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

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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...
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\(^1\)) and oral netupitant in combination with palonosetron (Akynzeo\(^8\)) 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 pneumopenitoneum 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 21\(^{\text{st}}\) 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](image-url)
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. 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], 25 full text articles were screened further for eligibility. Two articles were excluded for being observational studies, of which Hache et al. did not involve the comparison of aprepitant. Six references were excluded as the drugs of interest were trialled only on open procedures. 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. One was found to be an abstract of another full text article and hence excluded. Finally, seven articles on aprepitant were included for our systematic review.

Study characteristics

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

Four studies 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. 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 or 11 point scales) and various definitions of severe nausea (verbal rating score (VRS) of ≥four or ≥seven), they could not be combined in a meta‑analysis. One study that investigated aprepitant 125 mg 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 and increased in the study on abdominal and pelvic oncology procedures. This last-mentioned study had included patients at high risk of PONV.

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, I² = 0%, and P = 0.89) [Figure 2] in the aprepitant (80 mg) group. Within 2–24 hours, a lower percentage of patients reported nausea in the aprepitant 80 mg group and our pooled analysis also found a reduced risk of nausea (RR 0.42, 95% CI: 0.21–0.81, I² = 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. 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 [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, adhesiolysis, myomectomy, vaginal hysterectomy, salpingostomy) | General anesthesia | Group I (control): 130±52; Group II (aprepitant): 125±43 | Group I: 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 periprotative 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 | Laparoscopic 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 I: 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 I-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 I: 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 |

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 |
|----------------------------------------|--------------|--------------|-----------------|-------------------|-------------------------------|----------------------------------|------------------------|---------------------------------------------|
| 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 (ind 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 mg 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/ adnexitomy, nephrectomy, hemicolectomy, partial gastrectomy) | General anesthesia and neuraxial block | Group I: (control): 367.5 (145-600) Group II: (treatment): 437.5 (131-610) | | Group I: Oral starch po 1 hr Ondansetron 4-8 mg IV at end of surgery Group II: 80 mg aprepitant po 1 hr pre-induction 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 |
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, I² = 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, I² = 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 1: Contd...

| Author, year of publication and country | Study design | Type of surgery | Type of anesthesia | Duration of surgery (minutes) | Participants | Intervention & comparison | Postoperative regular and rescue antiemetic | Number of participants/ demographics |
|----------------------------------------|-------------|-----------------|-------------------|-----------------------------|-------------|--------------------------|---------------------------------|---------------------------------|
| Bilgen et al., 2018; Turkey             | Double blind, randomised, placebo controlled trial | Laparoscopic gynaecological surgery or laparoscopic cholecystectomy | General anaesthesia | Group I: Dexamethasone-Ondansetron 67.1±24.5; Group II: Dexamethasone-Aprepitant 74.8±29.4 | 34; 35.3±7.9; 66.8±14.3 | Group I: Control group: oral placebo 1‑2 hr preinduction; IV dexamethasone 8 mg postinduction; 2 ml of IV saline last 30 minutes of surgery; Group II: Aprepitant 40 mg po 1‑2 hours preinduction, IV dexamethasone 8 mg postinduction; Ondansetron 4 mg IV | Ondansetron 4 mg IV | 33; 40±10.9; 66.9±13 |

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.
| Author, Year of publication | Intervention & comparison | Number of participants | Nausea [n (%)] | Vomiting [n (%)] | Scale of severity | MEASURED OUTCOMES | Need for rescue antiemetic medication [n (%)] | Other antiemetic medication | Adverse effects |
|----------------------------|---------------------------|------------------------|----------------|----------------|------------------|------------------|---------------------------------|-----------------------------|----------------|
| Kakuta et al., 2011 | Group I: Control group (no antiemetic); Group II: Aprepitant 80 mg po 3 hours before surgery | 30 | 0-2 hours: 19 (63.3); 2-24 hours: 8 (26.7) * | 0-2 hours: 4 (13.3); 2-24 hours: 2 (0.7) | 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: 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 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 | 34 | 0-2 hours: 10 (30.4); 2-24 hours: 4 (11.8) | 0-2 hours: 1 (0.03); 24 hours: 0 (0) | Nausea: 10‑point VRS scale from 0-11 = severe | 0-2 hours: VRS ≥ 4: 23 (67.6) 2-24 hours: VRS ≥ 4: 4 (11.8) | 0-2 hours: 1; 2-4 hours: 0 | | | |
| 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 (37.5); 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); 2-24 hours: Severe: 24 (75) | 0-24 hours: 9 (28.1) * | | |

Contd...
| Author, Year of publication | Intervention & comparison | Number of participants | Number of participants | Nausea [n (%)] | Vomiting [n (%)] | Scale of severity | MEASURED OUTCOMES |
|-----------------------------|--------------------------|------------------------|------------------------|----------------|----------------|------------------|----------------|
| 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: 0 (0); 24 hours: 5 (14) *; 0-24 hours: 5 (15) * | Severe nausea= VRS≥7 | 0-2 hours: 0 (0); 2-24 hours: Severe: 0 (0); 0-24 hours: 2-24 hours: Severe: 0 (0) | Complete response: VAS nausea score<4 and no use of rescue therapy | Complete response [n ( %)]: 0-24 hours: 3 (8.8) * | Ondansetron: 4 mg: 6 (17.7) Hypotension 8 mg: 28 (82.3) Pruritis 4 mg: 16 (47) 8 mg: 18 (53) |
| 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 | Complete response [n ( %)]: 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 | Complete response: VAS nausea score<4 and no use of rescue therapy | Complete response [n ( %)]: 0-24 hours: 13 (27.7) |
| Sinha et al., 2014 | Group I: 80 mg aprepitant po 60 mins before anesthesia. | 64 | Not reported | 11-point VRS score: 0=no nausea, 10=nausea as bad as possible | Defined as no nausea or vomiting, without requiring any additional rescue antiemetic for 72 hours. | Defined as complete response [n ( %)]: 0-24 hours: 27 (42.2) 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: 0.78±1.67; 24 hours: 1.31±2.67 | Defined as complete response: VAS nausea score<4 and no use of rescue therapy | Defined as complete response [n ( %)]: 0-24 hours: 26 (42.3) | Contd... |
| Author, Year of publication | Intervention & comparison | Number of participants | MEASURED OUTCOMES | | |
|---|---|---|---|---|
| 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 | Nausea [n (%)] | PACU: 12 (22); 0-24 hours: 33 (60) * |
| | | | Vomiting [n (%)] | PACU: 1 (2); 0-24 hours: 13 (24) |
| | | | Scale of severity | 11-point score: 0 = nausea as bad as possible |
| | | | Severity of Nausea | PACU: 0.9±1.8; PACU-6 hr: 1.3±2.3; 24-48 hr: 1.5±2.3; 24-48 hr: 0.9±1.8 |
| | | | Definition of complete response | Defined as no PONV and no rescue antiemetics up 48 hours |
| | | | Need for rescue antiemetic [n (%)] | PACU: 42 (76); 0-6 hours: 31 (56); 0-24 hours: 21 (38); 0-48 hours: 21 (38); |
| | | | Other antiemetic medication | Headache: 32 (58); Dizziness: 0.9±1.8; Sedation: 1.6±2.9; Delayed flatus: 0.9±1.8 |
| | Group II: Placebo po 60 min before anesthesia. Ondansetron 4 mg IV 20 min before end of surgery | 55 | Nausea [n (%)] | PACU: 25 (45); 0-24 hours: 44 (80) * |
| | | | Vomiting [n (%)] | PACU: 5 (9); 0-24 hours: 20 (36) |
| | | | Scale of severity | 11-point VNRS score: 0 = nausea, 10 = nausea as bad as possible |
| | | | Severity of vomiting | PACU: 1.4±2.2; PACU-6 hr: 1.6±2.9; 24-48 hr: 0.6±1.4 |
| | | | Definition of complete response | Defined as no PONV and no rescue antiemetics up 48 hours |
| | | | Need for rescue antiemetic [n (%)] | PACU: 27 (50); 0-24 hours: 32 (58); 0-48 hours: 27 (50); |
| | | | Other antiemetic medication | Headache: 12 (22); Dizziness: 1.4±2.2; Sedation: 1.6±2.9; Delayed flatus: 1.6±2.9 |
| | | | Adverse effects | Headache: 25 (45); Dizziness: 3 (8); Sedation: 0.6±1.4 |
| | | | Other antiemetic medication | Headache: 24 (61); Dizziness: 1.4±2.2; Sedation: 1.6±2.9 |
| | Jung et al., 2013 | Group I: Control group no prophylactic antiemetic | 40 | Nausea [n (%)] | 0-2 hours: 25 (63); 0-24 hours: 16 (40) |
| | | | Vomiting [n (%)] | 2-24 hours: 3 (8); 0-24 hours: 8 (20) |
| | | | Scale of severity | 11-point VRS score: 0 = nausea, 10 = nausea as bad as possible |
| | | | Severity of vomiting | 48 hours: Median (range): 6 (0-10) |
| | | | Definition of complete response | Defined as no nausea, retching or vomiting and no need for rescue therapy |
| | | | Need for rescue antiemetic [n (%)] | 0-2 hours: 15 (38); 0-48 hours: 11 (28); 0-48 hours: 22 (56) * |
| | Group II: Aprepitant 80 mg po 2 hour before anesthesia | 40 | Nausea [n (%)] | 0-2 hours: 14 (35) *; 2-24 hours: 2 (24) |
| | | | Vomiting [n (%)] | 0-2 hours: 0 (0); 0-24 hours: 0 (0) |
| | | | Scale of severity | 48 hours: Median (range): 4 (0-10) |
| | | | Severity of vomiting | 0-2 hours: 26 (65) *; 0-48 hours: 22 (56) * |
| | | | Definition of complete response | Defined as no nausea, retching or vomiting and no need for rescue therapy |
| | | | Need for rescue antiemetic [n (%)] | 0-2 hours: 26 (65) *; 0-48 hours: 25 (63) * |
| | | | Other antiemetic medication | Headache: 1.2 (31); Dizziness: 0.6±1.4; Sedation: 1.4±2.2; Delayed flatus: 0.6±1.4 |
| | Group III: Aprepitant 125 mg po 2 hour before anesthesia | 40 | Nausea [n (%)] | 0-2 hours: 14 (35) *; 2-24 hours: 8 (20) |
| | | | Vomiting [n (%)] | 0-2 hours: 0 (0); 0-24 hours: 0 (0) |
| | | | Scale of severity | 48 hours: Median (range): 4 (0-10) |
| | | | Severity of vomiting | 0-2 hours: 26 (65) *; 0-48 hours: 25 (63) * |
| | | | Definition of complete response | Defined as no nausea, retching or vomiting and no need for rescue therapy |
| | | | Need for rescue antiemetic [n (%)] | 0-2 hours: 26 (65) *; 0-48 hours: 25 (63) * |
| | | | Other antiemetic medication | Headache: 1.2 (31); Dizziness: 0.6±1.4; Sedation: 1.4±2.2; Delayed flatus: 0.6±1.4 |

VRS: verbal rating scale; PACU: Postanesthesia care unit; VNRS: verbal numerical rating scale; VAS: visual analogue scale; *: statistically significant (p<0.05)
reported to be vomiting at 72 hours in a study on laparoscopic bariatric procedures. 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. Similar finding has also been reported by Ham et al., 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., 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). Similarly, more patients in the aprepitant group had less-intense nausea compared to the control group in the study by Kakuta et al. 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 palonosetron group (P < 0.05). However, our meta-analysis revealed no significant difference in the severity of nausea in the first two hours or the need for rescue antiemetics in the first 24 hours 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 up to 24 hours or 48 hours.

**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. 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. 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), I² = 0.0%, P = 0.70) and first 48 hours (n = 190; pooled RR: 2.00 (1.28, 3.13), I² = 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.

**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. A lower incidence of pruritis in the apreptant group has also been reported by two studies [29,32] [Table 2].

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**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.
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 HT3 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,

| 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 | Unclear | Low | Unclear | Low | Poor |
| de Morais et al., 2018 | Low | Low | Low | Low | Low | Low | Low | Poor |
| Moon et al., 2014 | Low | High | Low | Low | Unclear | Low | Low | Good |
| 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 |

SMD: standardized mean difference; RR: relative risk; CI: confidence intervals
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.\[^{11}\] 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 summed 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 NK1 receptor antagonists other than aprepitant or that compared NK1 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.

**Acknowledgments**

We would like to thank Chris Parker and Jana Waldmann, Librarians at the Prince Charles Hospital for their assistance with literature search and Dr. Margaret Soroka for proofreading the draft.

**Financial support and sponsorship**

Nil

**Conflicts of interest**

There are no conflicts of interest.

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