Can J Anesth/J Can Anesth (2015) 62:1268–1278
DOI 10.1007/s12630-015-0457-1

REPORTS OF ORIGINAL INVESTIGATIONS

Efficacy of palonosetron for preventing postoperative nausea and vomiting: a systematic review and meta-analysis

Efficacité du palonosétron pour la prévention des nausées et vomissements postopératoires: une revue systématique de la littérature et méta-analyse

Chao Xiong, MD · Guangyu Liu, MD · Ruolan Ma, MD · Jixiu Xue, MD · Anshi Wu, MD

Received: 30 March 2015 / Revised: 13 July 2015 / Accepted: 11 August 2015 / Published online: 22 August 2015

Abstract

Purpose *Palonosetron, a second-generation 5-hydroxytryptamine 3 receptor antagonist (5-HT$_3$RA), has unique characteristics relative to first-generation 5-HT$_3$RAs such as ondansetron. Nevertheless, it remains unclear if palonosetron is better than ondansetron for the prevention of nausea and vomiting during the first 24 hr after surgery and is thus the focus of this systematic review.*

Methods *We conducted a systematic search of the MEDLINE®, EMBASE™, Cochrane Central Register of Controlled Trials and Web of Science® databases to identify randomized controlled trials (RCTs) that addressed a comparison of the prophylactic antiemetic efficacy between palonosetron and ondansetron within 24 hr after surgery. The primary outcomes were the proportion of participants who experienced postoperative nausea (PON), postoperative vomiting (POV), or both, in the early (0-6 hr) or late (6-24 hr) period. The pooled relative risks (RRs) were calculated along with their corresponding 95% confidence intervals (CIs).*

Results *We identified nine RCTs that comprised 741 participants. Palonosetron was superior to ondansetron in the reduction of early PON [RR, 0.51; 95% CI, 0.37 to 0.71], late PON (RR, 0.53; 95% CI, 0.36 to 0.77), and late POV (RR, 0.41; 95% CI, 0.28 to 0.62), but not early POV (RR, 0.77; 95% CI, 0.45 to 1.34).*

Conclusion *Palonosetron provides more effective prophylaxis of early PON, late PON, and late POV compared with ondansetron. Future studies are required to investigate the role of palonosetron during 24-72 hr following surgery.*

Résumé

Objectif *Le palonosétron est un antagoniste du récepteur de la 5-hydroxytryptamine 3 (5-HT$_3$RA) de deuxième génération; il présente des caractéristiques uniques par rapport aux 5-HT$_3$RA de première génération tels que l'ondansétron. Néanmoins, il n'est pas certain que le palonosétron est meilleur que l'ondansétron pour la prévention des nausées et vomissements au cours des 24 premières heures suivant une chirurgie et cela est donc l'objet de cette revue systématique.*

Méthodes *Nous avons effectué une recherche systématique dans les bases de données MEDLINE®,*

Author contributions *Chao Xiong* and *Anshi Wu* were involved in the design of the study. *Anshi Wu* was involved in the conception of the study. *Chao Xiong* and *Guangyu Liu* helped extract the data. *Chao Xiong, Guangyu Liu,* and *Jixiu Xue* helped analyze and interpret the study data. *Chao Xiong, Guangyu Liu, Ruolan Ma,* and *Jixiu Xue* helped draft the article. *Ruolan Ma* was involved in the statistical analysis raised by the reviewers and in modifying the analysis part of the Method and Results sections. *Ruolan Ma* and *Jixiu Xue* were involved in checking the study data. *Chao Xiong* and *Guangyu Liu* contributed equally to the study. *Anshi Wu* helped critically revise the manuscript.

Electronic supplementary material The online version of this article (doi:10.1007/s12630-015-0457-1) contains supplementary material, which is available to authorized users.

C. Xiong, MD · A. Wu, MD (✉)
Department of Anesthesiology, Beijing Chaoyang Hospital, Capital Medical University, No. 8, Gongtinan Road, Chaoyang District, Beijing 100020, China
e-mail: wuanshi1965@163.com

G. Liu, MD · J. Xue, MD
Department of Anesthesiology, Xuan Wu Hospital, Capital Medical University, Beijing, China

R. Ma, MD
Department of Anesthesiology, Beijing Stomatological Hospital, Capital Medical University, Beijing, China

EMBASE™, le Registre central Cochrane des essais cliniques contrôlés et Web of Science® pour identifier les essais randomisés contrôlés qui ont abordé la comparaison de l'efficacité antiémétique dans les 24 premières heures suivant une chirurgie, du palonosétron et de l'ondansétron administrés à titre prophylactique. Les principaux critères d'évaluation étaient le pourcentage de participants éprouvant des nausées postopératoires (NPO), des vomissements postopératoires (VPO) ou les deux, dans la période précoce (0-6 heures) ou tardive (6-24 heures). Les risques relatifs (RR) regroupés ont été calculés avec leurs intervalles de confiance (IC) à 95 % correspondants.

Résultats *Nous avons identifié neuf essais cliniques randomisés ayant inclus 741 participants. Le palonosétron a été supérieur à l'ondansétron pour la réduction des NPO précoces [RR, 0,51; IC à 95 %, 0,37 à 0,71], des NPO tardives (RR, 0,53; IC à 95 %, 0,36 à 0,77), et des VPO tardifs (RR, 0,41; IC à 95 %, 0,28 à 0,62), mais pas pour les VPO précoces (RR, 0,77; IC à 95 %, 0,45 à 1,34).*

Conclusion *Le palonosétron assure une prophylaxie plus efficace que l'ondansétron sur les NPO précoces et tardifs, ainsi que sur les VPO tardifs. D'autres études sont nécessaires pour étudier le rôle du palonosétron au cours des 24 à 72 heures suivant une intervention chirurgicale.*

Postoperative nausea and vomiting (PONV), the big "little problem",[1] is the most common postoperative medical problem. From the perspective of both patients and healthcare providers, prophylaxis of PONV is equally as important as postoperative analgesia.[2,3] The incidence of PONV is estimated at 20-40% in adults,[4] and for patients with multiple risk factors, the rate of PONV can be as high as 79%.[5] Postoperative nausea and vomiting not only decreases patient satisfaction but also relates to rare but severe adverse consequences, including pulmonary aspiration, wound dehiscence, esophageal rupture, subcutaneous emphysema, and bilateral pneumothoraces.[6]

The main strategy for PONV prophylaxis is antiemetic drug therapy. The 5-hydroxytryptamine -3 receptor antagonists (5-HT_3RAs) are the most popular pharmacologic class of antiemetics for PONV. The first-generation 5-HT_3RAs have been shown to have similar efficacy and safety for PONV prophylaxis during the first 24 hr after surgery. The number needed to treat (NNT) with 5-HT_3RAs in order to prevent one additional patient from experiencing nausea, vomiting, or PONV compared with placebo has been reported to be approximately 7, 6, and 3, respectively.[7–11] Ondansetron was the first available 5-HT_3RA, and its wide use in the prevention of PONV may be related to its relatively lower cost compared with other agents in the same class.[7,8]

Numerous studies of different prophylactic agents have been published over the past 50 years; however, a significant percentage of surgical patients still suffer from PONV.[12] New antiemetic drugs continue to be introduced, including palonosetron, a 5-HT_3RA approved by the United States Food and Drug Administration (FDA) in 2008 for PONV prophylaxis up to 24 hr. In 2012, palonosetron was recommended for authorization by Health Canada for the prevention of acute and delayed chemotherapy-induced nausea and vomiting. Nevertheless, palonosetron has not yet been approved for the prophylaxis or treatment of PONV in Canada.

Compared with the first-generation 5-HT_3RAs, studies have shown that palonosetron has greater receptor binding affinity to 5-HT_3R and a longer plasma half-life.[13,14] In addition, Rojas *et al*.[15–17] showed features that differentiate palonosetron from other 5-HT_3RAs: allosteric binding and positive cooperativity with 5-HT_3R, triggering of 5-HT_3R internalization and prolonged inhibition of receptor function, and inhibition of substance P (a mediator of emesis)-mediated responses.[15–17] Due to these unique characteristics, palonosetron may be a promising agent that could achieve long-lasting efficacy in the prevention of PONV. Importantly, preliminary studies have already shown that palonosetron is safer and more effective than other 5-HT_3RAs in preventing chemotherapy-induced nausea and vomiting, although this requires more rigorous confirmation.[18,19]

In consideration of the above, we conducted this systematic review and meta- analysis to investigate whether the recommended palonosetron dose (0.075 mg *iv*)[20] has better efficacy than ondansetron ($\geq$ 4 mg *iv*), a widely used first-generation 5-HT_3RA, for the prophylaxis of nausea and vomiting during the first 24 hr following surgery.

Methods

This systematic review and meta-analysis included randomized controlled trials (RCTs) that compared the efficacy of palonosetron with ondansetron in the prevention of PONV. We reported the study in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[21,22]

Systematic search and strategy

We searched the MEDLINE®, EMBASE® Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science™ databases up to January 6, 2015 without

language limitations. We also searched the reference lists of included studies and grey literature using the System for Information on Grey Literature in Europe (SIGLE) database to identify potential RCTs.

The search strategy consisted of a combination of free text words and Medical Subject Headings (MeSH) terms as follows: "palonosetron", "drug therapy", "postoperative", "postanaesthetic", "postanesthetic", "surgical", "nausea", "emesis", "vomiting", "retching", "randomized controlled trial", "controlled clinical trial", "randomized", "randomly", and "trial". Details of our search strategy are provided in the Appendix.

Eligibility criteria

Studies were included in the systematic review if they were RCTs that evaluated the effect of palonosetron 0.075 mg relative to that of ondansetron $\geq$ 4 mg for the prophylaxis of PONV. Participants were adults (18 yr or older) receiving any type of elective surgery involving general anesthesia and palonosetron or ondansetron administration by intravenous injection, regardless of the timing.

Exclusion criteria were studies that did not define nausea or vomiting; studies that did not report the primary outcome separately in the early and late postoperative periods; studies of treatments for established PONV; or data from meeting abstracts, reviews, posters, case reports, comments, letters to the editor, and animal studies.

The primary outcome measures were the proportion of participants who experienced postoperative nausea (PON) or postoperative vomiting (POV) in the early or late period during the first 24 hr. If the 24-hr follow-up period was divided into two separate periods (e.g., 0-6 and 6-24 hr), we defined the first as the early period and the second as the late period. If the follow-up period was divided into three periods (e.g., 0-2, 2-8, and 8-24 hr), we defined the second as the early period and the third as the late period. The secondary outcome measures were the proportion of participants who experienced common adverse effects and the proportion of participants who received rescue antiemetics.

Nausea was defined as the subjectively unpleasant feeling associated with an awareness of the urge to vomit. Both vomiting (an actual physical phenomenon – the forceful expulsion of gastric contents from the mouth) and retching (laboured, spasmodic contractions of the respiratory muscle without expulsion of gastric contents) were defined as vomiting.[23] We did not consider these definitions as mandatory inclusion criteria of an RCT.

Study selection and data collection

Two reviewers (C.X. and G.Y.L.) independently scanned the titles and abstracts of all identified citations to exclude duplicates and those that obviously failed to meet our inclusion criteria. Full articles of the selected citations were retrieved for further screening. The two reviewers resolved all discrepancies through discussion, and if necessary, they contacted another author (A.S.W.) for a decision. We used the PRISMA flow diagram to summarize the processes of study selection.

The following data were extracted from each study: name of first author; publication year; country; sample size; age of participants and their American Society of Anesthesiologists physical status; risk factors for PONV;[5] anesthetic technique; type of surgery; dose and timing of target drug administration; dosage of administration. We also extracted the number of participants who experienced PON or POV in the early or late periods, those who received rescue antiemetics in the early or late periods, and those who experienced common adverse effects. All graphical data were converted into numerical data. Two reviewers (C.X. and G.Y.L.) were responsible for the extraction of all data mentioned above and another reviewer (J.X.X.) checked the extracted data.

Risk of bias in individual studies

We evaluated the overall risk of bias in individual studies with regard to the adequacy of randomization, concealment of allocation, blinding (of patients, healthcare providers, data collectors, and outcome assessors), incomplete outcome data, selective outcome reporting, and other sources of bias.

Summary measures and statistical analyses

Data of all primary and secondary outcomes were binary, and we used relative risks (RRs) and the NNTs with corresponding 95% confidence intervals (CIs) as the summary measures. If the 95% CI included the value 1.0, we assumed that the difference between the two groups was not statistically significant. The I^2 test was used to measure heterogeneity. For $I^2 \leq 40\%$ and $I^2 > 40\%$, fixed effects and random effects models were used, respectively, (Mantel-Haenszel method) to compute the summary measures.[24] The Egger regression asymmetry test was used to evaluate the existence of publication bias.

Substantial publication bias was considered to exist with $P < 0.05$ in the regression asymmetry test. If substantial heterogeneity ($I^2 > 40\%$) existed, we considered the possible reasons and performed a sensitivity analysis for the primary outcomes according to methodological quality, dose of ondansetron, type of anesthesia, and method for the combination of intervention effect estimates across studies. We used the software package STATA® (version 12.0) to conduct all statistical analyses.

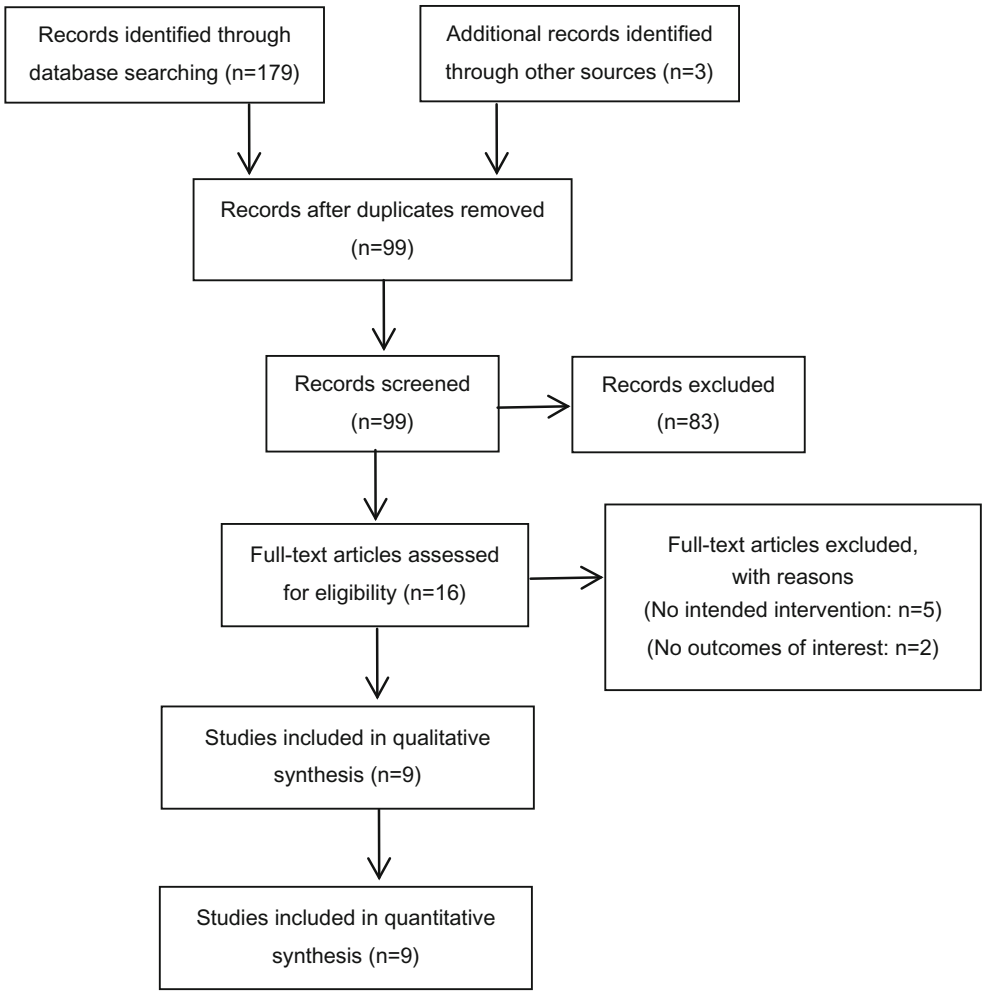


Fig. 1 Study selection flow diagram

Results

Study selection

Initially, we identified 179 citations by searching the MEDLINE, EMBASE, CENTRAL, and Web of Science databases, and we identified three additional citations through other sources. Of these, 83 were duplications and were excluded. Next, we scanned the abstracts of the remaining 99 citations and found that 83 clearly did not meet our inclusion criteria. We then retrieved the full texts of the remaining 16 citations and excluded seven of these citations because five among them had no intended interventions and two had no outcomes of interest. Altogether, nine studies[25–33] fulfilled the criteria for systematic review and meta-analysis. The study selection processes are shown in Fig. 1.

Study characteristics

The studies in this review comprised a total of 741 eligible participants; 371 patients received palonosetron 0.075 mg *iv* and 370 patients received ondansetron $\geq$ 4 mg *iv*. Three studies involved ondansetron 4 mg and six studies involved ondansetron 8 mg. Five studies were conducted in Korea and four in India.

These studies scored their participants for risk factors for PONV using Apfel's simplified risk factor scoring system.[5] Among these studies, patients' scores varied. Inhalation anesthesia was performed in eight studies and total intravenous anesthesia (TIVA) was used in one study. Palonosetron was administered before induction of anesthesia in eight studies and at the end of surgery in one study. Table 1 shows the characteristics of all included studies.

Table 1 Characteristics of included studies

First author, year	Country of origin	No. Of patients	Age (P/O) Mean (SD)	ASA PS	Risk factors of PONV	Type of Anesthesia (P/O)	Route of administ-ration	Timing of administration	Intervention/control	Definition of early period	Definition of late period
Bajwa *et al*., 2011[25]	India	60	32.22(1.58)yr/ 33.46(1.86)yr	I–II	≥1	TIVA	*iv*	before induction	P 0.07 5mg/O 8mg	1-6hr	6-24hr
Park *et al*., 2011[26]	Korea	90	42.4(10.0)yr/42.8 (7.3)yr	I–II	≥2	N_2O + Sevoflurane	*iv*	before induction	P 0.075mg/O 8mg	2-6hr	6-24hr
Moon *et al*., 2012[27]	Korea	100	45.9yr/43.8yr	I–II	≥3	N_2O +Sevoflurane	*iv*	end of surgery	P 0.075mg/ O 8mg *iv* + PCA16mg	0-2hr	2-24hr
Kim YY *et al*., 2012[28]	Korea	100	49.8(7.3)yr/51.2(7.8)yr	I–II	≥2	Sevoflurane	*iv*	before induction	P 0.075mg/O 8mg	0-2hr	2-24hr
Chakravarty *et al*, 2013[29]	India	60	38.9(9.76)yr/42.7(6.92)yr	I–II	≥1	N_2O + Sevoflurane	*iv*	before induction	P 0.075mg/O 4mg	0-6hr	6-24hr
Kim SH *et al*., 2013[30]	Korea	71	54.3(10.5)yr/53.3(10.9)yr	I–II	4	Sevoflurane	*iv*	before induction	P 0.075mg/O 4mg	1-6hr	6-24hr
Kim YY *et al*., 2013[31]	Korea	100	43.0(11.2)yr/41.1(11.3)yr	I–II	3	N_2O + Sevoflurane	*iv*	before induction	P 0.075mg/ O 8mg *iv* + PCA16mg	0-2hr	2-24hr
Shadangi *et al*., 2013[32]	India	60	39(9.68)yr/36.6(10.93)yr	I–II	≤2	Isoflurane	*iv*	before induction	P 0.075mg/O 8mg	2-8hr	8-24hr
Joshi *et al*., 2014[33]	India	100	36.67(12.05)yr/ 36.62(14.35)yr	I–II	≤2	N_2O + Isoflurane	*iv*	before induction	P 0.075mg/O 4mg	1-6hr	6-24hr

ASA PS = American Society of Anesthesiologists' physical status; PONV = postoperative nausea and vomiting; N_2O = nitrous oxide; P/O = palonosetron group/ondansetron group; P 0.075 mg = intravenous administration of palonosetron (0.075 mg); O 4 mg = intravenous administration of ondansetron (4 mg); O 8 mg = intravenous administration of ondansetron (8mg); O 8 mg *iv* + PCA 16 mg = 8 mg of ondansetron as a bolus and 16 mg of ondansetron through a patient-controlled analgesia device; TIVA = total intravenous anesthesia

Risk of bias within studies

The overall risk of bias within studies was low in two studies and unclear in seven (Fig. 2)

Syntheses of results

Fig. 3 shows that palonosetron 0.075 mg *iv* was significantly more effective than ondansetron for the prevention of early PON (RR, 0.51; 95% CI, 0.37 to 0.71; $I^2 = 36\%$) and late PON (RR, 0.53; 95% CI, 0.36 to 0.77; $I^2 = 56\%$). Fig. 4 indicates that palonosetron was more effective than ondansetron in preventing late POV (RR, 0.41; 95% CI, 0.28 to 0.62; $I^2 = 0\%$) but was similarly effective in the prevention of early POV (RR, 0.77; 95% CI, 0.45 to 1.34; $I^2 = 8\%$). As both the relative treatment effect and the prevalence of disease determine the clinical effectiveness of a given treatment, we estimated the NNT. The numbers needed to treat for early PON (NNT, 9.3; 95% CI, 6.4 to 31.7), late PON (NNT, 5.4; 95% CI, 4.0 to 11.1), and late POV (NNT, 9.7; 95% CI, 7.6 to 17.0) characterized the benefit of palonosetron when compared with ondansetron.

Six studies compared the need for rescue antiemetics between the treatment groups. The combined results of these studies failed to identify a statistically significant difference between palonosetron and ondansetron in the need of rescue antiemetics, either in the early period (RR, 0.67; 95% CI, 0.40 to 1.13; $I^2 = 0\%$) or in the late period (RR, 0.59; 95% CI, 0.30 to 1.20; $I^2 = 50\%$). The meta-analysis showed no difference between palonosetron and ondansetron with regard to the rates of common adverse effects (Table 2), such as headache (RR, 0.73; 95% CI, 0.52 to 1.03; $I^2 = 0\%$), dizziness (RR, 0.84; 95% CI, 0.56 to 1.25; $I^2 = 0\%$), or drowsiness (RR, 1.00; 95% CI, 0.53 to 1.87; $I^2 = 0\%$).

Publication bias and sensitivity analysis

None of the results of the Egger regression asymmetry tests for early PON, late PON, early POV, or late POV achieved statistical significance ($P = 0.50$, 0.14, 0.16, 0.34, respectively).

We performed four separate sensitivity analyses (Table 3) as follows: (1) excluding studies with an unclear or high risk of bias, (2) studies in which more than 4 mg of ondansetron were administered, (3) studies in which TIVA was used, and (4) a comparison of the fixed and random-effects estimates of the efficacy of palonosetron relative to ondansetron. In the subgroup analysis comparing different doses of ondansetron with palonosetron, each primary outcome showed that the RR was lower in the 4-mg group than in the 8-mg group, and the I^2 value was lower in each of the 4-mg and 8-mg groups than in the two groups combined.

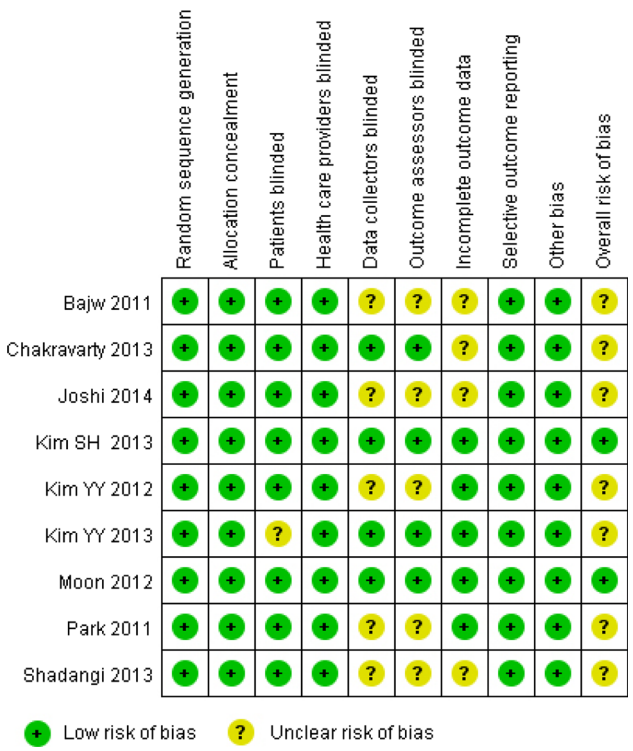


Fig. 2 Summary of the risk of bias of the included studies

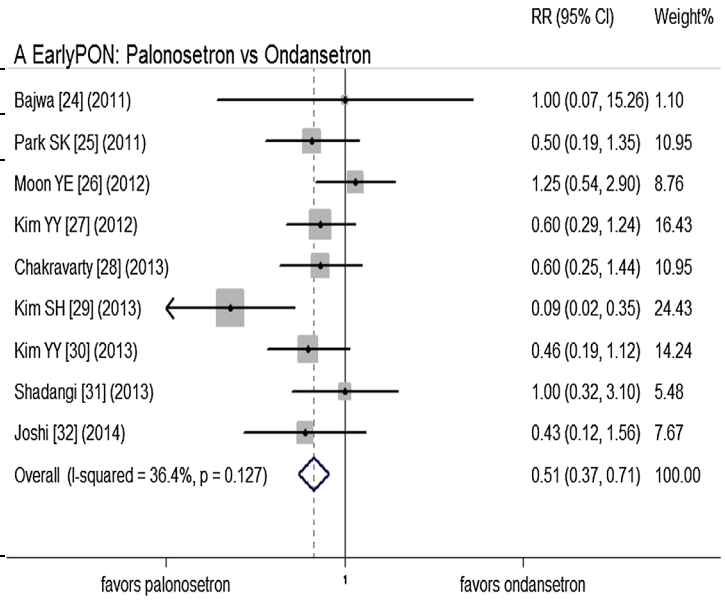
Discussion

With nine included RCTs, our study investigated the efficacy and safety profile of palonosetron relative to ondansetron for PONV prophylaxis during the first 24 hr. Our meta-analysis shows that palonosetron 0.075 mg *iv* compared with ondansetron $\geq$ 4 mg significantly reduces the incidence of early PON (RR, 0.51; 95% CI, 0.37 to 0.71), late PON (RR, 0.53; 95% CI, 0.36 to 0.77), and late POV (RR, 0.41; 95% CI 0.28 to 0.62) but shows no difference between groups for early POV (RR, 0.77; 95% CI, 0.45 to 1.34). Furthermore, palonosetron did not reduce the need for rescue antiemetics in either the early or the late postoperative periods. The NNTs of palonosetron are large, and the corresponding 95% CIs are fairly wide, raising a question regarding the clinical impact of these findings. Among all the included trials, the overall baseline risk for PONV (based on the 2014 consensus guidelines)[20] was variable. As the NNT is likely affected by the baseline incidence of PONV, the same intervention might achieve a smaller NNT if it included more studies with high-risk participants.

Our findings may be explained partially by the longer half-life and receptor binding characteristics of

A Early PON

Study	Palonosetron		vs.	Ondansetron	
	Events	Total		Events	Total
Bajwa SS,2011[24]	1	30		1	30
Park SK,2011[25]	5	45		10	45
Moon YE,2012[26]	10	50		8	50
Kim YY,2012[27]	9	50		15	50
Chakravarty,2013[28]	6	30		10	30
Kim SH,2013[29]	2	36		22	35
Kim YY,2013[30]	6	50		13	50
Shadangi,2013[31]	5	30		5	30
Joshi,2014[32]	3	50		7	50
Total	47	371		91	370



B Late PON

Study	Palonosetron		vs.	Ondansetron	
	Events	Total		Events	Total
Bajwa SS,2011[24]	1	30		2	30
Park SK,2011[25]	9	45		15	45
Moon YE,2012[26]	17	50		27	50
Kim YY,2012[27]	10	50		14	50
Chakravarty,2013[28]	5	30		14	30
Kim SH,2013[29]	6	36		26	35
Kim YY,2013[30]	20	50		16	50
Shadangi,2013[31]	5	30		13	30
Joshi,2014[32]	6	50		16	50
Total	79	371		143	370

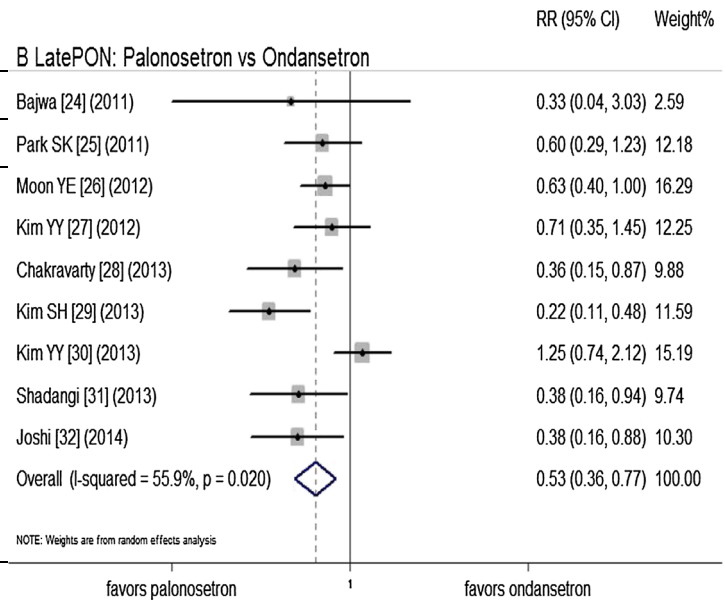


Fig. 3 Forest plot of meta-analysis for palonosetron *vs* ondansetron: (A) Early postoperative nausea (PON); (B) late PON. CI = confidence interval; RR = relative risk

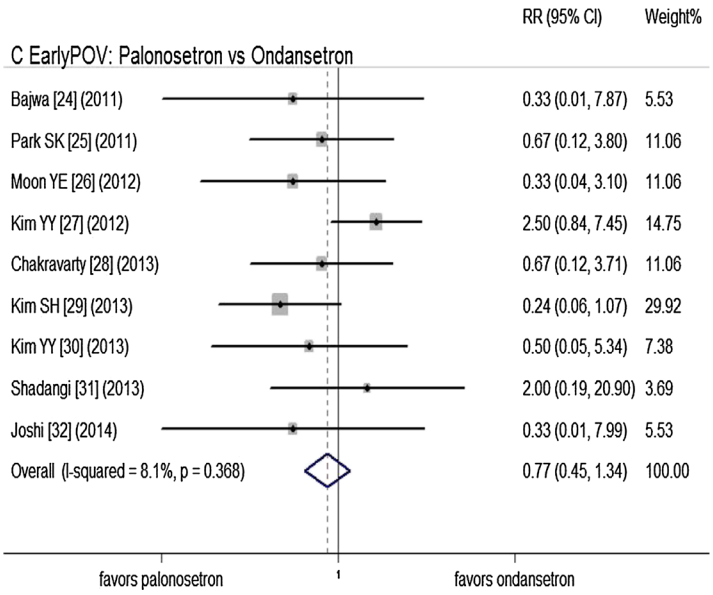
palonosetron.[13–17] Palonosetron may also have other advantages for perioperative care. For example, a recent study reported by Cho *et al.*[34] found that palonosetron 0.075 mg *iv* administered before induction of anesthesia reduced injection pain associated with rocuronium administration; the NNT was 2.94. Ondansetron was also found to be effective in reducing injection pain, with an NNT (2.78) similar to that of palonosetron,[35] but it might be inappropriate to administer ondansetron before induction due to its short duration of action.[36]

The recommended intravenous dose of ondansetron is 4 mg,[20] and the combined results of the dose-ranging studies[11] suggest no significant difference between 4 mg and 8 mg. Thus, we included studies in which at least 4 mg of ondansetron were administered in this meta-analysis. Nevertheless, in our subgroup analysis comparing palonosetron and ondansetron 4 mg, the difference between the two agents may be even bigger. This may explain some of the heterogeneity in this meta-analysis when combining studies of all doses of ondansetron.

The common adverse effects of palonosetron include headache, dizziness, drowsiness, constipation, and bradycardia.[37] Our study showed that palonosetron was no different than ondansetron in the rates of headache,

C Early POV

Study	Palonosetron		vs.	Ondansetron	
	Events	Total		Events	Total
Bajwa SS,2011[24]	0	30		1	30
Park SK,2011[25]	2	45		3	45
Moon YE,2012[26]	1	50		3	50
Kim YY,2012[27]	10	50		4	50
Chakravarty,2013[28]	2	30		3	30
Kim SH,2013[29]	2	36		8	35
Kim YY,2013[30]	1	50		2	50
Shadangi,2013[31]	2	30		1	30
Joshi,2014[32]	0	50		1	50
Total	20	371		26	370



D Late POV

Study	Palonosetron		vs.	Ondansetron	
	Events	Total		Events	Total
Bajwa SS,2011[24]	0	30		2	30
Park SK,2011[25]	4	45		6	45
Moon YE,2012[26]	5	50		13	50
Kim YY,2012[27]	7	50		8	50
Chakravarty,2013[28]	0	30		6	30
Kim SH,2013[29]	4	36		19	35
Kim YY,2013[30]	2	50		5	50
Shadangi,2013[31]	4	30		6	30
Joshi,2014[32]	2	50		4	50
Total	28	371		69	370

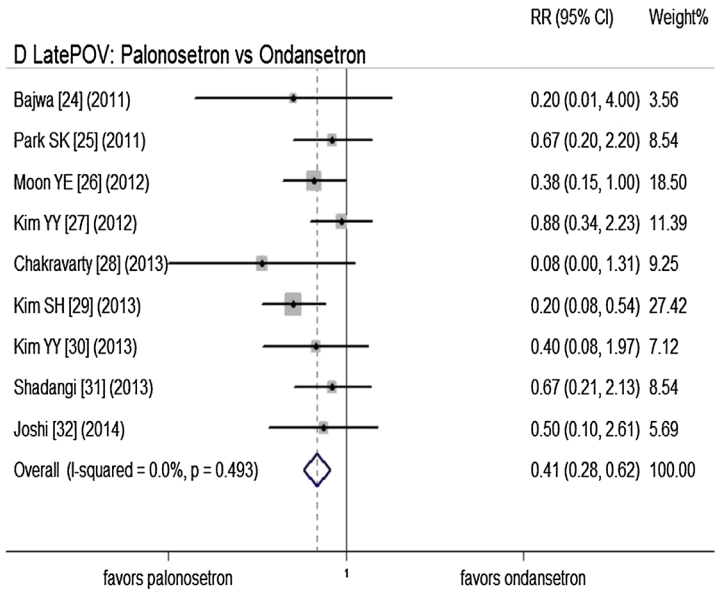


Fig. 4 Forest plot of meta-analysis for palonosetron *vs* ondansetron: (C) Early postoperative vomiting (POV); (D) late POV. CI = confidence interval; RR = relative risk

dizziness, or drowsiness. Previous meta-analyses showed that other 5-HT_3RAs, including ondansetron, granisetron, and ramosetron, had similar rates of adverse effects when used for the prevention of PONV,[10,38] and use of palonosetron did not result in a higher incidence of adverse effects compared with other 5-HT_3RAs for the prevention of chemotherapy-induced nausea and vomiting.[18,19] Nevertheless, we cannot easily draw a conclusion regarding the safety profile of palonosetron because the studies in this meta-analysis did not report the incidence of all common adverse effects or any rare but severe adverse events.

Reports of recent clinical studies[30,39–41] showed that granisetron, ramosetron, and palonosetron had similar rates of associated adverse effects when used to prevent PONV, and in general, the incidence of common adverse events seemed to be similar among different 5-HT_3RAs. With regard to serious adverse events, however, significant differences between palonosetron and ondansetron may exist. For example, in 2011, the FDA announced that the use of ondansetron may bring about abnormal heart rhythms[42] by prolonging the QT interval. This may lead to the potentially fatal abnormal heart rhythm, Torsade de Pointes, reported in some patients receiving ondansetron.[43] In contrast,

Table 2 Comparison of incidences of adverse effects between palonosetron and ondansetron

Adverse effects	Number of studies	Incidence of adverse effects/total number of patients		RR(95% CI)	References
		Palonosetron	Ondansetron		
Headache	8	43/321	59/320	0.73 (0.52 to 1.03)	25–32
Dizziness	8	36/321	43/320	0.84 (0.56 to 1.25)	25–32
Drowsiness	4	17/170	17/170	1.00 (0.53 to 1.87)	27,28,31,32
Constipation	2	4/75	4/75	1.00 (0.26 to 3.86)	25,26
Myalgia	2	1/75	2/75	0.67 (0.11 to 3.91)	25,26
Sedation	2	0/60	1/60	0.33 (0.01 to 7.87)	25,29
Pain	1	3/30	2/30	1.50 (0.27 to 8.34)	25
Anxiety	1	1/30	2/30	0.50 (0.05 to 5.22)	25
Dry mouth	1	1/30	0/30	3.00 (0.13 to 70.83)	25
Chest tightness	1	1/36	1/35	0.97 (0.06 to 14.94)	30
Fever	1	2/36	1/35	1.949 (0.19 to 20.49)	30
Pruritus	1	3/36	2/35	1.50 (0.27 to 8.45)	30

CI = confidence interval; RR = relative risk

Table 3 Sensitivity analysis

Subgroup	No. Of Studies	No. Of Patients	Early PON		Late PON		Early POV		Late POV	
			RR (95%CI)	I^2	RR (95%CI)	I^2	RR (95%CI)	I^2	RR (95%CI)	I^2
Risk of bias										
Low risk	2	171	0.35 (0.02 to 5.51)	92%	0.39 (0.14 to 1.10)	82%	0.27 (0.08 to 0.91)	0%	0.28 (0.14 to 0.54)	0%
High or unclear risk	7	570	0.57 (0.39 to 0.84)	0%	0.59 (0.38 to 0.89)	46%	1.13 (0.59 to 2.15)	0%	0.53 (0.32 to 0.88)	0%
Dosage of Ondansetron										
4mg *iv*	3	231	0.31 (0.09 to 0.99)	67%	0.30 (0.19 to 0.48)	0%	0.36 (0.13 to 1.00)	0%	0.22 (0.10 to 0.48)	0%
8mg *iv*	6	510	0.69 (0.47 to 1.02)	0%	0.71 (0.54 to 0.93)	26%	1.14 (0.58 to 2.24)	0%	0.56 (0.34 to 0.90)	0%
Type of Anesthesia										
TIVA	1	60	1.00 (0.07 to 15.26)	/	0.33 (0.04 to 3.03)	/	0.33 (0.01 to 7.87)	/	0.20 (0.01 to 4.00)	/
Volatile anesthesia	8	681	0.55 (0.35 to 0.88)	44%	0.53 (0.36 to 0.79)	61%	0.80 (0.46 to 1.40)	17%	0.42 (0.28 to 0.63)	2%
Comparison of fixed and random-effect model										
Fixed-effect model	9	741	0.51 (0.37 to 0.71)	36%	0.55 (0.43 to 0.69)	56%	0.77 (0.45 to 1.34)	8%	0.41 (0.28 to 0.62)	0%
Random-effect model	9	741	0.56 (0.36 to 0.87)	36%	0.53 (0.36 to 0.77)	56%	0.77 (0.41 to 1.47)	8%	0.45 (0.30 to 0.68)	0%

CI = confidence interval; PON = postoperative nausea; POV = postoperative vomiting; RR = relative risk; TIVA = total intravenous anesthesia

palonosetron thus far appears to be safe in terms of QT intervals. Results of a number of studies[44–46] revealed that palonosetron had no effect on the QT interval during surgery.

Serotonin syndrome is another serious adverse event associated with the use of 5-HT_3RAs.[47] Serotonin syndrome is a potentially life-threatening condition, even in young patients, and should be avoided in the perioperative settings. Importantly, according to the FDA review,[47] 29 cases of serotonin syndrome were reported with the use of ondansetron, but no such events have been associated with the use of palonosetron. Thus, palonosetron may be safer than ondansetron with regard to serious adverse events, but this idea requires further investigation.

Our study has several limitations. Both the number of RCTs included in our meta-analysis and the sample size were small, and all patients were Asian (Indian or Korean). Furthermore, the risk of bias within studies was low in only two studies, and we did not investigate the efficacy of prophylaxis with palonosetron combined with other antiemetics for PONV. The latter warrants investigation

because patients at high risk often require more aggressive intervention.[20]

Baseline risks for PONV were not identical among these included trials, and the definitions for the postoperative early and late periods varied. Our study did not consider patient satisfaction or intensity of nausea as primary or secondary outcomes because the scale used to measure these outcomes differed among studies and we could not find an appropriate way to combine the data. We also did not include economic data as an outcome, although it is important to consider since palonosetron is more costly than other drugs in its class.

We based our study on the presumption that the optimal intravenous dose of palonosetron was 0.075 mg; equipotent doses of palonosetron and ondansetron are unknown. In 2008, the FDA approved a single intravenous dose of palonosetron for PONV prophylaxis for up to 24 hours based on the results of two earlier dose-ranging studies.[48,49] Subsequently, most studies[25–33] chose palonosetron 0.075 mg as the dose to administer in their trials, which makes it difficult to re-evaluate the optimal dose of palonosetron.

A final limitation of the present meta-analysis is that, although palonosetron holds promise for application during the postoperative 24-72 hr, we did not investigate its prophylactic efficacy for that period. In previous studies reported by Candiotti *et al*.[45] and Kovac *et al*.,[46] there was no statistical difference between palonosetron 0.075 mg and placebo in the reduction of PONV during the postoperative 24-72 hr. Compared with ondansetron, the combined results of four studies indicated that palonosetron can significantly reduce the incidence of PON (RR, 0.53; 95% CI, 0.33 to 0.86) but not POV within 24 to 48 or 72 hr after surgery.[25,28,30,31] Given that the overall rate of POV (0-10%) is low at the 24-48 hr or 24-72 hr, these studies comparing palonosetron with placebo or ondansetron suffered from small sample sizes, and it was difficult to show a statistically significant difference. Thus, it is inappropriate to make conclusions regarding palonosetron's efficacy during the postoperative 24-72 hr; it calls for more RCTs to address this question.

In conclusion, compared with ondansetron, palonosetron 0.075 mg *iv* showed statistically better efficacy for the prophylaxis of early PON, late PON, and late POV, but there may be questions regarding the clinical significance of these results due to the large NNTs. Future studies should focus on evaluating the safety profile of palonosetron and investigate its prophylactic efficacy for PONV in the postoperative 24-72 hr.

Funding Dr. Xiong is supported by the Department of Anesthesiology, Beijing Chaoyang Hospital.

Competing interests None declared.

References

1. *Kapur PA*. The big "little problem". Anesth Analg 1991; 73: 243-5.
2. *van den Bosch JE*, *Bonsel GJ*, *Moons KG*, *Kalkman CJ*. Effect of postoperative experiences on willingness to pay to avoid postoperative pain, nausea, and vomiting. Anesthesiology 2006; 104: 1033-9.
3. *Lee A*, *Gin T*, *Lau AS*, *Ng FF*. A comparison of patients' and health care professionals' preferences for symptoms during immediate postoperative recovery and the management of postoperative nausea and vomiting. Anesth Analg 2005; 100: 87-93.
4. *Lerman J*. Surgical and patient factors involved in postoperative nausea and vomiting. Br J Anaesth 1992; 69: 24S-32S.
5. *Apfel CC*, *Laara E*, *Koivuranta M*, *Greim CA*, *Roewer N*. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. Anesthesiology 1999; 91: 693-700.
6. *Apfel CC*, *Korttila K*, *Abdalla M*, *et al*. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. N Engl J Med 2004; 350: 2441-51.
7. *Tramer MR*, *Reynolds DJ*, *Moore RA*, *McQuay HJ*. Efficacy, dose response, and safety of ondansetron in prevention of postoperative nausea and vomiting: a quantitative systematic review of randomized placebo-controlled trials. Anesthesiology 1997; 87: 1277-89.
8. *Figueredo ED*, *Canosa LG*. Ansetron in the prophylaxis of postoperative vomiting: a meta-analysis. J Clin Anesth 1998; 10: 211-21.
9. *Kranke P*, *Apfel CC*, *Eberhart LH*, *Georgieff M*, *Roewer N*. The influence of a dominating centre on a quantitative systematic review of granisetron for preventing postoperative nausea and vomiting. Acta Anaesthesiol Scand 2001; 45: 659-70.
10. *Mihara T*, *Tojo K*, *Uchimoto K*, *Morita S*, *Goto T*. Reevaluation of the effectiveness of ramosetron for preventing postoperative nausea and vomiting: a systematic review and meta-analysis. Anesth Analg 2013; 117: 329-39.
11. *Carlisle JB, Stevenson CA*. Drugs for preventing postoperative nausea and vomiting. Cochrane Database Syst Rev 2006; 19: CD004125.
12. *Gupta A*, *Wu CL*, *Elkassabany N*, *Krug CE*, *Parker SD*, *Fleisher LA*. Does the routine prophylactic use of antiemetics affect the incidence of postdischarge nausea and vomiting following ambulatory surgery?: A systematic review of randomized controlled trials. Anesthesi ology 2003; 99: 488-95.
13. *Wong EH*, *Clark R*, *Leung E*, *et al*. The interaction of RS 25259-197, a potent and selective antagonist, with 5-HT3 receptors, in vitro. Br J Pharmacol 1995; 114: 851-9.
14. *Stoltz R*, *Cyong JC*, *Shah A*, *Parisi S*. Pharmacokinetic and safety evaluation of palonosetron, a 5-hydroxytryptamine-3 receptor antagonist, in U.S. and Japanese healthy subjects. J Clin Pharmacol 2004; 44: 520-31.
15. *Rojas C*, *Stathis M*, *Thomas AG*, *et al*. Palonosetron exhibits unique molecular interactions with the 5-HT3 receptor. Anesth Analg 2008; 107: 469-78.
16. *Rojas C*, *Thomas AG*, *Alt J*, *et al*. Palonosetron triggers 5-HT 3 receptor internalization and causes prolonged inhibition of receptor function. Eur J Pharmacol 2010; 626: 193-9.
17. *Rojas C*, *Li Y*, *Zhang J*, *et al*. The antiemetic 5-HT3 receptor antagonist palonosetron inhibits substance P-mediated responses in vitro and in vivo. J Pharmacol Exp Ther 2010; 335: 362-8.
18. *Botrel TE*, *Clark OA*, *Clark L*, *Paladini L*, *Faleiros E*, *Pegoretti B*. Efficacy of palonosetron (PAL) compared to other serotonin

inhibitors (5-HT3R) in preventing chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately or highly emetogenic (MoHE) treatment: systematic review and meta-analysis. Support Care Cancer 2011; 19: 823-32.
19. *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: 1685-97.
20. *Gan TJ*, *Diemunsch P*, *Habib AS*, *et al*. Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg 2014; 118: 85-113.
21. *Liberati A*, *Altman DG*, *Tetzlaff J*, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 2009; 62: e1-34.
22. *Moher D*, *Liberati A*, *Tetzlaff J*. *Altman DG; PRISMA Group*. Reprint–preferred reporting items for systematic reviews and meta analyses: the PRISMA statement. Phys Ther 2009; 89: 873-80.
23. *Scuderi PE*. Pharmacology of antiemetics. Int Anesthesiol Clin 2003; 41: 41-66.
24. *Higgins JP, Green S*. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration, 2011. Available from URL: www.cochrane-handbook.org (accessed July 2015).
25. *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.
26. *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.
27. *Moon YE*, *Joo J*, *Kim JE*, *Lee Y*. Anti-emetic effect of ondansetron and palonosetron in thyroidectomy: a prospective, randomized, double-blind study. Br J Anaesth 2012; 108: 417-22.
28. *Kim YY*, *Song DU*, *Lee KH*, *et al*. Comparison of palonosetron with ondansetron in preventing postoperative nausea and vomiting after thyroidectomy during a 48-hour period. Anesth Pain Med 2012; 7: 312-6.
29. *Chakravarty N*, *Raghuwanshi SK*. Comparison between efficacy of palonosetron and ondansetron in postoperative nausea and vomiting in middle ear surgery: a randomized double blind study. Int J Pharma Bio Sci 2013; 4: B67-74.
30. *Kim SH*, *Hong JY*, *Kim WO*, *Kil HK*, *Karm MH*, *Hwang JH*. 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: 517-23.
31. *Kim YY*, *Moon SY*, *Song DU*, *Lee KH*, *Song JW*, *Kwon JE*. 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: 122-6.
32. *Shadangi BK*, *Agrawal J*, *Pandey R*, *et al*. A prospective, randomized, double-blind, comparative study of the efficacy of intravenous ondansetron and palonosetron for prevention of postoperative nausea and vomiting. Anaesth Pain Intensive Care 2013; 17: 55-8.
33. *Joshi H*, *Parmar P*, *Raval B*. Comparison of ondansetron v/s palonosetron for prevention of post-operative nausea and vomiting in laparoscopic surgery. Res J Pharm Biol Chem Sci 2014; 5: 54-63.
34. *Cho K*, *Lee SH*, *Lee W*, *et al*. Effect of pretreatment with palonosetron on withdrawal movement associated with rocuronium injection. Korean J Anesthesiol 2014; 66: 23-7.
35. *Memiş D*, *Turan A*, *Karamanlioglu B*, *Sut N*, *Pamukçu Z*. The prevention of pain from injection of rocuronium by ondansetron, lidocaine, tramadol, and fentanyl. Anesth Analg 2002; 94: 1517-20.
36. *Sun R*, *Klein KW*, *White PF*. The effect of timing of ondansetron administration in outpatients undergoing otolaryngologic surgery. Anesth Analg 1997; 84: 331-6.
37. *MGI Pharma*. 2008. ALOXI (Palonosetron HCl) prescribing information [online]. Available from URL: http://www.aloxi.com/docs/pdf/PI.pdf (accessed July 2015).
38. *Wu SJ*, *Xiong XZ*, *Lin YX*, *Cheng NS*. Comparison of the efficacy of ondansetron and granisetron to prevent postoperative nausea and vomiting after laparoscopic cholecystectomy: a systematic review and meta-analysis. Surg Laparosc Endosc Percutan Tech 2013; 23: 79-87.
39. *Bhattacharjee DP*, *Dawn S*, *Nayak S*, *Roy PR*, *Acharya A*, *Dey R*. A comparative study between palonosetron and granisetron to prevent postoperative nausea and vomiting after laparoscopic cholecystectomy. J Anaesthesiol Clin Pharmacol 2010; 26: 480-3.
40. *Chattopadhyay S*, *Goswami S*. Palonosetron versus ramosetron prophylaxis for control of postoperative nausea and vomiting after cesarean delivery under spinal anesthesia. J Obstet Gynaecol India 2015; 65: 28-33.
41. *Roh GU, Yang SY, Shim JK, Kwak YL* . Efficacy of palonosetron versus ramosetron on preventing opioid-based analgesia-related nausea and vomiting after lumbar spinal surgery: a prospective, randomized, and double-blind trial. Spine (Phila Pa 1976) 2014; 39: E543-9.
42. *U.S. Food and Drug Administration.* FDA Drug Safety Communication, 2011. Abnormal Heart Rhythms May be Associated With use of Zofran (ondansetron). Available from URL: http://www.fda.gov/Drugs/DrugSafety/ucm271913.htm (accessed July 2015).
43. *Ayad RF*, *Assar MD*, *Simpson L*, *Garner JB*, *Schussler JM*. Causes and management of drug-induced long QT syndrome. Proc (Bayl Univ Med Cent) 2010; 23: 250-5.
44. *Kim HJ*, *Lee HC*, *Jung YS*, *et al*. Effect of palonosetron on the QTc interval in patients undergoing sevoflurane anaesthesia. Br J Anaesth 2014; 112: 460-8.
45. *Candiotti KA*, *Kovac AL*, *Melson TI*, *Clerici G*. *Joo Gan T; Palonosetron 04-06 Study Group.* A randomized, double-blind study to evaluate the efficacy and safety of three different doses of palonosetron versus placebo for preventing postoperative nausea and vomiting. Anesth Analg 2008; 107: 445-51.
46. *Kovac AL*, *Eberhart L*, *Kotarski J*, *Clerici G*. *Apfel C; Palonosetron 04-07 Study Group.* A randomized, double-blind study to evaluate the efficacy and safety of three different doses of palonosetron versus placebo in preventing postoperative nausea and vomiting over a 72-hour period. Anesth Analg 2008; 107: 439-44.
47. *Christian Cao, Ali Niak, Ethan Hausman*. Serotonin Syndrome. FDA Pharmacovigilance Review, 2013. Available from URL: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM342225.pdf (accessed July 2015).
48. *Tang J*, *D'Angelo R*, *White PF*, *Scuderi PE*. The efficacy of RS-25259, a long-acting selective 5-HT3 receptor antagonist, for preventing postoperative nausea and vomiting after hysterectomy procedures. Anesth Analg 1998; 87: 462-7.
49. *White PF*, *Scuderi PE*. Prevention of postoperative nausea and vomiting (PONV): a dose-ranging study involving palonosetron, a potent 5-HT3 receptor antagonist. Anesthesiology 2005; 103: A703.