Systematic Review and Meta-Analysis

Comparison of aprepitant versus ondansetron for prevention of postoperative nausea and vomiting: A systematic review and meta-analysis with trial sequential analysis

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Submitted: 30-Jan-2024
Revised: 18-Jun-2024
Accepted: 19-Jun-2024
Published: 16-Aug-2024

Access this article online

Website: https://journals.lww.com/ijaweb

DOI: 10.4103/ija.ija_106_24

Quick response code

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ABSTRACT

Background and Aims: Postoperative nausea and vomiting (PONV) is a common complication after surgery. Preventing PONV in high-risk patients often requires a multimodal approach combining antiemetic drugs with diverse mechanisms. While aprepitant, a neurokinin-1 receptor antagonist, is recognised as highly effective for PONV prevention, uncertainties remain regarding its effectiveness. **Methods:** This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The analysis assessed the effectiveness of aprepitant (A), aprepitant plus ondansetron (AO) and aprepitant plus dexamethasone and ondansetron (ADO) in preventing PONV compared to ondansetron alone (O) or in combination with dexamethasone (DO). **Results:** In the analysis of 12 studies involving 2729 patients, aprepitant demonstrated significant efficacy in preventing PONV compared to ondansetron alone (A versus [vs.] O: PONV incidence 12.5% vs. 28.5%, relative risk [RR] = 0.45, $P < 0.001$; complete response rate 55.97% vs. 50.35%, RR = 1.13, $P = 0.010$). The combination of aprepitant with ondansetron (AO) also showed a significantly lower incidence of PONV compared to ondansetron alone (11.3% vs. 26.8%, RR = 0.43, $P < 0.001$) and a higher complete response rate (38.1% vs. 26.84%, RR = 1.41, $P = 0.020$). In addition, ADO significantly reduced PONV incidence compared to DO (ADO vs. DO: 13.63% vs. 35.38%, RR = 0.38, $P = 0.006$). **Conclusion:** Aprepitant, whether used alone or in combination with ondansetron or both ondansetron and dexamethasone, consistently outperforms ondansetron in achieving a complete response as it lowers vomiting rates and reduces the need for rescue therapy during the crucial 24–48-h postoperative period.

Keywords: Antiemetics, aprepitant, dexamethasone, neurokinin-1 receptor antagonist, ondansetron, postoperative nausea and vomiting, substance P

INTRODUCTION

Postoperative nausea and vomiting (PONV) is a prevalent complication occurring within 24 h postsurgery, particularly in the post-anaesthesia care unit, with a global prevalence of nearly 30%.[1,2] This phenomenon significantly contributes to postoperative morbidity, diminishing patient satisfaction and often leading to unforeseen hospital admissions following daycare surgeries. Recognised as a primary factor in

How to cite this article: Singh MP, Gurunthalingam MP, Gupta A, Singh J. Comparison of aprepitant versus ondansetron for prevention of postoperative nausea and vomiting: A systematic review and meta-analysis with trial sequential analysis. Indian J Anaesth 2024;68:762-75.

escalating hospitalisation costs, effective management of PONV is crucial.[3]

Various antiemetic drugs, categorised into classes like 5-hydroxytryptamine3 receptor antagonists, dopamine-2 receptor antagonists, neurokinin-1 (NK-1) receptor antagonists, corticosteroids, antihistamines and anticholinergics, exhibit varying efficacy.[4,5] Recent advancements in antiemetic drugs and preventive programmes aim to enhance safety, prolong drug effectiveness and improve overall efficacy.[6-8] A consensus on preventing PONV in high-risk patients advocates for a multimodal prevention approach, combining antiemetic drugs with different mechanisms.[9] Another meta-analysis was deemed necessary to investigate aprepitant's effectiveness in combination therapies further and to evaluate its comparative effectiveness against other antiemetic regimens, building upon the findings of Weibel *et al*.'s[5] meta-analysis, which identified aprepitant as highly effective and of high quality for preventing PONV. This approach aimed to enhance our understanding of the aprepitant's role in PONV prevention. Despite increasing studies on aprepitant's use in recent years, uncertainties persist regarding its effectiveness in preventing PONV.[10-13] The objectives of this meta-analysis were to evaluate the effectiveness of aprepitant (A), aprepitant plus ondansetron (AO) and aprepitant plus dexamethasone and ondansetron (ADO) in preventing PONV compared to ondansetron alone (O) or in combination with dexamethasone (DO). The analysis focuses on high-risk surgical patients and assesses outcomes such as the incidence of PONV, complete response rate and use of rescue antiemetics.

METHODS

The systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14] The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (ID: CRD42024501444).

Search strategy

A comprehensive systematic search was done on 11 January 2024 across databases, namely PubMed, Google Scholar, Clinical Trials Registry (https://clinicaltrials.gov/) and the Cochrane Library, encompassing clinical trials published in the English language from inception until 31 December 2023. The search was performed using the keywords: 'aprepitant' and 'ondansetron', and 'postoperative nausea and vomiting' (PONV) [MeSH Terms]) OR (Postoperative nausea and vomiting [MeSH Terms]) AND (aprepitant [MeSH Terms]) AND (ondansetron [MeSH Terms])). The complete search strings, including the MeSH terms used for searching, can be found in the supplementary file [Table S1]. Additional studies were identified through the reference lists of relevant articles. After eliminating duplicates and unrelated studies, two investigators (MPS and MPG) independently scrutinised the abstracts of each article to assess their suitability based on the inclusion criteria. Data extraction focused on qualitative aspects, including study characteristics, participant demographics, intervention details and outcomes of interest. Discrepancies were resolved through discussion or consultation with a third reviewer (AG). The study protocol and statistical analysis plan were also reviewed to identify critical information gaps. The PRISMA flowchart illustrates the selection process of studies [Figure 1].

Study selection

Randomised clinical trials involving postoperative patients aged >18 years, undergoing different surgeries under anaesthesia and comparing antiemetics aprepitant (A) given at any dose with ondansetron (O) in various phases of clinical trials were included. Studies with various designs and timings were included to evaluate comprehensively the aprepitant's role in PONV prevention.

Data extraction

Two review authors (MPS, MPG) performed data extraction using Microsoft Excel 2016. The extracted data included demographic information, inclusion and exclusion criteria, treatment schedules, study design and all outcomes. Any missing information was sourced from the protocol, statistical analysis plan and other published analyses. Subsequently, all relevant data were analysed using version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB-2) [Review Manager (RevMan) version 5.4 for Windows by the Cochrane Collaboration (London, UK)]. The risk of bias (RoB) for individual studies was assessed using RoB-2 assessment tools. The RoB tool was used to evaluate various biases.[15] Publication bias was assessed using a funnel plot for each outcome.

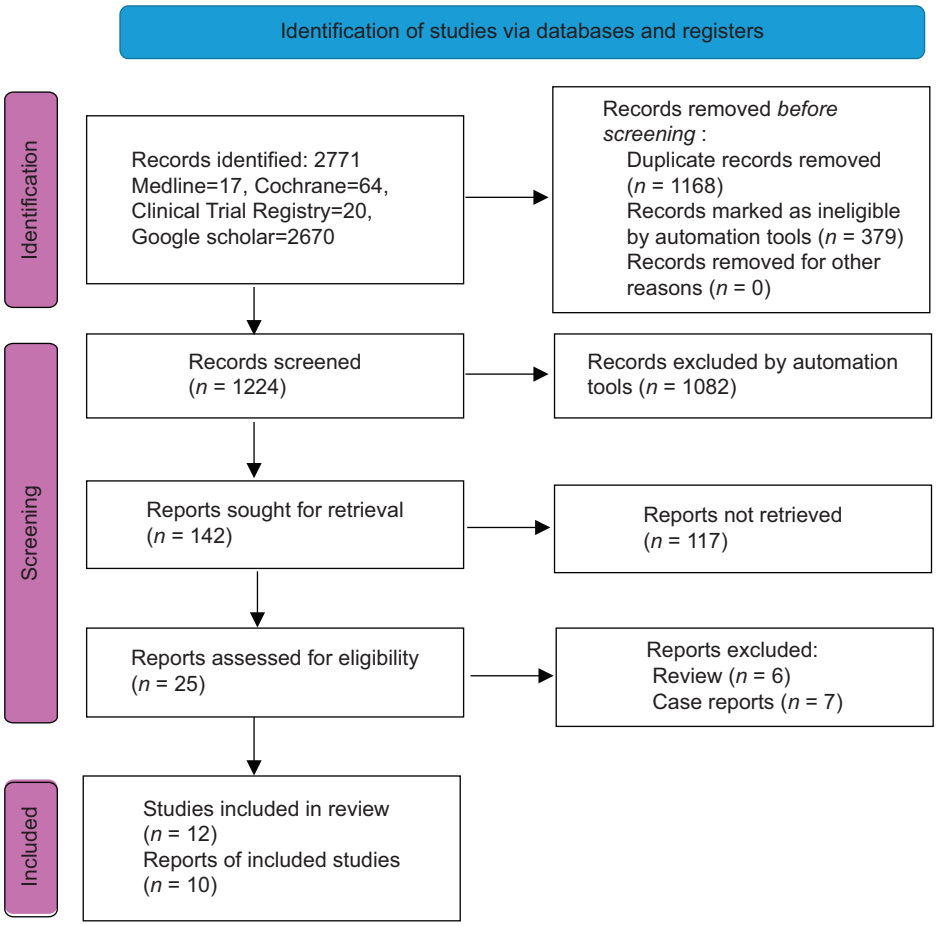

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection process

Outcomes

The efficacy and safety endpoints includes:

- Incidence of PONV: The incidences of nausea and vomiting in the included studies were calculated based on patient reports or direct observation following surgery, using standardised scales like the 11-point numerical rating scale/verbal rating scale (NRS/VRS) or Rhodes Index to quantify symptom severity.
- Number of patients with complete response (no vomiting and no need to use rescue antiemetics): Total number of participants who did not experience vomiting and did not require any additional antiemetic medications postoperatively.
- Number of patients not needing rescue antiemetics: Total number of participants who did not require additional antiemetic medications following surgery.

Statistical analysis

The meta-analysis employed relative risks (RRs) with 95% confidence intervals (CIs) for dichotomous data, adhering to established methodologies. Subsequently, I^2 statistics were utilised to assess the true heterogeneity among the included studies, with a significance level set at $P < 0.10$.[16] The random-effects model was selected for meta-analysis, acknowledging potential variability across studies. This approach accommodates within-study and between-study variability, enhancing the robustness of synthesised evidence. Publication bias was assessed using funnel plots to ensure the integrity of synthesised evidence. The quality of evidence for outcomes was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria.[17] This system classifies the quality of evidence into four categories: very low, low, moderate and high.

A trial sequential analysis (TSA) was performed for all the outcomes using TSA software version 0.9 beta (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark).[18] This was done to mitigate the risk of low sample sizes and the repeated inclusion of studies in the meta-analyses, which could otherwise increase the likelihood of

random errors. The required information size was adjusted for the current meta-analysis, and trial sequential monitoring boundaries were calculated to assess the reliability of the evidence in our meta-analysis. The effect measure was set to 'RR' and the model to 'fixed effect' as per the TSA software. A two-sided TSA was conducted to maintain a 5% risk for type I error and 80% power.

RESULTS

Baseline characteristics

The study includes 2729 patients from 12 randomised clinical trials [Figure 1]. Two trials contributed 64.82% of participants.[17,18] The mean age of patients was 43.5 years, and 76.8% were female. The significant reasons for excluding studies were narrative and systematic reviews. The baseline information of the included studies is listed in Table 1.

In this meta-analysis, the efficacy of aprepitant was evaluated across various treatment modalities, encompassing both monotherapy and combination therapies. Specifically, the analysis investigated aprepitant's effectiveness in isolation and combination with other drugs, including ondansetron and dexamethasone. This comprehensive approach allowed for a nuanced assessment of the comparative effectiveness of different drug combinations in managing the targeted condition. Aprepitant is given as a capsule before surgery to prevent PONV, whereas ondansetron is given via intravenous (IV) route perioperatively or postoperatively for management of PONV. Review authors included aprepitant in a 40, 80 and 125 mg dose compared to ondansetron 4 mg and dexamethasone 4–8 mg. The RoB-2 analysis is presented in Table 2. Two trials had some concerns, mainly about the risk related to the randomisation process.

Outcomes

Aprepitant (A) versus ondansetron (O)

The incidence of PONV was lower in the A group compared to the O group (12.5% vs. 28.5%; RR: 0.45, 95% CI: 0.29, 0.72; $P < 0.001$) [Figure 2a]. In TSA, the cumulative Z-curve crosses the upper monitoring boundary early, indicating a significant reduction in the incidence of PONV for 'A' compared to 'O', suggesting that sufficient evidence exists to conclude that 'A' significantly reduces the incidence of PONV and no further trials might be necessary as the evidence is conclusive. A symmetrical funnel chart showed no publication bias, but significant heterogeneity was observed with $I^2 = 75\%$ ($P = 0.003$) [Figure S1]. Complete

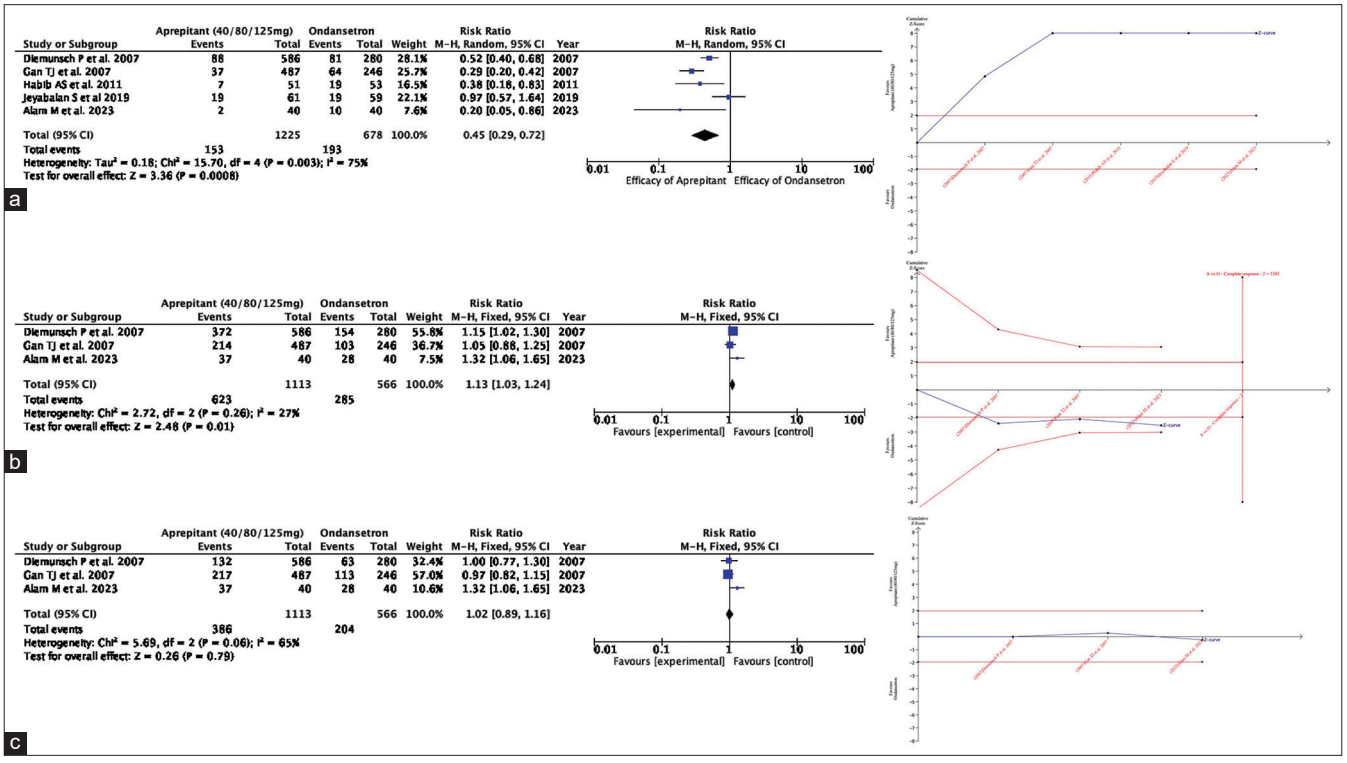

Figure 2: Forest plot and trial sequential analysis graph for comparison between aprepitant (A) versus ondansetron (O). (a) Comparison between Aprepitant (A) versus Ondansetron (O) for incidence of PONV, (b) Comparison between Aprepitant (A) versus Ondansetron (O) for Complete Response, (c) Comparison between Aprepitant (A) versus Ondansetron (O) for no use of Rescue Antiemetics. CI = confidence interval, M-H = Mantel–Haenszel

Table 1: Summary of included studies

Study	Study type	Country	No. of participants	Average age (in years)	Sex (male: female)	Surgery type
Alam *et al*. 2023[21]	Randomised, double blind	Iran	80	A: 33 (11.7) O: 34 (10.7)	50:50	Lefort I maxillary advancement osteotomy and bilateral sagittal split osteotomy mandibular setback surgery with the Dalpont method
Spaniolas *et al*. 2020[13]	Randomised, open label	USA	83	Intervention: 41.3 (9.7) Control: 43 (13)	34: 66	SG
de Morais *et al*. 2018[11]	Randomised, double blind, placebo controlled	Brazil	66	Treatment group: 60.5 (31–87) Control group: 50.5 (19-77)	All females	Laparoscopic procedures to treat abdominal or pelvic cancer
Bergese *et al*. 2016[22]	Randomised, double blind	USA	95	A: 52.1 (14.5) O: 51.4 (16.8)	46.5:53.5	Craniotomy under general anaesthesia
Thanuja *et al*. 2016[23]	Randomised controlled trial	India	96	Group A: 27 (25–31) Group DO: 28 (26–32.5) Group ADO: 27 (25–30)	All females	Daycare gynaecological laparoscopy
Sinha *et al*. 2014[24]	Randomised, double blind	USA	124	Group A: 43.09 (12.45) Group P: 43.20 (12.70)	35:65	Laparoscopic bariatric surgery
Vallejo *et al*. 2012[25]	Randomised, double blind	USA	150	A + O: 43.7 (14.3) O: 45.3 (16.3)	30:70	Ambulatory plastic surgery patients
Habib *et al*. 2011[26]	Randomised, double blind	USA	104	A: 51 (13) O: 48 (13)	44:56	Elective craniotomy under general anaesthesia
Ham *et al*. 2011[7]	Randomised, double blind	Korea	118	A + O: 40 (22–55) O: 42 (23–61)	All females	Laparoscopic gynaecological surgery
Diemunsch *et al*. 2007[19]	Randomised, double blind	Multicentric	922	A 40 mg: 46 (11) A 125 mg: 46 (11) O 4 mg: 45 (11)	9:91	Open abdominal surgery
Gan *et al*. 2007[20]	Randomised, double blind	Multicentric	766	A 40 mg: 46 (11.2) A 125 mg: 44 (9.4) O 4 mg: 45 (11.2)	6:94	Open abdominal surgery
Jeyabalan *et al*. 2019[27]	Randomised, double blind	India	125	O: 42.5 (11.5) A: 45.4 (11.1)	All female	Thyroid or breast surgery

Study	No. of arms	Arms	Outcome	Result
Alam *et al*. 2023[21]	2	1. Aprepitant capsule 80 mg + IV distilled water 2. Placebo capsule + ondansetron 4 mg IV	• Incidence and severity of PONV • Duration of surgery • Total amount of administered narcotics • Incidence of vomiting • Use of rescue drugs • Complete response to study drugs • Side effects (drowsiness, abdominal pain)	• No significant differences in surgery duration or opioid use during surgery • The aprepitant group had significantly lower incidence and severity of nausea within 0–2 h and 12–24 h after surgery • Lower incidence of vomiting in the aprepitant group • A higher number of patients in the ondansetron group requested rescue drugs • The aprepitant group showed a significantly higher rate of complete response to study drugs • Most frequently reported side effect was drowsiness; one patient in the aprepitant group experienced abdominal pain
Spaniolas *et al*. 2020[13]	2	1. Aprepitant 80 mg orally + scopolamine (transdermal patch) + IV dexamethasone 8 mg + IV ondansetron 4 mg (intervention)	• PONV-related delay in hospital discharge • Severity of PONV • Self-rated quality of recovery at 24 h	• PONV-related delay in discharge: control group: 9.5%, intervention group: 0 (P=0.119)

Contd...

Table 1: Contd...

Study	No. of arms	Arms	Outcome	Result
		2. IV dexamethasone 8 mg + IV ondansetron 4 mg (control)	• PONV-related readmissions, ED visits and discharge delays within the overall enhanced recovery cohort	• PONV scores in intervention group: significantly lower at all in-hospital time points (P=0.0392 for verbal scores and P<0.0001 for Rhodes Index) • Self-rated quality of recovery at 24 h: significantly higher in the intervention group (Quality of Recovery-15 instrument, P<0.05)
de Morais *et al*. 2018[11]	2	1. Treatment group: aprepitant 80 mg + IV dexamethasone 4–8 mg + IV ondansetron 4–8 mg 2. Control group: oral starch (placebo + IV dexamethasone 4–8 mg + IV ondansetron 4–8 mg)	• Incidence of PONV • Severe nausea and vomiting in the first 24 h • Rescue antiemetic requirements	• Incidence of vomiting in the first 24 h: control group: 40.6%, treatment group: 2.9% (P=0.0002, 95% CI: 18%–54%) • Severe nausea and vomiting in the control group (severe nausea: 6.3%, severe vomiting: 12.5%) • Severe vomiting in the treatment group: one patient in the first 24 postoperative hours
Bergese *et al*. 2016[22]	2	1. Aprepitant 40 mg + IV placebo saline + IV promethazine 25 mg + IV dexamethasone 10 mg 2. IV ondansetron 4 mg + placebo capsule + IV promethazine 25 mg + IV dexamethasone 10 mg	• Nausea and/or vomiting during the first 24 h after a surgical procedure	• No statistically significant differences in the number of vomiting episodes, incidence or severity of nausea, need for rescue antiemetics or complete response at various time intervals • Median time to first emetic and significant nausea episodes and first rescue medication did not show statistically significant differences between aprepitant and ondansetron groups
Thanuja *et al*. 2016[23]	3	1. Group A: aprepitant 80 mg 2. Group DO: placebo capsule + IV ondansetron 4 mg + IV dexamethasone 8 mg 3. Group ADO: aprepitant 80 mg + IV ondansetron 4 mg + IV dexamethasone 8 mg	• Incidence of nausea and/or vomiting in the first 4 h following surgery • Severity of symptoms and side effect profiles of drugs	• PONV incidence: no statistically significant difference in PONV incidence between Group ADO and groups A and DO • Severity of PONV and need for rescue treatment was comparable among groups • Postoperative adverse effects (pain, agitation, lethargy) within the first 4 h were comparable • Time to discharge not significantly different between groups (Group A=7.2±1, Group DO=7.3±7.4, Group ADO=7.5±0.8 h; P=0.43)
Sinha *et al*. 2014[24]	2	1. Aprepitant 80 mg + IV ondansetron 4 mg (Group A) 2. Similar-appearing placebo tablet 1 h before surgery + IV ondansetron 4 mg (Group P)	• Cumulative incidence of vomiting at 72 h • Time to first vomiting • Odds ratio for vomiting in Group P compared to Group A • Complete absence of nausea or vomiting • Nausea scores at measured time points	• Cumulative incidence of vomiting at 72 h: Group A: 3%, Group P: 15% (P=0.021) • Odds ratio for vomiting: Group P compared to Group A: 5.47 times • Time to first vomiting: significantly delayed in Group A (P=0.019) • Complete absence of nausea or vomiting: Group A: 42.18%, Group P: 36.67% • Nausea scores: no significant difference between groups at measured time points
Vallejo *et al*. 2012[25]	2	1. IV ondansetron 4 mg + oral aprepitant 40 mg 2. IV ondansetron 4 mg alone	1. Occurrence of vomiting for up to 48 h postoperatively 2. Severity of nausea for up to 48 h postoperatively	• Vomiting incidence: aprepitant group: 9.3%, placebo group: 29.7% • Increased incidence of emesis in patients receiving ondansetron alone compared to ondansetron and aprepitant (P=0.006) • Severity of nausea: higher in those receiving ondansetron alone compared to ondansetron and aprepitant

Contd...

Table 1: Contd...

Study	No. of arms	Arms	Outcome	Result
Habib *et al*. 2011[26]	2	1. Aprepitant 40 mg orally + 2 ml saline placebo IV 2. Oral placebo + ondansetron 4 mg IV (2 ml)	• Cumulative incidence of vomiting at 48 h • Incidence of vomiting at 2 and 24 h • Incidence and severity of nausea • Need for rescue antiemetics • Complete response for 0–2 h, 0–24 h and 0–48 h	• Aprepitant group showed a significantly lower hazard ratio for vomiting within 48 h compared to ondansetron (*P*=0.0086) • Aprepitant group demonstrated lower incidence and number of vomiting episodes at various time intervals • No significant differences in nausea, rescue antiemetics, sedation scores or patient satisfaction
Ham *et al*. 2011[7]	2	1. Oral aprepitant 80 mg + IV ondansetron 4 mg 2. Intravenous ondansetron 4 mg alone	• Complete response up to 48 h after surgery (defined as no PONV and no rescue antiemetics) • Incidence of retching/ vomiting and nausea • Severity of nausea (measured by an 11-point verbal numeric rating scale (VNRS) • Use of rescue antiemetics and analgesic drugs • Incidence of adverse events • VNRS scores for pain • Time to first PONV during the first 48 h after surgery	• No statistical difference in overall complete response during the first 48 h after surgery (33% vs. 16%, *P*=0.05) • Proportion of complete responses in the aprepitant and ondansetron groups was higher in PACU and up to 24 h after surgery • No differences in incidence of retching/ vomiting, severity of nausea, use of rescue antiemetics, adverse events or VNRS scores for pain between the two groups
Diemunsch *et al*. 2007[19]	3	1. Aprepitant 40 mg 2. Aprepitant 125 mg 3. Ondansetron 4 mg	• Complete response (no vomiting and no use of rescue therapy) over 0–24 h after surgery • No vomiting over 0–24 h after surgery • No vomiting over 0–48 h after surgery • No use of rescue therapy in the first 24 h after surgery • Peak nausea score on the VRS at various time points • Time to first vomiting in the first 48 h	• Non-inferiority of both aprepitant doses to ondansetron for complete response was demonstrated: 64% (aprepitant 40 mg), 63% (aprepitant 125 mg) and 55% (ondansetron) • Both aprepitant doses were superior to ondansetron for no vomiting over 0–24 h and 0–48 h • Aprepitant delayed the time to first vomiting compared to ondansetron • Both aprepitant groups showed lower peak nausea scores than ondansetron • Similar rates of adverse events across treatment groups; no significant tolerability concerns observed
Gan *et al*. 2007[20]	3	1. Aprepitant 40 mg 2. Aprepitant 125 mg 3. Ondansetron 4 mg	• Proportion of patients with complete response (no vomiting, no rescue therapy) in the 24 h after surgery • No vomiting 0–24 h • No rescue therapy 0–24 h • No vomiting 0–48 h • Safety assessment	• Both aprepitant doses also had higher incidences of no vomiting over 0–48 h (*P*<0.001) • Similar complete response across all groups • No difference in side effect profile among all groups
Jeyabalan *et al*. 2019[27]	2	1. Ondansetron 8 mg 2. Aprepitant 40 mg	• The incidence of postoperative vomiting in 0–2, 2–12 and 12–24 h after the surgery • The number of emetic episodes • Severity of postoperative nausea	• Immediate postoperative period: 79.7% of patients in Group I and 85.2% in Group II were free of emesis (*P*=0.49). • Request for first rescue antiemetic (min) for ondansetron was 90 (45–147) min versus aprepitant 147 (11–457) min (*P*=0.80)

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Table 1: Contd...

Study	No. of arms	Arms	Outcome	Result
			• Timing of the first vomiting episode • Use of rescue antiemetics • Patient satisfaction rating	• Time of first emetic episode (min) for ondansetron was 90 (45–147) min versus aprepitant 160 (26–490) min (*P*=0.20) • Aprepitant delayed the time to first vomiting compared to ondansetron • No significant differences in nausea or patient satisfaction

A=aprepitant, ADO=aprepitant+dexamethasone+ondansetron, AO=aprepitant+ondansetron, CI=confidence interval, D=dexamethasone, DO=dexamethasone+ondansetron, ED=emergency department, IV=intravenous, O=ondansetron, PACU=post-anaesthesia care unit, PONV=postoperative nausea and vomiting, SG=sleeve gastrectomy, VNRS=verbal numeric rating scale, VRS=verbal rating scale

Table 2: RoB summary

Trial (study, year)	RoB arising from randomisation process	RoB due to deviations from the intended intervention	RoB due to missing outcome data	RoB in the measurement of the outcome	RoB in the selection of the reported result	Overall RoB
Alam *et al*. 2023[21]	Low	Low	Low	Low	Low	Low
De Morais *et al*. 2018[11]	Low	Low	Low	Low	Low	Low
Diemunsch *et al*. 2007[19]	Low	Low	Low	Low	Low	Low
Gan *et al*. 2007[20]	Some concerns	Low	Low	Low	Low	Some concerns
Habib *et al*. 2011[26]	Low	Low	Low	Low	Low	Low
Ham *et al*. 2011[7]	Low	Low	Low	Low	Low	Low
Jeyabalan *et al*. 2019[27]	Low	Low	Low	Low	Low	Low
Sinha *et al*. 2014[24]	Low	Low	Low	Low	Low	Low
Thanuja *et al*. 2016[23]	Low	Low	Low	Low	Low	Low
Valeejo *et al*. 2012[25]	Some concerns	Low	Low	Some concerns	Low	Some concerns

RoB=Risk of bias

response was observed more in the A group compared to the O group (55.97% vs. 50.35%; RR: 1.13, 95% CI: 1.03, 1.24; $P = 0.010$) with moderate but not significant heterogeneity ($I^2 = 27\%$, $P = 0.260$) [Figure 2b]. In TSA, the cumulative Z-curve does not cross the monitoring boundaries, initially declining to suggest a lack of significant evidence for a complete response when comparing 'A' to 'O', then stabilising but remaining inconclusive, indicating the need for further trials to determine a conclusive effect. The publication bias was not seen for this outcome as there was a symmetrical funnel chart [Figure S2]. The outcome of no use of rescue antiemetics was observed more in the A group than the O group (34.58% vs. 36.04%; RR: 1.02, 95% CI: 0.89, 1.16; $P = 0.790$) [Figure 2c]. In TSA, the cumulative Z-curve remains very close to the zero line and within the monitoring boundaries, indicating no significant difference between 'A' and 'O' regarding the use of rescue antiemetics, thus suggesting the evidence is inconclusive and more trials may be needed to determine a significant effect. The funnel chart for this outcome was symmetrical, hence not showing publication bias, but significant heterogeneity was observed: $I^2 = 65\%$, $P = 0.060$ [Figure S3]. The certainty of the evidence for the incidence of PONV was moderate, whereas for the complete response, it was high, and for no use of rescue medication was low [Table 3].

Aprepitant + ondansetron (AO) versus ondansetron (O)

The AO group had lower PONV incidence than the O group (11.3% vs. 26.8%; RR: 0.43, 95% CI: 0.27, 0.67; $P < 0.001$) [Figure 3a]. Heterogeneity was observed for this outcome, but it was not significant ($I^2 = 41\%$, $P = 0.190$), whereas the publication bias for this outcome was not seen as there was a symmetrical funnel plot [Figure S4]. TSA findings indicate that the cumulative Z-curve starts below zero and rises steadily but remains within the monitoring boundaries, suggesting inconclusive evidence and the need for more trials to determine if 'AO' significantly reduces the incidence of PONV compared to 'O'. Complete response was also higher in the AO group (38.1% vs. 26.84%; RR: 1.41, 95% CI: 1.05, 1.90; $P = 0.020$) [Figure 3b]. There was no publication bias, but heterogeneity was there, which was not significant ($I^2 = 34\%$, $P = 0.220$) [Figure S5]. In TSA, the cumulative Z-curve initially drops, then rises within boundaries, with a crossing of a futility boundary suggesting further trials might be futile, concluding that 'AO' lacks significant

Table 3: Summary of findings Aprepitant versus Ondansetron

Certainty assessment						Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With O	With A		Risk with O	Risk difference with A
A vs O-PONV											
1903 (5 RCTs)	not serious	serious[a]	not serious	not serious	none	⊕⊕⊕◯ Moderate	193/678 (28.5%)	153/1225 (12.5%)	RR 0.45 (0.29-0.72)	193/678 (28.5%)	157 fewer per 1,000 (from 202 fewer to 80 fewer)
A vs O- Complete Response											
1679 (3 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ High	285/566 (50.4%)	623/1113 (56.0%)	RR 1.13 (1.03-1.24)	285/566 (50.4%)	65 more per 1,000 (from 15 more to 121 more)
A vs O- No use of Rescue Antiemetics											
1679 (3 RCTs)	not serious	serious[a]	not serious	serious[b]	none	⊕⊕◯◯ Low	204/566 (36.0%)	386/1113 (34.7%)	RR 1.02 (0.89-1.16)	204/566 (36.0%)	7 more per 1,000 (from 40 fewer to 58 more)

CI: confidence interval; RR: risk ratio. [a]Significant heterogeneity; I^2=65 percent, P=0.06. [b]Wide confidence interval

impact compared to 'O' in achieving a complete response. The AO group had more patients without rescue antiemetics than the O group (53.09% vs. 52.1%; RR: 1.02, 95% CI: 0.84, 1.23; $P = 0.860$) [Figure 3c]. This outcome›s heterogeneity was insignificant ($I^2 = 0\%$, $P = 1.00$), with a symmetrical funnel chart showing no publication bias [Figure S6]. The cumulative Z-curve in TSA stays near the zero line within monitoring boundaries, indicating no significant difference between 'AO' and 'O' in the absence of rescue antiemetics, suggesting inconclusive evidence and potentially diminishing the likelihood of significant differences in further trials. The certainty of evidence for the incidence of PONV, for complete response and for no use of rescue medication was moderate [Table 4].

Aprepitant + dexamethasone + ondansetron (ADO) versus dexamethasone + ondansetron (DO)

The incidence of PONV was less in the ADO group compared to the DO group (13.63% vs. 35.38%; RR: 0.38, 95% CI: 0.19, 0.76; $P = 0.006$) [Figure 4a]. There was no significant heterogeneity ($I^2 = 0\%$, $P = 0.850$) and no publication bias [Figure S7]. The cumulative Z-curve in TSA crosses the conventional boundary, indicating a significant difference between ADO and DO for the incidence of PONV. This suggests sufficient evidence has been obtained, and further trials are unlikely to alter these findings. ADO group had more patients without rescue antiemetics than the O group (89.39% vs. 76.92%; RR: 1.16, 95% CI: 0.99, 1.36; $P = 0.060$) [Figure 4b]. Publication bias was not seen for this outcome, whereas heterogeneity was seen, which was not significant ($I^2 = 11\%$, $P = 0.290$) [Figure S8]. The cumulative Z-curve in TSA stays near the zero line within monitoring boundaries, indicating no significant difference between ADO and DO in the absence of rescue antiemetics, suggesting inconclusive evidence and potentially diminishing the likelihood of significant differences in further trials. There were two studies in which other antiemetics like scopolamine and promethazine were also used, along with aprepitant and ondansetron. Hence, quantitative analysis for these studies could not be done. The certainty of evidence for the incidence of PONV and for no use of rescue medication was moderate. [Table 5]

DISCUSSION

This comprehensive meta-analysis, integrating data from 12 trials involving 2729 patients, evaluates strategies for PONV. The NK-1 receptor antagonist aprepitant emerges as a highly efficacious agent,

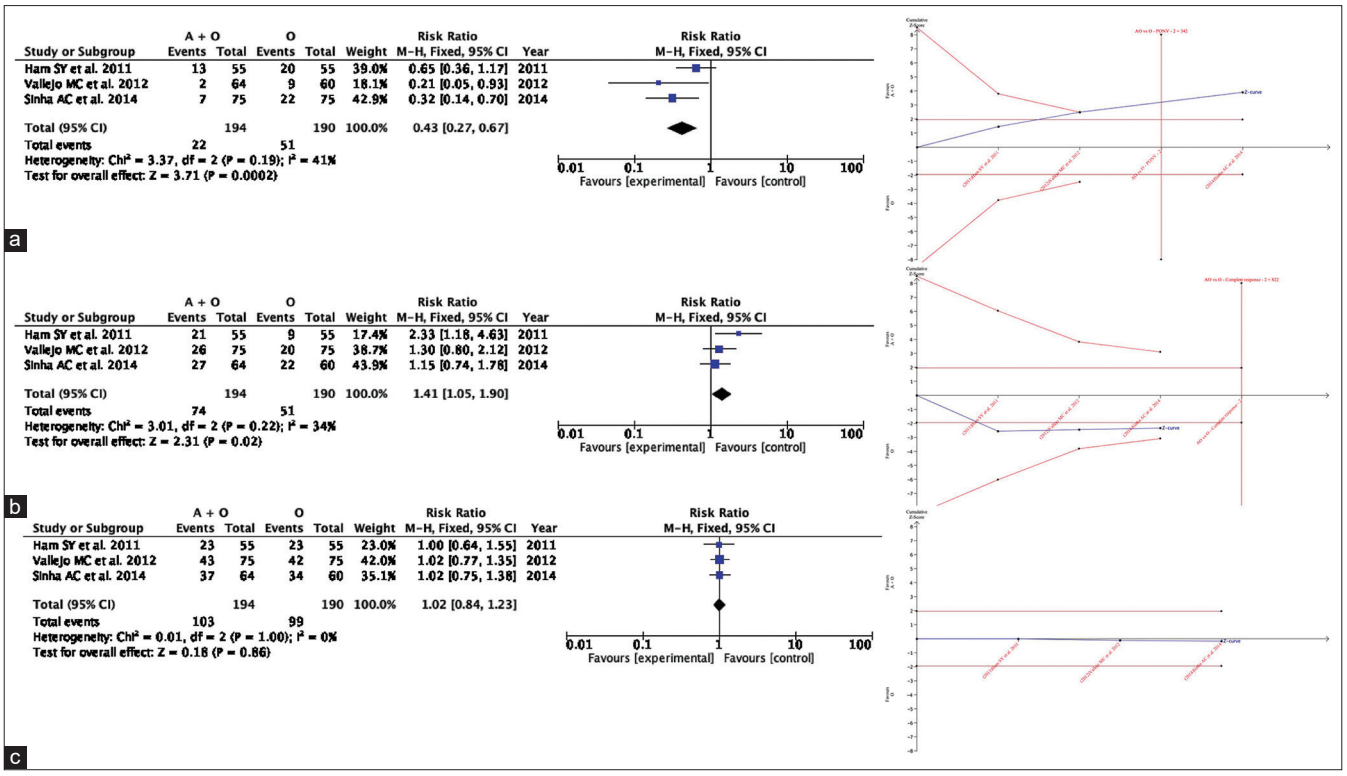

Figure 3: Forest plot and trial sequential analysis graph for comparison between A + O versus O. (a) Comparison between Aprepitant+Ondansetron (AO) vs Ondansetron (O) for incidence of PONV, (b) Comparison between Aprepitant+Ondansetron (AO) vs Ondansetron (O) for Complete Response, (c) Comparison between Aprepitant+Ondansetron (AO) vs Ondansetron (O) for no use of Rescue Antiemetics. A + O = aprepitant + ondansetron, CI = confidence interval, M-H = Mantel–Haenszel, O = ondansetron

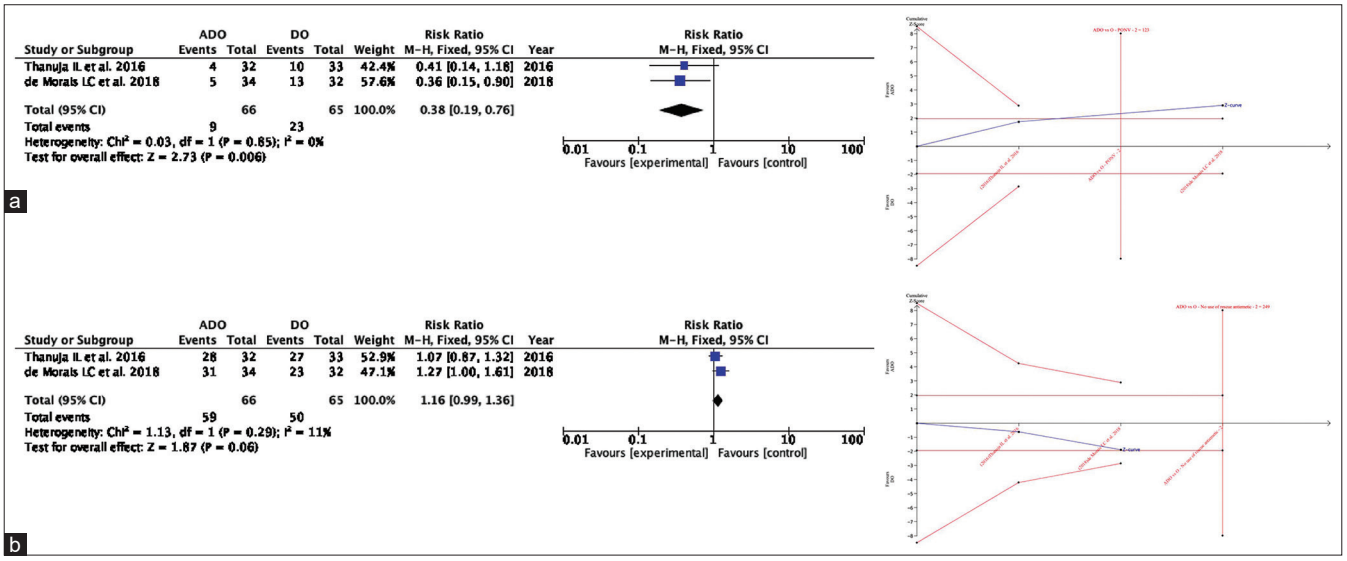

Figure 4: Forest plot and trial sequential analysis graph for comparison between ADO versus DO. (a) Comparison between Aprepitant+Dexa methasone+Ondansetron (ADO) vs Dexamethsone+Ondansetron (DO) for incidence of PONV, (b) omparison between Aprepitant+Dexamet hasone+Ondansetron (ADO) vs Dexamethsone+Ondansetron (DO) for no use of Rescue Antiemetics. ADO = aprepitant + dexamethasone + ondansetron, CI = confidence interval, M-H = Mantel–Haenszel, DO = Dexamethsone+ondansetron

consistently demonstrating superior prophylactic potential compared to the conventionally used ondansetron. Notably, combining aprepitant (80 mg) with dexamethasone and ondansetron exhibits synergistic effects, bolstering its efficacy and advocating for adopting multimodal approaches in PONV management.

Recognising diverse dosing practices and regional differences in drug availability, we grouped varying

Table 4: Summary of findings Aprepitant-Ondansetron versus Ondansetron

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%) With O	Study event rates (%) With AO	Relative effect (95% CI)	Anticipated absolute effects Risk with O	Anticipated absolute effects Risk difference with AO
AO vs O- Incidence of PONV											
384 (3 RCTs)	not serious	not serious	not serious	serious[a]	none	⊕⊕⊕◯ Moderate	51/190 (26.8%)	22/194 (11.3%)	RR 0.43 (0.27-0.67)	51/190 (26.8%)	153 fewer per 1,000 (from 196 fewer to 89 fewer)
AO vs O- Complete Response											
384 (3 RCTs)	not serious	not serious	not serious	serious[a]	none	⊕⊕⊕◯ Moderate	51/190 (26.8%)	74/194 (38.1%)	RR 1.41 (1.05-1.90)	51/190 (26.8%)	110 more per 1,000 (from 13 more to 242 more)
AO vs O- No need of rescue medication											
384 (3 RCTs)	not serious	not serious	not serious	serious[a]	none	⊕⊕⊕◯ Moderate	99/190 (52.1%)	103/194 (53.1%)	RR 1.02 (0.84-1.23)	99/190 (52.1%)	10 more per 1,000 (from 83 fewer to 120 more)

CI: Confidence interval; RR: Risk ratio, AO: Aprepitant-Ondansetron, O: Ondansetron. [a]Wide confidence interval

Table 5: Summary of findings Aprepitant-Dexamethsone-Ondansetron versus Ondansetron

ADO compared to DO

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%) With DO	Study event rates (%) With ADO	Relative effect (95% CI)	Anticipated absolute effects Risk with DO	Anticipated absolute effects Risk difference with ADO
ADO vs DO- Incidence of PONV											
131 (2 RCTs)	not serious	not serious	not serious	serious[a]	none	⊕⊕⊕◯ Moderate	23/65 (35.4%)	9/66 (13.6%)	RR 0.38 (0.19-0.76)	23/65 (35.4%)	219 fewer per 1,000 (from 287 fewer to 85 fewer)
ADO vs DO- No use of Rescue Antiemetics											
131 (2 RCTs)	not serious	not serious	not serious	serious[a]	none	⊕⊕⊕◯ Moderate	50/65 (76.9%)	59/66 (89.4%)	RR 1.16 (0.99-1.36)	50/65 (76.9%)	123 more per 1,000 (from 8 fewer to 277 more)

CI: Confidence interval; RR: Risk ratio, ADO: Aprepitant-Dexamethsone-Ondansetron, O: Ondansetron, DO: Dexamethsone-Ondansetron. [a]Wide confidence interval

doses of aprepitant and ondansetron to compare comprehensively. This mitigated the challenge posed by dose variability and ensured the inclusion of a broader range of studies for analysis, thus offering valuable insights into their comparative efficacy and safety in preventing PONV.

During data analysis, we considered the overall occurrences of nausea and vomiting throughout the study. This was necessary because some studies did not report these events separately. However, in cases where nausea and vomiting were reported as separate events, we prioritised the higher value. This decision was based on the understanding that the occurrence of one symptom does not exclude the other. Therefore, we refrained from adding up the nausea and vomiting events, recognising them as distinct experiences requiring individual consideration.

The RR value of 0.45 for aprepitant versus ondansetron aligns harmoniously with Liu Y's odds ratio of 0.34, indicating a substantial reduction in PONV incidence with aprepitant.[28] Furthermore, the RR values for the combination regimens (AO vs. O; RR: 0.43; ADO vs. O; RR: 0.38) reinforce the enhanced efficacy of aprepitant when employed in multimodal antiemetic strategies.

On performing TSA, encompassing all three distinct comparisons – A versus O, AO versus O and ADO versus DO – we uncovered diverse outcomes across various postoperative measures. Firstly, when comparing ADO and DO regarding PONV incidence, we observed that further trials are unlikely to alter these findings significantly. Conversely, evaluating the absence of rescue antiemetics between ADO and DO yielded inconclusive evidence. TSA suggests a lack of substantial difference between the two interventions, potentially diminishing the likelihood of significant disparities in subsequent trials. Moreover, comparing A versus O and AO versus O demonstrated inconclusive results for PONV incidence and complete response, emphasising the complex nature of treatment efficacy determination. These findings underscore the critical need for continued research to elucidate the true effectiveness of interventions across various postoperative outcomes, thereby informing clinical practice with precision and confidence.

Recent studies by Kienbaum *et al*.[29] and Weibel *et al*.[30.31] reinforce the effectiveness of aprepitant for preventing PONV, aligning with our meta-analysis findings. Personalised approaches advocated by Kienbaum *et al*.[29] underscore aprepitant as a leading option, while Weibel *et al*.'s[30,31] Cochrane reviews confirm its efficacy, bolstering the evidence base. Murakami *et al*.'s[32] 2020 study focused on NK-1 receptor antagonists, including aprepitant, and emphasised the need for further research to address existing knowledge gaps and improve antiemetic strategies. Singh *et al*.'s[33] findings highlighted the continuity of evidence over time, further solidifying aprepitant's standing as a reliable and effective prophylactic option. Liu *et al*.'s[34] insightful meta-analysis from 2015 provides valuable contributions to understanding the role of NK-1 receptor antagonists, with a specific focus on aprepitant, in preventing PONV.

A critical indicator of aprepitant's effectiveness is its ability to achieve a complete response, defined as the absence of vomiting and the absence of the need for rescue therapy. Studies by Diemunsch *et al*.[19]and Alam *et al*.[21] demonstrate the non-inferiority and potential superiority of aprepitant (40 and 125 mg, respectively) compared to ondansetron, showing higher complete response rates over the 0–24 h postoperative period. Gan *et al*.'s[20] trial comparing oral aprepitant to IV ondansetron consistently shows lower vomiting incidence with aprepitant in diverse surgical settings, indicating not only non-inferiority, but also potential superiority in reducing vomiting incidence within the initial 24 h after surgery. In addition, Sinha *et al*.'s trial in laparoscopic bariatric surgery reveals a significantly lower cumulative incidence of vomiting at 72 h with aprepitant.[24]

These findings emphasise aprepitant's strong and consistent antiemetic efficacy across surgical contexts and timeframes. The evidence underscores its potential as a reliable and versatile prophylactic antiemetic, contributing significantly to understanding effective PONV management strategies.

Cavaye *et al*.'s[35] meta-analysis further strengthens the case for aprepitant's efficacy, emphasising its effectiveness in reducing the risk of nausea and vomiting in the critical postoperative period. Specifically, the meta-analysis underscores the benefits of preoperative oral administration of aprepitant, demonstrating a significant reduction in the risk of nausea and vomiting within the initial 2 h, with this effect sustained up to 24 h after adult laparoscopic surgery. This sustained decrease in symptoms is particularly relevant in enhancing the overall postoperative experience for patients.

In studies where aprepitant is compared or combined with other drugs like palonosetron, ramosetron and dexamethasone for PONV, a consistent reduction in PONV is observed. While the reduction may not always reach statistical significance, the cumulative evidence suggests that aprepitant plays a valuable role in combination therapies for PONV.[10,12,36-38] This highlights the versatility of aprepitant in multimodal antiemetic approaches, potentially offering tailored solutions for different patient populations and surgical contexts.

Despite the comprehensive analysis, several limitations must be acknowledged. Firstly, the heterogeneity among the included studies, in terms of methodologies, patient populations and surgical contexts, may have introduced variability in the findings. Moreover, the potential for publication bias and the variability in aprepitant dosages and administration routes could have influenced the observed efficacy. Due to the limited number of studies available for each outcome, we could not conduct a meta-regression analysis, even though we utilised varying doses of aprepitant for comparison. The highest number of studies available for a single outcome was only five, which posed a significant constraint. With such a small number of studies, there exists a considerable risk of obtaining spurious or unreliable conclusions through meta-regression analysis, as the statistical power to detect meaningful associations is greatly diminished. In addition, due to specific inclusion criteria and lack of long-term follow-up in some studies, the limited generalisability of the findings may restrict their applicability across diverse patient populations and surgical settings. Addressing these limitations in future research endeavours will be crucial for enhancing the understanding of aprepitant's effectiveness in preventing PONV and optimising its clinical utility.

CONCLUSION

Aprepitant, whether alone or combined with ondansetron or ondansetron and dexamethasone, consistently surpasses ondansetron in achieving a complete response, with lower vomiting rates and reduced need for rescue therapy in the critical 24–48 h postoperatively. In addition, aprepitant delays the onset of the first vomiting episode, leading to improved early recovery outcomes.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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SUPPLEMENTARY FILE

Table S1: Search strategies:

Medline – 17

(PONV [MeSH Terms]) OR (Postoperative nausea and vomiting [MeSH Terms]) AND (aprepitant [MeSH Terms]) AND (ondansetron [MeSH Terms])).

Cochrane – 64

(aprepitant):ti AND (ondansetron):ti AND (postoperative nausea and vomiting):ti

Clinical Trial Registry – 20

(aprepitant) AND (ondansetron) AND (postoperative nausea and vomiting)

Google Scholar – 2670

(aprepitant) AND (ondansetron) AND (postoperative nausea and vomiting)

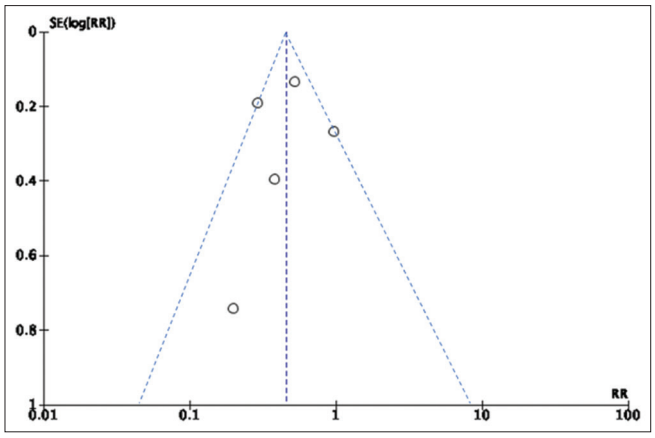

Figure S1: Funnel plot of A versus O for incidence of PONV. A = aprepitant, O = ondansetron, PONV = postoperative nausea and vomiting, RR = relative risk

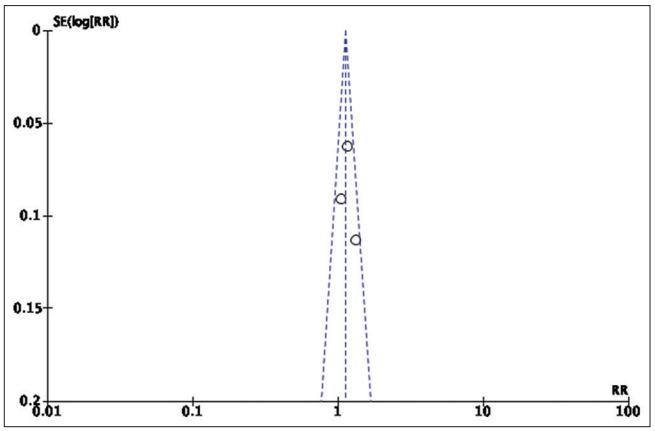

Figure S2: Funnel plot of A versus O for complete response. A = aprepitant, O = ondansetron, RR = relative risk

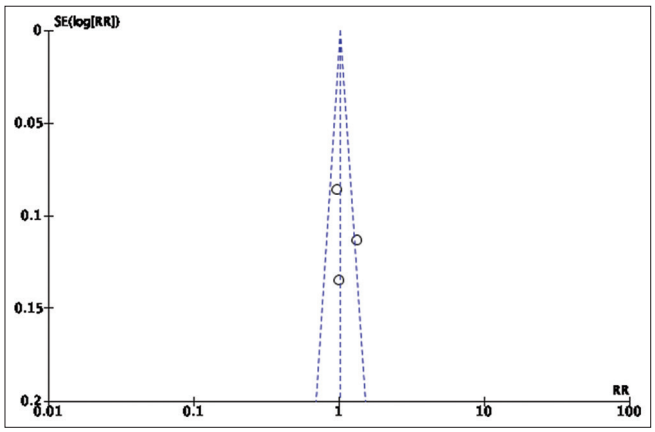

Figure S3: Funnel plot of A versus O for no need of rescue antiemetics. A = aprepitant, O = ondansetron, RR = relative risk

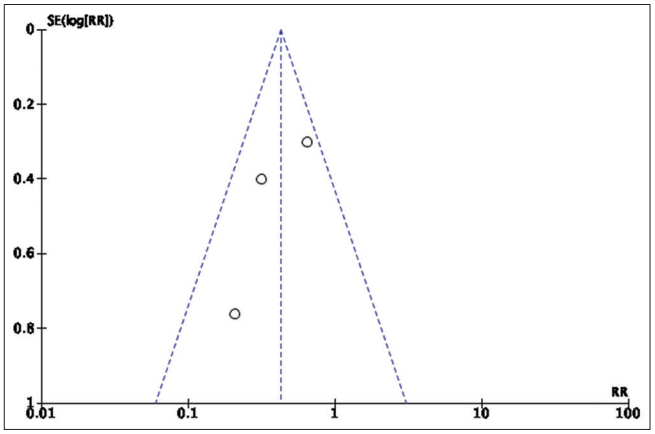

Figure S4: Funnel plot of AO versus O for the incidence of PONV. AO = aprepitant + ondansetron, O = ondansetron, PONV = postoperative nausea and vomiting, RR = relative risk

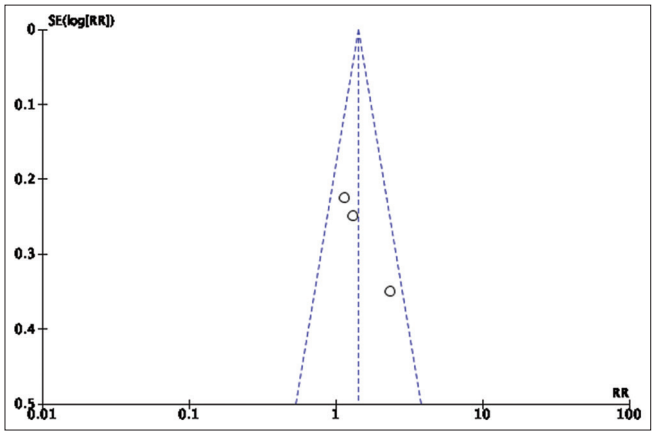

Figure S5: Funnel plot of AO versus O for complete response. AO = aprepitant + ondansetron, O = ondansetron, RR = relative risk

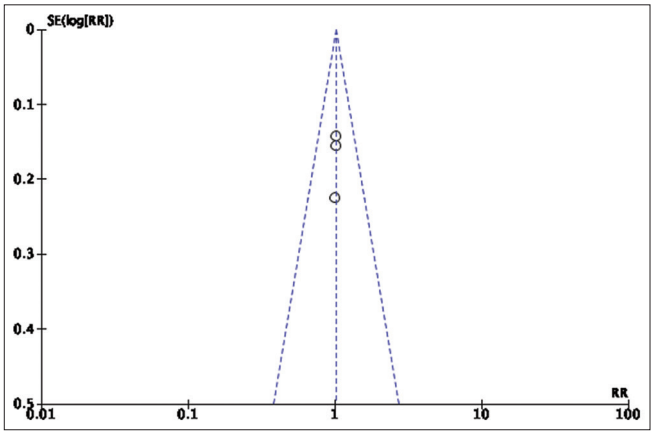

Figure S6: Funnel plot of AO versus O for no need of rescue antiemetics. AO = aprepitant + ondansetron, O = ondansetron, RR = relative risk

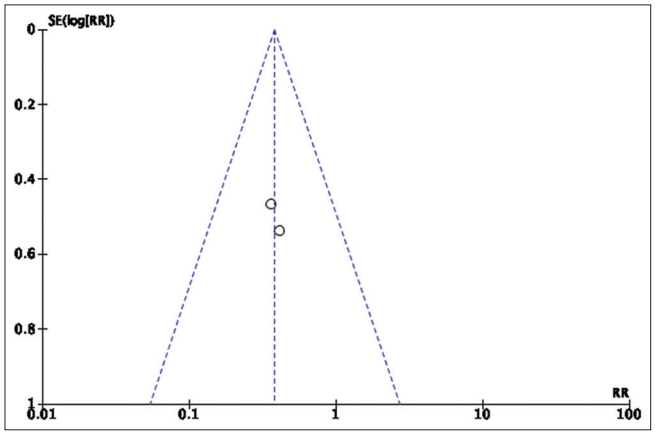

Figure S7: Funnel plot of ADO versus O for the incidence of postoperative nausea and vomiting. ADO = aprepitant + dexamethasone + ondansetron, O = ondansetron, RR = relative risk

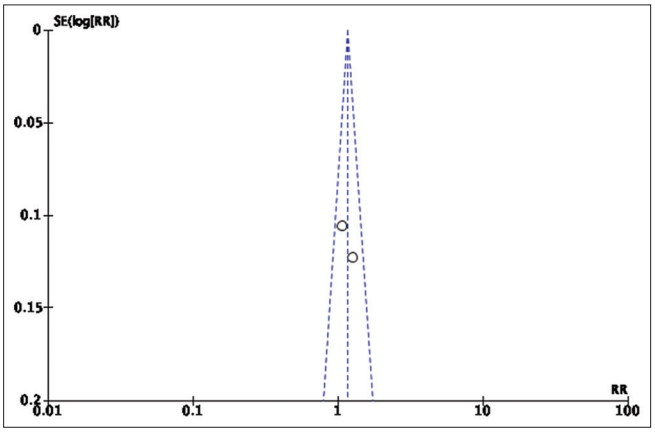

Figure S8: Funnel plot of ADO versus O for no need of rescue antiemetics. ADO = aprepitant + dexamethasone + ondansetron, O = ondansetron, RR = relative risk