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Symptom Management and Supportive Care

A Systematic Review and Meta-Analysis of Intravenous Palonosetron in the Prevention of Chemotherapy-Induced Nausea and Vomiting in Adults

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ABSTRACT

Objectives. **We performed a systematic review and meta-analysis to compare treatment effectiveness and adverse effects in cancer patients receiving chemotherapy with palonosetron to prevent chemotherapy-induced nausea and vomiting (CINV).**

Methods. **We identified randomized controlled clinical trials (RCT) comparing palonosetron with first-generation 5-HT3RA in the prevention of CINV in cancer patients. Meta-analyses were performed on homogeneous studies. Fixed or random-effects models were used to combine data.**

Results. **Eight eligible trials were identified, reporting outcomes on 3,592 patients. Meta-analyses showed statistically significant differences in favor of palonosetron compared with first-generation 5-HT3RA in prevention of acute CINV ($p = .0003$), delayed CINV ($p < .00001$), and overall phase of CINV ($p < .00001$). Subgroup analyses showed statistically significant differences in favor of both 0.25 mg and 0.75 mg of palonosetron in prevention of all phases of CINV. There were no statistically significant differences between 0.25 and 0.75 mg of palonosetron. Compared with the first-generation 5-HT3RA, 0.75 mg of palonosetron showed a statistically significant difference in the occurrence of constipation ($p = .04$).**

Interpretation. **The use of palonosetron should be considered an integral part of adjuvant therapy for prevention of the acute, delayed, and overall phases of CINV. The 0.25 mg intravenous palonosetron dose is as effective as the 0.75 mg intravenous palonosetron dose. However, 0.75 mg intravenous palonosetron causes constipation more frequently than the first-generation 5-HT3RA.** ***The Oncologist*** 2011;16:207–216

INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) is a serious problem associated with poor health-related quality of life [1], especially in patients who experience more than two episodes [2]. As such, it might reduce therapeutic compliance [3]. Patients surveyed state that

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nausea and vomiting are the most feared effects of chemotherapy [4].

CINV can be divided into an acute phase, defined as vomiting that occurs within 24 hours after chemotherapy, delayed CINV that takes place 24–120 hours after chemotherapy, and anticipatory CINV, which occurs before chemotherapy. Without adequate antiemetic prophylaxis, more than 90% of patients who receive highly emetogenic chemotherapy (HEC) will experience emesis [5]. Characteristics that increase the risk of CINV include female gender, younger age, previous exposure to chemotherapy, history of alcohol abstention, and presence of nausea and vomiting with prior chemotherapy [6].

The 5-hydroxytryptamine3 (5-HT3) receptor plays a pivotal role in the process of emesis. Chemotherapy initiates the release of serotonin from enterochromaffin cells in the small intestine, activating 5-HT3 receptors located on vagal afferents, and thus causing emesis [7]. The efficacy and low incidence of side effects have established the 5-HT3 receptor antagonists (5-HT3RA) as first-line treatments for preventing acute CINV. Complete response of first-generation 5-HT3RA as monotherapy for prophylaxis against acute CINV has ranged from 41% to 71% [8–14], but for prophylaxis against delayed CINV it has ranged from 27% to 43% [8, 9, 11, 15]. Combining first-generation 5-HT3RA with corticosteroids, such as dexamethasone, can bring acute and delayed CINV response rates to 68%–90% [9–14] and 47%–63.8% [8, 9, 11, 14, 15], respectively. However, meta-analysis shows that adding a first-generation 5-HT3RA to dexamethasone is no more effective than dexamethasone for preventing delayed emesis [16].

Guidelines recommend a three-drug regimen of dexamethasone, a 5-HT3RA, and aprepitant/fosaprepitant for the prevention of acute CINV associated with HEC, and a three- or two-drug regimen of dexamethasone and a 5-HT3RA (with or without aprepitant/fosaprepitant) for the prevention of acute CINV associated with moderately emetogenic chemotherapy (MEC) [5, 17–19]. Meta-analysis confirms that there is no difference in efficacy between first-generation 5-HT3RAs (ondansetron, granisetron, dolasetron, and tropisetron) for prevention of acute CINV [20].

Palonosetron is a second-generation 5-HT3RA characterized by much higher binding affinity (Pki = 10.45 for palonosetron, 8.39 for ondansetron, 8.91 for granisetron, and 7.60 for dolasetron) and longer serum half-life compared with first-generation 5-HT3RAs (40 hours for palonosetron, 4 hours for ondansetron, 9 hours for granisetron, and 7.3 hours for dolasetron) [21]. In contrast to ondansetron and granisetron, which bond to one site on the 5-HT3 receptors and act in synergy with competing antagonistic agents, palonosetron binds to two sites on the 5-HT3 receptor, and also has a positive synergistic effect. Moreover, prolonged inhibition of Ca^{2+} has been observed in palonosetron [22]. With these unique characteristics, palonosetron has been demonstrated to be more effective than first-generation 5-HT3RAs in the prevention of the delayed and overall phases of CINV [23, 24]. However, the advantage of palonosetron in prevention of acute CINV and the optimal dosage remain controversial. Whether adding a corticosteroid to palonosetron is beneficial is also unclear. We performed a systematic review and meta-analysis to evaluate the effectiveness and adverse effects of palonosetron in the prevention of CINV.

METHODS

Trial Identification

We searched for RCTs in the English or Chinese literature that compared palonosetron with first-generation 5-HT3RA in (a) MEDLINE (1950 through March 2010), (b) EMBASE (1966 through March 2010), (c) Chinese VIP database (1989 through March 2010), (d) Evidence-based Medicine Review, (e) Cochrane Central Register of Controlled Trials, (f) Current Controlled Trials, (g) The National Research Register, and (9) Clinicaltrials (clinicaltrials.gov). Search terms included the combination of palonosetron with "chemotherapy induced nausea and vomiting," "chemotherapy-induced nausea or vomiting," and "CINV." We excluded RCTs of pediatric patients.

Outcomes

The primary outcome was complete response (CR) of the acute, delayed, and overall phases of CIVN after chemotherapy. Complete response was defined as no emetic episodes and no rescue medication. Overall phase was defined as 0–120 hours after chemotherapy. Secondary outcomes included adverse effects of palonosetron.

Statistical Analysis

For nonheterogenerous trials, we performed meta-analysis with Review Manager (Revman 4.2) using fixed or random effects models. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. A heterogeneity test $p > .05$ was interpreted as signifying a low level of heterogeneity suitable for meta-analysis.

Methodological Quality of Included Studies

We evaluated the methodological quality of included studies by assessing methods of randomization, allocation, concealment, and blinding.

Table 1. Exclusion reasons of excluded studies

Study	Year	Exclusion reason
Aapro et al. [25]	2005	Pooled analysis
Liu et al. [26]	2007	Only abstract is available
Kadota et al. [27]	2007	Included pediatric patients
Sepúlveda-Vildósola et al. [28]	2008	Included pediatric patients
Herrington et al. [29]	2008	Evaluate the effectiveness of aprepitant

Subgroup Analyses

We performed subgroup analyses by using different dosages of palonosetron (0.25 or 0.75 mg), and by either combining or not combining them with glucocorticoid. We also evaluated the effectiveness of palonosetron in differently emetogenic chemotherapy.

Results

Results of the Search Strategy

Of 235 references, 8 RCTs involving 3,592 patients were identified as eligible for inclusion in this review. We excluded 5 RCTs [25–29]. The reasons for exclusion are listed in Table 1.

Characteristics of Included Trials

Four studies evaluated the effectiveness of palonosetron in HEC [30–33] and 2 in MEC [23, 24]. Two studies included both HEC and MEC regimens [34, 35]. Two studies were published in Chinese [31, 34]; the rest were published in English. The female-to-male ratio varied from 0.58 to 4.58. Two studies did not mention chemotherapy-naive patients [31, 34]; one included more than 90% chemotherapy-naive patients [32].

Quality of Included Studies

Of the eight RCTs in the review, one failed to mention sample size calculation [34]. Six of the RCTs were designed as noninferiority trials, except for one study that used a superiority test for calculation of delayed CINV prevention [32]. All included studies were double-blinded trials with appropriate randomization methods. None mentioned allocation concealment. Two of the eight studies used a crossover design [34, 35]. We used the results for cycle 1 of one study [35]. "Intention to treat" was mentioned in six of the eight studies. The characteristics of included studies are summarized in Table 2.

Results of Included Studies

All included studies compared intravenous palonosetron with first-generation 5-HT3RA (one compared dolasetron, three compared ondansetron, and four compared granisetron).Three studies evaluated the effectiveness of both 0.25 and 0.75 mg of palonosetron [23, 24, 30]. Four studies evaluated the effectiveness of 0.25 mg of palonosetron [31, 33–35] and one evaluated 0.75 mg of palonosetron [32]. Corticosteroids were used before chemotherapy in two studies [30, 32]. Saito et al. investigated palonosetron combined with dexamethasone [32]. Intravenous dexamethasone (20 mg) before chemotherapy was permitted but not required in another study [30]. Yu et al. evaluated the effectiveness of 0.25 mg of palonosetron in the prevention of CINV in 0–24, 24–48, 48–72, 72–96, and 96–120 hours [33]; thus, the CR rates of delayed and overall phases were unavailable. The most common adverse events were headache and constipation. These interventions are summarized in Table 3.

Results of Meta-analyses

Primary Outcome

Effectiveness of Palonosetron Compared with First-Generation 5-HT3RA in Prevention of Acute CINV (Fig. 1)

All eight RCTs compared palonosetron with first-generation 5-HT3RA for prevention of acute CINV. There was no heterogeneity between included studies ($p = .80$). Meta-analysis that included 3,592 patients with 3,696 cycles showed that palonosetron reduced the risk of acute CINV by 24% (OR, 0.76; 95% CI, 0.66–0.88, $p = .0003$). Subgroup analysis showed that there were statistically significant differences in favor of both 0.25 mg of palonosetron (OR, 0.68; 95% CI, 0.56–0.83; $p = .0001$) and 0.75 mg of palonosetron (OR, 0.82; 95% CI, 0.69–0.99; $p = .03$).

Effectiveness of Palonosetron Compared with First-Generation 5-HT3RA in Prevention of Delayed CINV (Fig. 2)

Seven RCTs with 3,384 patients (3,488 cycles) compared palonosetron with first-generation 5-HT3RA in prevention of delayed CINV. The results showed no heterogeneity ($p = .59$) in any included studies (OR, 0.62; 95% CI, 0.54–0.71) in favor of palonosetron ($p < .00001$). Subgroup analyses indicated statistically significant differences in favor of both 0.25 mg of palonosetron (OR, 0.62; 95% CI, 0.51–0.75; $p < .00001$) and 0.75

Table 2. Quality of the included studies

Study	Year	Sample size calculation	Randomization	Blinding	Allocation concealment	Crossover study	Intention-to-treat analysis
Eisenberg et al. [23]	2003	Noninferiority	A	A	B	N	A
Gralla et al. [24]	2003	Noninferiority	A	A	B	N	A
Aapro et al. [30]	2006	Noninferiority	A	A	B	N	A
Chen et al. [31]	2007	Noninferiority	A	A	B	N	B
Saito et al. [32]	2009	Noninferiority for acute phase; superiority for delayed phase	A	A	B	N	A
Yu et al. [33]	2009	Noninferiority	A	A	B	N	A
Li et al. [34]	2009	Unclear	A	A	B	Y	A
Tian et al. [35]	2010	Noninferiority	A	A	B	Y	B

Abbreviations: *Randomization:* A, appropriate; B, unclear; 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. *Crossover study:* N, not; Y, yes. *Intention-to-treat analysis:* A, appropriate; B, unclear.

mg of palonosetron (OR, 0.61; 95% CI, 0.52–0.72; $p <$ .00001).

Effectiveness of Palonosetron Compared with First-Generation 5-HT3RA in Prevention of the Overall Phase of CINV (Fig. 3)

Seven RCTs compared palonosetron with first-generation 5-HT3RA in prevention of the overall phase of CINV. Meta-analysis showed an OR of 0.64 (95% CI, 0.56–0.74) in favor of palonosetron ($p <$ .00001). Subgroup analysis showed statistically significant differences in favor of both 0.25 mg of palonosetron (OR, 0.62; 95% CI, 0.51–0.75; $p <$ .00001) and 0.75 mg (OR, 0.65; 95% CI, 0.55–0.76; $p <$ .00001).

Effectiveness of 0.25 mg of Palonosetron Compared with 0.75 mg of Palonosetron

Meta-analysis included three studies (n = 1,202) showed no statistically significant differences between 0.25 and 0.75 mg of palonosetron in terms of preventing acute CINV (OR, 1.09; 95% CI, 0.85–1.38; p = .50), delayed CINV (OR, 1.05; 95% CI, 0.83–1.32; p = .68), or overall phase CINV (OR, 1.11; 95% CI, 0.88–1.40; p = .38).

Effectiveness of Palonosetron Plus Dexamethasone Compared with First-Generation 5-HT3RA Plus Dexamethasone

We extracted data from two studies on HEC that compared palonosetron plus dexamethasone with first-generation 5-HT3RA plus dexamethasone [30, 32]; one study allowed dexamethasone before chemotherapy by choice [30]. Meta-analyses of 1,561 patients showed a trend in favor of palonosetron plus dexamethasone in prevention of acute CINV (OR, 0.84; 95% CI, 0.67–1.05; p = .36). For prevention of delayed CINV and overall phase of CINV, the meta-analyses showed that palonosetron plus dexamethasone significantly reduced risk of CINV by 40% and 38% ($p <$ .00001), respectively.

Effectiveness of Palonosetron Compared with First-Generation 5-HT3RA for Prevention of CINV in Differently Emetogenic Chemotherapy

Results of meta-analyses for MEC [23, 24] showed that there were statistically significant differences in favor of palonosetron in the prevention of acute CINV (OR, 0.70; 95% CI, 0.54–0.91; p = .008), delayed CINV ($p <$ .00001), and overall phase CINV ($p <$ .0001).

Results of the meta-analyses for HEC [30–33] showed that there were statistically significant differences in favor of palonosetron for prevention of acute CINV (OR, 0.79; 95% CI, 0.64–0.96; p = .02), delayed CINV ($p <$ .00001), and overall phase CINV ($p <$ .00001). Meta-analysis of two studies [31, 33] showed a significant difference in favor of 0.25 mg of palonosetron in prevention of acute CINV in HEC (OR, 0.58; 95% CI, 0.36–0.93; p = .02).

Table 3. Interventions of included studies

Study	Year	Interventions	*N*
Eisenberg et al. [23]	2003	(a) 0.25 mg of palonosetron	189
		(b) 0.75 mg of palonosetron	189
		(c) 100 mg of dolasetron	191
Gralla et al. [24]	2003	(a) 0.25 mg of palonosetron	189
		(b) 0.75 mg of palonosetron	189
		(c) 32 mg of ondansetron	185
Aapro et al. [30]	2006	(a) 0.25 mg of palonosetron; 20 mg of dexamethasone was allowed before chemotherapy	223
		(b) 0.75 mg of palonosetron; 20 mg of dexamethasone was allowed before chemotherapy	223
		(c) 32 mg of ondansetron; 20 mg of dexamethasone was allowed before chemotherapy	221
Chen et al. [31]	2007	(a) 0.25 mg of palonosetron	111
		(b) 3 mg of granisetron	112
Saito et al. [32]	2009	(a) 0.75 mg of palonosetron plus intravenous dexamethasone (16 mg on day 1, 8 mg intravenously for cisplatin chemotherapy on day 2 and day 3, 4 mg orally for AC/EC chemotherapy on day 2 and day 3)	555
		(b) 40 μg/kg granisetron plus intravenous dexamethasone (16 mg on day 1, 8 mg intravenously for cisplatin chemotherapy on day 2 and day 3, 4 mg orally for AC/EC chemotherapy on day 2 and day 3)	559
Yu et al. [33]	2009	(a) 0.25 mg of palonosetron	104
		(b) 3 mg of granisetron	104
Li et al. [34]	2009	(a) 0.25 mg of palonosetron	104
		(b) 16 mg of ondansetron	104
Tian et al. [35]	2010	(a) 0.25 mg of palonosetron	72
		(b) 3 mg of granisetron	72

Abbreviations: AC/EC, anthracyclines (doxorubicin or epirubicin) plus cyclophosphamide chemotherapy regimen; *N*, number of patients in arms.

Analyses of Adverse Effects

Constipation

Seven RCTs reported constipation as an adverse event. Meta-analysis showed that palonosetron increased the risk of constipation by 39% (OR, 1.39; 95% CI, 1.08–1.78; $p = .01$). Subgroup analyses showed significant differences between 0.75 mg of palonosetron and first-generation 5-HT3RA ($p = .04$), but not between 0.25 mg of palonosetron and first-generation 5-HT3RA ($p = .20$).

Headache

Data showed no significant difference between palonosetron and first-generation 5-HT3RA on the occurrence of headache (OR, 1.16; 95% CI, 0.89–1.53; $p = .27$). Subgroup analyses also showed no significant differences between first-generation 5-HT3RA and palonosetron (0.25 and 0.75 mg).

Discussion

Guidelines indicate that all 5-HT3RAs (ondansetron, granisetron, dolasetron, and palonosetron) have similar effectiveness for control of acute emesis [5]. In our analyses, most of the RCTs indicated that the second-generation 5-HT3RA, palonosetron, has significant advantages in the prevention of the delayed and overall phases of CINV. All but one RCT [24] showed that palonosetron was not superior to first-generation 5-HT3RA for prevention of acute CINV. Our meta-analysis, however, showed that palonosetron was more effective than the first-generation 5-HT3RA in prevention of acute CINV. We noticed that all the RCTs on prevention of acute CINV were designed for noninferior tests. That might make the sample sizes insufficient to determine differences. Our meta-analysis also demonstrated the superiority of 0.25 mg of palonosetron over first-generation 5-HT3RA in the prevention of acute CINV in HEC. Because of its synergism with other agents, dexamethasone has been prescribed with 5-HT3RA to prevent acute CINV.

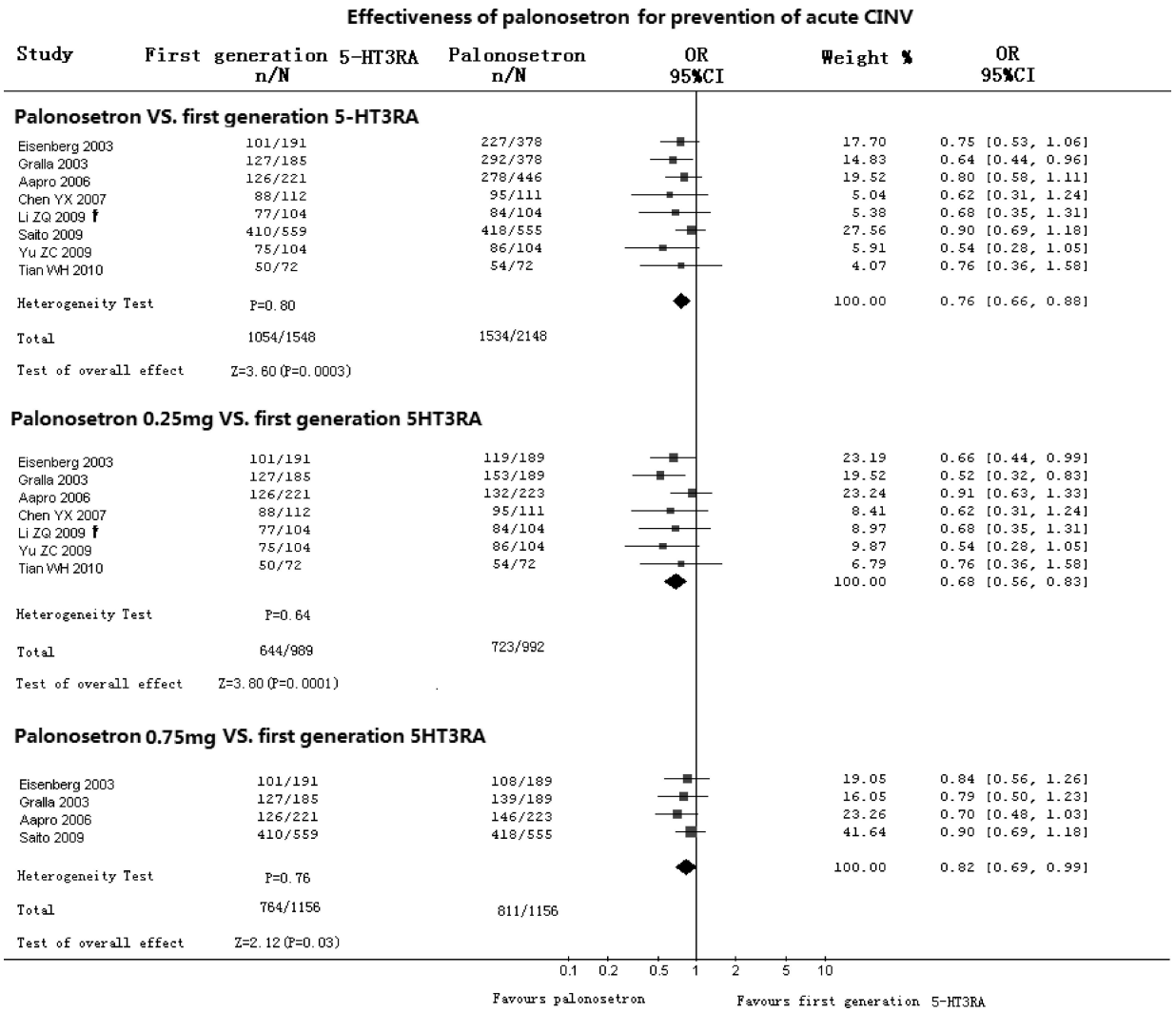

Figure 1. Effectiveness of palonosetron compared with first-generation 5-HT3RA in prevention of acute CINV. Abbreviations: CI, confidence interval; CINV, chemotherapy-induced nausea and vomiting; CR, complete response; *n*, number of CRs; *N*, number of groups; OR, odds ratio; †, from crossover data.

Our analysis showed a trend in favor of palonosetron plus dexamethasone in prevention of acute CINV in HEC, but it did not reach statistical significance ($p = .36$).

The advantage of palonosetron in prevention of delayed CINV was of value for at least two important reasons. First, a high percentage of patients experienced emesis despite prophylaxis. Second, adding a first-generation 5-HT3RA to dexamethasone was not superior to dexamethasone in prevention of delayed CINV. Two RCTs included dexamethasone in the interventions. One compared palonosetron plus dexamethasone with the first-generation 5-HT3RA plus dexamethasone. Dexamethasone was used before chemotherapy, and on days 2 and 3 [32]. The other study allowed for, but did not require, use of dexamethasone before chemotherapy [30]. Our subgroup analyses proved that palonosetron plus dexamethasone was superior to the first-generation 5-HT3RA plus dexamethasone in prevention of the delayed and overall phases of CINV. In a double-blinded RCT [36], 0.25 mg of intravenous palonosetron plus 8 mg of dexamethasone were given as prophylaxis before chemotherapy, with 4 mg of dexamethasone twice a day orally or placebo administered on days 2 and 3. In this trial of 300 patients, the CR rate was similar in the overall period. The authors suggested a reduction in dexamethasone. However, acute and delayed CINV might have overlapped. CR rate in the overall phase was probably a more useful endpoint [37].

In our analyses, both 0.25 and 0.75 mg of palonosetron were superior to first-generation 5-HT3RA in the overall phase of CINV. A phase II study found that there was no difference between 10 and 30 μg/kg palonosetron in the prevention of all phases of CINV [38]. The doses 0.25 and 0.75 mg of palonosetron were commonly used. Our subgroup analyses

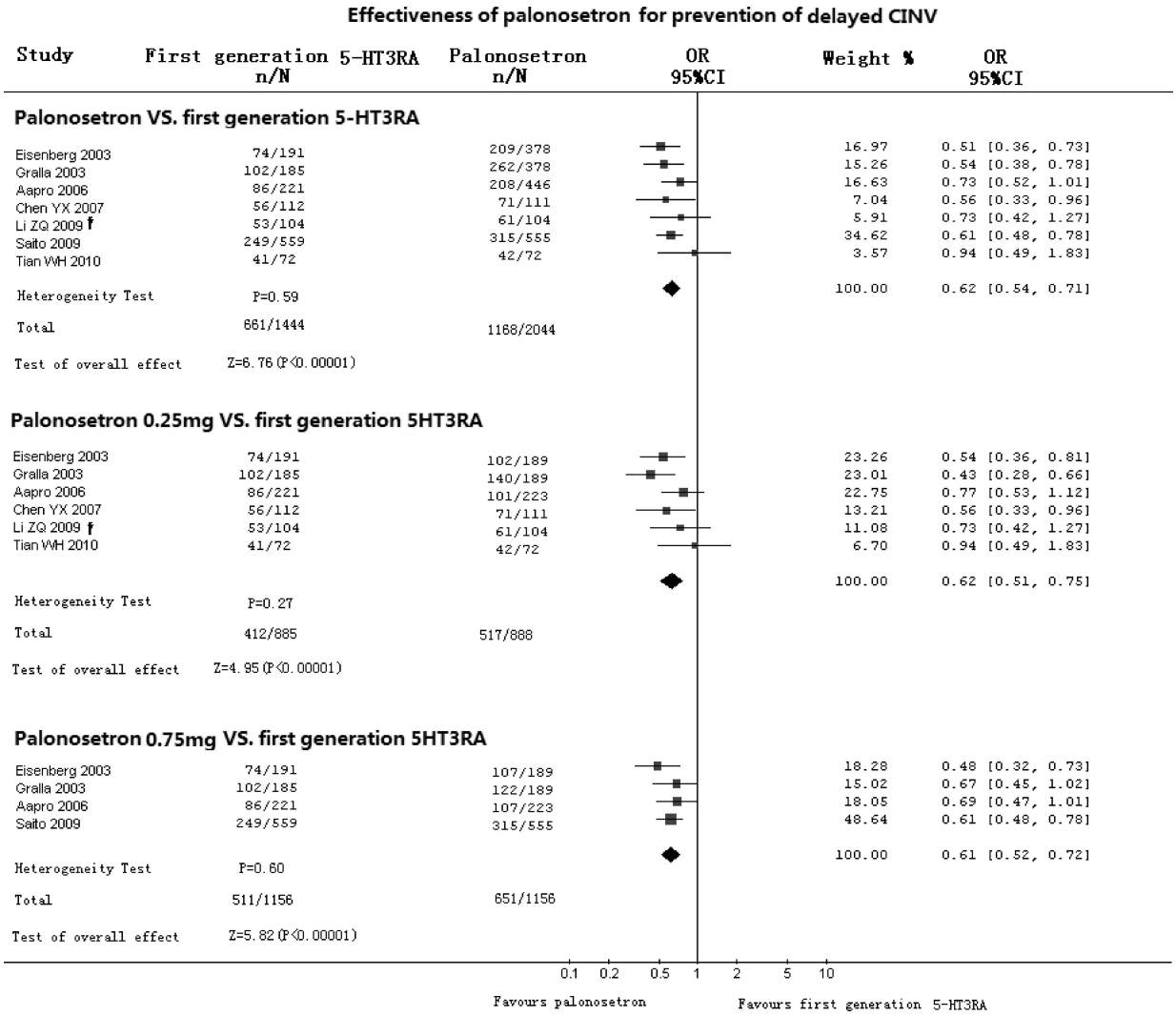

Figure 2. Effectiveness of palonosetron compared with first-generation 5-HT3RA in prevention of delayed CINV. Abbreviations: CI, confidence interval; CINV, chemotherapy-induced nausea and vomiting; CR, complete response; *n*, number of CRs; *N*, number of groups; OR, odds ratio; †, from crossover data.

showed that both palonosetron doses were more efficient than the first-generation 5-HT3RA, and that 0.25 mg of palonosetron was as effective as 0.75 mg of palonosetron.

Constipation and headache were the most common adverse effects. Our meta-analyses showed that patients treated with palonosetron experienced more constipation than those who received the first-generation 5-HT3RA ($p = .01$), but there was no significant difference in headaches.

Further subgroup analyses showed no significant difference in constipation between 0.25 mg of palonosetron and the first-generation 5-HT3RA, whereas 0.75 mg of palonosetron caused more constipation than the first-generation 5-HT3RA ($p = .04$), indicating that a higher dose of palonosetron might cause more constipation. The reason might rely on that 5-HT3RA prolongs the whole gut transit time [39] and inhibits postprandial colonic motor function [40]. However, in a recent study [41], patients treated with palonosetron took adequate caloric intake. The reasons might be that 5-HT3RA did not change the volume of meal tolerated, fasting, or postprandial gastric volumes [42], nor did it change gastric emptying [43].

In summary, the results of our meta-analyses indicate that palonosetron is an effective and safe drug for prevention of CINV. Both 0.25 and 0.75 mg of intravenous palonosetron are more efficacious than first-generation 5-HT3RA in prevention of the acute, delayed, and overall phases of CINV. The 0.25 mg dose of palonosetron is preferred. In the prevention of acute CINV in HEC, 0.75 mg of palonosetron plus dexamethasone is as effective as the first-generation 5-HT3RA, but palonosetron at that dose may increase the risk of constipation. Intravenous palonosetron plus dexamethasone is more efficacious than the first-gen-

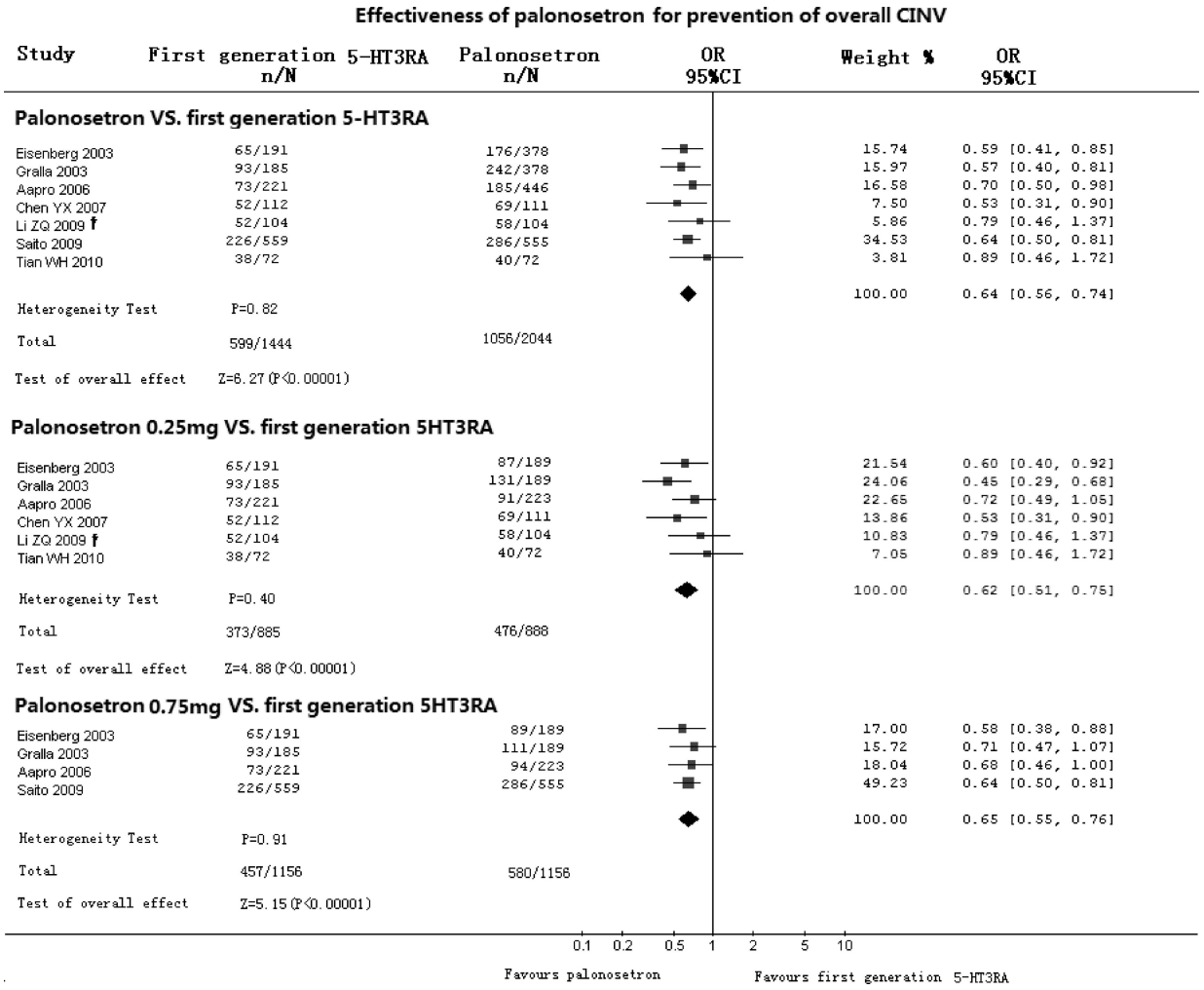

Figure 3. Effectiveness of palonosetron compared with first-generation 5-HT3RA in prevention of overall phase of CINV. Abbreviations: CI, confidence interval; CINV, chemotherapy-induced nausea and vomiting; CR, complete response; *n*, number of CRs; *N*, number of groups; OR, odds ratio; †, from crossover data.

eration 5-HT3RA plus dexamethasone in prevention of the delayed and overall phases of CINV.

This study has some limitations. We did not evaluate the effectiveness of 0.25 mg of palonosetron plus dexamethasone because of limited data. In addition, we searched studies published only in English and Chinese. Although 0.25 mg of palonosetron is preferred for prevention of CINV, a direct comparison between 0.25 mg of palonosetron plus dexamethasone and the first-generation 5-HT3RA plus dexamethasone is needed.

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Zhou Likun, Jing Xiang, and Ba Yi contributed equally to this work.

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Final approval of manuscript: Zhou Likun, Jing Xiang, Ba Yi

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