A Meta-Analysis of Palonosetron for the Prevention of Postoperative Nausea and Vomiting in Adults

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Purpose: The aim of this meta-analysis was to evaluate the effectiveness and adverse effects of palonosetron in the prevention of postoperative nausea and vomiting (PONV).

Design: A meta-analysis using a systematic search strategy was performed.

Methods: A meta-analysis of randomized controlled clinical trials was performed to compare palonosetron with first-generation 5-hydroxytryptamine 3 receptor antagonist (5-HT3RA) or placebo to prevent PONV. Fixed or random effect models were used to combine homogenous data.

Findings: A total of 10 randomized controlled clinical trials including 1,827 patients were identified. The data showed statistically significant differences in favor of palonosetron (0.075 mg) in the prevention of acute PONV ($P < .00001$) and delayed PONV ($P < .002$), reducing the risk of PONV by 49% and 51%, respectively. Subgroup analyses indicated significant differences in favor of palonosetron compared with placebo ($P < .00001$) or first-generation 5-HT3RA ($P = .002$). There were no significant differences in the occurrence of headache, dizziness, and constipation between palonosetron and control groups ($P = .85$, $P = .22$, and $P = .30$, respectively).

Conclusions: The results of this meta-analysis suggest that intravenous palonosetron could become a prophylactic antiemetic 5-HT3RA in the prevention of PONV compared with first-generation 5-HT3RAs or placebo. No increased risk of side effects with palonosetron were found.

Keywords: palonosetron, prophylaxis, PONV, 5-HT3RA, meta-analysis.

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POSTOPERATIVE NAUSEA AND VOMITING (PONV), defined as nausea or vomiting within 24 hours of surgery, has an incidence rate ranging between 20% and 30%. Four primary risk predictors have been reported as female gender, history of motion sickness, nonsmoking, and the use of postoperative opioids. The simplified score by Apfel et al suggests that patients with at least two of the four previously mentioned risk factors should be considered to receive a prophylactic antiemetic strategy. If untreated, PONV occurs in 20% to 30% of general surgical strategy. Among high-risk patients, the incidence of PONV will rise to as frequent as 70% to 80%. Evidence-based guidelines have been established to identify the primary risk factors for PONV and give optimal approaches for PONV prophylaxis.

Several first-generation 5-hydroxytryptamine 3 receptor antagonists (5-HT3RAs), such as ondansetron (recommended dose is 4 mg), dolasetron (12.5 mg), granisetron (0.35 to 1.5 mg), and tropisetron (2 mg), have been marketed and frequently used. Ondansetron was suggested to be more effective than others for preventing PONV in a meta-analysis. However, the short life of the first-generation 5-HT3RAs limits their utilization as prophylactic antiemetics. Palonosetron is a second-generation 5-HT3RA with a unique pharmacodynamic mechanism of allosteric binding with higher binding affinity and longer half-life and duration of action compared to standard 5-HT3RAs. As of this publication, the US Food and Drug Administration has approved a single injection of a 0.075 mg dose for PONV prevention for up to 24 hours after surgery. Numerous randomized controlled clinical trials (RCTs) have been performed to assess the efficacy and safety of palonosetron for preventing PONV as compared to other first-generation 5-HT3RAs or placebo after different kinds of surgery.

In an effort to seek supportive evidence for the prophylactic use of palonosetron, this systemic review was performed to evaluate the effectiveness of prophylaxis and adverse effects associated with the use of palonosetron in different time periods.

Materials and Methods

Data Sources
PubMed (1966-April 2014), Cochrane Library, Google Scholar, Wanfang Data (Chinese 1998-April 2014), and China National Knowledge infrastructure electronic databases (1994-April 2014) were searched for RCTs. Search terms included “post-operative nausea and vomiting,” “post-operative nausea and vomiting,” and “PONV.” We excluded unpublished data and RCTs of pediatric patients with PONV.

Selection Criteria and Outcomes
Primary outcomes of interest included complete response (CR) of acute (0 to 24 hours) and delayed (24 to 72 hours) periods of PONV by palonosetron. CR was defined as no emesis and no rescue medication during the different phases mentioned previously. The adverse effects of palonosetron were also investigated.

Methodological Quality and Statistical Analysis
Included studies were evaluated for methodological quality by the methods of randomization, allocation, and blinding. The meta-analysis was performed on the nonheterogeneous trials with Review Manager (RevMan 5.0; Nordic Cochrane Centre, Rigshospitalet, Denmark) using fixed or random effect models. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. The heterogeneity test (P > .05) was considered as the low level of heterogeneity. Funnel plots were used to assess for possible publication bias. Statistical significance was considered as P value less than .05.

Subgroup Analyses
We performed subgroup analyses using two different control criteria versus palonosetron during first 24 hours as follows: first-generation 5-HT3RA and placebo, respectively.

Results
Ten RCTs including 1,827 patients were considered, with eight studies in English and two in
Chinese, (Figure 1). Six studies involved palonosetron for PONV after gynecological laparoscopic surgery; two involved laparoscopic cholecystectomy; one thyroid surgery, and one mastectomy procedures. Six trials compared palonosetron with first-generation 5-HT3RA (ondansetron, granisetron, and tropisetron) and two compared it with placebo as control. The reasons for exclusions were as follows (three in English and two in Chinese): (1) One study\textsuperscript{20} in 2013 established the evaluation of nausea in patients by visual analog scale scores, not by CR; (2) The other RCT\textsuperscript{21} performed opioid-based intravenous patient-controlled analgesia after lumbar spinal surgery, which is an significant risk factor impacting 5-HT3RA therapy results; (3) A clinical study\textsuperscript{22} compared palonosetron with ondansetron plus dexamethasone in the prevention of PONV; (4) No incidence of overall PONV was reported in the palonosetron or control group in the two Chinese RCTs,\textsuperscript{23,24} respectively.

**Descriptive Analysis**

Of these 10 RCTs included (Table 1), eight (six in English and two in Chinese) evaluated prevention of PONV in the acute phase (the first 24 hours) and two in the delayed phase (24 to 72 hours). Among the eight trials in the acute phase, four studies examined the use of palonosetron for preventing PONV as compared with placebo; the other four studies compared palonosetron with the first-generation 5-HT3RA. Two different dosages were used in the 10 English RCTs (0.075 mg) and in the two Chinese (0.25 mg) studies. The funnel plot indicated no publication bias (Figure 2).

**Meta-Analyses Results**

**THE EFFECTIVENESS OF PALONOSETRON IN THE PREVENTION OF ACUTE PONV.** Eight RCTs with 1,163 patients compared palonosetron with the first-generation 5-HT3RA or placebo for preventing acute PONV during the first 24 hours postoperatively (Figure 3). The data showed that there was no heterogeneity ($P = .83$) within these eight RCTs and also demonstrated that palonosetron ($P < .00001$) more effectively reduced the risk of PONV by 49% (OR, 0.51; 95% CI, 0.40 to 0.64). Owing to the different dosage used in the Chinese RCTs (0.25 mg) as compared to the English trials (0.075 mg), a separate meta-analysis was performed without Chinese trials, indicating no heterogeneity ($P = .66$) within the eight included studies (OR, 0.50; 95% CI, 0.39 to 0.64), which also favored palonosetron ($P < .00001$; Figure 3). Subgroup analyses demonstrated significant differences in favor of palonosetron compared with placebo (OR, 0.52; 95% CI, 0.40 to 0.69, $P < .00001$) or first-generation 5-HT3RA (OR, 0.41; 95% CI, 0.23 to 0.73, $P = .002$).

![Figure 1](image.png)

*Figure 1.* Based on the inclusion criteria, we enrolled 10 final studies (eight in English and two in Chinese) in our systematic review. RCT, randomized controlled clinical trial.
THE EFFECTIVENESS OF PALONOSETRON IN THE PREVENTION OF DELAYED PONV. RCTs were also analyzed for effectiveness in the prevention of delayed PONV. The results showed no heterogeneity between two studies \((P = .74)\), and palonosetron reduced the risk of delayed PONV by 51% in 460 patients with PONV during 24 to 72 hours postoperatively \((OR, 0.49; 95\% CI, 0.31 to 0.78, P < .002; Figure 3)\).

**Adverse Effects**

**HEADACHE AND DIZZINESS.** Eight RCTs reported headache as an adverse effect in the palonosetron and control arms. Meta-analyses showed that there was almost the same risk with palonosetron and first-generation 5-HT3RAs or placebo \((OR = 0.96, 95\% CI, 0.66 to 1.42)\), with no significant difference between them \((P = .85; Figure 4)\).

No significant difference was shown in the occurrence of dizziness between palonosetron and control groups \((OR = 0.73, 95\% CI, 0.45 to 1.20, P = .22)\) in the meta-analyses of five trials (Figure 4).

**CONSTIPATION.** Six RCTs with 914 patients were examined for the risk of occurrence of constipation. Data demonstrated that palonosetron did not increase the risk of constipation \((OR = 1.45, 95\% CI, 0.72 to 2.91)\), with no significant difference between them \((P = .30; Figure 4)\).

**Discussion**

5-HT3RAs have been recommended as one of the first-line prophylactic drugs and the only drugs for the treatment of existing PONV.\(^9\)\(^{19}\) Palonosetron, a newer secondary 5-HT3RA, has been evaluated for its efficacy in the prevention of PONV after different types of surgery.\(^10\)\(^{19}\) In these meta-analyses, eight RCTs showed palonosetron was superior to first-generation 5-HT3RAs or

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**Table 1. Descriptive Analysis of 10 RCTs**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Sample Size Calculation</th>
<th>Randomization</th>
<th>Blinding</th>
<th>Allocation Concealment</th>
<th>Intention-to-Treat Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kovac et al(^13)</td>
<td>2008</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>Candiotti et al(^10)</td>
<td>2008</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>Bhattacharjee et al(^11)</td>
<td>2010</td>
<td>C</td>
<td>A</td>
<td>A</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>Park and Cho(^15)</td>
<td>2011</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>Park and Cho(^16)</td>
<td>2011</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>Moon et al(^14)</td>
<td>2012</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>Park et al(^7)</td>
<td>2013</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>Yang and Li(^19)</td>
<td>2013</td>
<td>C</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>Ma et al(^18)</td>
<td>2013</td>
<td>C</td>
<td>B</td>
<td>D</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>Chun et al(^12)</td>
<td>2014</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
</tbody>
</table>

RCT, randomized controlled clinical trial.

Sample size calculation: A: superiority; B: Noninferiority; C: unclear.

Randomization: A: appropriate; B: randomization mentioned in the Materials and Methods section but without details; C: quasi-randomization; D: inappropriate.

Blinding: A: double blind; B: blinding of participants or investigators; C: blinding of analyst only; D: unclear; E: not blinded.

Allocation concealment: A: concealed; B: unclear; C: not concealed.

Intention-to-treat analysis: A: appropriate; B: unclear; C: not performed.
placebo in control arms for preventing acute PONV. The first-generation 5-HT3RAs enrolled in our study were ondansetron, ramosetron, granisetron, and tropisetron, which were the most common drugs for the prevention of PONV in clinical practice. However, there was no evidence of any difference in the efficacy of various first-generation 5-HT3RAs in the prophylaxis of PONV in a consensus guideline.\textsuperscript{5} Our subgroup analyses indicated that first-generation 5-HT3RAs or placebo were inferior to palonosetron in the prevention of PONV during the first 24 hours, respectively. One RCT from China also suggested that palonosetron has a significant antiemetic effect superior to ondansetron plus dexamethasone within 48 hours after gynecological laparoscopic surgery.\textsuperscript{22}

Dose range selection for intravenous palonosetron (form 0.1 to 90 mcg/kg) was evaluated in several RCTs\textsuperscript{10,13,26} in healthy subjects from the United States and Japan.\textsuperscript{27} The pharmacokinistics of palonosetron was evidenced to be independent of dosage.\textsuperscript{27} However, Tang et al\textsuperscript{28} suggested 30 mcg/kg of palonosetron is the most effective for reducing postoperative vomiting. The recommended initial dose for palonosetron for the prevention of chemotherapy-induced nausea and vomiting (CINV) is 0.25 mg, whereas for PONV, the minimum effective dose, which was approved by the US Food and Drug Administration,\textsuperscript{29,30} is 0.075 mg, which is more effective than granisetron 1 mg\textsuperscript{11} and ondansetron 4 mg.\textsuperscript{16} The dosage of 0.25 mg used in our two Chinese trials was not consistent with the dosage used (0.075 mg) in other trials. When these trials were removed from the analysis, the meta-analyses finally demonstrated the superiority of 0.075 mg of palonosetron over first-generation 5-HT3RAs or placebo for prophylaxis of acute PONV.

For the evaluation of effectiveness of palonosetron in delayed PONV, two RCTs comparing palonosetron with placebo during the 24 to 72 hours after surgery were analyzed. The risk of delayed PONV was significantly reduced by palonosetron compared to placebo (OR = 2.02). It is possible
that the improved effects of palonosetron on PONV may be due to the long half-life (approximately 40 hours) and strong binding affinity to the 5-HT3RA (pKi is 10.4) based on its unique properties. In previous meta-analyses involving comparison of first-generation 5-HT3RAs, palonosetron has been reported as more effective and safer for the prevention of delayed CINV. Among all RCTs, PONV with various surgery types were found to be prevented by palonosetron. Previous studies reported the incidence of PONV was associated with various surgery-related factors, including types of surgery and opioid-based therapy. Thyroid surgery and lumbar spinal surgery have a high incidence of PONV, likely due to a high proportion of female patients and higher opioid utilization. Palonosetron was shown to be superior to ondansetron, tropisetron, or placebo in thyroidectomy, breast surgery, and abdominal laparoscopic surgery, but to be inferior to ramosetron in lumbar spinal surgery. The reason may be related to the opioid used for analgesia after lumbar spinal surgery. However, another study by Candiotti KA 2008, Chiu AC 2008, Na GS 2013, Moon YJ 2012, Park SK 2011 A, Park SK 2011 B, and Park SK 2013 compared the adverse effects of palonosetron compared with placebo or first-generation 5-HT3RA in prevention of PONV, including headache, dizziness, and constipation. 5-HT3RA, 5-hydroxytryptamine 3 receptor antagonist; PONV, postoperative nausea and vomiting; OR, odds ratio; n/N, number; CI, confidence interval. This figure is available in color online at www.jopan.org.

Figure 4. The adverse effects of palonosetron compared with placebo or first-generation 5-HT3RA in prevention of PONV, including headache, dizziness, and constipation. 5-HT3RA, 5-hydroxytryptamine 3 receptor antagonist; PONV, postoperative nausea and vomiting; OR, odds ratio; n/N, number; CI, confidence interval. This figure is available in color online at www.jopan.org.
Park and Cho\textsuperscript{15} found that palonosetron plus inhalational anesthesia was almost as effective as total intravenous anesthesia with remifentanil and propofol for reduction of the incidence of PONV. Thus, different types of surgical, anesthetic procedure and opioid-based analgesia are critical factors to consider when evaluating palonosetron for the prevention of PONV.

Adverse effects such as headache, dizziness, and constipation with palonosetron and other 5-HT3RAs were mild and transient in clinical practice. Data from this study showed no significant difference between palonosetron and first-generation or placebo in occurrence. However, the trend of incidence of headache and dizziness with palonosetron was addressed, but no statistical difference was found. 5-HT3RAs were recommended to be more effective and associated with lower risk of headache when combined with other antiemetic drugs which act on different pathways, such as butyrophenones (droperidol) and corticosteroids (dexamethasone).\textsuperscript{8,34,35} The optimal antiemetic dosing with combination therapy should be further established. The lack of increased risk for constipation in palonosetron in PONV was not consistent with the previous meta-analyses evaluating use in the prevention of CINV.\textsuperscript{20} The different dosage used in previous and recent analyses (0.75 mg vs 0.075 mg) could attribute to the outcome.

Limitations were shared in these trials. Some possible concomitant medications, such as antihypertensives and antidiabetic medications will influence the compared results in efficacy of palonosetron and other 5-HT3RAs. Additionally, the risk factors such as age, gender, weight, and history of opioid usage should be considered in patients with PONV. CR, defined as no emesis and no use of rescue medications, was generally considered as the efficacy end point of palonosetron in the treatment of PONV.\textsuperscript{13} However, other end points have also been analyzed in some reports, including emesis and nausea rates and a reduction in nausea severity, even visual analog scale scores for evaluation of effectiveness of palonosetron.\textsuperscript{20,23,24} In this study, the excluded RCTs\textsuperscript{20–24} used these end points to compare palonosetron with control arms, which could not be combined together with other trials enrolled in these meta-analyses.

In conclusion, results from this study provide strong evidence that intravenous palonosetron is more efficacious than first-generation 5-HT3RAs or placebo in the prevention of acute and delayed PONV.

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References


