Review Article

NK1 receptor antagonists versus other antiemetics in the prevention of postoperative nausea and vomiting following laparoscopic surgical procedures: a systematic review and meta-analysis

John Cavaye[1,2*], Bryan Dai[1,2*], Karthik Gurunathan[3], Rachel M. Weir[4], Stephanie Yerkovich[1], Usha Gurunathan[1,2]

[1]Faculty of Medicine, University of Queensland, [2]Department of Anaesthesia and Perfusion Services, The Prince Charles Hospital, [3]School of Pharmacy, Queensland University of Technology, [4]Department of Anaesthesia, Sunshine Coast University Hospital, Queensland, Australia
*Both contributed equally.

Abstract

A systematic electronic search of MEDLINE, EMBASE, and CINAHL databases aimed at comparing neurokinin-1 receptor antagonists with other antiemetics in their prevention of postoperative nausea and vomiting in adult patients undergoing laparoscopic surgery identified seven randomized controlled trials for review and meta-analysis. Preoperative aprepitant 80 mg was found to reduce nausea (RR: 0.56, 95% CI: 0.41–0.75, I^2 = 0%, P = 0.89) and vomiting (RR: 0.20, 95% CI: 0.05–0.77, I^2 = 0%, P = 0.96) and resulted in complete response (RR: 1.61 (1.25-2.08), I^2 = 0%, P = 0.70) within the first 2 hours following surgery as well as vomiting in 2–24 hours (RR: 0.09, 95% CI: 0.02-0.36, I^2 = 0%; P = 0.81) when compared to placebo or no antiemetic therapy. Preoperative aprepitant 80 mg has a superior overall effect compared to placebo or other antiemetics in the first two hours postoperatively, and thereafter reduces the risk of vomiting alone in the first 24 hours following laparoscopic surgeries.

Keywords: Aprepitant, neurokinin-1 receptor antagonists, postoperative nausea and vomiting

Postoperative nausea and vomiting (PONV) continue to be a challenge to manage following anesthesia, despite advances in the use of anesthetic drugs and techniques. PONV is reported to occur in up to 30% of all surgical patients and 70–80% of high-risk patients following surgery with no prophylactic antiemetic therapy.[1] PONV can result in numerous adverse events, including, fluid and electrolyte imbalances, wound dehiscence, esophageal tears, and raised intracranial pressure.[2] In addition, PONV increases patient discomfort and dissatisfaction as well as delays recovery and discharge, resulting in increased healthcare costs.[2,3]

Neurokinin-1 (NK-1) receptor antagonists such as aprepitant, rolapitant, casopitant, fosaprepitant, netupitant and maropitant belong to a class of compounds that possess anxiolytic, antidepressant, and antiemetic properties.[4] They act by blocking NK-1 receptors at the area postrema, nucleus of tractus solitaries, and areas of reticular formation. The NK-1

Address for correspondence: Dr. Usha Gurunathan, Department of Anaesthesia and Perfusion Services, The Prince Charles Hospital, Rode Road, Chermside, Queensland, Australia.
E-mail: usha.gurunathan@health.qld.gov.au

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receptors have both central and peripheral mechanisms of action.[5] Large studies have demonstrated their superiority in preventing significant postoperative vomiting than nausea.[6,7] A recent Cochrane review has demonstrated the superiority of NK-1 receptor antagonists and a comparable efficacy of a single NK-1 receptor antagonist to other drug combinations in preventing vomiting.[8] Aprepitant was the first oral NK-1 receptor antagonist to be marketed in the USA and Europe for chemotherapy-induced nausea and vomiting.[5,9] It has a 3000-fold selectivity for NK-1 receptors compared to serotonin, corticosteroid, or dopamine receptors. Aprepitant undergoes extensive metabolism and its metabolites are not renally excreted, making it safe for those with severe renal insufficiency.[10] Its serum half-life is 40 hours, reaching the peak plasma concentration at approximately 4 hours and its bioavailability is 60–65% after oral administration.[10,11] Currently, only oral aprepitant is approved for the prevention of PONV. Intravenous fosaprepitant (Emend®) and oral netupitant in combination with palanosetron (Akynzeo®) are marketed for emesis following cytotoxic chemotherapy. These drugs have been well researched in the prevention of nausea and vomiting following cancer chemotherapy; however, their use to prevent PONV is much less studied.

Previous systematic reviews that reported on the efficacy of NK-1 receptor antagonists in the prevention of PONV were limited by their heterogeneity as they combined different types of surgery.[12-14] The type of surgery is considered a risk factor for PONV.[11] Laparoscopic cholecystectomy and gynecological laparoscopy have a high incidence of PONV with several proposed contributing factors including pneumoperitoneum and female sex.[15] Hence, we performed a systematic review and meta-analysis to compare NK-1 receptor antagonists with other antiemetics in the prevention of PONV in adult patients undergoing laparoscopic surgeries. Our primary outcomes were the incidence of nausea and vomiting at different time points until the first 48 hours following surgery. Additional outcomes were the use of rescue antiemetics, pain scores and opioid requirement, adverse effects and the incidence of complete response, defined as complete absence of nausea and vomiting with no requirement for any rescue antiemetic therapy.

Material and Methods

Search strategy and eligibility criteria

A systematic electronic search of MEDLINE, EMBASE and CINAHL databases was performed by the investigators J.C and B.D. Articles on human studies limited to adult populations, published in English until 21st December 2020 were identified with the following search terms and their modifications: postoperative nausea and vomiting, neurokinin-1 receptor antagonists or blockers or inhibitors, aprepitant or fosaprepitant or casopitant or ezlopitant or netupitant or rolapitant or their commercial names. Search terms were modified appropriate to the search engine implemented. All the titles and abstracts were reviewed, and the relevant articles were independently identified by the investigators J.C and B.D and verified by U.G.

Randomized controlled trials (RCT) that compared NK-1 receptor antagonists with other antiemetics or placebo in the prevention of PONV in adult patients undergoing laparoscopic surgery were included. Nonhuman studies, observational studies, opinion papers, case reports, editorials, irrelevant studies, studies on pediatric population, adults undergoing open surgery, or those having concurrent chemotherapy were excluded. Unpublished studies were not reviewed. A single attempt was made to contact authors through email when there were ambiguities regarding the nature of surgery. Any discrepancy was resolved by discussion among all the investigators. Full texts of the articles were obtained, and the references were manually searched for further relevant literature. The results of the search are shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram [Figure 1].[16] This study was registered with the PROSPERO database at the Centre for Reviews and Dissemination (CRD), University of York (No: CRD42020147998).

Data abstraction and quality assessment

The following data were extracted in a standardized form by the investigators J.C and B.D, and verified for accuracy by the rest:

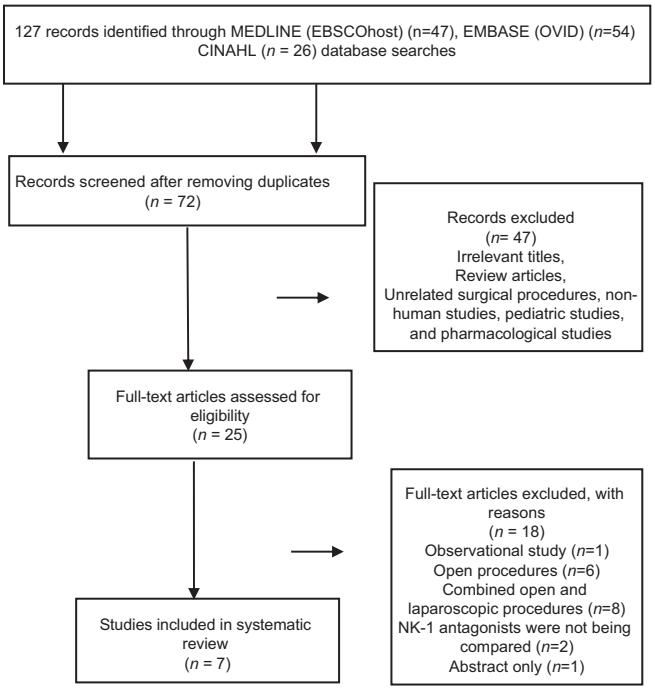

Figure 1: Study flow diagram based on PRISMA recommendations

Author, year of publication, country, study design, details on participants, nature of surgery, duration of surgery, anesthetic details, postoperative analgesia, intervention and comparison, postoperative regular and rescue antiemetics, and the outcomes of interest. Seven studies were finally selected for analysis.

For outcomes with an adequate number of homogeneous studies, a random effect meta-analysis was conducted using the "metan" package in the Stata statistical software (Version 15). I^2 statistic was used to measure the heterogeneity between the studies with <40%, 40–60%, and >60% representing low, moderate, and high heterogeneity, respectively, and their significance was determined with a *P* value of 0.05. However, it was noted that the number of studies that reported comparable outcomes in a consistent format were insufficient to justify a meta-analysis for most outcomes of interest. These were considered for a systematic review.

Risk of bias assessment

The Cochrane tool was used to assess the methodological quality and the risk of bias in the studies selected for analysis.[17] This tool comprised eight questions. The studies were scored for their likelihood of bias as definitely yes (low risk of bias), mostly yes, mostly no, and definitely no (high risk of bias) as per Cochrane examples and topic-specific predetermined criteria agreed by the authors K.G and R.W. Analysis and interpretation of results were carried out by S.Y and U.G. All the listed authors contributed in drafting this article and reviewing the final version of the manuscript.

Results

Search details

The initial search identified a total of 127 citations. The search strategies with the databases are given in the appendix. After excluding citations for reasons given in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) diagram [Figure 1][16], 25 full text articles were screened further for eligibility. Two articles were excluded for being observational studies,[18,19] of which Hache *et al.*[18] did not involve the comparison of aprepitant. Six references were excluded as the drugs of interest were trialled only on open procedures.[6,7,20-23] Eight studies seemed to have included open and laparoscopic procedures. Of these, five investigator groups were emailed to confirm the nature of the surgery and resolve uncertainty. However, as we received no reply, based on the consensus between the authors, all those studies were excluded from review. Two were excluded as aprepitant was not being compared with other antiemetics in those studies.[24,25] One was found to be an abstract of another full text article[26] and hence excluded. Finally, seven articles on aprepitant were included for our systematic review [Table 1].

Study characteristics

There was one study from Japan,[27] three from Korea,[28-30] one from USA,[31] one from Brazil,[32] and one from Turkey.[26] They were all single-center RCT. Two studies[26,30] investigated the efficacy of 40 mg of aprepitant and the rest compared 80 mg of aprepitant with no antiemetic or identical placebo.

Four studies[27-29,32] were included in the quantitative review for early PONV. One study was excluded for the 0–2 hours vomiting outcome as no events were observed in either group.[32] A qualitative review was performed when the outcomes reported were not in a consistent format [Table 2]. For instance, due to the differences in the scales for the severity of nausea (4-point[27] or 11 point[28,29,31,32] scales) and various definitions of severe nausea (verbal rating score (VRS) of ≥four[31] or ≥seven[32]), they could not be combined in a meta-analysis. One study that investigated aprepitant 125 mg[28] was also included in the systematic review but not for meta-analysis.

Early onset nausea (0-24 hours)

In the reviewed studies, the incidence of nausea at 0–2 hours was 3–63% (control arm) and 0–40% (aprepitant 80 mg), while at 2–24 hours, the incidence was 27–40% (control arm) and 0–28% (aprepitant 80 mg) [Table 2]. Interestingly, compared to the first two hours after surgery, the overall number of patients with nausea had reduced in 2–24 hours in the studies on laparoscopic gynecological procedures[27-29] and increased in the study on abdominal and pelvic oncology procedures.[32] This last-mentioned study had included patients at high risk of PONV.[32]

Within 0–2 hours of surgery, there was a markedly reduced risk of nausea (n = 316, RR: 0.56, 95% CI: 0.41–0.75, I^2 = 0%, and *P* = 0.89) [Figure 2] in the aprepitant (80 mg) group.[27-29,32] Within 2–24 hours, a lower percentage of patients reported nausea in the aprepitant 80 mg group,[27,28,32] and our pooled analysis also found a reduced risk of nausea (RR 0.42, 95% CI: 0.21–0.81, I^2 = 26.3%, *P* = 0.26) with a low level of heterogeneity observed between the studies [Figure 2]. No significant difference in nausea was reported between aprepitant 40 mg and placebo with the coadministration of ondansetron and dexamethasone at 0–2 and 2–24 hours.[26] Aprepitant 125 mg also showed a significant benefit over the control group for nausea 0–2 hour; however, it was not different from 80 mg[28] [Table 2].

Early onset vomiting (0–24 hours)

Compared to nausea, the incidence of overall vomiting was found to be low [Table 2]. The incidence of vomiting within 0–2 hours ranged between 0–13% (control arm) and 0–3% (aprepitant 80 mg), while within 2–24 hours, the incidence ranged between 0.1–40% (control arm)

Table 1: Characteristics of the studies reviewed

Author, year of publication and country	Study design	Participants	Type of surgery	Type of anaesthesia	Duration of surgery (minutes)	Number of participants/ demographics	Intervention & comparison	Postoperative regular and rescue antiemetic
Kakuta *et al.*, 2011; Japan	Prospective randomised controlled trial	Inclusion criteria: ASA I/II; Females: 20-70 years; Exclusion criteria: BMI>33 kg/ m2, pregnancy, steroid use; abnormal liver or renal function, neuronal disease	Laparoscopic gynecological surgery (ovarian cystectomy/ tumorectomy, adhesioloysis, myomectomy, vaginal hysterectomy, salpingostomy)	General anesthesia	Group I (control): 130±52; Group II (aprepitant): 125±43	Group 1: Number: 30; Age (y): 38±13; Wt (kg): 53±7 Group II: Number: 30; Age (y): 35±11; Wt (kg): 54±8	Group I: Control group (no antiemetic); Group II: Aprepitant 80 mg po 3 hours before surgery	Metoclopramide
Jung *et al.*, 2013; Korea	Double blind randomised control trial	Inclusion criteria: ASA I/II, 21-60 years; Exclusion criteria: Liver, neurologic, active pulmonary disease; cardiac arrhythmia; allergies to perioperative medications used in the study	Elective laparoscopic total hysterectomy	General anesthesia	Group I (control): 102±54 Group II (aprepitant 80 mg): 102±33 Group III (aprepitant 125 mg): 96±38	Group I: Number: 40; Age (y):46±6; Weight (kg): 59±8 Group II: Number: 40; Age (y): 46±5; Weight (kg): 58±9 Group III: Number: 40; Age (y): 46±5; Weight (kg): 59±7	Group I: Control group: No drugs Group II: Aprepitant 80 mg po 2 hour before anesthesia Group III: Aprepitant 125 mg po 2 hour before anesthesia	Dexamethasone 5 mg IV 1st line, metoclopramide 10 mg IV 2nd line
Moon *et al.*, 2014; Korea	Prospective randomised controlled trial	Inclusion criteria: ASA 1-2, Aged 20-60; Exclusion criteria: Pregnant, weight<45 kg or>100 kg, smokers, history of PONV, serious medical ailment of cardiovascular system, kidney, liver or hepatic disorder.	Laproscopic gynecological surgery	General anesthesia	Group I: (aprepitant): 71.5±37.7 Group II: (palanosetron): 79.2±42.2	Group I: Number: 46 Age (y): 37.9±11.1 Weight (kg): 56.2±5.6 Group II: Number: 47 Age (y): 37.6±8.0 Weight (kg): 54.8±5.8	Group 1: 40 mg aprepitant po with 30 mL water, 90 min before anesthesia; Saline (control for palanosetron) administered postintubation Group II: 0.075 mg palanosetron IV postintubation	VAS score>4: 10 mg metoclopramide IV first line, 5 mg dexamethasone IV second line
Sinha *et al.*, 2014; USA	Prospective randomised controlled trial	Inclusion criteria: ASA 1-3; >18 yrs, high risk PONV Exclusion criteria: Allergy to aprepitant or ondansetron, pregnant, breast feeding females, substance abuse, significant psychiatric disease, history of	Elective upper gastrointestinal surgery (banding or bypass)	General anesthesia	Group I: (aprepitant) 153.05±43.82; Group II: (placebo): 141.97±41.80	Group I: Number: 64; Age (y): 43.09±12.45 BMI (kg/m2): 50.11±8.28 Group II Number: 60; Age (y): 43.20±12.70 BMI (kg/m2: 48.07±6.72	Group I: 80 mg aprepitant po 60 mins before anesthesia. Group II: Placebo po 60 mins before anesthesia. Both the groups received 4 mg ondansetron IV prior to cessation of surgery	4 mg ondansetron, 4 mg dexamethasone, 10 mg metoclopramide or 0.0625 mg droperidol as per institutional policy

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Table 1: Contd...

Author, year of publication and country	Study design	Participants	Type of surgery	Type of anesthesia	Duration of surgery (minutes)	Number of participants/ demographics	Intervention & comparison	Postoperative regular and rescue antiemetic
		chronic nausea/ vomiting, taking meds with known antiemetic properties or known interactions with study drugs						
Yeon Ham., 2016; Korea	Randomised, double-blind controlled trial	Inclusion criteria: ASA 1/2; Females undergoing laparoscopic gynecological surgery with planned IV PCA fentanyl; Exclusion criteria: Allergy to components of aprepitant, taking drugs that interact with aprepitant (incl pimozide, terfenadine, astemizole, cisapride, warfarin), taking other antiemetics before surgery, hepatic dysfunction, psychiatric disease, mental retardation	Laparoscopic gynecological surgery (total hysterectomy, ovarian cystectomy, ovarian cyst enucleation, myomectomy, salpingo-oopherectomy)	General anesthesia		Group I: Number: 55; Age (y): 40 (22 to 55); Wt (kg): 55.4±7.9 Group II: Number: 55; (y): 42 (23 to 61); (kg): 55.5±9.0	Group I: 80 mg aprepitant po 60 min before anesthesia. Ondansetron 4 m iv 20 min before end of surgery Group II: Placebo po 60 min before anesthesia. Ondansetron 4 mg iv, 20 min before end of surgery	PACU: IV Metoclopramide 10 mg; Continued nausea: PCA ceased. Ward: IV Metoclopramide or Ramosetron
de Morais *et al.*, 2017; Brazil	Single centre, prospective, randomised controlled trial	Inclusion criteria: ASA 1-2 with 3/4 Apfel risk scores, >18 yrs; Exclusion criteria: Open surgery, administration of inhalation agents, postoperative endotracheal intubation, cardiovascular instability in the immediate postoperative period	Elective laparoscopic intermediate procedures for abdominal or pelvic cancer (hysterectomy/ adnexectomy, nephrectomy, hemicolectomy, partial gastrectomy)	General anesthesia and neuraxial block	Group I: (control): 367.5 (145-600) Group 2: (treatment): 437.5 (131-610)	Group I: Number: 32 median age (y): 50.5 (min: 19; max: 77) BMI (kg/m2: 29.7 (min: 19; max: 39) Group II Number: 34 median age (y): 60.5 (min: 31; max: 87) BMI (kg/m2: 31.2 (min 16; max: 47)	Group I: Oral starch po 1 hr Ondansetron 4-8 mg IV at end of surgery. Group II: 80 mg aprepitant po 1 hr preinduction Both groups received IV dexamethasone IV at induction and IV ondansetron 4-8 mg IV at the end of surgery.	Ondansetron IV 4 mg q8 h; Droperidol 0.625 mg IV prn for the first 24 hr

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Table 1: Contd...

Author, year of publication and country	Study design	Participants	Type of surgery	Type of anesthesia	Duration of surgery (minutes)	Number of participants/ demographics	Intervention & comparison	Postoperative regular and rescue antiemetic
Bilgen *et al.*, 2018; Turkey	Double blind, randomised, controlled trial	Inclusion criteria: ASA 1/2, 18-60 yrs; Exclusion criteria: Hypersensitivity or contraindication to study medications, preoperative administration of antiemetic or steroid drug 24 hrs, history of diabetes mellitus, pregnancy or lactation	Laparoscopic gynecological surgery or laparoscopic cholecystectomy	General anesthesia	Group I: Dexamethasone-Ondansetron 67.1±24.5; Group II: Dexamethasone-Aprepitant 74.8±29.4	Group I: Number: 34; Age (y): 35.3±7.9; Wt (kg): 66.8±14.3 Group II: Number: 33; (y): 40±10.9; (kg): 66.9±13	Group I: Control group: oral placebo 1-2 hr preinduction; IV dexamethasone 8 mg postinduction; ondansetron 4 mg last 30 minutes of surgery; Group II: Aprepitant 40 mg po 1-2 hours preinduction, IV dexamethasone 8 mg postinduction; 2 ml of IV saline last 30 minutes of surgery	Ondansetron 4 mg IV

ASA: American society of anesthesiologists; Wt: weight; BMI: Body mass index; PONV: postoperative nausea and vomiting; VAS: visual analogue score; PACU: postanesthesia care unit; PCA: patient controlled analgesia; IV: Intravenous

Figure 2: Forest plots of the included studies for nausea in the first 24 hours following surgery. (a) Nausea 0–2 hours following surgery. (b) Nausea 2–24 hours following surgery. (c)Nausea 0–24 hours following surgery

and 0–3% (aprepitant 80 mg). Our pooled analysis showed that there was a significant reduction in the risk of vomiting (n = 250, RR: 0.20, 95% CI: 0.05–0.77, $I^2 = 0\%$, $P = 0.96$) within 0–2 hours[27-29] and 2–24 hours in the 80 mg aprepitant group[27,28,32] (n = 206, RR: 0.09, 95% CI: 0.02–0.36, $I^2 = 0\%$; $P = 0.81$) [Figure 3]. However, no significant benefit with vomiting has been reported with the administration of aprepitant 40 mg[26] [Table 2].

Delayed vomiting (>24 hours)

Higher number of patients in the placebo group than the aprepitant 80 mg group (OR: 5.5, 95% CI: 1.3–26.5, $P = 0.03$) were

Table 2: Outcomes of the included studies

Author, Year of publication	Intervention & comparison	Number of participants	MEASURED OUTCOMES									
			Nausea [*n* (%)]	Vomiting [*n* (%)]	Scale of severity	Severity of Nausea	Severity of vomiting	Definition of complete response	Complete response [*n* (%)]	Need for rescue antiemetic [*n* (%)]	Other antiemetic medication	Adverse effects
Kakuta *et al.*, 2011	Group I: Control group (no antiemetic);	30	0-2 hours: 19 (63.3); 2-24 hours: 8 (26.7) *	0-2 hours: 4 (13.3); 2-24 hours: 2 (0.07)	4-point scale: 0=none; 1=mild; 2=moderate; 3=severe	0-2 hours: None-Mild: 17 (56.7) 2-24 hours: None-Mild: 28 (93.3)				0-2 hours: 6; 2-24 hours: 3		
	Group II: Aprepitant 80 mg po 3 hours before surgery	30	0-2 hours: 12 (40); 2-24 hours: 0 (0)	0-2 hours: 1 (0.03);2-24 hours: 0 (0)		0-2 hours: None-Mild: 25* (83.3)) 2-24 hours: None-Mild: 30 (100)				0-2 hours: 1 2-24 hours: 0		
Bilgen *et al.*, 2018	Group I: Control group: oral placebo 1-2 hr preinduction; IV dexamethasone 8 mg postinduction; ondansetron 4 mg last 30 minutes of surgery	34	0-2 hours: 10 (30.4); 2-24 hours: 4 (11.8)	0-2 hours: 0;2-24 hours: 1 (3.0)	Nausea: 10-point VRS scale from 0-11≥4 = severe	0-2 hours: VRS≥4: 10 (30.4); 2-24 hours: VRS≥4: 4 (11.8)			23 (67.6)	0-24 hours: 9 (26.5)		
	Group II: Aprepitant 40 mg po 1-2 hours preinduction, IV dexamethasone 8 mg postinduction; 2 ml of IV saline last 30 minutes of surgery	33	0-2 hours: 11 (33.3); 2-24 hours: 3 (9.1)	0-2 hours: 1 (2.9);2-24 hours: 1 (3.0)		0-2 hours: VRS≥4: 11 (33.3); 2-24 hours: VRS≥4: 3 (9.1)			23 (69.7)	0-24 hours: 10 (30.3)		
de Morais *et al.*, 2018	Group I: Oral starch po 1 hr+4-8 mg IV dexamethasone preinduction. Ondansetron 4-8 mg IV at end of surgery.	32	0-2 hours: 1 (3); 2-24 hours: 12 (37)*; 0-24 hours: 13 (40)*	0-2 hours: 0 (0);2-24 hours: 13 (40)	11-point scale: 0=no nausea, 10=as bad as possible; Severe nausea: ≥ 7; Severe vomiting: ≥ 3 episodes	0-2 hours: None- moderate: 1 (3.1); Severe: 0 (0); 2-24 hours: Severe: 2 (6.3)	0-2 hours: 0 (0); 2-24 hours: Severe: 4 (12.5)			0-24 hours: 9 (28.1) *	Ondansetrron: 4 mg: 8 (25) 8 mg: 24 (75) Dexamethasone: 4 mg: 16 (50) 8 mg: 16 (50)	Hypotension 1 (3.1) Pruritis 10 (31.3)

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Table 2: Contd...

Author, Year of publication	Intervention & comparison	Number of participants	MEASURED OUTCOMES									
			Nausea [*n* (%)]	Vomiting [*n* (%)]	Scale of severity	Severity of Nausea	Severity of vomiting	Definition of complete response	Complete response [*n* (%)]	Need for rescue antiemetic [*n* (%)]	Other antiemetic medication	Adverse effects
	Group II: 80 mg aprepitant po 1 hr pre-induction+4-8 mg IV dexamethasone. Ondansetron 4-8 mg IV at end of surgery.	34	0-2 hours: 0; 2-24 hours: 5 (14) * ; 0-24 hours: 5 (15)*	0-2 hours: 0 (0);2-24 hours: 1 (2.9)	Severe nausea= VRS≥7	0-2 hours: Severe: 0 (0) 2-24 hours: Severe: 0 (0)	0-2 hours: 0 (0); 2-24 hours: Severe: 1 (2.9)			0-24 hours: 3 (8.8) *	Ondansetrron: 4 mg: 6 (17.7) 8 mg: 28 (82.3) Dexamethasone: 4 mg: 16 (47) 8 mg: 18 (53)	Hypotension 1 (2.9) Pruritis 7 (20.5)
Moon *et al.*, 2014	Group 1: 40 mg aprepitant po with 30 mL water, 90 min before anesthesia. Saline (control for palanosetron) administered post intubation	46			11-point VAS score: 0=no nausea, 10=nausea as bad as possible	Mean±SE; 0 hr=11.2±2.1*; 2 hrs=9.7±2.1*		Complete response: VAS nausea score<4 and no use of rescue therapy		0-24 hours: 13 (28.2)		
	Group II: 0.075 mg palanosetron iv after endotracheal intubation.	47				Mean±SE; 0 hr=19.0±2.2; 2 hrs=19.4±3.5 No sig diff at 24 hrs; further details not provided				0-24 hours: 13 (27.7)		
Sinha *et al.*, 2014	Group I: 80 mg aprepitant po 60 mins before anesthesia.	64	Not reported	Reported at 72 hrs: 2 (3.1) *	11-point VRS score: 0=no nausea, 10=nausea as bad as possible Severe nausea≥4	Mean VRS at 2 hrs: 0.78±1.67; 24 hours: 1.31±2.67		Defined as no nausea or vomiting, without requiring any additional rescue antiemetic for 72 hours.	27 (42.2)	0-24 hours: 27 (42.2)	Ondansetron 4 mg, Dexamethasone 4 mg; Metoclopramide 10 mg; Droperidol 0.625 mg	
	Group II: placebo po 60 mins before anesthesia. Both groups received 4 mg ondansetron IV prior to cessation of surgery	60	Not reported	At 72 hrs: 9 (15) *		Mean VRS at 2 hrs: 1.20±2.33; 24 hrs: 1.27±2.42			22 (36.7)	0-24 hours: 26 (42.3)		

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Table 2: Contd...

Author, Year of publication	Intervention & comparison	Number of participants	MEASURED OUTCOMES									
			Nausea [*n* (%)]	Vomiting [*n* (%)]	Scale of severity	Severity of Nausea	Severity of vomiting	Definition of complete response	Complete response [*n* (%)]	Need for rescue antiemetic [*n* (%)]	Other antiemetic medication	Adverse effects
Yeon Ham *et al.*, 2014	Group I: 80 mg aprepitant po 60 min before anesthesia. Ondansetron 4 mg IV 20 min before end of surgery	55	PACU: 12 (22) *; 0-24 hours: 33 (60) *	PACU: 1 (2); 0-24 hours: 13 (24)	11-point VNRS score: 0=no nausea, 10=nausea as bad as possible	PACU: 0.9±1.8; PACU-6 hr: 1.3±2.3; 6-24 hr: 1.5±2.3; 24-48 hr: 0.9±1.8		Defined as no PONV and no rescue antiemetics upt 48 hours	PACU: 42 (76) 0-6 hours: 31 (56); 0-24 hours: 21 (38); 0-48 hours: 18 (33)	0-24 hours: 32 (58)		Headache: 15 (27); Dizziness: 37 (67); Sedation: 15 (27); Delayed flatus: 28 (52); Pruiritis: 2 (4)
	Group II: Placebo po 60 min before anesthesia. Ondansetron 4 mg IV, 20 min before end of surgery	55	PACU: 25 (45) *; 0-24 hours: 44 (80) *	PACU: 5 (9); 0-24 hours: 20 (36)		PACU: 1.4±2.2; PACU - 6 hr: 1.6±2.9; 6-24 hr: 2.1±2.4; 24-48 hr: 0.6±1.4			PACU: 27 (50) 0-6 hours: 18 (33); 0-24 hours: 9 (16); 0-48 hours: 9 (16)	0-24 hours: 32 (58)		Headache: 12 (22); Dizziness: 28 (52); Sedation: 11 (20); Delayed flatus: 24 (61); Pruritus: 5 (9)
Jung *et al.*, 2013	Group I: Control group no prophylactic antiemetic	40	0-2 hours: 25 (63); 2-24 hours: 16 (40)	0-2 hours: 3 (8); 2-24 hours: 8 (20)	11-point VRS score: 0=no nausea, 10=worst possible nausea	48 hours: Median (range): 6 (0-10)		Defined as no nausea, retching or vomiting and no need for rescue therapy	0-2 hours: 15 (38) 0-48 hours: 11 (28)	0-48 hours: 8 (20)		Dizziness 1; Headache 3; Dyspepsia 0; Abdominal distension 0
	Group II: Aprepitant 80 mg po 2 hour before anesthesia	40	0-2 hours: 14 (35) *; 2-24 hours: 11 (28)	0-2 hours: 0 (0); 2-24 hours: 0 (0)		48 hours: Median (range): 4 (0-10)			0-2 hours: 26 (65) *; 0-48 hours: 22 (56) *	0-48 hours: 3 (8)		Dizziness 1; Headache 1; Dyspepsia 2; Abdominal distension 0
	Group III: Aprepitant 125 mg po 2 hour before anesthesia	40	0-2 hours: 14 (35) *; 2-24 hours: 8 (20)	0-2 hours: 0 (0); 2-24 hours: 0 (0)		48 hours: Median (range): 4 (0-10)			0-2 hours: 26 (65) *; 0-48 hours: 25 (63) *	0-48 hours: 4 (10)		Dizziness 3; Headache 1; Dyspepsia 0; Abdominal distension 1

*VRS: verbal rating scale; PACU: Postanesthesia care unit; VNRS: verbal numerical rating scale; VAS: visual analogue scale; *: statistically significant ($p<0.05$)*

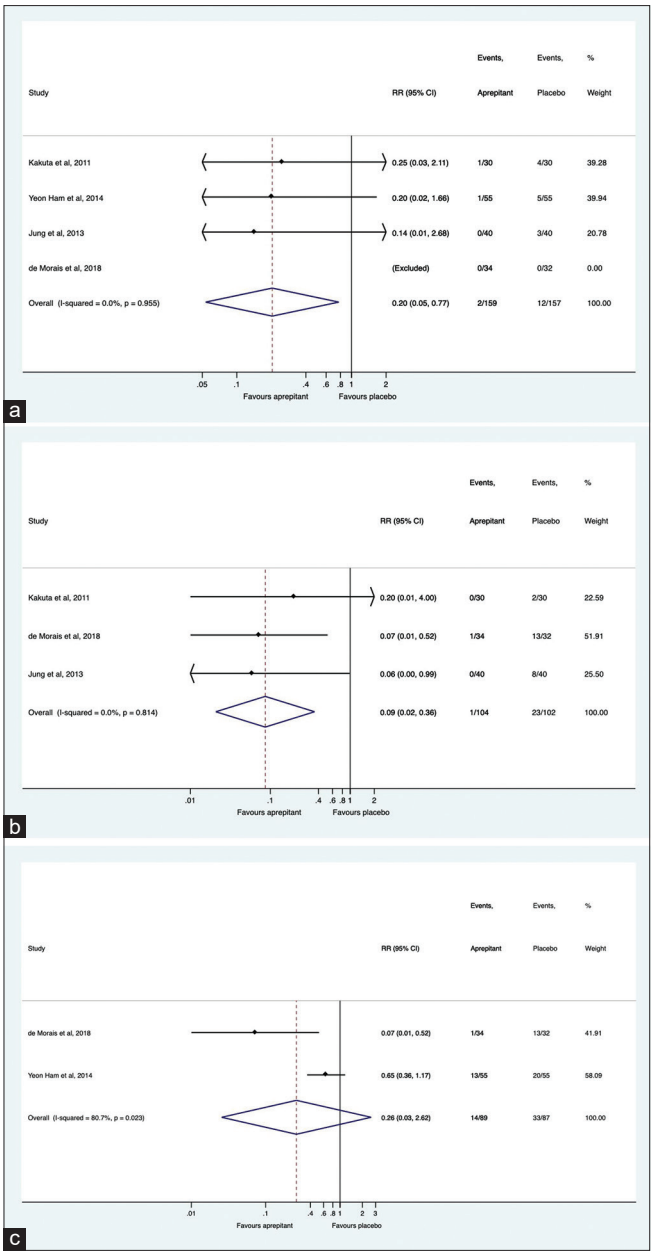

Figure 3: Forest plots of the included studies for vomiting in the first 24 hours following surgery. (a) Vomiting 0–2 hours following surgery. (b)Vomiting 2–24 hours following surgery. (c) Vomiting 0–24 hours following surgery

reported to be vomiting at 72 hours in a study on laparoscopic bariatric procedures.[31] This study included patients with high risk for PONV and all had received ondansetron as per protocol[31] [Table 2].

Secondary outcomes

Time to first vomiting

In the study by Sinha *et al.*, the placebo group had earlier onset of vomiting than the aprepitant group.[31] Similar finding has also been reported by Ham *et al.*,[29] with significantly delayed time to first PONV in the aprepitant group ($P = 0.014$).

Severity of PONV within 0–24 hours and the need for rescue antiemetics

In the study on laparoscopic abdominopelvic cancer surgery by de Morais *et al.*,[32] with ondansetron and dexamethasone intraoperative antiemetic protocol, there was no significant difference in the number of patients with severe PONV between the control vs aprepitant group. However, a higher number of aprepitant participants exhibited absence of vomiting during the first 24 hours ($p = 0.003$). In addition, there was a lesser need for rescue antiemetics in the aprepitant vs control group (8.8% vs 28.1% respectively, $P = 0.02$).[32] Similarly, more patients in the aprepitant group had less-intense nausea compared to the control group in the study by Kakuta *et al.*[26] in the first two hours ($P < 0.05$). Interestingly, significantly lower nausea scores have also been reported in the first two hours, in the 40 mg aprepitant group vs the palanosetron group ($P < 0.05$).[30] However, our meta-analysis revealed no significant difference in the severity of nausea in the first two hours[29,31] or the need for rescue antiemetics in the first 24 hours[29,32] between the groups [Table 3]. This lack of difference was also reported by the studies that measured the severity of PONV by VRS scores with aprepitant 80 mg or 125 mg upto 24 hours[29,31] or 48 hours.[28]

Complete response

A higher incidence of complete response in the aprepitant 80 mg and 125 mg groups compared with the no antiemetic group was observed by Jung *et al.*[28] at 2 hours ($p = 0.025$) and at 48 hours ($p = 0.007$ and $P = 0.003$, respectively) following surgery. Findings from other studies did not achieve statistical significance in spite of more aprepitant patients getting complete relief from PONV compared to the control group.[29,31] Our meta-analysis showed that aprepitant 80 mg had a higher likelihood of complete response in the first two hours ($n = 190$; Pooled RR: 1.61 (1.25, 2.08), $I^2 = 0.0\%$, $P = 0.70$) and first 48 hours ($n = 190$; pooled RR: 2.00 (1.28, 3.13), $I^2 = 0.0\%$, $P = 1.00$) compared to the control group [Table 3].

Pain scores and opioid consumption

No significant differences have been reported between the control group and treatment group (aprepitant 80 mg) with pain scores or opioid consumption.[27,29,32]

Adverse effects

No major adverse effects have been reported in the aprepitant group. However, according to one study, a greater number of aprepitant patients had headache, dizziness, sedation, and delayed flatus.[29] A lower incidence of pruritis in the aprepitant group has also been reported by two studies[29,32] [Table 2].

Risk of bias in the studies

Of the studies we reviewed, three studies were of good quality[26,29,32] and four were poor-quality studies.[27,28,30,31] But for Kakuta *et al.*,[27] all the studies were of low risk of bias in terms of random sequence generation and blinding with outcome assessment. One study was considered to have a high risk of bias with allocation concealment and selective reporting of outcomes[30] and the others fell under low or unclear risk of bias [Table 4].

Funnel plots were avoided due to the insufficient number of eligible studies in our meta-analysis.[33]

Discussion

Our meta-analysis demonstrated that 80 mg aprepitant lowers the risk of nausea by 44% and vomiting by 80% (0–2 hours) and 91% (2–24 hours) in comparison with the control patients that were administered either placebo or no antiemetic following laparoscopic procedures in adult patients. This risk reduction was evident even when other antiemetics such as ondansetron were given as per the protocol in two of the reviewed studies.[29,32] Due to lack of sufficient evidence, we are unable to make any conclusions about the antiemetic efficacy of the other drugs or dosages. Similar to our review, Liu *et al.*[12] observed the superiority of 80 mg over placebo and found all doses of aprepitant to be more effective against postoperative vomiting than against nausea.[12] Two large multicenter studies also concluded that NK-1 receptor antagonists (aprepitant and rolapitant) were better for controlling vomiting than nausea.[6,7] In fact, based on evidence across various surgical procedures, the number of patients needed to be treated with aprepitant to prevent one episode of nausea and vomiting was found to be 12 and 6, respectively, when used instead of 5 HT_3 antagonists.[34]

Although aprepitant is available in various strengths, the recommended dose of aprepitant is 40 mg within 3 hours of preinduction for the prevention of PONV.[10] In our review, the two studies[26,30] that investigated the 40 mg dose have not found any superiority of aprepitant treatment over 5HT-3 antagonists, except for a reduction in nausea intensity up to 2 hours in the aprepitant group.[30] In a large multicenter study,

Table 3: Meta-analysis of the included studies for the secondary outcomes

Study	Sample size	RR (95% CI)	% weight
Complete response 0-2 hours			
Yeon Ham *et al.*, 2014	110	1.56 (1.14,2.11)	69.25
Jung *et al.*, 2013	80	1.73 (1.09, 2.75)	30.75
Overall	n=190; Pooled RR: 1.61 (1.25,2.08) I^2=0.0%, P=0.699)		100
Complete response 0-48 hours			
Yeon Ham *et al.*, 2014	110	2.00 (0.99, 4.06)	39.86
Jung *et al.*, 2014	80	2.00 (1.12, 3.56)	60.14
Overall	n=190; Pooled RR: 2.00 (1.28,3.13) I^2=0.0%, P=1.00)		100
Severity of nausea 0-2 hours			
Sinha *et al.*, 2014	124	-0.21# (-0.56, 0.14)	53.02
Yeon Ham *et al.*, 2014	110	-0.25 # (-0.62, 0.13)	46.98
Overall	n=234; pooled SMD: -0.23 (-0.48, 0.03) I^2=0.0%, P=0.878		100
Need for rescue antiemetic 0-24 hours			
de Morais *et al.*, 2018	66	0.31 (0.09, 1.06)	38.00
Yeon Ham *et al.*, 2014	110	1.10 (0.73, 1.37)	62.00
Overall	n=176; pooled RR: 0.64 (0.20, 2.06) I^2=72.5%, P=0.06		100

SMD: standardized mean difference; RR: relative risk; CI: confidence intervals

Table 4: Cochrane risk of bias assessment of the included studies

Study	Random sequence generation	Allocation concealment	Selective reporting	Other sources of bias	Blinding (participants and personnel)	Blinding (outcome assessment)	Incomplete outcome data	Conclusion about quality
Sinha *et al.*, 2014	Low	Unclear	Unclear	Unclear	Low	Low	Low	Poor
Jung *et al.*, 2013	Low	Unclear	Unclear	Low	Unclear	Low	Unclear	Poor
De Morais *et al.*, 2018	Low	Low	Low	Low	Low	Low	Low	Good
Moon *et al.*, 2014	Low	High	High	Low	Unclear	Low	Low	Poor
Bilgen *et al.*, 2018	Low	Unclear	Low	Low	Low	Low	Low	Good
Kakuta *et al.*, 2011	Unclear	Unclear	Unclear	Unclear	High	Unclear	Unclear	Poor
Ham *et al.*, 2018	Low	Low	Unclear	Low	Low	Low	Low	Good

on open abdominal surgery (n = 805) comparing aprepitant 40 and 125 mg with ondansetron, aprepitant at both the doses was found to be superior for the prevention of vomiting up to 48 hours. There was no difference between aprepitant and ondansetron groups with nausea or the use of rescue antiemetics or with complete response.[6] A similar finding was reported by Sinha *et al.* in laparoscopic bariatric procedures, although aprepitant 80 mg was administered as a standard dose and not calculated as per the body weight.[31] There are no currently available dose–response studies[34] or recommendations on weight-based dosing for aprepitant among bariatric patients.[19]

To our knowledge, this is the first meta-analysis investigating NK1 receptor antagonists for PONV exclusively in laparoscopic surgery. A previous meta-analysis[13] had concluded the superiority of aprepitant; however, they had pooled studies on various surgical procedures (e.g., open abdominal surgery, joint replacements, and neurosurgery), various doses of aprepitant, and various comparators, with a high level of heterogeneity despite multiple subgroup analyses. Nevertheless, their conclusions[12,13] regarding the efficacy of 80 mg aprepitant were consistent with our findings. We have strictly included only prospective randomized controlled trials on laparoscopic surgical procedures. The main conclusions that we have presented are based on homogeneous pooling and hence can be considered robust, albeit this strict selection process had limited the number of studies that could be pooled.

Our meta-analysis had some limitations. Our selection criteria may have resulted in publication and language bias. The number of studies suitable for pooling was low and hence certain outcomes were only considered for systematic review. We did not attempt funnel plots for the same reason. The studies were small and may have been less precise by themselves. It is possible that the bias induced by poor-quality trials may have influenced the results. Not every outcome of our interest could be summated for quantitative analysis, for reasons such as outcomes not being reported or the use of different outcome scales. Hence, they were reported as such. We could not find any suitable study that investigated NK-1 receptor antagonists other than aprepitant or that compared NK-1 receptor antagonists with other antiemetics.

Conclusion

When compared to placebo or no antiemetics, preoperative oral aprepitant 80 mg led to significant reduction in the risk of nausea and vomiting in the first two hours and thereafter, the risk of vomiting alone until the first 24 hours following adult laparoscopic surgery. However, further studies are needed to evaluate its superiority over other antiemetics or for the management of PONV after 24 hours. There was lack of any evidence to draw conclusions on the anti-PONV efficacy of other NK1 receptor antagonists or other doses of aprepitant in adult laparoscopic surgery.

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Conflicts of interest

There are no conflicts of interest.

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