction of patients and their families.

With the predominance of two or three risk factors for PONV, according to the risk score proposed by Apfel et al.,[3] approximately 85% of patients in the present study had a likelihood of up to 60% of developing these symptoms. Even though around 50% of patients presented PONV, there was a considerable drop after 12 hours that supports the choice of a 24-hour assessment period after surgery, as it would be unnecessary to keep patients in the hospital for more than 1 day in the absence of significant symptoms.

According to the guidelines proposed by Gan et al.,[21] the use of ondansetron combined with dexamethasone should always be considered for PONV prophylaxis or treatment mainly in patients at moderate to high risk for PONV. Dexamethasone, whose mechanism of action seems to be associated with prostaglandin synthesis and endorphin release, has also been shown to be effective in postoperative pain control by significantly reducing the need for analgesics after laparoscopic cholecystectomy.[22]

In a meta-analysis, Tramer et al.[10] suggested 8-mg intravenous ondansetron as the optimal dose to prevent PONV, because increasing the dose from 4 mg to 8 mg led to a decrease of more than 20% in the number of patients who required rescue medication for nausea and vomiting up to 48 hours after surgery, but further increasing the dose to 16 mg led to no clinically relevant improvement. Therefore, 8 mg ondansetron was used in the present study based on evidence that the recommended doses for pediatric patients range from 0.1 $mg.kg^{-1}$ to 0.3 $mg.kg^{-1}$[23] and, according to Paventi et al.,[24] that ondansetron 8 mg is more effective than ondansetron 4 mg when administered intravenously in a single dose to prevent PONV after laparoscopic cholecystectomy. In addition, it has been shown that the use of 8-mg intravenous ondansetron does not increase the risk of cardiac abnormalities.[25]

Similar studies comparing the efficacy or duration of effect of intravenous ondansetron for PONV in laparoscopic surgery have been performed with the administration of a single dose.[6–9] In the present study, we opted for the administration of ondansetron at 8-hour intervals, intravenously, in order to maintain the effect of this antiemetic for the 24 hours during which PONV assessments were performed, because the plasma concentration of ondansetron shows a maximum peak of effect after 2 hours and duration of effect of 6 to 8 hours.[26] Thus, compared with palonosetron, which has a prolonged half-life of 40 hours, when administered intravenously, both groups remained under the effect of antiemetics for the 24 hours during which they were evaluated. Our study is novel in this respect and provides support for the non-inferiority method, since it provides a fair comparison with respect to the periods of action of these drugs. In addition, ondansetron has a high potential to reduce PONV, proven to be superior to placebo[11–15] and, maintaining its effective plasma concentration for 24 hours, we could speculate that its effect could be even greater than that of palonosetron, justifying the non-inferiority study/hypothesis.

In the present study, the use of rescue medication was higher between 2 and 6 hours after surgery than in all other postoperative periods, supporting the need for supplemental antiemetic therapy during this postoperative period. However, in the two treatment arms, we also observed that, in the 2- to 6-hour period, the rates for incidence of PONV (36.8% and 43.4%) were higher than those for use of rescue medication (29.2% and 25.5%). Some patients reported sudden improvement of nausea after a single episode of vomiting. This is in accordance with the pathophysiology of the vomiting mechanism, when patients often report absence of nausea soon after vomiting,[27] and do not require any further rescue medication.

Several aspects have already been discussed here with regard to carrying out a non-inferiority trial, such as practicality of drug administration and occurrence of fewer or less severe adverse effects. However, an advantage of using a drug defined as non-inferior would be a substantially lower cost, which would compensate for the difference in the non-inferiority margin. In this respect, we made a cost comparison analysis [https://consultaremedios.com.br/cloridrato-de-ondansetrona/pa, in US dollars; currency exchange rate, Brazilian Reais (R$) to US dollars (US$): R$ 5.00 US$ 1.00, December 21, 2020] of intravenous palonosetron (0.075 mg) versus intravenous ondansetron (8 mg), which cost, on average, approximately US$ 15.00 and US$ 1.20 per dose, respectively. According to the present study, the in-hospital cost of treatment would be US$ 15.00 with palonosetron and US$ 3.60 with ondansetron. Considering a scenario of discharge from hospital within 12 hours of surgery and home-maintenance of the antiemetic effect for 24 hours, initial prophylaxis with ondansetron (8 mg) would lead to a final antiemetic cost of US$ 14.40 – as two 8-mg ampoules would be used in the hospital within 12 hours (US$ 2.40), and one or two tablets of ondansetron (8 mg, orally) would be used at home within the subsequent 24 hours (at a cost to patients of approximately US$ 12.00 for purchasing a 10-tablet package). Initial prophylaxis with palonosetron, however, would lead to a final antiemetic cost of US$ 15.00, but at no cost to patients – they would be discharged home with no prescription for antiemetics, as they would still be under the action of the drug for 36 hours after surgery.

Also, to be considered is palonosetron patent expiration, which will occur on July 30, 2024.[28] This may result in a decrease in its market value, which would make palonosetron more accessible and a likely option to replace ondansetron for PONV prophylaxis in the coming years, due to its practical administration (single dose) and, at the very least, non-inferior effects.

The use of a dichotomous assessment of nausea can be seen as a limitation of the present study, since it is known that there are different intensities of nausea, which could be rated on a numerical scale or even qualitatively as mild, moderate, and severe. However, we chose this type of assessment for understanding that nausea is a subjective unpleasant sensation, and a single postoperative episode may not be easy to rank. Another possible limitation is that we did not evaluate patient satisfaction; however, this is sometimes complex to evaluate, and also considered a surrogate end point. Nonetheless, we followed Apfel et al.'s

recommendations on the conduction of studies on PONV in all aspects, thus ensuring good external validity.[29]

In conclusion, palonosetron is non-inferior to ondansetron when used in patients at risk of PONV undergoing laparoscopic cholecystectomy. Therefore, palonosetron provides a good option of antiemetic agent for PONV prophylaxis in patients at increased risk for these events when undergoing laparoscopic cholecystectomy, as it can be administered in a single dose.

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Conflicts of interest

The authors declare no conflicts of interest.

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