Original Article

Use of dexamethasone and a 5-HT3 receptor antagonist with or without aprepitant to prevent chemotherapy-induced nausea and vomiting among patients with lung cancer who are treated with platinum-based chemotherapy: a systematic review and meta-analysis of randomized controlled trials

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Background: Researchers have not clearly determined whether adding aprepitant (ADH) to dexamethasone and one 5-HT3 receptor antagonist (DH) is clinically effective at preventing chemotherapy-induced nausea and vomiting (CINV) among patients with lung cancer (LC) treated with platinum-based chemotherapy (PBC). Therefore, we conducted a meta-analysis to examine the efficacy and safety of ADH and DH.

Methods: We searched the PubMed, ScienceDirect, Cochrane Library, and Scopus databases, among others, for relevant studies. The primary outcomes were the complete response (CR) and the no nausea rate (NNR). The secondary endpoints were the number of patients who needed rescue antiemetic treatment (RAT), adverse events (AEs), and the Functional Living Index Emesis (FLIE) score.

Results: We initially screened 2,118 articles; ultimately, four randomized controlled trials (RCTs) with 518 patients were included. The ADH group had a superior overall CR [risk ratio (RR): 1.16 (1.06, 1.27), P=0.002] and a lower number of patients who needed RAT [RR: 0.44 (0.29, 0.65), P<0.0001]. The ADH group also had a better overall NNR [RR: 1.11 (0.97, 1.26), P=0.12] and delayed CR [RR: 1.12 (0.97, 1.31), P=0.13]. No significant differences were observed in acute CR, acute NNR, or delayed NNR. In the subgroup analysis of the overall CR and NNR, ADH was superior in certain clinical characteristics (China, cisplatin-based chemotherapy, 2nd-generation 5-HT3 receptor antagonist, ADC <50%, and Eastern Cooperative Oncology Group (ECOG) score of 0-2). No significant differences in the AEs characterized as hematological or nonhematological toxicity were observed between the groups.

Conclusions: Compared with DH, ADH appears to be superior at preventing CINV and achieving a better CR among patients with LC treated with PBC.

Keywords: Aprepitant; chemotherapy; nausea; vomiting; lung cancer (LC); meta-analysis

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Introduction

Lung cancer (LC) is the most widespread cancer in the world and has higher mortality rates than all other cancers (1,2). Guidelines for treating LC (3,4) indicate that the first-line treatment for LC is platinum-based chemotherapy (PBC). This treatment has been confirmed to be beneficial for patients. However, chemotherapy-induced nausea and vomiting (CINV) is the most common adverse event (5). CINV exerts a significant negative effect on quality of life (QoL) and even stops patients from undergoing chemotherapy treatment (6). Dexamethasone and one type of 5-HT3 receptor antagonist (DH) is commonly used as a standard and classical antiemetic treatment to prevent CINV. However, some of its effects have yet to be confirmed in the clinic.

Aprepitant is a neurokinin-1 (NK-1) RA that functions in both the gut and the central nervous system by antagonizing the interaction of substance P (chemotherapy-related increase) and NK-1 receptors to prevent CINV (7). Some clinical trials have suggested that adding aprepitant (ADH) to DH has achieved excellent effects (8). However, researchers have not clearly determined whether ADH is better than DH at preventing CINV in patients with LC (9,10). Several trials have been conducted to examine this issue. In one randomized controlled trial (RCT), Wu reported a better overall complete response (CR) and a lower rate of rescue antiemetic treatment (RAT) in the ADH group, but the no nausea rate (NNR) was similar in the two groups (11). Aksu also reported that ADH led to a better CR and lower Functional Living Index Emesis (FLIE) scores in patients with LC (12). However, Kusagaya and Ito reported similar CRs and NNRs in the acute, delayed and overall phases between the ADH and DH groups (13,14).

A meta-analysis was performed to compare the CR and NNR of patients with LC treated with PBC to examine the effects and safety of ADH and DH.

We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/apm-20-2290).

Methods

This meta-analysis was performed in accordance with the PRISMA guidelines (15,16) (Registration information: PROSPERO CRD42020162227).

Search strategy

The following eight databases were used to search for relevant articles: (I) PubMed, (II) ScienceDirect, (III) The Cochrane Library, (IV) Scopus, (V) Web of Science, (VI) Embase, (VII) Ovid MEDLINE, and (VIII) Google Scholar.

Two researchers conducted separate searches of the databases and manual searches in duplicate to search for all relevant research documents published between January 1990 and July 2020. Our search was conducted from database inception to July 30, 2020. “Aprepitant”, “Dexamethasone”, and “Chemotherapy” were used as key terms (Figure S1) illustrates the search strategy. The reference lists of the retrieved articles were manually searched for additional relevant studies. All searches were performed without language barriers.

Selection criteria

We formulated the inclusion criteria in accordance with the principle of PICOS: (I) population: patients who have been diagnosed with LC and treated with PBC were guided by the Eastern Cooperative Oncology Group (ECOG); (II) intervention and comparison: ADH versus DH; (III) outcomes: CR, NNR, RAT, adverse events (AEs) and FLIE score; (IV) study design: RCTs. We excluded reviews without raw data (conducted by screening the full text), meta-analyses, animal-based experiments, abstracts, and duplicate studies.

Data extraction

The following data were collected and summarized separately by two researchers (MYH and RXX): primary author’s name, publication date, research period, nation, study planning, number of recipients, recipient characteristics (age, sex, ECOG status, treatment arm, chemotherapy regimen, and pathological type), efficacy indices (CR, NNR, RAT, and FLIE score) and AEs. A third

reviewer resolved all the discrepancies (ZWX).

Outcome assessments

The CR and NNR were assessed as the primary outcomes. The CR was subdivided into the overall CR (days 1 to 5), acute CR (day 1) and delayed CR (days 2 to 5). The NNR was subdivided into the overall NNR, acute NNR and delayed NNR.

We performed a further subgroup analysis stratified according to the severity and type of AEs. For severity, AEs were classified into total AEs and grade 3–5 AEs. AE types were divided into hematological toxicity (leukopenia, neutropenia, anemia, and thrombocytopenia) and nonhematological toxicity (hepatotoxicity, nephrotoxicity, constipation, allergic reaction, hiccups, fatigue, diarrhea, decreased appetite, and abdominal pain).

Quality assessment

The Cochrane Risk of Bias Tool (CRBT) and Jadad scale were applied to assess the quality of RCTs. The evaluation indicators of the CRBT include randomization sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting. Study quality was classified as high, low, or unclear (17). Three key terms are included in the evaluation indicators of the Jadad scale: randomness, blackout, and follow-up management. A score ≥3 indicates high quality (18).

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to examine the quality of the outcomes. The evaluation indicators include the risk of bias, nonuniformity, inconsistency, inaccuracy and publication bias. The outcome quality was classified as high, medium, low or very low (19).

Statistical analysis

Review Manager (Ver. 5.4) and STATA (Ver. 15.1) software were used to carry out the meta-analysis. P≤0.05 was considered statistically significant. Data were summarized using risk ratios (RRs) with 95% CIs for the CR, NNR, FLIE scores (RR >1 prefers ADH; RR <1 prefers DH), and the number of patients who needed RAT (RR >1 prefers DH; RR <1 prefers ADH). We considered P<0.05 a statistically significant difference. Mantel-Haenszel (MH) was used for pooling variances (17). An AE analysis was performed to indicate the distinction among each reported symptom. Subgroup analyses of the CR and NNR were performed to identify in which scenario the outcomes varied based on the nation, chemotherapy regimen, 5-HT3 RA type, ADC (%) and performance status. We used Begg's and Egger's tests to explore publication bias. Heterogeneity was assessed using the χ^2 test and I^2 statistic. Significant heterogeneity was indicated by the results of the χ^2 test as being significant at P<0.1 or by an I^2>50%, and in these cases, the random effects model was adopted; otherwise, the fixed effects model was adopted.

Results

Search results and study quality assessment

We preliminarily screened 2118 potential qualified studies. Four studies assessing 518 patients (ADH group, 261 patients; DH group, 257 patients) were ultimately included in the analysis (*Figure 1*) (11-14). All the studies were RCTs. One study was conducted in China, two were conducted in Japan, and one was conducted in Turkey. The study characteristics are presented in *Table 1*. Based on the CRBT and Jadad scores, all of the included trials were of high quality (Figure S2 and Table S1). According to the GRADE framework, all the outcomes were of high or medium quality (Table S2).

Complete response

We considered nonvomiting and nonuse of emergency medicines as CR standards and assessed the efficacy of the CR based on the overall CR, acute CR and delayed CR. Four studies compared the overall CR (heterogeneity: P=0.80, I^2=0%). The ADH group had a significantly better CR than the DH group (RR: 1.16, 95% CI: 1.06–1.27, P=0.002; *Figure 2A*). Two studies compared the acute CR (heterogeneity: P=0.66, I^2=0%). No significant difference was observed between groups (RR: 0.99, 95% CI: 0.95–1.03, P=0.61; *Figure 2B*). Two studies compared the delayed CR (heterogeneity: P=0.46, I^2=0%), and the ADH group showed a better CR, but the difference was not significant (RR: 1.12, 95% CI: 0.97–1.31, P=0.13, I^2=0%; *Figure 2C*).

No nausea rate

We assessed the efficacy of the NNR between the ADH and DH groups based on the overall NNR, acute NNR, and delayed NNR. Three studies compared the overall NNR

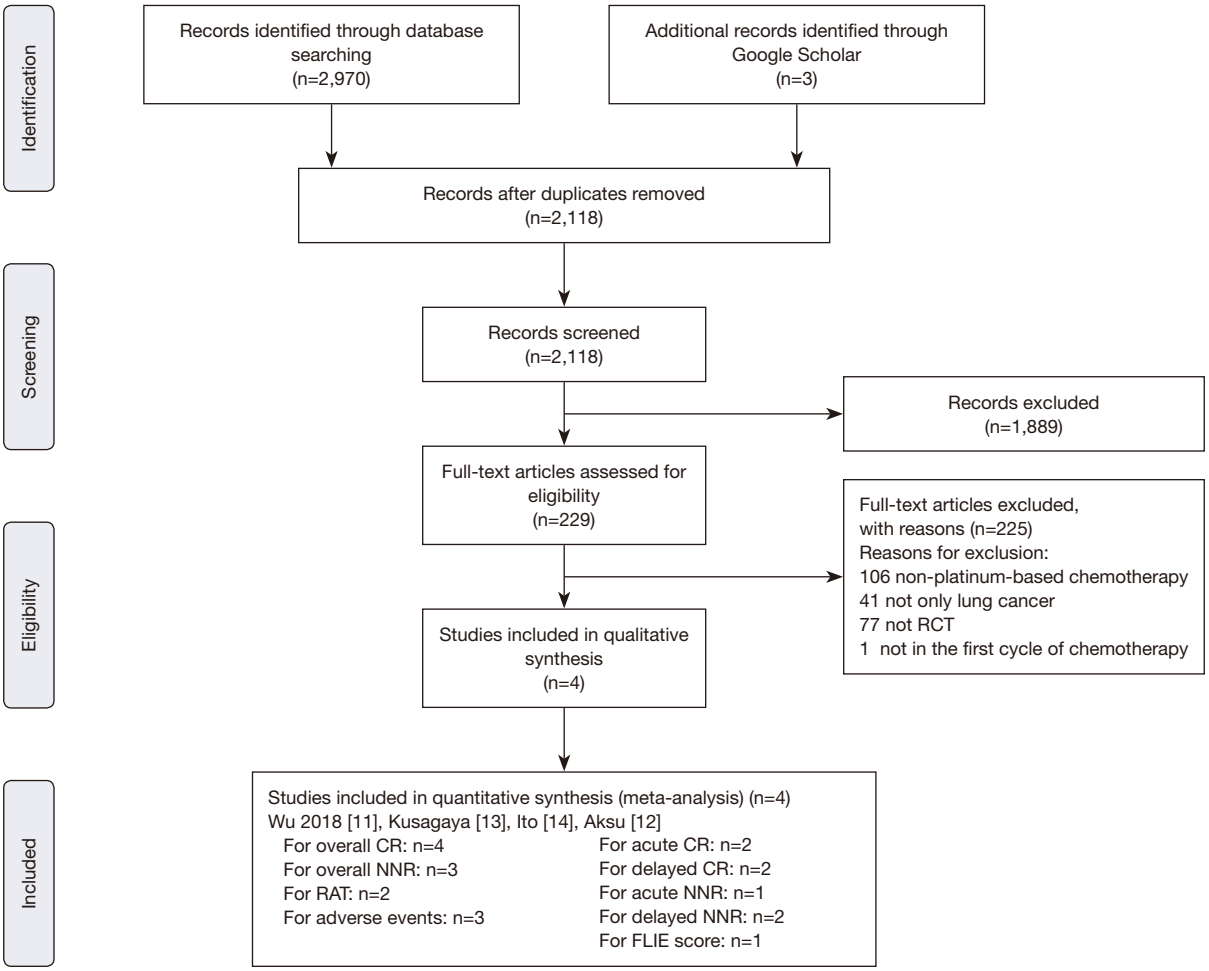

Figure 1 Flow chart of study selection.

(heterogeneity: P=0.67, I^2=0%), and the results showed a better NNR in the ADH group, but this difference was not significant (RR: 1.11, 95% CI: 0.97–1.26, P=0.12; *Figure 3A*). Only one study compared the acute NNR. No significant difference was observed between the two groups (RR: 0.93, 95% CI: 0.77–1.11, P=0.41; *Figure 3B*). Two studies compared the delayed NNR (heterogeneity: P=0.62, I^2=0%). No significant difference was found between the two groups (RR: 1.15, 95% CI: 0.92–1.43, P=0.22; *Figure 3C*).

Rescue antiemetic treatment

Two studies compared the proportion of patients who received RAT (heterogeneity: P=0.52, I^2=0%); A significantly lower number of patients in the ADH group received RAT than patients in the DH group (RR: 0.44, 95% CI: 0.29–0.65, P<0.0001). In the subgroup analysis of chemotherapy regimens, for patients taking cisplatin (RR: 0.40, 95% CI: 0.25–0.65, P=0.0002) and carboplatin + pemetrexed (RR: 0.45, 95% CI: 0.19–1.02, P=0.06), the ADH group showed a significantly lower need for RAT than the DH group. For patients receiving carboplatin + paclitaxel, no significant difference was observed between the two groups (RR: 1.06, 95% CI: 0.26–4.26, P=0.94; *Figure 4*).

Adverse events

Three studies including 458 patients recorded AEs. We classified the listed AEs in terms of severity (total AEs and grade 3–5 AEs) and type (hematological and nonhematological toxicity) and performed subgroup analyses of the listed AEs.

In the subgroup analysis of total AEs, ADH did not differ from DH in hematological toxicity (leukopenia,

Table 1 Summary of the baseline characteristics of the included studies

Study	Nation	Period (year)	Groups	Recipients	Gender (M/F)	Recipient's mean age (year)	Performance status ECOG	Treatment	Chemotherapy regimen	ADC (%)	Quality (score)
Wu (11), 2018	China	2014.02–2017.02	ADH	122	101/21	57.1	0, 1, 2	Aprepitant + dexamethasone + palonosetron	Cisplatin plus etoposide or docetaxel or paclitaxel or gemcitabine	28	5
			DH	122	104/18	56.2		Placebo + dexamethasone + palonosetron		38	
Kusagaya (13), 2015	Japan	2013.04–2015.02	ADH	41	29/12	70	0, 1	Aprepitant + dexamethasone + palonosetron	Carboplatin plus paclitaxel or pemetrexed or S-1 (+/– bevacizumab)	66	4
			DH	39	28/11	73		Dexamethasone + palonosetron		64	
Ito (14), 2014	Japan	2011.01–2013.02	ADH	67	56/11	67	0, 1, 2	Aprepitant + dexamethasone + 1st generation 5-HT3 antagonist	Carboplatin plus paclitaxel or pemetrexed (+/– bevacizumab)	75	4
			DH	67	54/13	66		Dexamethasone + 1st generation 5-HT3 antagonist		75	
Aksu (12), 2013	Turkey	2010.03–2012.11	ADH	31	56/4	58	–	Aprepitant + dexamethasone + ondansetron	Cisplatin plus docetaxel	–	3
			DH	29				Dexamethasone + ondansetron		–	

ECOG, Eastern Cooperative Oncology Group; ADC, adenocarcinoma; ADH, aprepitant, dexamethasone and a 5-HT3 receptor antagonist; DH, dexamethasone and a 5-HT3 receptor antagonist.

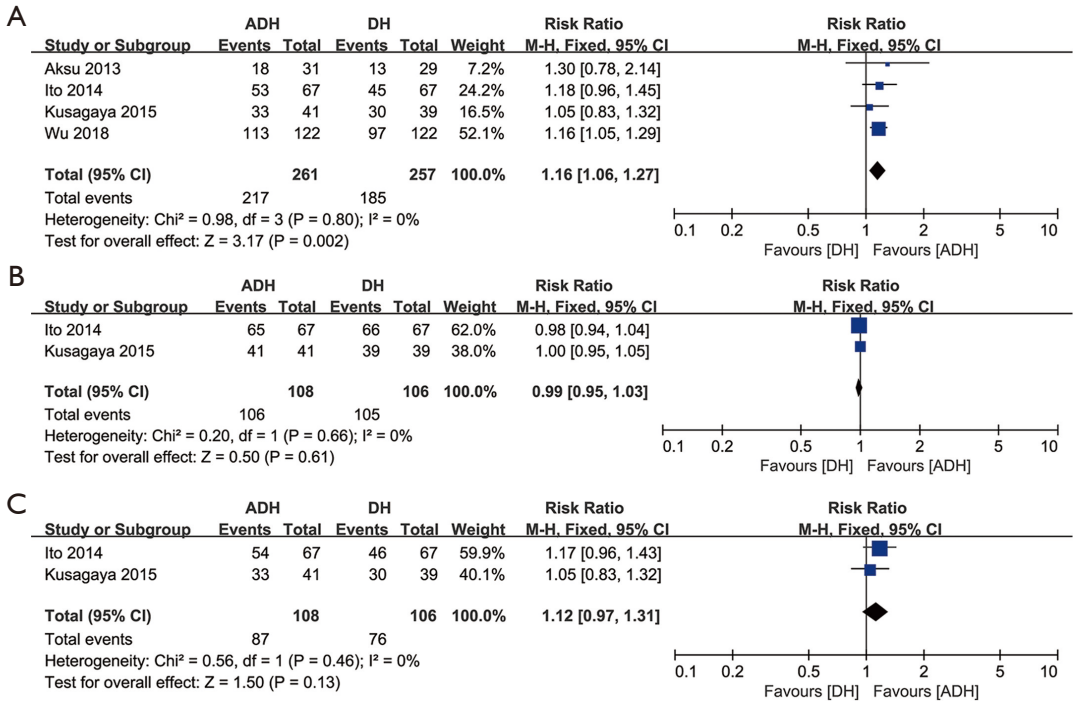

Figure 2 Forest plot of RR of CR associated with ADH versus DH. RR, risk ratio; CR, complete response; ADH, aprepitant, dexamethasone and a 5-HT3 receptor antagonist; DH, dexamethasone and a 5-HT3 receptor antagonist.

neutropenia, anemia, and thrombocytopenia) and nonhematological toxicity (hepatotoxicity, nephrotoxicity, constipation, allergic reaction, hiccups, fatigue, diarrhea, decreased appetite, and abdominal pain; Table S3).

In the subgroup analysis of grade 3–5 AEs, the ADH group did not differ from the DH group in hematological toxicity (leukopenia, neutropenia, anemia, and thrombocytopenia) and nonhematological toxicity (hepatotoxicity, nephrotoxicity, constipation, allergic reaction, hiccups, fatigue, diarrhea, decreased appetite, and abdominal pain; Table S4).

FLIE score

One study adopted the FLIE score to evaluate nausea and vomiting; lower scores indicate better QoL among patients. The median FLIE score (24.97 *vs.* 38.1, P=0.022), total score greater than 50 (3.2% *vs.* 31%, P=0.011) and total score greater than 20 (16.1% *vs.* 44.8%, P=0.015) were compared. Better results were recorded for the ADH group in all three comparisons.

Subgroup analysis

For the primary endpoints, i.e., the CR and NNR, we performed subgroup analyses based on the following classification variables: nation, chemotherapy regimen, 5-HT3 RA, ADC (%) and performance status. A subgroup analysis of the overall CR showed that ADH was superior in some groups stratified by specific clinical features (China, cisplatin-based chemotherapy, 2nd-generation 5-HT3 RA, ADC <50%, and ECOG score of 0–2). In the subgroup analysis of overall NNR, we did not observe significant differences between groups (*Table 2*).

Sensitivity analysis

No obvious heterogeneity was identified in the analysis of the overall CR and overall NNR. We assessed the stability and sensitivity of the combined result based on degree of influence of individual studies that examined each outcome. The analysis showed that the results related to the CR (Figure S3A) and NNR (Figure S3B) were reliable and stable.

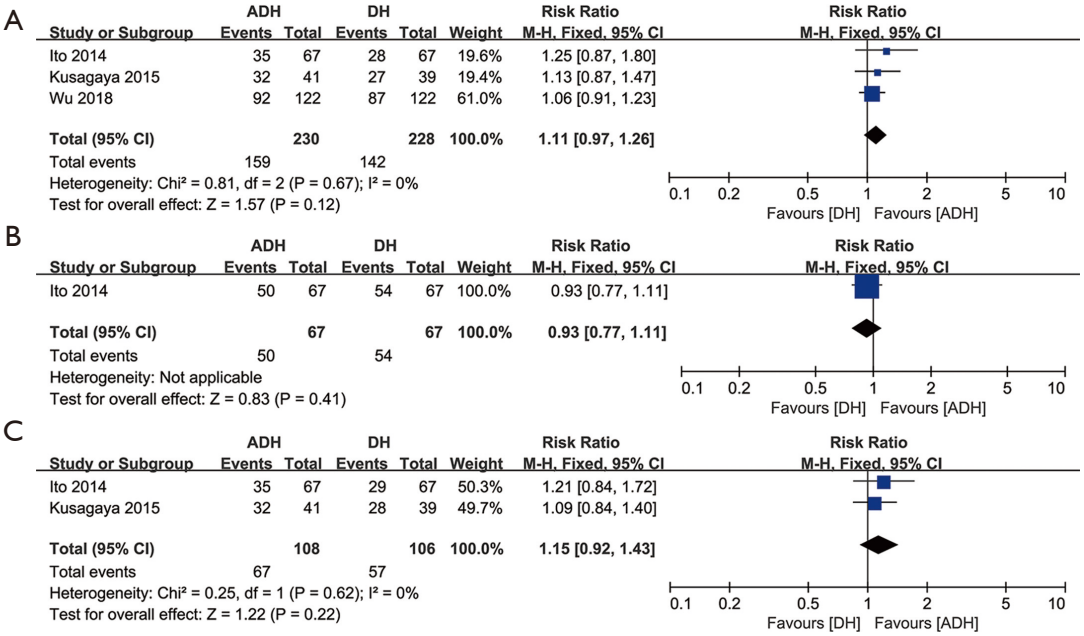

Figure 3 Forest plot of RR of NNR associated with ADH versus DH. RR, risk ratio; NNR, no nausea rate; ADH, aprepitant, dexamethasone and a 5-HT3 receptor antagonist; DH, dexamethasone and a 5-HT3 receptor antagonist.

Publication bias

No evidence of publication bias was observed for the overall CR (Begg's test P=0.734; Egger's test P=0.961, Figure S4A) and overall NNR (Begg's test P=0.296; Egger's test P=0.135, Figure S4B).

Discussion

CINV is the most common complication experienced by patients with LC treated with PBC, and it exerts a significant negative effect on treatment and patients' QoL. Researchers have not yet clearly determined whether adding aprepitant to DH increases the effectiveness of this treatment. This meta-analysis is the first to compare the effectiveness of ADH and DH among patients with LC receiving PBC based on data from RCTs. Based on our results, the ADH group had a better overall CR and a lower number of patients who needed RAT than the DH group. ADH also showed better trends for the overall NNR and delayed CR. No significant differences in the acute CR, acute NNR, and delayed NNR were observed between the two groups. In the subgroup analysis of the overall CR and overall NNR, ADH was superior in some groups stratified based on specific clinical features (China, cisplatin-based chemotherapy, 2nd-generation 5-HT3 RA, ADC <50%, and ECOG score of 0–2). AEs showed no significant difference in the hematological or nonhematological toxicity.

Our meta-analysis showed that ADH is superior to DH in terms of a better overall CR and overall NNR, as observed in two included RCTs (11,12). Dupuis *et al.* (20) and Yokoe *et al.* (21) showed that ADH led to a better CR and NNR. Albany *et al.* (22) suggested that ADH led to a better CR and NNR, but the differences were not significant. Some studies also showed similar results in patients with different cancers who received different chemotherapy regimens and were of different ages (8,23). We propose two likely explanations for the results: (I) 5-HT3 RA combined with 5-HT3 (a major pathogenic factor in acute CINV) is effective for the acute CR and NNR; aprepitant is an NK-1 RA, mainly for substance P (major pathogenic factor in delayed CINV), which predominates in the delayed phase to improve the CR and NNR. The combination of the two drugs exerts a synergistic effect to prevent CINV in the overall phase (14,20). (II) Aprepitant may be involved in the excretion of 5-HT3 together with central and exerts an antagonistic effect on chemotherapy-induced emetogenic effects (24). By analyzing the secondary endpoints, we also found that the number of patients receiving RAT and the FLIE score (lower means less CINV) were significantly lower in the ADH

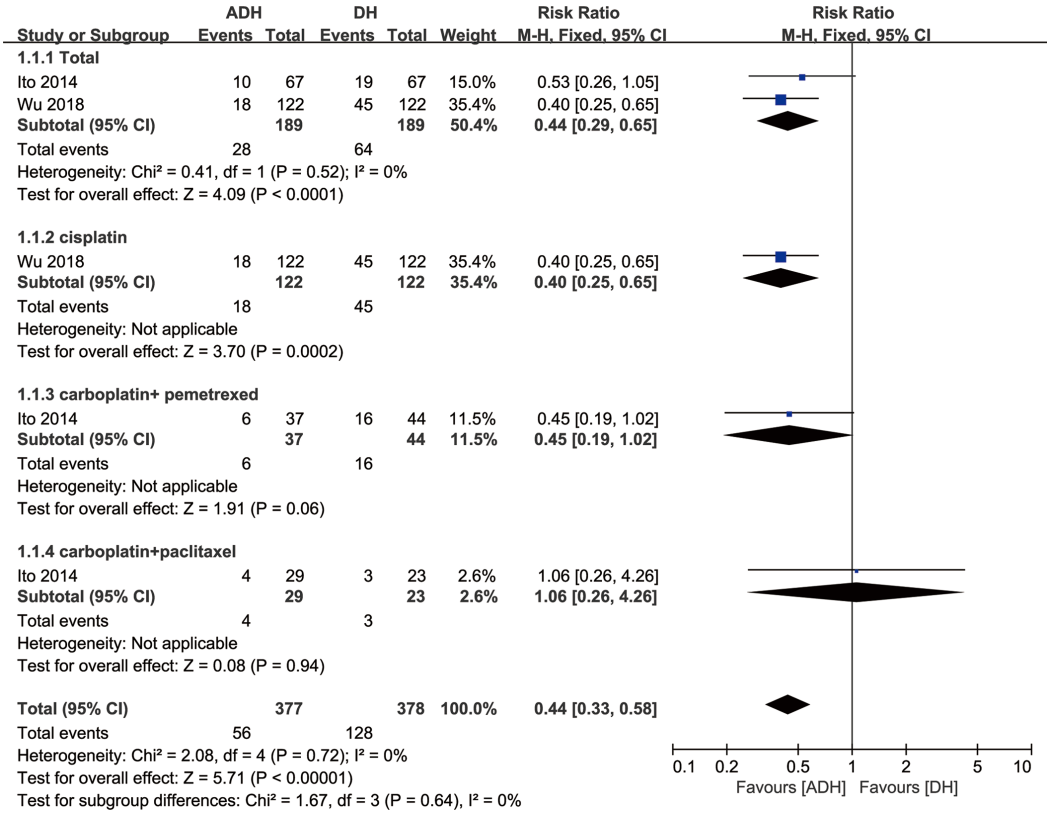

Figure 4 Forest plot of RR of RAT associated with ADH versus DH. RR, risk ratio; RAT, rescue antiemetic treatment; ADH, aprepitant, dexamethasone and a 5-HT3 receptor antagonist; DH, dexamethasone and a 5-HT3 receptor antagonist.

group than in the DH group, which indirectly indicates that ADH is more effective than DH at preventing CINV. In summary, the analysis of the main indicators and secondary indicators jointly proved that ADH is more effective at preventing CINV than DH and that ADH leads to a better overall CR and overall NNR.

In the subgroup analysis of chemotherapy regimens, different platinum drugs produced different results: the cisplatin subgroup showed a significantly higher overall CR, while the overall CR of the carboplatin subgroup was not significantly different. Two included RCTs (13,14) showed a better CR and NNR in the ADH group, but the differences were not significant. Albany *et al.* (22) and Miya *et al.* (8) reported that the ADH group had an effective CR and NNR after treatment with two different chemotherapy regions (cisplatin and carboplatin). We propose several explanations for these findings. Cisplatin-based chemotherapy is regarded as highly emetogenic chemotherapy (HEC), carboplatin-based chemotherapy is regarded as moderately emetogenic chemotherapy (MEC), and the anti-CINV effect of ADH on patients receiving HEC is more obvious (9,10). In summary, our subgroup analysis found that the results may be related to platinum drugs, and ADH has a greater relative advantage in patients receiving HEC. A subgroup analysis of combination therapy showed no significant difference, suggesting that combination therapy had little effect on the CR and NNR. Therefore, ADH was more effective at preventing CINV among patients undergoing HEC (cisplatin, for example). The subgroup of 5-HT3 RA showed that the result was different between 5-HT3 RAs, among which, the second generation 5-HT3 RA was more suitable for ADH than the 1st-generation 5-HT RA. This difference may be due to the factors listed below. (I) With a longer half-life, the 2nd-generation 5-HT3 RA has a longer effective period and it also has a greater receptor binding affinity, resulting higher drug availability (13). (II) The 2nd-generation 5-HT3 RA differentially inhibits NK-1/5-HT3 crosstalk, and thus it exerts a better synergistic effect with aprepitant in the delayed phase (25). In conclusion, we suggested that ADH

Table 2 Subgroup analysis of overall CR and overall NNR

Group	Overall CR				Overall NNR			
	No. of studies	RR (95% CI)	P	I^2 (%)	No. of studies	RR (95% CI)	P	I^2 (%)
Total	4	1.16	0.002	0	3	1.11	0.12	0
Nation								
China	1	1.16	0.004	–	1	1.06	0.47	–
Japan	2	1.12	0.14	0	2	1.19	0.14	0
Turkey	1	1.3	0.31	–	–	–	–	–
Chemotherapy regimen								
Cisplatin	2	1.18	0.003	0	1	1.06	0.47	–
Carboplatin	2	1.12	0.14	0	2	1.19	0.14	0
Carboplatin + pemetrexed ± bevacizumab	2	1.21	0.39	69	–	–	–	–
Carboplatin + paclitaxel ± bevacizumab	2	0.88	0.24	0	–	–	–	–
Carboplatin + S-1	1	1.2	0.36	–	–	–	–	–
5-HT3 RA								
1st-generation	2	1.2	0.07	0	1	1.25	0.23	–
2nd-generation	2	1.14	0.008	0	2	1.07	0.28	0
ADC								
<50%	1	1.16	0.004	–	1	1.06	0.47	–
>50%	2	1.12	0.14	0	2	1.19	0.14	0
Unclear	1	1.3	0.31	–	–	–	–	–
Performance status								
ECOG 0-2	3	1.15	0.002	0	3	1.11	0.12	0
Unclear	1	1.3	0.31	–	–	–	–	–

ADC, adenocarcinoma; CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; NNR, no nausea rate; RR, risk ratio; 5-HT3 RA, 5-hydroxytryptamine-3 receptor antagonist.

was more effective at preventing CINV among patients undergoing treatment with HEC (cisplatin, for example) and 2nd-generation 5-HT3 RA.

In the subgroup analysis of AEs, no significant difference was observed in hematological toxicity and nonhematological toxicity. Among AEs classified as hematological toxicity, the most common complications were leukopenia, neutropenia, anemia and thrombocytopenia. Among AEs classified as nonhematological toxicity, the most common complications were hepatotoxicity, constipation, hiccups, fatigue and decreased appetite. Hashimoto *et al.* (26) and Pasricha *et al.* (27) did not observe significant differences in patients treated with ADH and DH. The most commonly reported AEs of aprepitant were asthenia/fatigue, hiccups, constipation, diarrhea and anorexia (28,29). Our results showed no significant difference among these AEs. Some articles reported that aprepitant may be secondary to anaphylactic shock and cardiac arrest (30). One of our included RCTs also reported one case of anaphylactic shock, but no significant difference was found (14); however, additional high-quality RCTs are necessary to analyze and

confirm this conclusion. In general, the subgroup analysis of AEs showed no significant difference between the ADH and DH groups, confirming that ADH achieved similar safety to that of DH.

The analysis still has some limitations that would affect the results. On the one hand, although the four included articles were all high-quality RCTs, the reliability of the outcomes might be affected by the limited numbers of articles and patients. On the other hand, all articles were published in English, and language bias may exist. Moreover, the applicability of the results may be affected by the fact that the data we collected were obtained from Asian patients residing in three nations (China, Japan, and Turkey). In addition, different doses or types of 5-HT3 RAs and dexamethasone may affect the accuracy of the results. Furthermore, the applicability of the results may be reduced because the obtained patients were mainly middle-aged and elderly people, which may be related to the incidence of LC. Last but not least, the articles did not specify the type of LC, and thus the representativeness of the results may be influenced. These limitations should be used to guide future research.

Conclusions

Compared with DH, ADH appears to be superior for patients with LC who are treated with PBC in terms of a CR for CINV. Subgroup analyses showed advantages in some groups with specific clinical features (China, cisplatin-based chemotherapy, 2nd-generation 5-HT3 RA, ADC <50%, and ECOG score of 0-2). No significant difference was observed in the hematological toxicity and non-hematological toxicity between total AEs and grade 3–5 AEs. However, because of the potential deficiency of our meta-analysis, more large-scale, high-quality RCTs are required to verify this conclusion.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-2290). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

PubMed
The database was searched on July 30, 2020, n=302.
Search Strategy:
(Aprepitant[Title/Abstract] OR Emend[Title/Abstract] OR MK869[Title/Abstract] OR MK0517[Title/Abstract] OR L754030[Title/Abstract]) AND (Dexamethasone[Title/Abstract] OR Methylfluorprednisolone[Title/Abstract] OR Hexadecadrol[Title/Abstract] OR Decameth[Title/Abstract] OR Decaspray[Title/Abstract] OR Dexasone[Title/Abstract] OR Dexpak[Title/Abstract] OR Maxidex[Title/Abstract] OR Millicorten[Title/Abstract] OR Oradexon[Title/Abstract] OR Decaject[Title/Abstract] OR Hexadrol[Title/Abstract]) AND (Chemotherapy[Title/Abstract] OR Chemotherapies[Title/Abstract] OR Drug Therapy[Title/Abstract] OR Drug Therapies[Title/Abstract] OR Pharmacotherapy[Title/Abstract] OR Pharmacotherapies[Title/Abstract])

Web of Science
The database was searched on July 30, 2020, n=637.
Search Strategy:
1 TOPIC: (“Aprepitant” OR “Emend” OR “MK869” OR “MK0517” OR “ L754030”) (25318)
2 TOPIC: (“Dexamethasone” OR “ Methylfluorprednisolone” OR “Hexadecadrol ” OR “Decameth” OR “Decaspray” OR “Dexasone” OR “Dexpak” OR “ Maxidex” OR “Hexadecadrol ” OR “Millicorten” OR “Oradexon” OR “Decaject” OR “Hexadrol”) (117406)
3 TOPIC:(“Chemotherapy” OR “Chemotherapies” OR “Drug Therapy” OR “Drug Therapies” OR “Pharmacotherapy” OR “Pharmacotherapies”) (6107413)
4 #1 AND #2 AND #3 (637)

EMBASE
The database was searched on July 30, 2020, n=639.
Search Strategy:
('Aprepitant':ti,ab,kw OR 'Emend':ti,ab,kw OR 'MK869':ti,ab,kw OR 'MK0517':ti,ab,kw OR 'L754030':ti,ab,kw) AND ('Dexamethasone':ti,ab,kw OR 'Methylfluorprednisolone':ti,ab,kw OR 'Hexadecadrol':ti,ab,kw OR 'Decameth':ti,ab,kw OR 'Decaspray':ti,ab,kw OR 'Dexasone':ti,ab,kw OR 'Dexpak':ti,ab,kw OR 'Maxidex':ti,ab,kw OR 'Millicorten':ti,ab,kw OR 'Oradexon':ti,ab,kw OR 'Decaject':ti,ab,kw OR 'Hexadrol':ti,ab,kw) AND ('Chemotherapy':ti,ab,kw OR 'Chemotherapies':ti,ab,kw OR 'Drug Therapy':ti,ab,kw OR 'Drug Therapies':ti,ab,kw OR 'Pharmacotherapy':ti,ab,kw OR 'Pharmacotherapies':ti,ab,kw)

Cochrane Library
The database was searched on July 30, 2020, n=368.
Search Strategy:
(“Aprepitant” OR “Emend” OR “MK869” OR “MK0517” OR “L754030”): ti,ab,kw AND (“Dexamethasone” OR “Methylfluorprednisolone” OR “Hexadecadrol” OR “Decameth” OR “Decaspray” OR “Dexasone” OR “Dexpak” OR “Maxidex” OR “Millicorten” OR “Oradexon” OR “Decaject” OR “Hexadrol”): ti,ab,kw AND (“Chemotherapy” OR “Chemotherapies” OR “Drug Therapy” OR “Drug Therapies” OR “Pharmacotherapy” OR “Pharmacotherapies”): ti,ab,kw - (Word variations have been searched)

Ovid MEDLINE
The database was searched on July 30, 2020, n=295.
Search Strategy:
1 Aprepitant (1279)
2 MK869 (38)
3 MK0517 (0)
4 Emend (1279)
5 L754030 (10)
6 or/1-5 [Aprepitant] (1303)
7 Dexamethasone (71778)
8 Methylfluorprednisolone (3)
9 Hexadecadrol (38)
10 Decameth (2)
11 Decaspray (2)
12 Dexasone (16)
13 Dexpak (2)
14 Maxidex (28)
15 Millicorten (7)
16 Oradexon (10)
17 Decaject (2)
18 Hexadrol (9)
19 or/7-18 [Dexamethasone] (71793)
20 Chemotherapy (444985)
21 Chemotherapies (5758)
22 Drug Therapy (2302637)
23 Drug Therapies (4479)
24 Pharmacotherapy (30468)
25 Pharmacotherapies (3636)
26 or/20-25 [Chemotherapy] (2535245)
27 6 and 19 and 26 (347)
28 limit 27 to humans (295)

ScienceDirect
The database was searched on July 30, 2020, n=146.
Search Strategy:
Title, abstract, keywords: ((“Aprepitant” OR “Emend” OR “MK869” OR “MK0517” OR “L754030”) and (“Dexamethasone” OR “Methylfluorprednisolone” OR “Hexadecadrol” OR “Decameth” OR “Decaspray” OR “Dexasone” OR “Dexpak” OR “Maxidex” OR “Millicorten” OR “Oradexon” OR “Decaject” OR “Hexadrol”) and (“Chemotherapy” OR “Chemotherapies” OR “Drug Therapy” OR “Drug Therapies” OR “Pharmacotherapy” OR “Pharmacotherapies”))

Scopus
The database was searched on July 30, 2020, n=583.
Search Strategy:
TITLE-ABS-KEY ((“Aprepitant” OR “Emend” OR “MK869” OR “MK0517” OR “L754030”) and (“Dexamethasone” OR “Methylfluorprednisolone” OR “Hexadecadrol” OR “Decameth” OR “Decaspray” OR “Dexasone” OR “Dexpak” OR “Maxidex” OR “Millicorten” OR “Oradexon” OR “Decaject” OR “Hexadrol”) and (“Chemotherapy” OR “Chemotherapies” OR “Drug Therapy” OR “Drug Therapies” OR “Pharmacotherapy” OR “Pharmacotherapies”))

Figure S1 Search strategy. The combined text and medical subject heading (MeSH) terms used were: “Aprepitant”, “Dexamethasone”, “Chemotherapy”.

http://dx.doi.org/10.21037/apm-20-2290

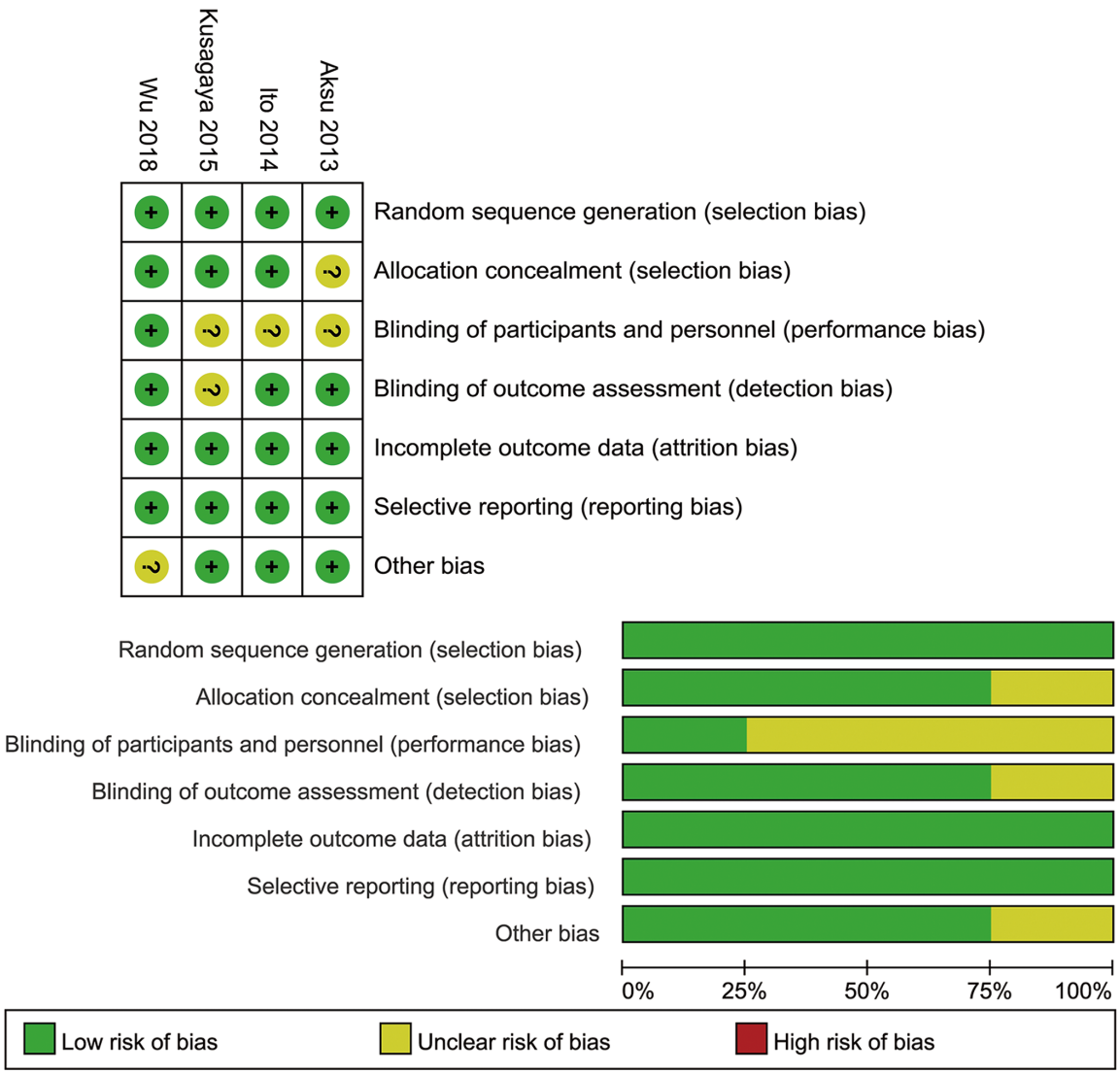
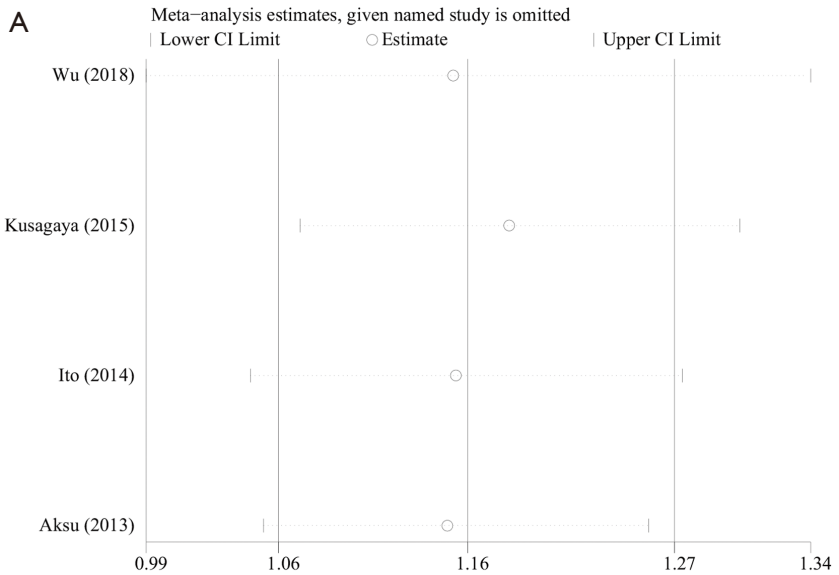
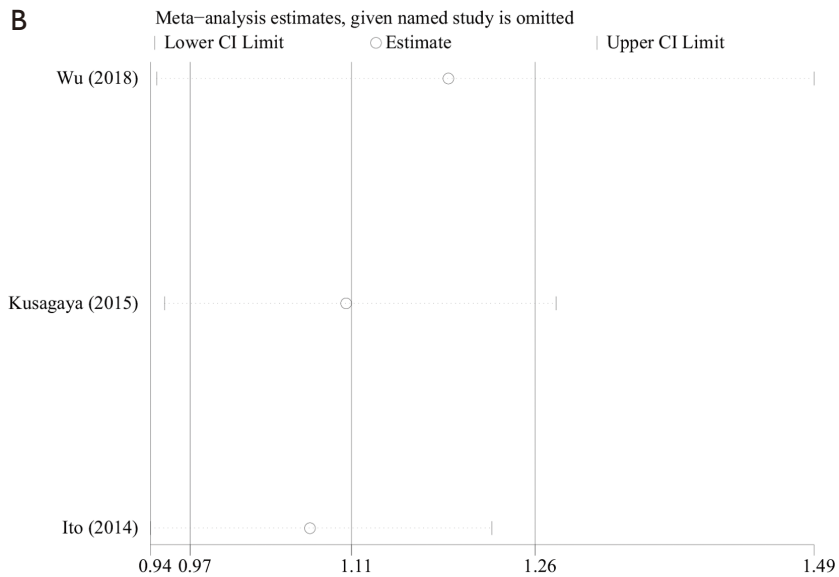


Figure S2 Risk of Bias Assessment of all included studies.

http://dx.doi.org/10.21037/apm-20-2290



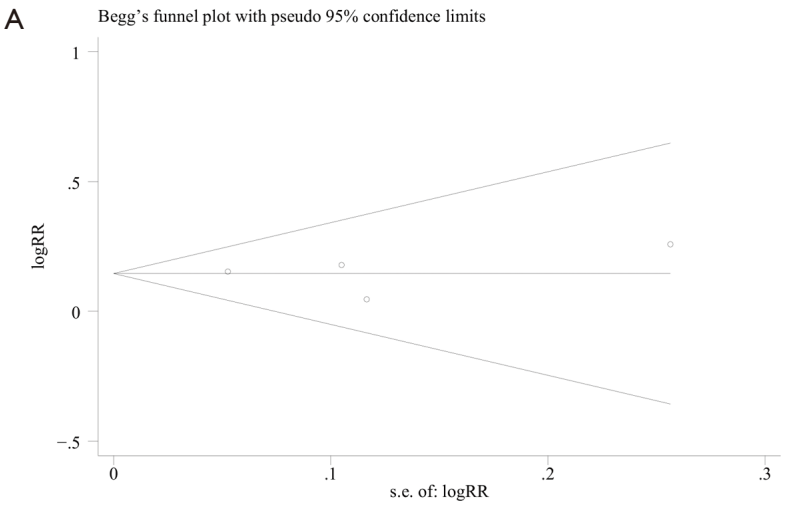
Study omitted	Estimate	[95% Conf.	Interval]
Wu (2018)	1.1501589	.98713946	1.3400998
Kusagaya (2015)	1.1799271	1.0688907	1.302498
Ito (2014)	1.1515169	1.0424714	1.271969
Aksu (2013)	1.1471781	1.0494994	1.2539477
Combined	1.1578641	1.0574725	1.2677865



Study omitted	Estimate	[95% Conf.	Interval]
Wu (2018)	1.1890435	.94742149	1.4922868
Kusagaya (2015)	1.1043478	.95390934	1.2785115
Ito (2014)	1.0743406	.94200504	1.2252669
Combined	1.1088137	.97492803	1.2610858

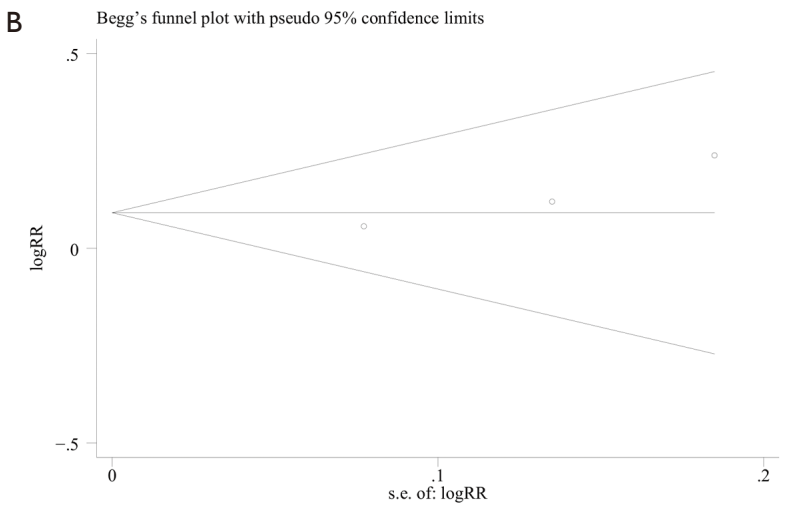
Figure S3 Meta-based influence analysis for comparisons of overall CR (A) and overall NNR (B). CR, complete response; NNR, no nausea rate.

http://dx.doi.org/10.21037/apm-20-2290



Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.1422169	.0660048	2.15	0.164	-.141779	.4262129
bias	.0424427	.767706	0.06	0.961	-3.26073	3.345615



Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	-.0651905	.0358218	-1.82	0.320	-.5203501	.3899691
bias	1.525643	.3279887	4.65	0.135	-2.641849	5.693134

Figure S4 Begg's and Egger's tests for comparisons of overall CR (A) and overall NNR (B). CR, complete response; NNR, no nausea rate.

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Table S1 Quality assessment of the included studies according to the Jadad scale

Study	Randomness	Blackout	Follow-up management	Quality (score)
Wu 2018 (11)	**	**	*	5
Kusagaya 2015 (13)	**	*	*	4
Ito 2014 (14)	**	*	*	4
Aksu 2013 (12)	*	*	*	3

Table S2 GRADE Quality assessment by therapeutic strategy and study design for the outcomes

Primary outcomes	No. of Studies	No. of participants		Differences[a] (95% CI)	Quality assessment					Quality
		ADH	DH		Risk of bias[b]	Nonuniformity	Circuitous	Inaccuracy	Publication bias[c]	
CR										
Overall	4	217/261	185/257	1.16 [1.06, 1.27]	Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
Acute	2	106/108	105/106	0.99 [0.95, 1.03]	Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
Delayed	2	87/108	76/106	1.12 [0.97, 1.31]	Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
NNR					Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
Overall	3	159/230	142/228	1.11 [0.97, 1.26]	Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
Acute	1	50/67	54/67	0.93 [0.77, 1.11]	Serious (-1)	No nonuniformity	No circuitous	No inaccuracy	Unlikely	Medium
Delayed	2	67/108	57/106	1.15 [0.92, 1.43]	Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
RAT	2	28/189	64/189	0.44 [0.29, 0.65]	Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
Total AEs										
Hematologic toxicity										
Leukopenia	2	50/108	55/106	0.92 [0.60, 1.40]	Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
Neutropenia	2	52/108	54/106	0.98 [0.56, 1.70]	Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
Anemia	2	42/108	35/106	1.18 [0.82, 1.69]	Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
Thrmbocytopenia	2	39/108	38/106	1.00 [0.71, 1.42]	Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
Non-hematologic toxicity										
Hepatotoxicity	2	21/108	23/106	0.90 [0.53, 1.52]	Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
Nephrotoxicity	2	3/108	4/106	0.74 [0.17, 3.23]	Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
Constipation	2	32/108	30/106	1.04 [0.69, 1.59]	Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
Allergic reaction	2	2/108	2/106	1.00 [0.15, 6.89]	Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
Hiccups	2	16/108	12/106	1.20 [0.39, 3.67]	Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
Fatigue	3	45/230	48/228	1.11 [0.50, 2.47]	Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
Diarrhea	3	3/230	5/228	0.63 [0.17, 2.35]	Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
Grade3-5 AEs										
Hematologic toxicity										
Leukopenia	2	12/108	18/106	0.66 [0.34, 1.29]	Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
Neutropenia	2	16/108	20/106	0.79 [0.43, 1.43]	Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
Anemia	2	4/108	2/106	1.77 [0.38, 8.18]	Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
Thrombocytopenia	2	9/108	12/106	0.73 [0.32, 1.68]	Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
Non-hematologic toxicity										
Hepatotoxicity	2	0/108	2/106	0.33 [0.03, 3.08]	Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
Nephrotoxicity	2	0/108	0/106	–	Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
Constipation	2	2/108	0/106	4.76 [0.24, 96.16]	Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
Allergic reaction	2	1/108	0/106	3.00 [0.12, 72.35]	Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
Hiccups	2	0/108	0/106	–	Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
Fatigue	3	1/230	3/228	0.33 [0.04, 3.12]	Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
Diarrhea	3	0/230	0/228	–	Low	No nonuniformity	No circuitous	No inaccuracy	Unlikely	High
FLIE score										
>50	1	1/31	9/29	0.10 [0.01, 0.77]	Serious (-1)	No nonuniformity	No circuitous	No inaccuracy	Unlikely	Medium
>20	1	5/31	13/29	0.36 [0.15, 0.88]	Serious (-1)	No nonuniformity	No circuitous	No inaccuracy	Unlikely	Medium

[a], Differences: risk ratios (RR) for CR, NNR, RAT, Total AEs, Grade3-5 AEs and FLIE score. [b], Risk of bias assessed using the Jadad Scale for randomized controlled trials. [c], Publication bias was assessed by Egger's and Begg's tests. ADH, aprepitant, dexamethasone and a 5-HT3 receptor antagonist; AEs, Adverse events; CI, confidence interval; CR, complete response; DH, dexamethasone and a 5-HT3 receptor antagonist; FLIE, Functional Living Index Emesis; NNR, no nausea rate; RAT, Rescue antiemetic treatment.

http://dx.doi.org/10.21037/apm-20-2290

Table S3 Total grade adverse effects associated with ADH versus DH

Adverse effects	Studies involved	ADH group		DH group		Total incidence	Risk ratio	95% CI	I^2	P
		Event/total	%	Event/total	%					
Hematologic toxicity										
Leukopenia	2	50/108	46.30%	55/106	51.89%	49.07%	0.92	0.60–1.40	58%	0.68
Neutropenia	2	52/108	48.15%	54/106	50.94%	49.53%	0.98	0.56–1.70	75%	0.94
Anemia	2	42/108	38.89%	35/106	33.02%	35.98%	1.18	0.82–1.69	0%	0.38
Thrmbocytopenia	2	39/108	36.11%	38/106	35.85%	35.98%	1.00	0.71–1.42	0%	1.00
Non-hematologic toxicity										
Hepatotoxicity	2	21/108	19.44%	23/106	21.70%	20.56%	0.90	0.53–1.52	0%	0.70
Nephrotoxicity	2	3/108	2.78%	4/106	3.77%	3.27%	0.74	0.17–3.23	0%	0.69
Constipation	2	32/108	29.63%	30/106	28.30%	28.97%	1.04	0.69–1.59	0%	0.84
Allergic reaction	2	2/108	1.85%	2/106	1.89%	1.87%	1.00	0.15–6.89	–	1.00
Hiccups	2	16/108	14.81%	12/106	11.32%	13.08%	1.20	0.39–3.67	56%	0.75
Fatigue	3	45/230	19.57%	48/228	21.05%	20.31%	1.11	0.50–2.47	66%	0.79
Diarrhea	3	3/230	1.30%	5/228	2.19%	1.75%	0.63	0.17–2.35	15%	0.49
Decreased appetite	1	25/122	20.49%	22/122	18.03%	19.26%	1.14	0.68–1.90	–	0.63
Pain-abdominal	1	0/122	0.00%	0/122	0.00%	0.00%	–	–	–	–

ADH, aprepitant, dexamethasone and a 5-HT3 receptor antagonists; CI, confidence interval; DH, dexamethasone and a 5-HT3 receptor antagonists.

Table S4 Grade 3–5 adverse effects associated with ADH versus DH

Adverse effects	Studies involved	ADH group		DH group		Total incidence	Risk ratio	95% CI	I^2	P
		Event/total	%	Event/total	%					
Hematologic toxicity										
Leukopenia	2	12/108	11.11%	18/106	16.98%	14.02%	0.66	0.34–1.29	0%	0.23
Neutropenia	2	16/108	14.81%	20/106	18.87%	16.82%	0.79	0.43–1.43	0%	0.43
Anemia	2	4/108	3.70%	2/106	1.89%	2.80%	1.77	0.38–8.18	0%	0.47
Thrmbocytopenia	2	9/108	8.33%	12/106	11.32%	9.81%	0.73	0.32–1.68	50%	0.47
Non-hematologic toxicity										
Hepatotoxicity	2	0/108	0.00%	2/106	1.89%	0.93%	0.33	0.03–3.08	0%	0.33
Nephrotoxicity	2	0/108	0.00%	0/106	0.00%	0.00%	–	–	–	–
Constipation	2	2/108	1.85%	0/106	0.00%	0.93%	4.76	0.24–96.16	–	0.31
Allergic reaction	2	1/108	0.93%	0/106	0.00%	0.47%	3.00	0.12–72.35	–	0.50
Hiccups	2	0/108	0.00%	0/106	0.00%	0.00%	–	–	–	–
Fatigue	3	1/230	0.43%	3/228	1.32%	0.87%	0.33	0.04–3.12	–	0.34
Diarrhea	3	0/230	0.00%	0/228	0.00%	0.00%	–	–	–	–
Decreased appetite	1	0/122	0.00%	0/122	0.00%	0.00%	–	–	–	–
Pain-abdominal	1	0/122	0.00%	0/122	0.00%	0.00%	–	–	–	–

ADH, aprepitant, dexamethasone and a 5-HT3 receptor antagonists; CI, confidence interval; DH, dexamethasone and a 5-HT3 receptor antagonists.

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