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Efficacy and safety of Aprepitant-containing triple therapy for the prevention and treatment of chemotherapy-induced nausea and vomiting

A meta-analysis

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Abstract

Background: Most cancer patients suffer from the pain of chemotherapy-induced nausea and vomiting (CINV). This meta-analysis was performed to evaluate the efficacy and safety of a regimen consisting of aprepitant, dexamethasone, and 5-HT3 receptor antagonists in the prevention and treatment of CINV.

Methods: A systematic literature search was conducted across multiple databases, including PubMed, EMbase, Cochrane Library, MEDLINE, CENTRAL, HEED, CNKI, Wanfang, and VIP, to identify randomized controlled trials (RCTs) investigating the use of triple therapy (aprepitant, 5-HT_3 receptor antagonist, and dexamethasone) to prevent and treat CINV. Meta-analysis was performed using RevMan 5.4 and Stata17 software, employing either a fixed-effect or random-effect model based on statistical heterogeneity.

Results: A meta-analysis of 23 randomized controlled trials (RCTs) involving 7956 patients was conducted. Efficacy: Results showed significantly improved complete responses (CRs) for CINV in the test group versus the control group in the overall, acute, and delayed phases. Furthermore, in the test group, substantial alleviation of nausea symptoms was observed in the delayed and overall phases but not in the acute phase. Safety: There was no statistically significant difference in the incidence of febrile neutropenia, diarrhea, anorexia, and headache between the 2 groups. The incidence of fatigue and hiccups in the test group was higher than that in the control group; however, the incidence of constipation was significantly lower.

Conclusions: Aprepitant-containing triple therapy is highly effective in the prevention and treatment of CINV, with reliable medication safety.

Abbreviations: 5-HT_3 RA = 5-hydroxytryptamine 3 receptor antagonist, CINV = chemotherapy-induced nausea and vomiting, CR = complete response, NK-1 RA = neurokinin-1 antagonist, RCTs = randomized controlled trials.

Keywords: aprepitant, CINV, CR, meta-analysis, triple therapy

1. Introduction

According to the latest global cancer burden data (2020) released by the International Agency for Research on Cancer (IARC) of the World Health Organization, there were 4.57 million newly-diagnosed cancer cases and 3 million deaths in China, ranking first globally.[1] Nowadays, cancer has emerged as the leading cause of death, posing a significant threat and economic burden to human life.[2,3] Chemotherapy is the primary treatment for advanced-stage cancer; however, it is often accompanied by adverse reactions that significantly affect the patients' quality of life. One such common adverse reaction is chemotherapy-induced nausea and vomiting (CINV), which occurs in response to anti-tumor drugs. Frequent nausea and vomiting can result in anorexia, metabolic disorders, and nutritional imbalances, inflicting severe physical and psychological distress in patients, which hinders treatment compliance and, consequently, affects the efficacy of chemotherapy.[4–8]

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The study did not involve human or animal experiments, and thus not required to obtain the informed consent and approval from the ethics committee.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Supplemental Digital Content is available for this article.

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Based on the incidence of vomiting caused by chemotherapy drugs, it is classified into 4 risk levels: high (≥90%), moderate (30–90%), low (10–30%), and minimal (<10%).[9,10] Given the intricate pathogenesis of CINV and significant inter-individual variations among patients,[11] a combination of drugs should be administered as a prophylactic measure against vomiting in patients undergoing moderate or highly emetic chemotherapy (MEC/HEC).[9,10,12–20] The commonly used antiemetic drugs in clinics mainly include 5-HT_3 receptor antagonists (5-HT_3 RA), neurokinin-1 antagonists (NK-1 RA), glucocorticoids, dopamine receptor antagonists, and certain psychotropic drugs.[9-10,12-15] It has been demonstrated that various neurotransmitters are involved in the different phases of CINV. For example, 5-HT_3 plays an important role in acute CINV (0–24 hours), whereas substance P, a peptide that binds to NK receptors, mediates the occurrence of delayed CINV (2–5 days).[13–15] Aprepitant, the first commercially available NK-1 RA,[16] can traverse the blood-brain barrier to inhibit the interaction between substance P and the NK-1 receptor in the central nervous system, thus preventing chemotherapy-induced vomiting. Although both domestic and international CINV treatment guidelines recommend triple therapy consisting of 5-HT_3 RA, dexamethasone, and NK-1 RA (such as aprepitant) for the prevention and treatment of moderate-to-severe nausea and vomiting,[17–20] noncompliance with medication guidelines frequently occurs in clinical practice, and the combination of 5-HT_3 RA and dexamethasone is widely utilized.[21–23] This study conducted a meta-analysis of randomized controlled trials on aprepitant for the prevention and treatment of CINV published before December 2022, and evaluated the efficacy and safety of aprepitant-containing triple therapy. This study aimed to provide evidence-based support for the use of NK-1 receptor antagonists.

2. Materials and Methods

2.1. Literature search strategy and selection criteria

A comprehensive search was conducted across multiple databases including PubMed, EMbase, Cochrane Library, MEDLINE, CENTRAL, HEED, CNKI, Wanfang, and VIP. This study aimed to identify randomized controlled trials (RCTs) investigating the use of triple therapy for the prevention and treatment of chemotherapy-induced nausea and vomiting (CINV). The search was limited to RCTs published prior to December 2022. The search queries used were as follows: "aprepitant" AND ("5-HT_3 receptor antagonist" OR "5-HT_3 RA") AND ("dexamethasone" OR "triple therapy") AND ("chemotherapy-induced nausea and vomiting" OR "CINV").

The eligibility criteria for RCTs were as follows: patients were given the MEC or HEC regimen, regardless of age or tumor type, excluding those with co-infection, brain metastasis, or recent vomiting within 24 hours prior to chemotherapy; intervention: test groups received a combination of aprepitant, 5-HT_3 receptor antagonist, and dexamethasone; and comparison: control groups received a combination of a 5-HT_3 receptor antagonist and dexamethasone with or without placebo.

The primary outcomes included complete response (CR) to CINV (absence of vomiting events, with no use of rescue drugs for nausea or vomiting) in the overall, acute, and delayed phases. Secondary outcomes included total control (the absence of vomiting, without the need for rescue therapy, and visual analog scale (VAS) < 5 mm) and/or complete protection (the absence of vomiting, without the need for rescue therapy, and VAS < 25 mm) in the overall, acute, and delayed phases; the incidence of anorexia, diarrhea, constipation, headache, fatigue/weakness, hiccups, and febrile neutropenia.

2.2. Data extraction and quality assessment

Two researchers screened the literature, extracted data independently using a standardized table, and crosschecked the information. The table includes relevant information, such as author's name, region, publication time, tumor type, chemotherapy, sample size, average age, intervention measures, and outcomes. Any discrepancies in data interpretation were resolved through consensus with the assistance of a third researcher if necessary. The consent or approval from the ethics committee is not necessary for human or animal experiments are not involved.

The Cochrane Risk of Bias Assessment Tool 5.1.0[24] was used to evaluate the quality of each included RCT with the following aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias. The judgment for each bias was categorized as "low risk," "high risk," and "unclear risk."

2.3. Statistical analysis

Meta-analysis was performed using Review Manager 5.4 and Stata 17 software. Potential heterogeneity among the studies was assessed using the χ^2-based Q test and the I^2 index. If the results indicated $P > .1$ and $I^2 \leq 50\%$, it suggested the absence of statistical heterogeneity among the research findings, and a fixed-effect model was applied for analysis. Conversely, if $P < .05$ or $I^2 > 50\%$, a random-effect model was employed. Additionally, if the heterogeneity was deemed substantial, further investigation of the source was conducted. The odds ratios (OR) and 95% confidence intervals (CI) were calculated, and $P < .05$. Publication bias was evaluated using funnel plots.

3. Results

3.1. Results of search process and study characteristics

A total of 398 studies were initially identified through the retrieval of literature from the Chinese and English databases after excluding duplicate records. Of these, 145 were Chinese and 253 were English. After reviewing titles and abstracts, 189 references were excluded. After a full-text review based on the inclusion criteria, 183 references were removed. Ultimately, 26 studies were included in this meta-analysis. The screening process is illustrated in Figure 1.

3.2. Characteristics of included studies

A total of 23 high-quality randomized controlled trials (RCTs) were identified in 26 studies.[25–50] Among these studies, 3[25,28,35] specifically targeted children and adolescents, whereas the remaining studies focused exclusively on adults. All included studies were blinded to both the patients and researchers, thus minimizing the risk of performance and detection bias. Furthermore, information on patients who were lost to follow-up, withdrew, or lacked desired outcomes was recorded, indicating a low risk of attrition and reporting bias. Table 1 provides detailed information on the RCTs, while Figure 2 and Supplemental Digital Content 1, http://links.lww.com/MD/K627 present an assessment of the risk of bias.

3.3. Meta-analysis

3.3.1. CR of CINV in the overall, acute, and delayed phases. The heterogeneity analysis for CR of CINV (7956 patients[25–50]) in the overall phase revealed a moderate level of heterogeneity, as indicated by $P = .007$ and $I^2 = 47\%$. The

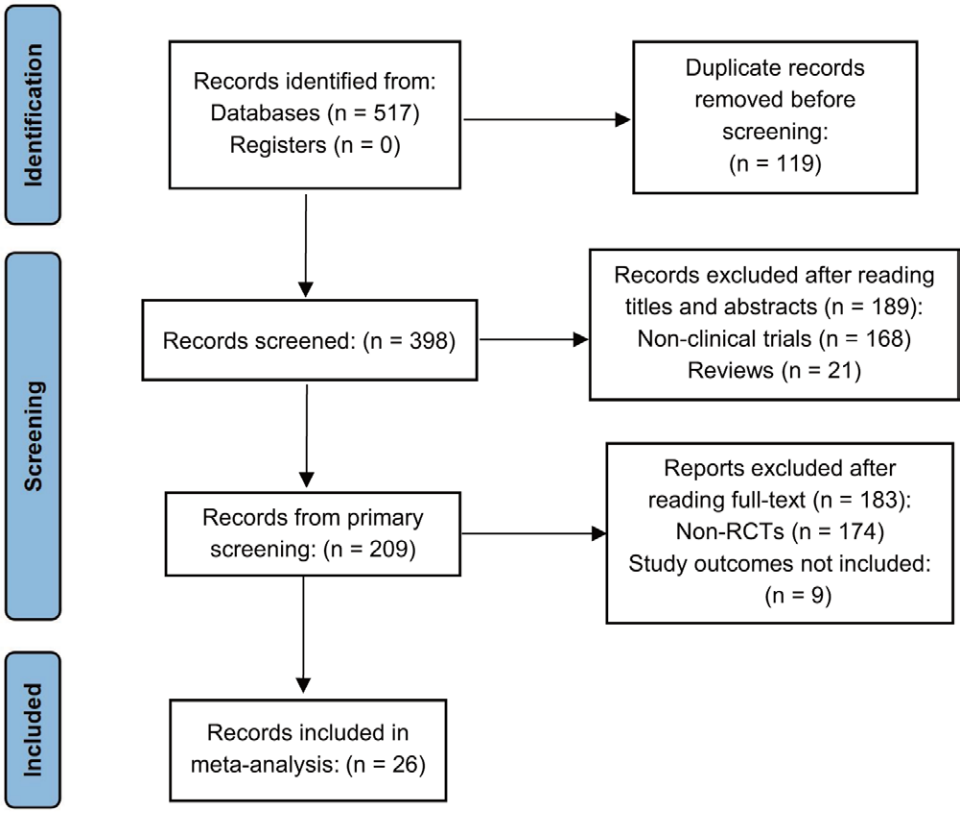

Figure 1. The PRISMA flow diagram of studies' screening and selection.

meta-analysis was performed using the random-effect model, with significant statistical differences (OR = 2.02, 95% CI: 1.76–2.33, $P < .0001$), as depicted in Figure 3. Similar results were obtained for CR in the acute phase (Fig. 4), with 7580 patients from previous studies,[25,27–42,44–47,49,50] demonstrating moderate statistical heterogeneity ($P = .01$, $I^2 = 47\%$) and significant differences (acute CR: OR = 1.91, 95% CI: 1.58–2.31, $P < .0001$). As shown in Figure 5, moderate statistical heterogeneity was also observed in the delayed phase, involving 7404 patients[25,27–41,44–47,49,50] ($P = .0005$, $I^2 = 59\%$), and significant differences were found (delayed CR: OR = 2.00, 95% CI: 1.70–2.36, $P < .0001$) among the RCTs.

3.3.2. Total control and/or complete protection of CINV in the overall phase. The fixed-effect model was employed for insignificant heterogeneity in total control (4899 patients,[27,28,30–33,37,40,44–50] $P = .19$ and $I^2 = 25\%$) and complete protection(5927 patients,[27,30–33,37–41,44–47,49,50] $P = .17$, and $I^2 = 27\%$) of CINV throughout the overall phase. The meta-analysis demonstrated significant differences between the 2 groups in both analyses: total control (OR = 1.31, 95% CI: 1.16–1.48, $P < .00001$) and complete protection (OR = 1.44, 95% CI: 1.28–1.61, $P < .00001$). Detailed results can be found in Supplemental Digital Content 2, http://links.lww.com/MD/K628 and Supplemental Digital Content 3, http://links.lww.com/MD/K629.

3.3.3. Total control and/or complete protection of CINV in the acute and delayed phases. Studies regarding total control in the delayed phase, including 3060 patients,[27,33,37,44,47,49,50] were analyzed using the random-effect model ($P = .07$, $I^2 = 49\%$), which indicated a significant difference (OR = 1.36, 95% CI: 1.09–1.71, $P = .007$) between the 2 groups (Supplemental Digital Content 4, http://links.lww.com/MD/K630). However, for the acute phase of 2537 patients,[27,33,44,47,49,50] it can be inferred that Yahata's study[49] might be the source of high heterogeneity ($P < .0001$, $I^2 = 91\%$). Consequently, as Supplemental Digital Content 5, http://links.lww.com/MD/K631 and 6, http://links.lww.com/MD/K632 show, the fixed-effect model was applied after excluding this reference ($P = .66$, $I^2 = 0\%$), with no significant statistical difference ($P = .1$). In terms of complete protection against CINV during the acute (3021 patients,[27,33,41,44,47,49,50] $P = .32$ and $I^2 = 14\%$) and delayed phases (3544 patients,[27,33,37,41,44,47,49,50] $P = .12$, $I^2 = 39\%$), insignificant heterogeneity between the 2 groups was found, and significant statistical differences were reported in Supplemental Digital Content 7, http://links.lww.com/MD/K633 and 8, http://links.lww.com/MD/K634 (acute: OR = 1.84, 95% CI: 1.46–2.33, $P < .0001$; delayed: OR = 1.47, 95% CI: 1.27–1.71, $P < .0001$).

3.3.4. Incidence of adverse reactions. Common adverse reactions caused by prevention and treatment of CINV include anorexia, diarrhea, constipation, headache, fatigue/weakness, and hiccup. Among these, febrile neutropenia is the most frequently-reported serious adverse effect. Given the low statistical heterogeneity in the analyses, a fixed-effect model was used to determine the incidence of adverse reactions. In Supplemental Digital Contents 9–12, http://links.lww.com/MD/K635, http://links.lww.com/MD/K636, http://links.lww.com/MD/K637, http://links.lww.com/MD/K638, meta-analyses revealed no significant differences in the incidence of diarrhea (7122 patients,[25–27,30–32,34–39,41,42,44–50] $P = .76$, $I^2 = 0\%$), anorexia (5464 patients,[25–27,34,36–39,41,44–48,50] $P = .95$, $I^2 = 0\%$), headache (3103 patients,[25,27,30–32,37–39,42,50] $P = .98$, $I^2 = 0\%$), or febrile neutropenia (5692 patients,[25,27,28,30–33,35,37–39,41,44,47,50] $P = .88$, $I^2 = 0\%$). As shown in Supplemental Digital Contents 13–15, http://links.lww.com/MD/K639, http://links.lww.com/MD/K640, http://links.lww.com/MD/K641, for other adverse reactions with significant

Table 1

Characteristics of studies included in the meta-analysis.

Author	Region	Publication time	Tumor type	Chemotherapy	Sample size		Average age		Intervention		Outcomes
					Test	Control	Test	Control	Test	Control	
Bakhshi [25]	India	2015	Malignant tumor	ABVD, AVD or VAdC	52	44	12.7 ± 3.45	13.1 ± 3.54	APR + OND + DEX	Placebo + OND + DEX	①②⑥
Bubalo[26]	America	2018	Leukemia	Cyclophosphamide	20	20	46	46	APR + OND + DEX	Placebo + OND + DEX	①⑥
Chawla[27]	Multi-center	2003	Solid tumor	Cisplatin (≥70 mg/m^2)	A:134 B:120	127	A: 56.0 ± 13.0 B: 58.4 ± 13.4	53.7 ± 13.2	A: APR (125/80) + OND + DEX B: APR (40/25) + OND + DEX	Placebo + OND + DEX	①②③④⑤⑥
Gore[28]	Multi-center	2009	Malignant tumor	Not Mentioned	32	18	15 ± 1.73	15 ± 1.91	APR + OND + DEX	Placebo + OND + DEX	①②③⑥
Gralla[29]	Multi-center	2005	Solid tumor	Cisplatin (≥70 mg/m^2)	70	72	/	/	APR + OND + DEX	OND + DEX	①②
Herrstedt [30] Warr[31,32]	Multi-center	2005/2011	Breast cancer	Cyclophosphamide	438	428	53.1 ± 10.7	52.1 ± 10.9	APR + OND + DEX	Placebo + OND + DEX	①②③⑥
Hesketh [33]	Multi-center	2003	Solid tumor	Cisplatin (≥70 mg/m^2)	264	266	59 ± 12	58 ± 12	APR + OND + DEX	Placebo + OND + DEX	①②③④⑤⑥
Hu[34]	China	2014	Solid tumor	Cisplatin (≥70 mg/m^2)	189	199	53.1 ± 10.1	53.6 ± 10.6	APR + GRA + DEX	Placebo + GRA + DEX	①②⑥
Kang[35]	Multi-center	2015	Solid tumor	MEC or HEC	155	152	7.2	7.6	APR + OND + DEX	Placebo + OND + DEX	①②⑥
Kim[36]	Korea	2017	Solid tumor	Carboplatin, oxaliplatin or Irinotecan	244	250	59.7 ± 11.4	60.9 ± 11.5	APR + OND + DEX	Placebo + OND + DEX	①②⑥
Poli- Bigelli[37]	Latin America	2003	Solid tumor	Cisplatin (≥70 mg/m^2)	283	286	54 ± 13	53 ± 14	APR + OND + DEX	Placebo + OND + DEX	①②③④⑤⑥
Rapoport [38,39]	Multi-center	2010/2014	Solid tumor	AC or non-AC	430	418	57.1 ± 11.8	55.9 ± 12.6	APR + OND + DEX	Placebo + OND + DEX	①②③⑥
Schmitt [40]	Germany	2014	Multiple myeloma	Melphalan	181	181	58.3	57.9	APR + GRA + DEX	Placebo + GRA + DEX	①②③⑥
Schmoll [41]	Multi-center	2006	Solid tumor	Cisplatin (≥70 mg/m^2)	244	245	59 ± 11	58 ± 11	APR + OND + DEX	Placebo + OND + DEX	①②③⑤⑥
Stiff[42]	America	2013	Malignant tumor	Cisplatin (≥70 mg/m^2)	92	89	50	51	APR + OND + DEX	Placebo + OND + DEX	①②⑥
Svanberg [43]	Sweden	2015	Lymphoma, myeloma	BEAM, BEAC, or melphalan	49	47	58.11 ± 8.84	56.52 ± 8.25	APR + TRO + BET	Placebo + TRO + BET	①
Takahashi [44]	Japan	2010	Solid tumor	Cisplatin (≥70 mg/m^2)	A:151 B:151	151	A: 60.5 ± 9.7 B: 3.3 ± 9.4	62.2 ± 9.8	APR + GRA + DEX	Placebo + GRA + DEX	①②③④⑤⑥
Tanioka [45]	Japan	2013	Gynecologic cancer	Combination with carboplatin	47	47	53	59	APR + GRA + DEX	Placebo + GRA + DEX	①②③⑥
Wang[46]	China	2021	Gastrointestinal cancer	FOLFIRI or FOLFOX	124	124	40.01 ± 7.42	40.17 ± 7.27	APR + PAL + DEX	Placebo + PAL + DEX	①②③⑥
Warr[47]	Multi-center	2005 (b)	Solid tumor	Cisplatin (≥70 mg/m^2)	520	523	56	55	APR + OND + DEX	Placebo + OND + DEX	①②③④⑤⑥
Wu[48]	China	2018	Lung cancer	Cisplatin (≥70 mg/m^2)	122	122	57.1 ± 8.6	56.2 ± 8.4	APR + PAL + DEX	Placebo + PAL + DEX	①③⑥
Yahata[49]	Japan	2016	Gynecologic cancer	Combination with TC	155	152	59	59	APR + OND/GRA +DEX	Placebo + OND/GRA + DEX	①②③④⑤⑥
Yeo[50]	China	2009	Breast cancer	Doxorubicin and Cyclophosphamide	62	62	46.5	48.5	APR + OND + DEX	OND + DEX	①②③④⑤⑥

① CR of CINV in the overall phase; ② CR of CINV in the acute or delayed phase; ③ total control and/or complete protection in the overall phase; ④ total control in the acute or delayed phase; ⑤ complete protection in the acute or delayed phase; ⑥ incidence of adverse reactions.

ABVD = doxorubicin + bleomycin + vinblastine + dacarbazine, AC = anthracycline antibiotics + cyclophosphamide, APR = aprepitant, AVD = vincristine + doxorubicin + cyclophosphamide, BEAC = carmustine + etoposide + cytarabine + cyclophosphamide, BEAM = carmustine + etoposide + cytarabine + melphalan, BET = betamethasone, DEX = dexamethasone, FOLFIRI = fluorouracil + calcium folinate + irinotecan, FOLFOX = fluorouracil + calcium folinate + oxaliplatin, GRA = granisetron, HEC = highly emetic chemotherapy, MEC = moderate emetic chemotherapy, OND = ondansetron, PAL = palonosetron., TC = paclitaxel + carboplatin, TRO = tropisetron, VAdC = vincristine + actinomycin-D1 + cyclophosphamide.

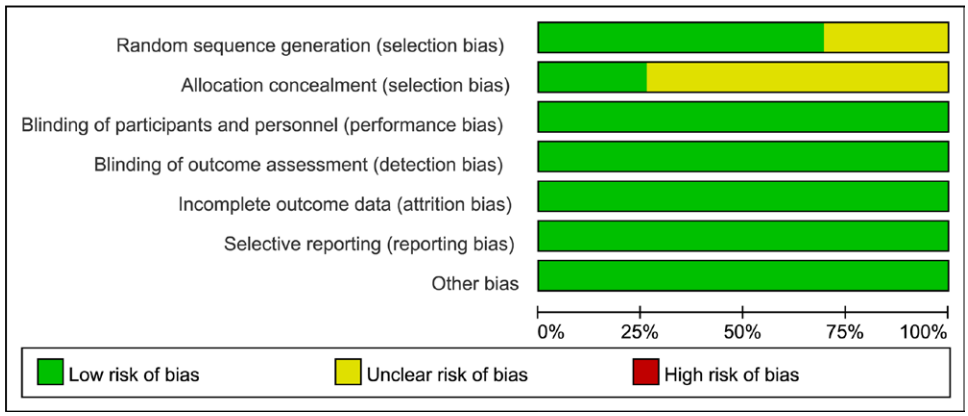

Figure 2. Risk of bias graph that review authors' judgements about each risk of bias item presented as percentages across all included studies according to Cochrane's bias assessment tool.

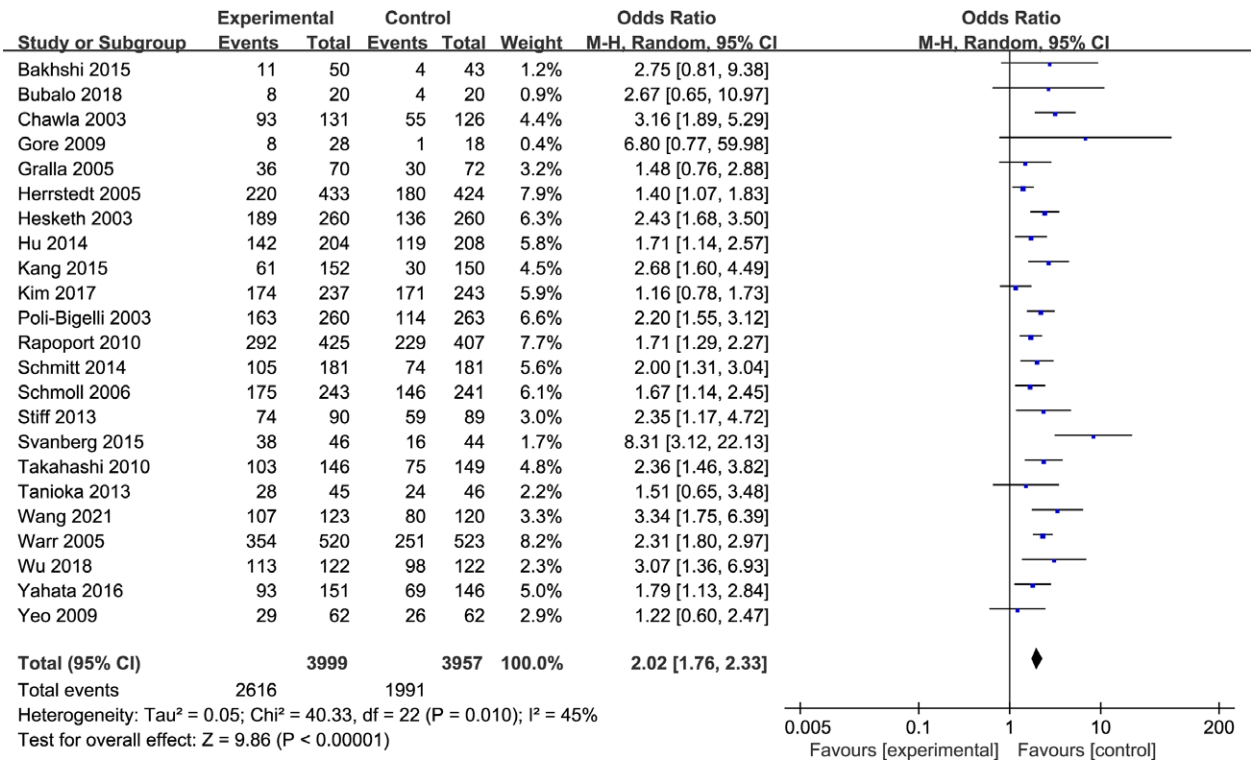

Figure 3. Forest plot for the complete response of CINV in the overall phase. CINV = chemotherapy-induced nausea and vomiting.

statistical differences observed, the OR value of constipation (7765 patients,[25–27,30–42,44–47,49,50] P = .11, I^2 = 30%) was less than 1 (OR = 0.78, 95% CI: 0.68–0.90, P = .0004). For fatigue (7060 patients,[26,27,30–34,36–42,44,45,47,48,50] P = .37, I^2 = 7%) and hiccup (3804 patients,[27,33,35,36,41,42,44,47] P = .14, I^2 = 37%), however, the OR value was greater than 1 (fatigue: OR = 1.38, 95% CI: 1.20–1.60, P < .0001; hiccup: OR = 1.61, 95% CI: 1.29–2.01, P < .0001).

3.4. Publication biases

Funnel plots of outcomes in section 3.3 were generated using Stata 17. As shown in Figure 6A, the majority of the studies exhibited a symmetrical distribution within the plots, suggesting a relatively low occurrence of publication bias. However, as shown in Figure 6B, when examining the proportion of patients with total control during the acute phase, a reference was identified outside the funnel plot, and exclusion resulted in a notable decrease in heterogeneity (P = .66, I^2 = 0%).

3.5. Sensitivity analysis

A sensitivity analysis was performed by sequentially eliminating one study in Figure 7A and B. With the exception of the analysis of patients with total control in the acute phase, the OR value and CI for other analyses remained within a consistent range, supporting the reliability of the meta-analysis. It can be inferred that the study conducted by Yahata[49] was the primary source of the observed heterogeneity deviation.

4. Discussion

CINV commonly occurs during the treatment of malignant cancer and seriously disturbs patient compliance. The underlying

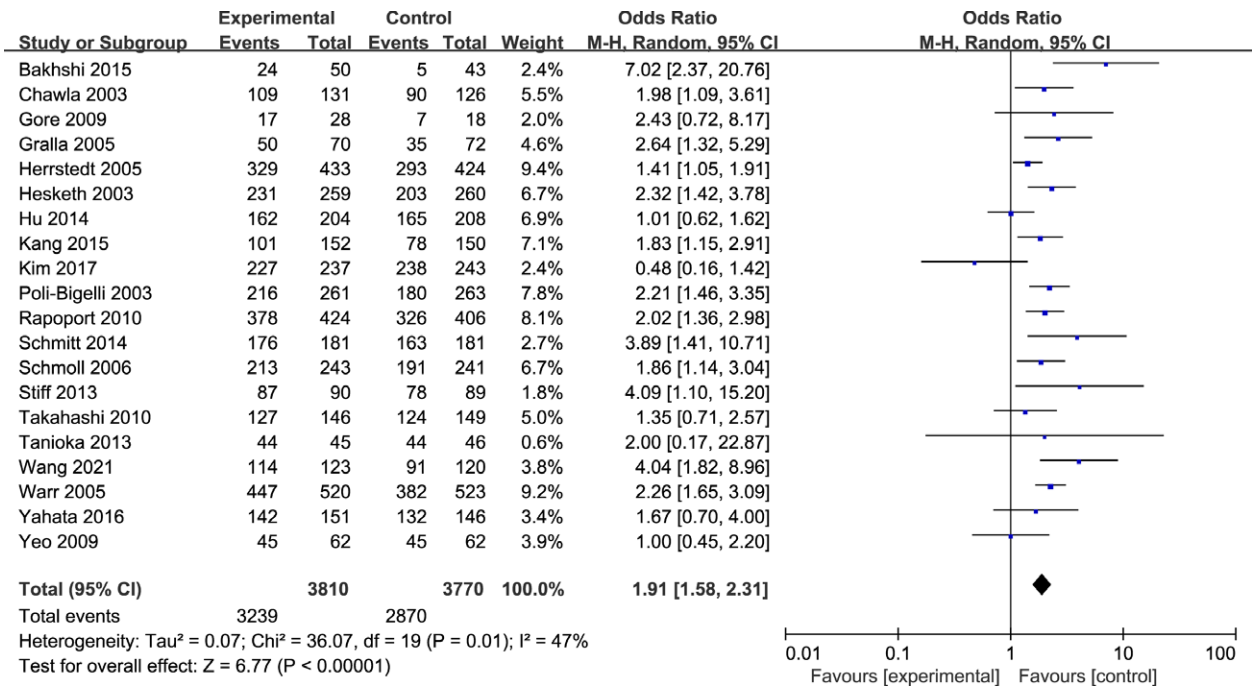

Figure 4. Forest plot for the complete response of CINV in the acute phase. CINV = chemotherapy-induced nausea and vomiting.

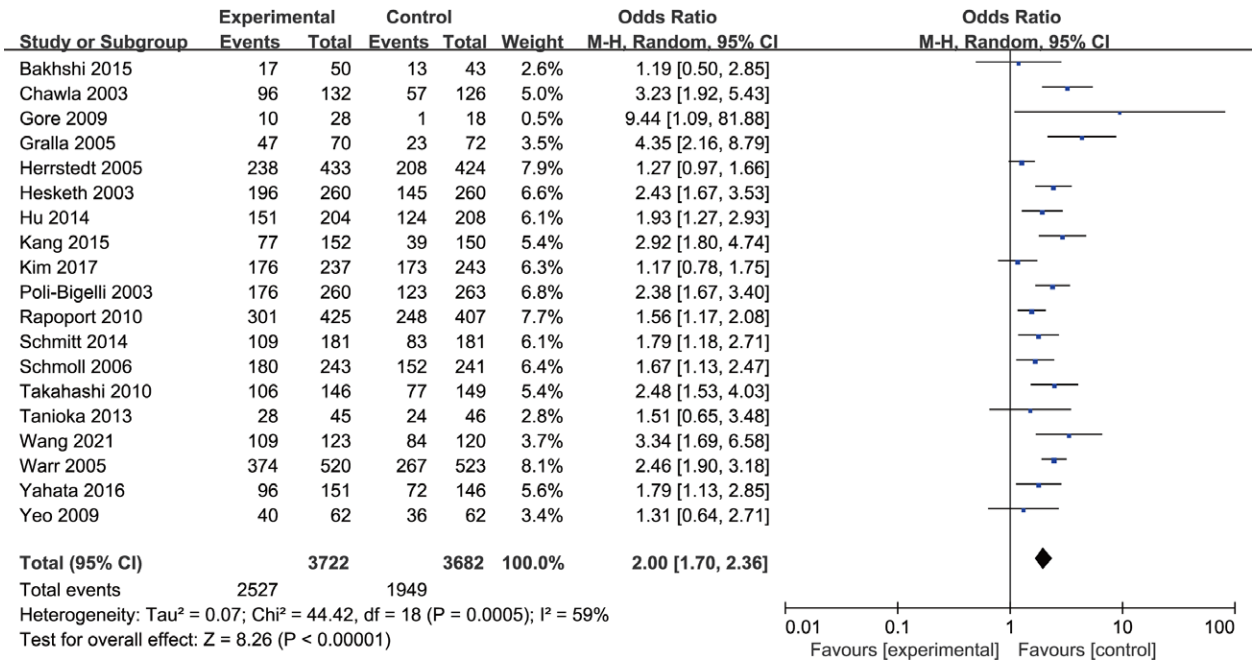

Figure 5. Forest plot for the complete response of CINV in the delayed phase. CINV = chemotherapy-induced nausea and vomiting.

mechanisms may involve the following: chemotherapeutic drugs that facilitate the release of 5-HT_3 from gastrointestinal chromaffin cells, leading to the transmission of nerve impulses that induce acute CINV; stimulation of the central nervous system and gastrointestinal chromaffin cells, triggering the release of substance P, which may contribute to delayed nausea and vomiting; and direct activation of the chemoreceptor trigger zone (CTZ) in the medulla oblongata by chemotherapeutic drugs, resulting in nausea and vomiting.[51–53] Considering the distinct targets of NK-1 and 5-HT_3 receptor antagonists, their combination significantly enhances the antiemetic efficacy. The role of dexamethasone in antiemetic treatment remains unclear and its efficacy is unsatisfactory when used alone. It is important to note that as a CYP3A4 enzyme inducer, the dosage of dexamethasone should be reduced when co-administered with NK-1 receptor antagonists.[51]

The combination of antiemetic drugs with diverse mechanisms is strongly recommended for the prevention and treatment of CINV. This study conducted a comprehensive comparison of the efficacy and safety of triple- and two-drug therapies, using multiple outcomes as measures. Meta-analysis was employed to assess binary variables, with odds ratios (OR) and 95%

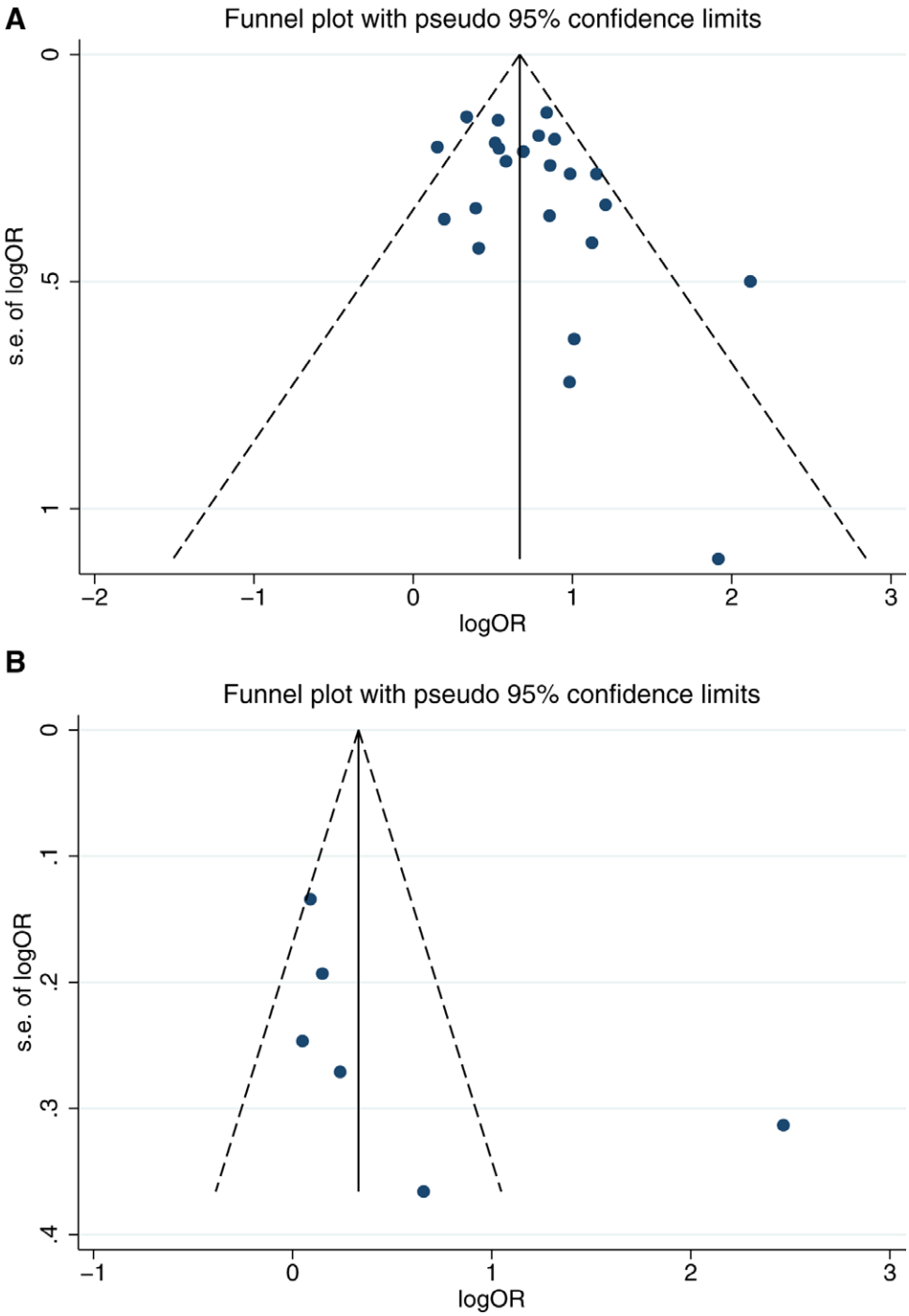

Figure 6. A. Funnel plot for the complete response of CINV in the overall phase. B. Funnel plot for the total control of CINV in the acute phase. CINV = chemotherapy-induced nausea and vomiting.

confidence intervals (CI) utilized as evaluation metrics. The formula for calculating the OR is as follows:

$$\mathrm{OR} = \frac{\left(\begin{array}{c}\text{number of patients exposed}\\ /\text{number of people not exposed}\end{array}\right)\text{in the test group}}{\left(\begin{array}{c}\text{number of people exposed}\\ /\text{number of people not exposed}\end{array}\right)\text{in the control group}}$$

If OR was > 1, the incidence of an event in the test group was higher than that in the control group, in contrast to the case when OR was < 1.[54,55] Therefore, when interpreting the results of the meta-analysis, it is essential to consider both OR values and the properties of outcomes for accurate judgements.

The analysis in Section 3.3 consisted of 4 parts: the first 3 were efficacy indicators, while the final part focused on safety. Favorable outcomes were associated with efficacy indicators, where an odds ratio (OR) greater than 1 was desired. Except for the analysis of patients with total control of acute CINV, OR > 1 and $P < .05$ was observed in the other analyses for efficacy. This suggests that aprepitant-containing therapy, in comparison to 5-HT_3 antagonists and dexamethasone alone, significantly alleviated chemotherapy-induced nausea and vomiting. The aim of safety indicators is to lower the incidence of adverse reactions. A meta-analysis indicated that aprepitant did not increase the occurrence of febrile neutropenia, diarrhea, anorexia, or headache. Furthermore, it may improve the safety

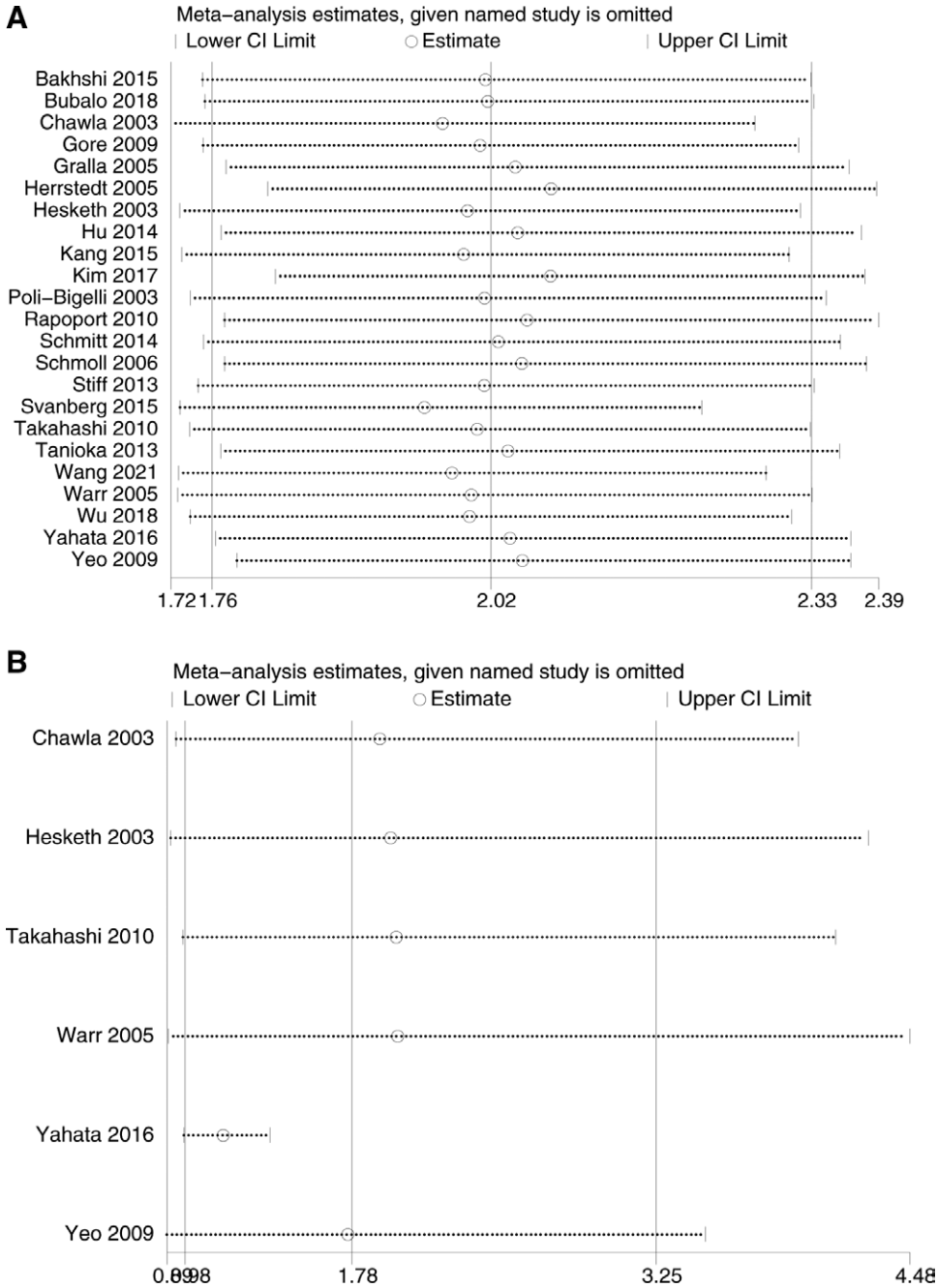

Figure 7. A. Sensitivity analysis plot for the complete response of CINV in the overall phase. B. Sensitivity analysis plot for the total control of CINV in the acute phase. CINV = chemotherapy-induced nausea and vomiting.

of constipation. Although the incidence of fatigue and hiccups was higher in the test group, experts confirmed the overall safety of triple therapy.

The findings of this study align with those of previously reported meta-analyses, demonstrating that the addition of aprepitant to standard two-drug therapy (5-HT_3 receptor antagonist and dexamethasone) significantly enhanced the CR rates of CINV in the overall/acute/delayed phase.[56–59] Furthermore, aprepitant exhibits notable efficacy in alleviating nausea symptoms, except for acute nausea,[58,59] on account of its mechanism of action as an NK-1 receptor antagonist that impedes substance P binding. Regarding adverse reactions, no significant differences were observed between the 2 therapies, except for a higher incidence of fatigue and hiccups. Considering relevant meta-analyses,[57–60] our analysis of adverse reactions in this study supports the conclusion that aprepitant-containing triple therapy does not lead to an increased occurrence of common adverse reactions.

In conclusion, the combination of aprepitant, a 5-HT_3 receptor antagonist, and dexamethasone has remarkable efficacy and safety in the prevention and treatment of CINV, as supported by available evidence. However, our study had several limitations. First, moderate heterogeneity was observed in some outcomes, potentially affecting the reliability of the results. Second, the inclusion of studies was limited to English and Chinese literature, resulting in inadequate representation of different racial populations. Additionally, some studies lacked detailed reporting of random sequence generation and allocation concealment, which may have introduced a potential bias. Despite these limitations, our analysis included 23

randomized controlled trials (RCTs) and performed a comprehensive assessment of the efficacy and safety outcomes, providing relatively reliable results for the use of aprepitant in clinical practice.

5. Conclusion

This study conducted a systematic comparison between standard therapy and aprepitant-containing triple therapy for the treatment of chemotherapy-induced nausea and vomiting (CINV). This study included 23 randomized controlled trials (RCTs) involving 7956 patients. The results demonstrated that aprepitant-containing triple therapy exhibited significantly superior efficacy for the prevention and treatment of CINV. Furthermore, the medication safety of this approach has been endorsed by experts and supported by multiple meta-analyses, providing robust evidence for the use of aprepitant. Our future work will aim to assess the economic feasibility of aprepitants in clinical practice by examining the relevant economic data.

Author contributions

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Writing – review & editing: Min Zhang.

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