Effects of palonosetron and ondansetron on preventing nausea and vomiting after laparoscopic surgery

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Abstract

Background: This meta-analysis was performed to evaluate the efficacy and safety of palonosetron and ondansetron in preventing postoperative nausea and vomiting (PONV) in patients undergoing laparoscopic surgery with general anesthesia.

Methods: We searched for randomized controlled clinical trials in PubMed, Embase, and The Cochrane Library.

Results: Nine studies were enrolled in this meta-analysis and showed no statistically significant difference between palonosetron and ondansetron in the prevention of PONV in the first 24 hours after surgery (relative risk [RR], 0.62; 95% confidence interval [CI], 0.35–1.10). Palonosetron more effectively prevented vomiting at various time intervals during the first 24 hours postoperatively than did ondansetron: 0–2 hours (RR, 0.45; 95% CI, 0.26–0.78), 2–6 hours (RR, 0.74; 95% CI, 0.39–1.40), and 6–24 hours (RR, 1.20; 95% CI, 0.55–2.64). No significant differences in side effects were found between palonosetron and ondansetron (RR, 0.67; 95% CI, 0.40–1.14).

Conclusion: This meta-analysis demonstrated that palonosetron is not more efficacious than ondansetron in the prevention of early PONV. However, palonosetron was more efficacious than ondansetron in the prevention of vomiting after laparoscopic surgery.

Keywords

Palonosetron, ondansetron, postoperative nausea and vomiting, meta-analysis, laparoscopic surgery, general anesthesia

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Introduction

During the last few decades, more effective drugs have been introduced into anesthesia practice and anesthetic techniques have rapidly improved. However, postoperative nausea and vomiting (PONV) in patients...
undergoing laparoscopic surgery remains one of the most common problems of anesthesia, occurring at an incidence of up to 70%.

PONV may be related to activation of the following four vomiting centers: the vestibular system, the chemoreceptor trigger zone, the gastrointestinal vagal nervous system, and the cortical center. A variety of neurotransmitters in these four areas transmit nerve impulse information to a vomiting center in the medulla. This completes a series of visceral and physical reactions that include nausea and vomiting. PONV not only causes pain but also gives rise to dehydration, anxiety, acid–base imbalance, electrolyte imbalance, and wound dehiscence; some patients even develop esophageal tears, hernias, aspiration pneumonia, and pneumothorax. PONV can prevent postoperative recovery and utilize enormous hospital resources.

Many recent studies have confirmed that 5-HT3 antagonists, which are anti-emetic agents, can prevent PONV. Thus, these drugs have been widely applied for this purpose. The most common 5-HT3 antagonists currently in use include ondansetron, ramosetron, tropisetron, and granisetron. Additionally, palonosetron hydrochloride is a novel long-acting 5-HT3 receptor antagonist. In 2003, the US Food and Drug Administration approved palonosetron for the treatment of acute and delayed nausea as well as vomiting and PONV. Ondansetron and palonosetron, as first- and second-generation 5-HT3 antagonists, respectively, have been broadly used in clinical practice. These two drugs exercise inhibition via presynaptic 5-HT3 receptors in the peripheral nervous system, thus effectively preventing nausea and vomiting. Compared with ondansetron, palonosetron has a longer half-life (about 40 hours), which increases its affinity to the 5-HT3 receptor by about 30 to 100 times. However, the results of many recent studies on the efficacy of ondansetron and palonosetron in preventing PONV in patients undergoing laparoscopic surgery are controversial. Therefore, the present meta-analysis was performed to evaluate the effectiveness of ondansetron and palonosetron in the prevention of PONV in patients undergoing laparoscopic surgery.

Materials and Methods

Inclusion criteria

The inclusion criteria for this meta-analysis were as follows. (1) The study was a randomized controlled trial (RCT) using either allocation concealment or a blinding method; no language limitations were enforced. (2) The study subjects were patients undergoing laparoscopic surgery. (3) With respect to the intervention, either the experimental group received palonosetron while the control group received ondansetron, or the experimental group received palonosetron plus other drugs while the control group received ondansetron plus other drugs. (4) The measurement indices were the incidence of nausea and vomiting within 24 hours, postoperative dizziness, headache, and constipation.

Search strategy

The PubMed, Embase, and Cochrane Library databases were searched from January 1995 to June 2016. English search terms included palonosetron, nausea, vomiting, ondansetron, and laparoscopic surgery. The PubMed, Embase, and Cochrane Library databases were searched from January 1995 to June 2016. English search terms included palonosetron, nausea, vomiting, ondansetron, and laparoscopic surgery.

Literature screening and data extraction

We screened the literature based on the above-mentioned inclusion and exclusion criteria. After reading the titles and abstracts, we excluded unqualified articles. We then read the full texts of the articles that were potentially consistent with the inclusion criteria to determine their eligibility. Next, we checked the results of the included articles. Additionally, we extracted complete data from eligible RCTs. Two reviewers...
independently performed the above steps and cross-checked each other, consulting a third party when a disagreement was encountered. The two researchers extracted information in accordance with pre-established forms and employed a Jadad scale to evaluate the quality, specifically with regard to (1) whether the randomization method was appropriate, (2) whether randomization concealment was appropriate, (3) whether the blinding method was appropriate, and (4) whether reasons for withdrawals and drop-outs were indicated.

**Statistical methods**

RevMan 5.1 software (Cochrane Collaboration, Copenhagen, Denmark) was used to conduct the meta-analysis. Heterogeneity of each enrolled study was evaluated using the $\chi^2$ test. When statistical homogeneity was found ($P > 0.1, I^2 < 50\%$), a fixed-effects model was used for the analysis; when statistical heterogeneity was found ($P < 0.1, I^2 > 50\%$), we analyzed the sources of heterogeneity and conducted a subgroup analysis according to potential factors that could have resulted in heterogeneity. A fixed-effects model was employed when high similarity was found among studies of subgroups and between subgroups ($P > 0.1, I^2 < 50\%$). A random-effects model was used when there was significant heterogeneity but no clinical heterogeneity or statistical significance. Descriptive analysis was used if heterogeneity between the two groups was too large. If necessary, sensitivity analysis was adopted to test the stability of the results.

**Results**

**Basic information of included studies**

In total, 64 related articles were evaluated using the above-described literature search method, and 11 were included after reading of the titles and abstracts. However, one article without full text and one without specific data were excluded. Therefore, nine RCTs were included in the meta-analysis (Figure 1). Basic information on these nine studies is shown in Table 1.
| Author and year            | Patients (n) | Grouping                  | Surgical setting                          | Jadad score | Blinding | Concealment allocation | Randomized | Follow-up |
|---------------------------|--------------|---------------------------|-------------------------------------------|-------------|----------|------------------------|------------|-----------|
| Joshi et al. 2014         | 100          | Palonosetron              | Laparoscopic surgery                      | 5           | 2        | 1                      | 1          | 1         |
| Bajwa et al. 2011         | 60           | Ondansetron, Palonosetron | Laparoscopic tubal ligation surgery        | 6           | 2        | 1                      | 2          | 1         |
| Bhalla et al. 2015        | 100          | Ondansetron, Palonosetron | Laparoscopic cholecystectomy               | 6           | 2        | 1                      | 2          | 1         |
| Candiotti et al. 2014     | 98           | Palonosetron, Ondansetron | Laparoscopic abdominal or gynecological surgery | 5           | 1        | 1                      | 2          | 1         |
| Kim YY 2013               | 100          | Palonosetron              | Gynecological laparoscopic surgery         | 5           | 2        | 1                      | 1          | 1         |
| Kim S 2013                | 109          | Ondansetron, Palonosetron | Laparoscopic surgery                      | 6           | 2        | 1                      | 2          | 1         |
| Park and Cho 2011         | 90           | Palonosetron, Ondansetron | Laparoscopic surgery                      | 6           | 2        | 1                      | 2          | 1         |
| Swaika et al. 2011        | 87           | Palonosetron              | Laparoscopic cholecystectomy               | 6           | 2        | 1                      | 2          | 1         |
| Sharma and Shankaranarayana 2015 | 90       | Ondansetron, Ramosetron, Palonosetron + dexamethasone | Laparoscopic hysterectomy                   | 6           | 2        | 1                      | 2          | 1         |
**Methodological quality assessment**

Among the nine enrolled RCTs, eight used blinding methods exclusively and seven specifically used randomization. All studies provided a written record of withdrawals and dropouts and of adverse reactions to drugs. The results of the methodological quality assessments are shown in Table 1.

**Outcomes**

**Primary outcome: PONV.** PONV was recorded at different time intervals among the nine studies. The meta-analysis revealed no statistically significant difference in PONV between the palonosetron and ondansetron groups within 24 hours after surgery (relative risk [RR], 0.78; 95% confidence interval [CI], 0.50–1.24) (Figure 2). The $I^2$ value of 76% implied significant heterogeneity. Further subgroup analyses based on different routes and doses of ondansetron and palonosetron showed little influence over the pooled results, and all of these analyses were also affected by heterogeneity.

However, the meta-analysis revealed a statistically significant difference in PONV between the palonosetron and ondansetron groups during the first 24 hours postoperatively (RR, 0.30; 95% CI, 0.15–0.60; $P=0.0006$) (Figure 2).

Palonosetron was no more effective than ondansetron in the prevention of postoperative nausea during several time periods within 24 hours after surgery: 0–2 hours (RR, 0.92; 95% CI, 0.42–2.01), 2–6 hours (RR, 0.62; 95% CI, 0.27–1.42), and 6–24 hours (RR, 0.45; 95% CI, 0.20–1.03) (Figure 3). The $I^2$ value of 38% suggested no significant heterogeneity.

However, during several different time periods within the first 24 hours after surgery, palonosetron tended to be more effective than ondansetron in preventing postoperative vomiting: 0–2 hours (RR, 0.45; 95% CI, 0.26–0.78; $P=0.004$).

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*Figure 2.* Forest plot of relative risk of postoperative nausea and vomiting between palonosetron and ondansetron treatment.
2–6 hours (RR, 0.74; 95% CI, 0.39–1.40), and 6–24 hours (RR, 1.20; 95% CI, 0.55–2.64) (Figure 4). The I² value of 19% indicated no significant heterogeneity. A 2013 study by Laha et al.⁶ was not included in our meta-analysis because no detailed PONV outcomes were provided. Additionally, the results indicated that preoperative administration of a single intravenous dose of palonosetron was as effective as ondansetron in reducing the incidence of PONV.

Secondary outcomes: Side effects of palonosetron and ondansetron. The four studies with secondary outcomes provided full data on the side effects (e.g., headache, dizziness) of palonosetron and ondansetron after surgery. No fewer side effects were recorded for palonosetron than ondansetron (RR, 0.67; 95% CI, 0.40–1.14) (Figure 5). Moreover, no substantial heterogeneity was observed (I² = 0%). Other studies, without offering detailed data on side effects, also revealed no statistically significant difference between palonosetron and ondansetron.

Publication bias analysis. A funnel plot analysis was conducted on all enrolled studies and showed good symmetrical results. This indicated that the meta-analysis is unlikely to have been affected by publication bias.

Discussion
This meta-analysis showed no difference between the effects of palonosetron and
### Figure 4.
Forest plot of relative risk of postoperative vomiting between palonosetron and ondansetron treatment.

| Study or Subgroup | Experimental Events | Control Events | Total Events | Weight | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|---------------------|----------------|--------------|--------|-----------------------------|
| 3.1.1 0-2 h       |                     |                |              |        |                             |
| Kim YY 2013       | 6                   | 50             | 13           | 50     | 0.46 [0.19, 1.12]          |
| Park 2011         | 4                   | 45             | 12           | 45     | 0.33 [0.12, 0.96]          |
| Sharma 2015       | 0                   | 29             | 8            | 29     | 0.06 [0.00, 0.97]          |
| Swaiwa 2011       | 6                   | 45             | 3            | 45     | 2.00 [0.53, 7.51]          |
| Subtotal (95% CI) | 169                 | 169            | 100.0%       | 0.45   [0.26, 0.78]        |
| Total events      | 16                  | 36             |              |        |                             |
| Heterogeneity: Chi² = 7.21, df = 3 (P = 0.07); I² = 58% |
| Test for overall effect: Z = 2.85 (P = 0.004) |

| 3.1.2 2-6 h       |                     |                |              |        |                             |
| Park 2011         | 5                   | 45             | 10           | 45     | 0.50 [0.19, 1.35]          |
| Sharma 2015       | 3                   | 29             | 3            | 29     | 1.00 [0.22, 4.55]          |
| Swaiwa 2011       | 6                   | 45             | 6            | 45     | 1.00 [0.35, 2.67]          |
| Subtotal (95% CI) | 119                 | 119            | 100.0%       | 0.74   [0.39, 1.40]        |
| Total events      | 14                  | 19             |              |        |                             |
| Heterogeneity: Chi² = 1.07, df = 2 (P = 0.50); I² = 0% |
| Test for overall effect: Z = 0.93 (P = 0.35) |

| 3.1.3 8-24 h      |                     |                |              |        |                             |
| Park 2011         | 9                   | 45             | 5            | 45     | 1.80 [0.65, 4.95]          |
| Sharma 2015       | 0                   | 29             | 0            | 29     | Not estimable              |
| Swaiwa 2011       | 3                   | 45             | 5            | 45     | 0.60 [0.15, 2.36]          |
| Subtotal (95% CI) | 119                 | 119            | 100.0%       | 1.20   [0.55, 2.64]        |
| Total events      | 12                  | 10             |              |        |                             |
| Heterogeneity: Chi² = 1.60, df = 1 (P = 0.21); I² = 37% |
| Test for overall effect: Z = 0.45 (P = 0.65) |

Test for subgroup differences: Chi² = 4.18, df = 2 (P = 0.12), I² = 52.1%

### Figure 5.
Forest plot of relative risk of side effects between palonosetron and ondansetron treatment.

| Study or Subgroup | Experimental Events | Control Events | Total Events | Weight | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|---------------------|----------------|--------------|--------|-----------------------------|
| 2.1.1 Headache    |                     |                |              |        |                             |
| Bajwa 2011        | 2                   | 30             | 6            | 30     | 0.33 [0.07, 1.52]          |
| Bhatta 2015       | 3                   | 50             | 10           | 50     | 0.30 [0.09, 1.03]          |
| Kim SH 2013       | 2                   | 36             | 3            | 35     | 0.65 [0.12, 3.65]          |
| Park 2011         | 3                   | 45             | 4            | 45     | 0.75 [0.18, 3.16]          |
| Subtotal (95% CI) | 161                 | 160            | 100.0%       | 0.43   [0.21, 0.88]        |
| Total events      | 10                  | 23             |              |        |                             |
| Heterogeneity: Chi² = 1.23, df = 3 (P = 0.75); I² = 0% |
| Test for overall effect: Z = 2.31 (P = 0.02) |

| 2.1.2 Dizziness   |                     |                |              |        |                             |
| Bajwa 2011        | 1                   | 30             | 2            | 30     | 0.50 [0.05, 5.22]          |
| Bhatta 2015       | 6                   | 50             | 4            | 50     | 1.50 [0.45, 4.99]          |
| Kim SH 2013       | 4                   | 36             | 3            | 35     | 1.30 [0.31, 5.38]          |
| Park 2011         | 5                   | 45             | 5            | 45     | 1.00 [0.31, 3.22]          |
| Subtotal (95% CI) | 161                 | 160            | 100.0%       | 1.14   [0.47, 2.25]        |
| Total events      | 16                  | 14             |              |        |                             |
| Heterogeneity: Chi² = 0.75, df = 3 (P = 0.86); I² = 0% |
| Test for overall effect: Z = 0.36 (P = 0.72) |

Test for subgroup differences: Chi² = 3.69, df = 1 (P = 0.05), I² = 72.9%
ondansetron in preventing PONV in patients undergoing laparoscopic surgery. Additionally, no differences were found between the two groups in the prevention of adverse reactions after laparoscopic surgery. However, palonosetron was more efficacious than ondansetron in the prevention of vomiting after laparoscopic surgery.

The PONV mechanism involves a variety of chemical mediators and receptors such as 5-HT3 receptors, dopamine, and histamine, with 5-HT3 receptors playing a major role. 5-HT3 receptors, mainly distributed in the central nervous system, can activate the chemoreceptor trigger zone in the small intestinal wall. Palonosetron produces a positive synergistic effect through allosteric and competitive inhibition, thus affecting the 5-HT3 receptor, while ondansetron (a first-generation 5-HT3 receptor antagonist) only selectively inhibits the 5-HT3 receptor. Palonosetron suppresses activation of the presynaptic 5-HT3 receptor in the central nervous system, thus stopping signal transmission to the 5-HT3 receptor and reducing the incidence of nausea and vomiting. Ondansetron is also a 5-HT3 antagonist. This means that it can selectively bind with 5-HT3 receptors and reduce neuronal excitability in the nucleus of the solitary tract as well as in other parts of the vomiting center, thereby preventing nausea and vomiting.

The most common adverse reactions associated with PONV-preventing agents are constipation and headache, followed by diarrhea, fatigue, dizziness, and bloating. The present meta-analysis showed no significant differences in any of these adverse reactions between palonosetron and first-generation 5-HT3 receptor antagonists. Some studies have implied that 5-HT3 receptor antagonists can prolong the Q-T interval, leading to arrhythmias and even cardiac arrest. Popovic et al. proved that palonosetron is safer than first-generation 5-HT3 receptor antagonists. Additionally, a recent systematic analysis found no significant differences in the incidence of arrhythmias during administration, and the clinical value of electrocardiographic monitoring for all patients thus remains unclear. Therefore, further studies are needed.

Finally, although 5-HT3 receptors play an essential role in the pathogenesis of PONV, no relationship between the pathogenesis of PONV and 5-HT3 receptors was found when multiple risk factors were combined.

Several limitations of this meta-analysis should be considered. First, each study had issues regarding quality and design. Furthermore, the dosages and measurement times were not uniform. This may have given rise to clinical heterogeneity among the studies. In addition, wide differences in patients’ conditions may have been present because the inclusion criteria varied among the studies. More high-quality RCTs are needed to provide better clinical evidence with which to help clinicians make more rational clinical decisions and thus offer more precise and effective choices in the prevention of PONV in patients undergoing laparoscopic surgery.

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Declaration of conflicting interest
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References

1. Pierre S, Benais H and Pouymayou J. Apfel’s simplified score may favourably predict the risk of postoperative nausea and vomiting. *Can J Anaesth* 2002; 49: 237–242.

2. Fujii Y. The utility of antiemetics in the prevention and treatment of postoperative nausea and vomiting in patients scheduled for laparoscopic cholecystectomy. *Curr Pharm Des* 2005; 11: 3173–3183.

3. Navari RM. Palonosetron for the treatment of chemotherapy-induced nausea and vomiting. *Expert Opin Pharmacother* 2014; 15: 2599–2608.

4. Kloth DD. New pharmacologic findings for the treatment of PONV and PDNV. *Am J Health Syst Pharm* 2009; 66(Suppl 1): S11–S18.

5. Gurha P, Kaur RD and Sanjay RR. Prophylactic intravenous palonosetron, granisetron and ondansetron in the prevention of post operative nausea and vomiting in laparoscopic surgeries. *Br J Anaesth* 2012; 108: ii376.

6. Laha B, Hazra A and Mallick S. Evaluation of antiemetic effect of intravenous palonosetron versus intravenous ondansetron in laparoscopic cholecystectomy: a randomized controlled trial. *Indian J Pharmacol* 2013; 45: 24–29.

7. Sharma AN and Shankaranarayana P. Postoperative Nausea and Vomiting: Palonosetron with Dexamethasone vs. Ondansetron with Dexamethasone in Laparoscopic Hysterectomies. *Oman Med J* 2015; 30: 252–256.

8. Bhalla J, Baduni N and Bansal P. Comparison of palonosetron with ondansetron for post-operative nausea and vomiting in patients undergoing laparoscopic cholecystectomy under general anesthesia. *J Minim Access Surg* 2015; 11: 193–197.

9. Candiotti KA, Ahmed SR, Cox D, et al. Palonosetron versus ondansetron as rescue medication for postoperative nausea and vomiting: a randomized, multicenter, open-label study. *BMC Pharmacol Toxicol* 2014; 15: 45.

10. Joshi H, Parmar P and Raval B. Comparison of ondansetron vs palonosetron for prevention of post-operative nausea and vomiting in laparoscopic surgery. *Research Journal of Pharmaceutical, Biological and Chemical Sciences* 2014; 5: 54–63.

11. Kim YY, Moon SY, Song DU, et al. Comparison of palonosetron with ondansetron in prevention of postoperative nausea and vomiting in patients receiving intravenous patient-controlled analgesia after gynecological laparoscopic surgery. *Korean J Anesthesiol* 2013; 64: 122–126.

12. Park SK and Cho EJ. A randomized, double-blind trial of palonosetron compared with ondansetron in preventing postoperative nausea and vomiting after gynecological laparoscopic surgery. *J Int Med Res* 2011; 39: 399–407.

13. Swaiika S, Pal A, Chatterjee S, et al. Ondansetron, ramosetron, or palonosetron: Which is a better choice of antiemetic to prevent postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy? *Anesth Essays Res* 2011; 5: 182–186.

14. Bajwa SS, Bajwa SK, Kaur J, et al. Palonosetron: A novel approach to control postoperative nausea and vomiting in day care surgery. *Saudi J Anaesth* 2011; 5: 19–24.

15. Kim S, Hong J, Kim WO, et al. Palonosetron has superior prophylactic antiemetic efficacy compared with ondansetron or ramosetron in high-risk patients undergoing laparoscopic surgery: a prospective, randomized, double-blinded study. *Korean J Anesthesiol* 2013; 64: 517–523.

16. Rawlinson A, Kitchingham N, Hart C, et al. Mechanisms of reducing postoperative pain, nausea and vomiting: a systematic review of current techniques. *Evid Based Med* 2012; 17: 75–80.

17. Rojas C, Stathis M, Thomas AG, et al. Palonosetron exhibits unique molecular interactions with the 5-HT3 receptor. *Anesth Analg* 2008; 107: 469–478.
18. Popovic M, Warr DG, Deangelis C, et al. Efficacy and safety of palonosetron for the prophylaxis of chemotherapy-induced nausea and vomiting (CINV): a systematic review and meta-analysis of randomized controlled trials. *Support Care Cancer* 2014; 22: 1685–1697.

19. Tricco AC, Soobiah C, Hui W, et al. Interventions to decrease the risk of adverse cardiac events for patients receiving chemotherapy and serotonin (5-HT3) receptor antagonists: a systematic review. *BMC Pharmacol Toxicol* 2015; 16: 1.