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Review Article

Does palonosetron have a positive effect than ramosetron on PONV? A meta-analysis of RCTs

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Abstract: Background: General anesthesia is associated with an appreciably high rate of postoperative nausea and vomiting (PONV). This study was designed to conduct a meta-analysis on the effect and safety of palonosetron versus ramosetron on preventing PONV via the most recently published randomized controlled trials (RCTs). Methods: We searched PubMed, EMbase, and The Cochrane Library for RCTs to compare the effect and safety of palonosetron with that of ramosetron. The meta-analysis was performed by employing Review Manager Version 5.2. Dichotomous outcomes were expressed as the relative risk (RR) with a 95% confidence interval (CI). Results: Seven studies, totaling 730 patients, were included in this study. The meta-analysis suggested that no statistically significant difference was found between ramosetron and palonosetron in the prevention of postoperative nausea (PON) and postoperative vomiting (POV) at different time periods within 48 hours after surgery. No significant side effects were observed between the two groups when the safety of ramosetron and palonosetron was compared (RR 1.10, 95% CI [0.75, 1.62]; P=0.64). Conclusion: This meta-analysis demonstrated that palonosetron was not superior to ramosetron on the prevention of POV and PON. In addition, no appreciable difference was recorded between the two groups on their side effects.

Keywords: Palonosetron, ramosetron, PONV, meta-analysis

Introduction

PONV is one of the most dreaded and distressing side-effects of general anesthesia, with an incidence of around 30% [1]. The incidences and risk factors for PONV are anesthesia-related and non-anesthesia-related. A lot of clinical studies have indicated that anesthesia-related risk factors for PONV include the administration of postoperative opioid analgesics and volatile anesthetics. However, the mechanism that underlies the two major risk factors, at present, still remains unclear [2].

In fact, failure to suppress PONV would increase the time to discharge, consume resource of the post-anesthesia care, and raise cost of medical care, though PONV is not a fatal medical complication [3]. Generally, cholinergic receptor antagonists, histamine receptor antagonists, 5 HT-3 receptor antagonists, dopamine antagonists, and other antiemetic drugs are employed to control PONV, of which, 5-HT3 receptor antagonists are most commonly used ones in post-anesthesia care. Palonosetron and ramosetron, the newly developed 5-HT3 receptor antagonists, show more prolonged and sustained activity than ondansetron, and they are very efficacious in preventing PONV [4, 5]. In order to present an updated evaluation of the effect of ramosetron, we conducted a meta-analysis on the effect and safety of ramosetron and palonosetron via the most recently published RCTs.

Material and methods

Inclusion and exclusion criteria

Research types randomized controlled trials (RCTs) Study subjects surgical patients Interventions group 1 was given palonosetron, while group 2 received ramosetron.

Outcome indicators the primary outcome included the incidence of PON and POV. The

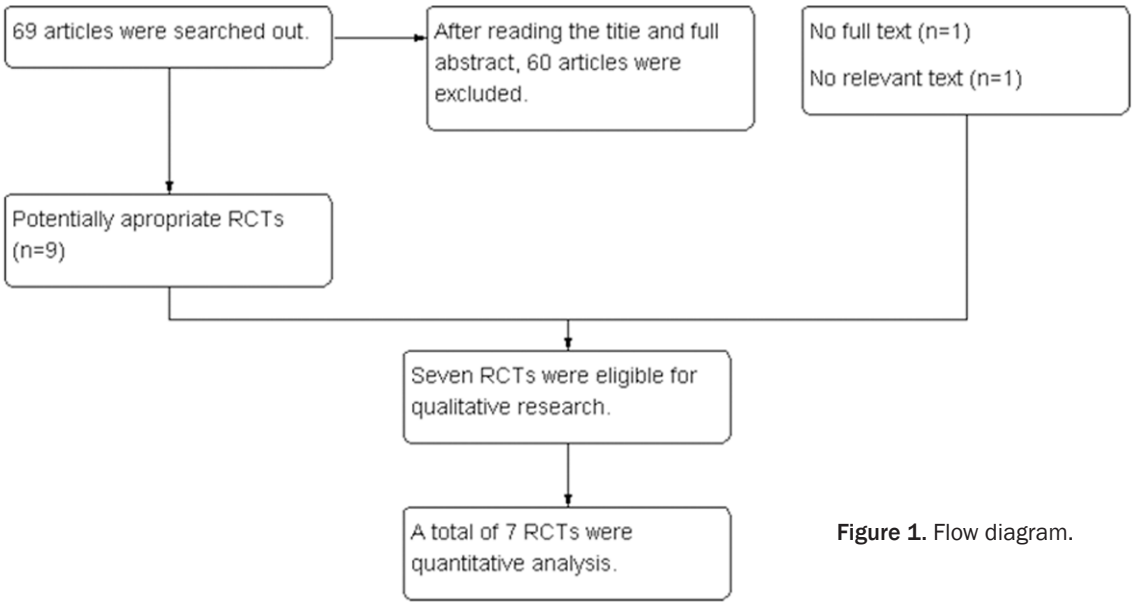

Figure 1. Flow diagram.

secondary outcome included side effects (including headache, dizziness, and pruritis) of palonosetron and ramosetron. Exclusion criteria repeated studies, studies with incomplete data, and non-English language articles.

Search strategy

PUBMED, The Cochrane Library, and EMBASE were searched for all relevant published RCTs. The following search terms were used: "nausea", "vomiting", "surgery", "palonosetron", and "ramosetron".

Literatures screening and data extraction

Two reviewers independently screened literatures and extracted data on the basis of inclusion and exclusion criteria, then cross-checked with each other. The two discussed or consulted a third party when there was a disagreement.

Quality evaluation

The quality of the enrolled studies was assessed by adopting the Jadad scale, which analyzes the randomization method, blinding method, allocation concealment, and withdrawals and dropouts in the study. Jadad score ≥3 means that the study is of high quality [6].

Statistical analysis

We conducted the meta-analysis via using RevMan 5.2. Enumeration data were presented as relative risk (RR) with a 95% CI, and measurement data were expressed as weighted mean difference (WMD) with a 95% CI. A heterogeneity test was done on included studies via χ^2 test, and when α=0.05 and $P \leq 0.05$, heterogeneity was considered present. Furthermore, a quantitative analysis was conducted on heterogeneity by adopting I^2 value, and heterogeneity existed when $I^2 \geq 50\%$. We adopted a fixed effects model to do a meta-analysis when there was no heterogeneity. A random-effects model was employed when each study showed statistical heterogeneity rather than clinical heterogeneity or when the differences had no significance. And a descriptive analysis approach was used when the heterogeneity was too large.

Results

Study identification and characteristics

We identified a total of 69 records by applying our search strategy. Studies published by Shin were excluded as there was no full text [7]. And one study, without relevant data, was excluded [8]. Only 7 studies were eligible for the meta-analysis after screening titles and abstracts and full texts of the included studies [9-15] (**Figure 1**). The characteristics of the included studies are presented in **Table 1**. Most of the studies, with a Jadad score of 5 or 6 (**Table 1**), were well designed RCTs.

Table 1. Characteristics and jadad score of the included studies in the meta-analysis

Author (Published year)	Country	Head-count	Grouping	Surgical setting	Jadad score	Ran-domized method	Conceal-ment al-location	Blind-ing
Chattopadhyay 2015	India	109	Palonosetron Ramosetron	Cesarean Delivery	6	2	1	2
Kim SH 2015	Korea	88	Palonosetron Ramosetron Placebo	Gynecological laparoscopic surgery	6	2	1	2
Lee 2015	South Korea	105	Palonosetron Ondansetron Ramosetron	Laparoscopic gynecologic surgery	6	2	1	2
Park 2013	Korea	100	Palonosetron Ramosetron	Gynecological laparoscopic surgery	5	1	1	2
Roh 2014	South Korea	196	Palonosetron Ramosetron	Lumbar Spinal Surgery	6	2	1	2
Swaika 2011	India	87	Palonosetron Ondansetron Ramosetron	Laparoscopic cholecystectomy	5	1	1	2
Kim SH 2013	Korea	109	Palonosetron Ondansetron Ramosetron	Laparoscopic surgery	5	1	1	2

Outcomes

Primary outcomes

PON and POV: Seven studies, totaling 730 patients, were enrolled to treat with antiemetic drugs after surgery. In the 7 included studies, PON and POV events were observed at different time intervals within 48 hours after surgery. The meta-analysis showed that no statistically significant difference was found between palonosetron group and ramosetron group in PON at different time intervals in 48 hours after surgery: 0-2 hours (RR 0.87, 95% CI [0.36, 2.09]; P=0.76), 0-6 hours (RR 1.03, 95% CI [0.56, 1.87]; P=0.93), 6-24 hours (RR 0.86, 95% CI [0.46, 1.60]; P=0.64) or 24-48 hours (RR 0.86, 95% CI [0.47, 1.58]; P=0.63). However, during the 2-24 hour time period after surgery, ramosetron showed to be more efficacious than palonosetron (RR 0.34, 95% CI [0.17, 0.70]; P=0.003). The I^2 value of 65% implied that there was significant heterogeneity. Moreover, the pooled results were not influenced by further subgroup analyses based on different routes and doses of palonosetron and ramosetron, and all of these analyses were also affected by heterogeneity (**Figure 2**).

Palonosetron was as effective as ramosetron on POV. During some of the time periods in the 48 hours after surgery, palonosetron was proved to be more effective than ramosetron on POV: 0-2 hours (RR 1.65, 95% CI [0.69, 3.90]; P=0.26), 0-6 hours (RR 0.66, 95% CI [0.30, 1.44]; P=0.29), 2-24 hours (RR 0.61, 95% CI [0.31, 1.23]; P=0.17), 6-24 hours (RR 1.53, 95% CI [0.63, 3.74]; P=0.35) and 24-48 hours (RR 0.64, 95% CI [0.37, 1.09]; P=0.10). The I^2 value of 28% suggested no significant heterogeneity. The study conducted by Kim SH 2015 [8] was not enrolled into our meta-analysis because detailed PON and POV outcomes were not provided. And their results indicated that preoperative administration of a single intravenous dose of palonosetron showed no efficacy than that of ramosetron in reducing the incidence of PONV after surgery (**Figure 3**).

Secondary outcome

Side effects of palonosetron and ramosetron: Among the included 7 studies, 3 of them offered full data on side effects (headache, dizziness, and pruritus) of palonosetron or ramosetron after surgery. It turned out that observable side effects of palonosetron was no more than that of ramosetron (RR 1.10, 95% CI [0.75, 1.62]; P=0.64). The I^2 value of 0% suggested that there was no significant heterogeneity. Other studies, without providing detailed data on side effects, however, mentioned that no statistically significant difference was observed between palonosetron and ramosetron in their results (**Figure 4**).

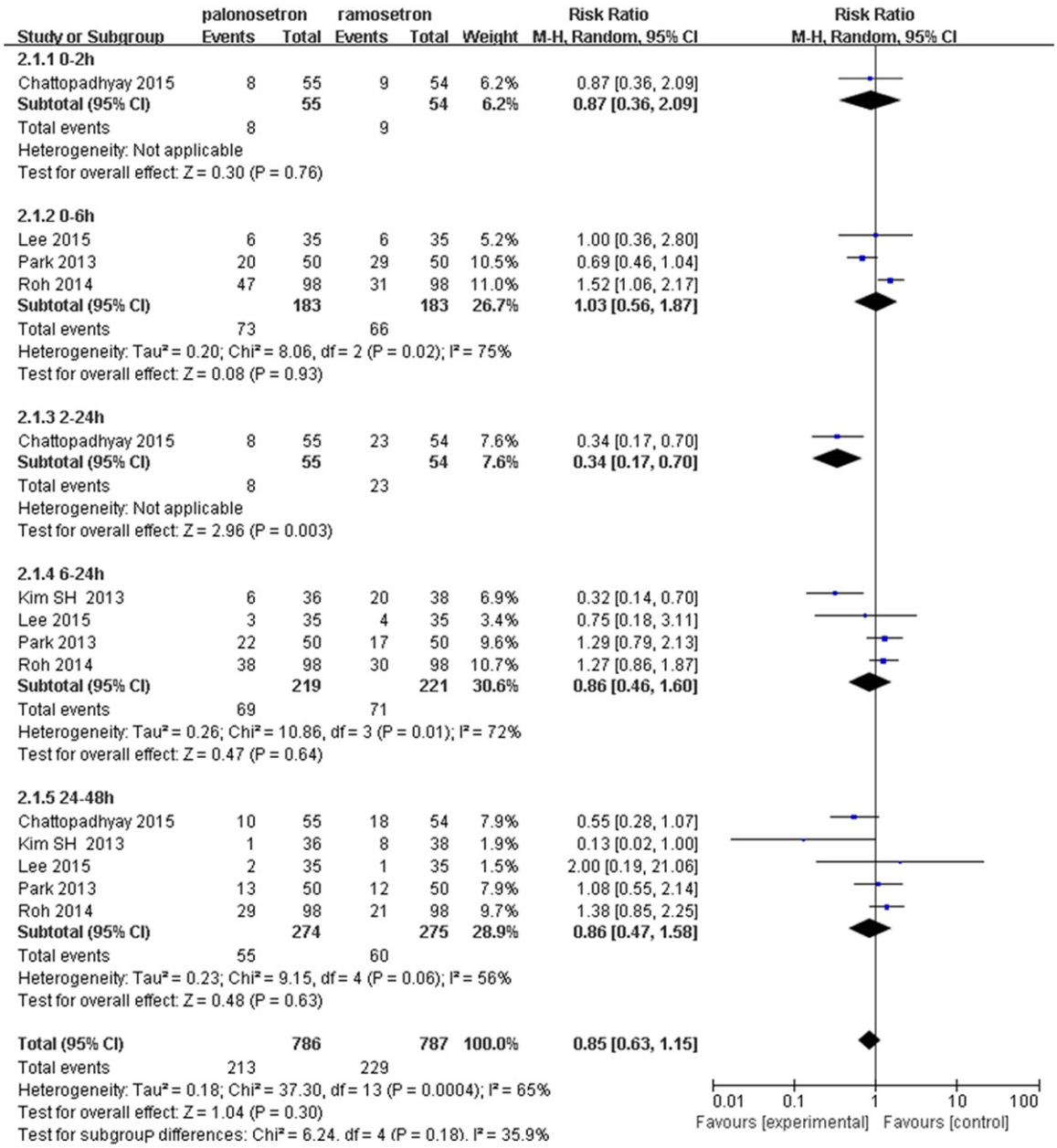

Figure 2. Forest plot of relative risk on PON between palonosetron and ramosetron treatment.

Publication bias

We adopted Begg's funnel plot to assess the potential publication bias of the included studies. And no publication bias was detected.

Discussion

This meta-analysis indicated that though ramosetron showed to be more effective than palonosetron in the 2-24 hours after treatment, no statistically significant difference was observed in the prevention of PON during any time periods within 48 hours after surgery between ramosetron and palonosetron. In addition, no statistically significant difference between palonosetron and ramosetron was found on the prevention of POV (0-2 hours, 0-6 hours, 2-24 hours, 6-24 hours, and 24-28 hours) during some of the time periods within 48 hours after surgery.

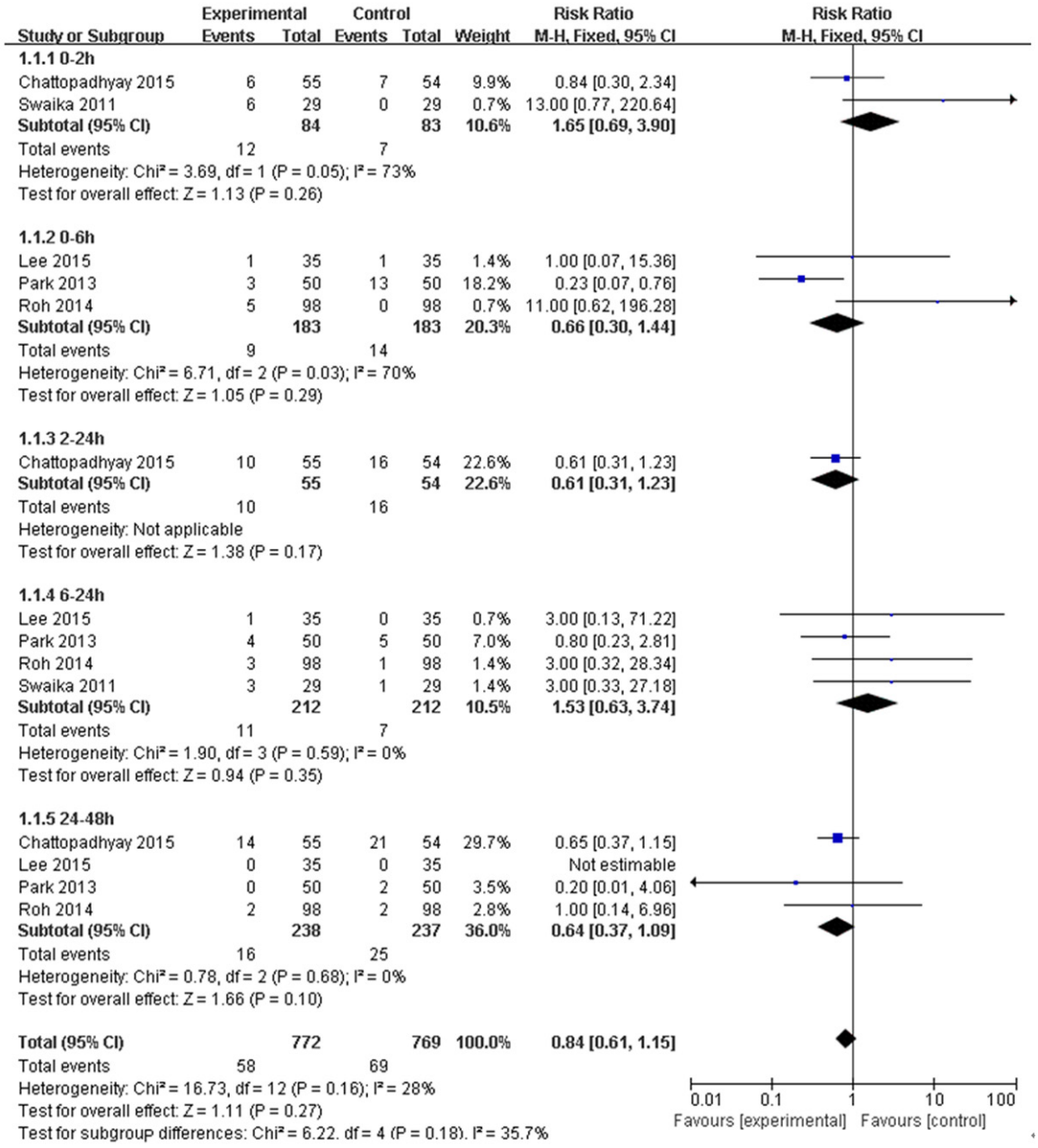

Figure 3. Forest plot of relative risk on POV between palonosetron and ramosetron treatment.

Side effects of palonosetron were no fewer than that of ondansetron after surgery, when the total number of side effects (including headache, dizziness, and pruritus) were compared.

At present, the mechanism of ramosetron and palonosetron in preventing PONV remains unclear, but the drugs may act on by prohibiting 5-HT3 receptors sites in nucleus of the solitary tract (NTS) and area postrema [16, 17]. The doses of ramosetron and palonosetron were on the basis of similar studies in the Indian context [18, 19] on dose-ranging studies with regard to optimal adult dose of ramosetron and palonosetron.

However, several limitations of this meta-analysis should be taken into consideration. Firstly, the sample size for each time period was small, as the total number of patients enrolled was only 730. As the etiology behind the PONV is complex and multifactorial, and anaesthetic technique may also influence the incidence of

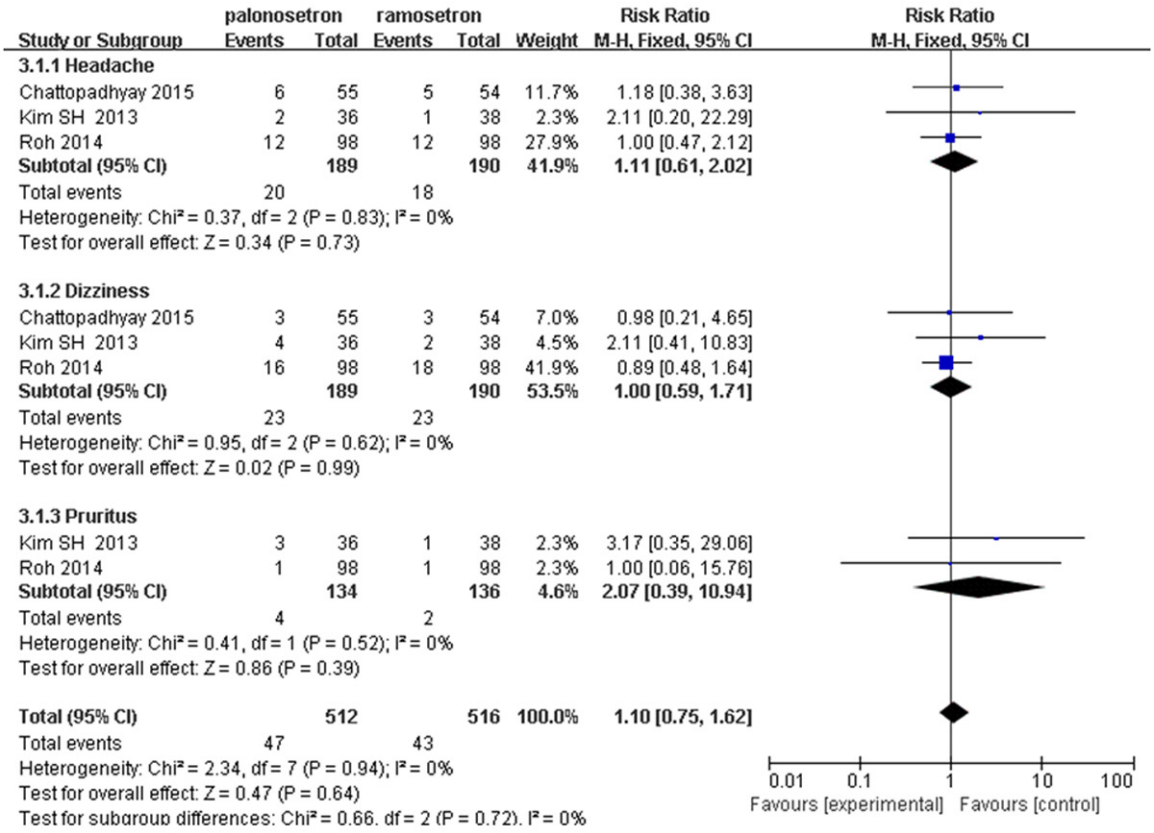

Figure 4. Forest plot of relative risk on side effects between palonosetron and ramosetron treatment.

PONV Moreover, different studies adopted different administrations of ramosetron and palonosetron. As a result, the possibility of biases remains.

In summary, this meta-analysis demonstrated that there were no statistically significant differences in efficacy between palonosetron and ramosetron on the prevention of PON and POV. Besides, there was no difference between their effects on preventing their side effects.

Disclosure of conflict of interest

None.

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