Neurokinin-1 Receptor Antagonists in Preventing Postoperative Nausea and Vomiting

A Systematic Review and Meta-Analysis

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Abstract: Newly developed neurokinin-1 receptor (NK-1R) antagonists have been recently tried in the prevention of postoperative nausea and vomiting (PONV). This systematic review and meta-analysis was conducted to explore whether NK-1R antagonists were effective in preventing PONV.

The PRISMA statement guidelines were followed. Randomized clinical trials (RCTs) that tested the preventive effects of NK-1R antagonists on PONV were identified by searching EMBASE, CINAHL, PubMed, and the Cochrane Library databases followed by screening. Data extraction was performed using a predefined form and trial quality was assessed using a modified Jadad scale. The primary outcome measure was the incidence of PONV. Meta-analysis was performed for studies using similar interventions. Network meta-analysis (NMA) was conducted to compare the anti-emetic effects of placebo, ondansetron, and aprepitant at different doses.

Fourteen RCTs were included. Meta-analysis found that 80 mg of aprepitant could reduce the incidences of nausea (3 RCTs with 224 patients, pooled risk ratio (RR) = 0.60, 95% confidence interval (CI) = 0.47 to 0.75), and vomiting (3 RCTs with 224 patients, pooled RR = 0.13, 95% CI = 0.04 to 0.37) compared with placebo. Neither 40 mg (3 RCTs with 1171 patients, RR = 0.47, 95% CI = 0.37 to 0.60) nor 125 mg (2 RCTs with 1058 patients, RR = 0.32, 95% CI = 0.13 to 0.78) of aprepitant showed superiority over 4 mg of ondansetron in preventing postoperative vomiting. NMA did not find a dose-dependent effect of aprepitant on preventing postoperative vomiting.

INTRODUCTION

Postoperative nausea and vomiting (PONV) is commonly seen after major surgery. It is estimated that about 30% of the surgical patients will suffer from PONV during the first postoperative day.1 The incidence of PONV can be as high as 70% in patients combined with several risk factors such as the use of inhaled anesthetics or opioids, female sex, nonsmoking, and pre-existing motion sickness.2–4 PONV is distressing to patients, costly and even affects the postoperative recovery profile.5 Moreover, successful prevention of PONV might greatly improve patients’ satisfaction.6

Several kinds of antiemetics including serotonin 5-HT3 receptor antagonists, dopamine receptor antagonists, histamine H2 receptor antagonists, anticholinergic agents, and corticosteroids have been tried, which have showed effects on the prevention of PONV.1 These drugs mainly act by interfering with neurotransmitter receptors signaling in the central nervous system and gastrointestinal tract except corticosteroids. However, none of the aforementioned antiemetics is universally effective and efficient enough in controlling PONV. In some cases, although several kinds of drugs were provided, they still experience PONV.7 Thereafter, more powerful antiemetics are still needed to further reduce the development of PONV.

Neurokinin-1 receptor (NK-1R) is widely expressed in human gastrointestinal vagal afferents and brain areas that are involved in the vomiting reflex such as the nucleus of solitary tract (NST).8 Substance P, the natural ligand of NK-1R, was found to be able to trigger NK-1R signaling, thereby causing nausea and vomiting.9,10 NK-1R antagonists are believed to provide antiemetic activity mainly by suppressing neuron activities at NST, the central regulator of visceral function.11 Several selective NK-1R antagonists have been developed for the prevention and control of nausea and vomiting including aprepitant, fosaprepitant, casopitant, rolapitant, and others. Aprepitant, a highly selective NK-1R antagonist with 9 to 14-hour half-life time, has been approved by FDA for
the management of PONV, whereas other ones like rolapitant and casopitant are still under clinical observation. Moreover, NK-1R antagonists have shown great antiemetic activities against chemotherapy-induced nausea and vomiting (CINV), which shared similar traits with PONV. These results encouraged the prophylactic use of NK-1R antagonists to avoid PONV. However, the clinical effects of NK-1R antagonists on PONV prevention remain inconclusive. To explore whether NK-1R antagonists are effective in preventing PONV, the current systematic review and meta-analysis is performed.

METHODS

This systematic review and meta-analysis was conducted following the guidelines of PRISMA statement. Ethical approval of our study was not necessary, as this systematic review and meta-analysis did not involve patients.

Search Strategy

We conducted a literature search of electronic EMBASE, CINAHL, PubMed, and the Cochrane Library databases for articles published before March 31, 2014. The search strategy consisted of a combination of the following free texts and MeSH terms: NK1 receptor antagonists (including neurokinin, NK1, NK1R, NK-1, NK-1R, aprepitant, fosaprepitant, casopitant, rolapitant, ezlopitant, netupitant, CP122721, or vestipitant), postoperative (including surger*, operation, postoperative, or surgical), and vomiting (including vomit*, nausea, queasiness, naupathia, retch*, emesis, or emeses). No language or region restriction was applied. Reference lists of the identified articles were further checked for potential relevant publications.

Study Selection

Two authors (M.L. and B.D.) independently read the titles and abstracts of the 471 articles returned from the initial search. Articles that were clearly irrelevant according to our predefined inclusion and exclusion criteria were excluded at this phase. Completed studies that met all the following criteria were considered eligible for inclusion in the systematic review and meta-analysis: randomized clinical trials (RCTs) assessing interventions to prevent PONV; participants at least 18 years old, with an American society of Anesthesiologists (ASA) physical status of I to III; and trials comparing the antiemetic effects of NK-1R antagonists with that of other drugs or placebo. Research articles were excluded if they recruited patients with nausea and vomiting before surgery or prophylactic drug administration; were trial protocols or unfinished studies; included nonsurgical patients groups; or enrolled patients with intraoperative chemotherapy. Disagreements on inclusion were resolved by further discussion with a third investigator (X.S.).

Data Extraction

The primary outcome measure was the incidence of nausea and vomiting. The secondary outcome was the rate of complete response (CR, defined as the absence of vomiting and no need of any rescue antiemetics) and the time to first vomiting (hour). Incidences of using rescue drugs and adverse events were also analyzed if possible. The time point used for data syntheses and comparisons was 24 hours after surgery at which the outcome measures were most frequently reported in the included studies. For a single study, we described all the related outcomes according to the time points listed in the article.

Two authors (M.L. and H.Z.) independently extracted data of all identified trials using a predesigned data collection form. Disagreements were resolved by the third author consultation (X.S.). The following characteristics were collected: primary author, publication year, trial type (single-centered or multi-center trial), participant characteristics (age, sex, and number), types of surgery, anesthesia methods, analgesics and anesthetics, antiemetic prophylaxis (drugs and dosages), the incidence of PONV, the incidence of CR, the time to first vomiting (hour), the percent of using rescue antiemetics, and antiemetics-related adverse events. Dichotomous data were converted into incidences for data syntheses and continuous data were recorded using mean and standard deviation (SD). When incomplete data were encountered, we attempted to contact the authors for details. When no response or no detailed data was provided, we arbitrarily deemed their results as uncertain and ruled out the study for data synthesis.

Trial Quality Assessment

Two authors (H.F. and Z.Z.) independently read the full texts of included articles and assessed their validity using a modified Jadad scale that we previously described. The scale evaluated the study quality using the following indicators: randomization, allocation concealment, intervention blinding, withdrawal or dropouts, and intention-to-treat (ITT) analysis. For each indicator, except ITT analysis, 1 point was given when the study used proper methods, and another 1 point was given if the study described them adequately. Otherwise, no point was given. As we selected only randomized trials for analysis, the possible minimal score of an included trial was 1 and the maximum was 8. Studies were not excluded or weighted based on the quality scores in the meta-analysis.

Data Analysis

Meta-analysis was performed when ≥2 studies using similar interventions were identified. Two control groups were used in our study, placebo and ondansetron, with data analyzed separately. If one study additionally used some NK-1R antagonist to prevent PONV in the intervention group besides routine antiemetics, we arbitrarily classified this kind of studies as studies comparing the antiemetic effect of NK-1R antagonist to that of placebo. As there was no valid method to conduct dose conversion among different NK-1R antagonists (aprepitant, fosaprepitant, casopitant, ezlopitant, netupitant, CP122721, and vestipitant), we performed data syntheses for each drug at every single dose. If relevant data could not be analyzed quantitatively, we reported the results of each study qualitatively with the corresponding P values.

RevMan Version 5.2 software (Cochrane Collaboration) was used for data syntheses. Statistical heterogeneity was assessed with a standard $\chi^2$ and $I^2$ statistic. Significant heterogeneity was considered evident at $\chi^2 P < 0.10$ or $I^2 > 50\%$ (2-tailed). A fixed-effects parametric approach weighted with the inverse variance was performed when no significant heterogeneity was found. Otherwise, a random-effects model was taken. For dichotomous outcome measures, both pooled risk ratio (RR) and pooled incidence with 95% confidence intervals (CIs) were calculated. For continuous data, standard mean difference (SMD) was used. Publication bias was assessed by visually inspecting funnel plot and using Begg test if needed. For all the analyses, a $P$ value of less than 0.05 (2-tailed) was considered statistically significant.
A Bayesian random effects model for multiple treatment comparison was constructed to compare the anti-emetic effects of aprepitant at different doses. The network meta-analysis (NMA) was performed by calling WinBUGS 1.4.3 software (MRC Biostatistic Unit, Cambridge, UK) through the R statistical software using the R2WinBUGS package (R Foundation for Statistical Computing, Vienna, Austria). We used Markov chain Monte Carlo method in WinBUGS, running 3 chains with different starting values (see Supplemental Digital Content, which describes the R codes in detail). Odds ratio (OR) with 95% CI was presented as summary statistics, and a significant difference was deemed existed when 95% CI of the OR did not include 1.

RESULTS

Study Selection

The primary search yielded 471 articles. After abstract screening, 21 studies 8,13–15,20–36 that potentially met the inclusion criteria were identified. The full-text publications of these studies were examined at detail, and 7 trials were further excluded: 2 studies were not RCTs30,31; one study described ongoing trials32; one study used NK-1R antagonists for patients who already developed nausea or vomiting36; one study investigated the efficacy of NK-1R antagonists on post-discharge nausea and vomiting37; and 2 studies compared NK-1R antagonist alone to that combined with additional antiemetics.38,39 We finally included 14 RCTs8,13–15,20–29 in this systematic review and meta-analysis (Figure 1).

Study Characteristics

The characteristics and main outcomes of included 14 studies8,13–15,20–29 were listed in Tables 1 and 2, respectively. These studies, consisting of 5 multicenter studies14,20–23 and 9 single-centered studies,8,13,15,24–29 recruited from 6026 to 92220 patients. The earliest study was published in 2000 by Gesztesi et al.15 Thirteen studies were described in English with 1 in Spanish.26 The surgery types included otorhinolaryngological,13 plastic,27 gynecological,8,15,21,25,28 abdominal surgeries,14,20,21,23,26,29 and craniotomy.24 All surgeries were performed under general anesthesia using volatile anesthetics that included sevoflurane, isoflurane, desflurane, or N2O (Table 1). The efficacy of aprepitant was tried in ten trials8,13,14,20,24–29 with the dosage ranging from 40 to 125 mg. Two studies 21,22 tested the antiemetic role of different doses of casopitant. The antiemetic efficacy of different dosages of rolapitant20 and CP12272115 was tried respectively in the rest 2 trials.

Quality Scores of Included Studies

The scores of included studies were shown in Table 3. The average score was 5.43 with a standard deviation (SD) of 2.03. A score <3 was found in 2 studies.13,20 Two studies got a full score of 8,19,20

Quantitative Review and Meta-Analysis

Primary Outcomes

Incidence of Nausea

Of the 8 trials8,15,21,23–26,28 reporting the incidence of nausea, 3 studies8,25,28 with 224 patients tested the effects of 80 mg of aprepitant versus placebo on preventing postoperative nausea. Meta-analysis using the fixed-effects model showed that prophylactic aprepitant (80 mg) was effective in lowering the incidence of nausea compared with placebo (P < 0.001, Figure 2). The pooled incidence of nausea was 45.2% (95% CI = 36.2 to 56.5) in patients receiving 80 mg of aprepitant and was 76.1% (95% CI = 67.8 to 85.4) in patients taking placebo. Jung et al28 further showed that 125 mg of aprepitant was also effective in preventing nausea compared with placebo. There was no difference in the incidence of nausea between 2 doses of aprepitant (35% vs 35%; 80 vs 125 mg of aprepitant).28

The comparative effects of 80 mg aprepitant and 4 mg ondansetron in preventing postoperative nausea were tested by Alonso-Damian et al.26 Their study found that patients taking aprepitant had less nausea on arrival in the recovery room (3.3% vs 53.3%; P < 0.001) and 6 hours after surgery (none vs 33.3%; P = 0.002) compared with patients taking ondansetron. Moreover, the 2 groups showed similar incidences of nausea during the time intervals of 6 to 24 hours after surgery (0/30 vs 1/30; aprepitant vs ondansetron; P = 0.313). However, this study was low in trial quality with a modified Jadad score of 3, and recruited only 30 patients per group.26

When aprepitant was taken at a lower dose (40 mg), Habib et al24 did not find a significant difference in the incidence of nausea, the proportions of significant nausea or nausea scores between aprepitant and ondansetron (4 mg) at all 3 time points (0–2; 0–24, and 0–48 hours). Both groups of patients received 10 mg dexamethasone after the induction of general anesthesia. Based on their reported incidences of nausea, 708 patients per group were needed to get a significant difference in the incidence of nausea at 48 hours after surgery.

Singla et al21 reported that all 3 doses of casopitant (50, 100, or 150 mg) failed to decrease the incidence of nausea compared with placebo. Gan et al23 found no difference among 20, 70, and 200 mg of rolapitant and placebo in reducing the occurrence of postoperative nausea.

Incidence of Vomiting

Thirteen of the included 14 studies,8,13,14,20–29 reported the incidence of vomiting. The reported incidences ranged from...
TABLE 1. Characteristics of Included Studies

| Author, Year | Quality Score | Surgery | Anesthesia | Antiemetic Prophylaxis | Surgery Time (min, Mean ± SD) | Anesthesia Time (min, Mean ± SD) | Postoperative Analgesia | Age, y | Sex (F/M) | Multi-centered Study |
|--------------|---------------|---------|------------|------------------------|-----------------------------|-----------------------------|------------------------|-------|-----------|---------------------|
| Sinha, 201429 | 6              | Open ABD | Sevoflurane/desflurane | Ap 80 mg + Ondan 4 mg vs Ondan 4 mg | 153.1 ± 43.8 vs 141.9 ± 41.8 | N/A | IV morphine | 43.1 ± 12.5 vs 43.2 ± 12.7 | 42/22 vs 39/21 | No |
| Lim, 201313   | 2              | OTORI   | Desflurane/remifentanil | Ap 125 mg + Ondan 4 mg vs Ap 80 mg + Ondan 4 mg vs Ondan 4 mg | 55 ± 32 vs 83 ± 72 vs 62 ± 32 | 77 ± 31 vs 105 ± 73 vs 84 ± 33 | Ketracel | 41 ± 12 vs 45 ± 12 vs 45 ± 12 | 6/20 vs 10/18 vs 6/18 | No |
| Vallejo, 201227 | 6              | Plastic | Sevoflurane/fentanyl1 | Ap 40 mg + Ondan 4 mg placebo + Ondan 4 mg | 122.9 ± 73.3 vs 117.4 ± 65.4 vs 108 ± 46.9 | 164.3 ± 80.1 vs 153.2 ± 70.1 vs 158.8 ± 46.9 | IV analgesics | 43.7 ± 14.3 vs 45.3 ± 16.3 | 70/5 vs 70/4 | No |
| Lee, 201227   | 4              | GYN     | Desflurane/remifentanil/N2O | Ap 80 mg + Ramo 3 mg vs Rama 3 mg | 113.4 ± 61.6 vs 124 ± 48.7 | 145.0 ± 62.3 vs 158.8 ± 46.9 | IV fentanyl | 43.8 ± 8.2 vs 43.6 ± 10.4 | F42 vs F42 | No |
| Jung, 201328  | 5              | Endo GYN | Isoflurane | Ap 12.5 mg vs Ap 80 mg vs placebo | 96 ± 38 vs 102 ± 33 vs 102 ± 54 | 122 ± 38 vs 123 ± 37 vs 126 ± 53 | IV fentanyl ketorolae | 46 ± 6 vs 46 ± 5 vs 46 ± 5 | F40 vs F40 vs F40 | No |
| Alonso-Damian, 201226 | 2             | Open ABD | Sevoflurane/fentanyl1 | Ap 80 mg vs Ondan 4 mg | 125 ± 43 vs 130 ± 52 | 173 ± 45 vs 180 ± 59 | IV pentozone | 35 ± 11 vs 38 ± 13 | F30 vs F30 | No |
| Kakuta, 201125 | 2              | Endo GYN | Sevoflurane/fentanyl1 | Ap 80 mg vs placebo | 125 ± 43 vs 130 ± 52 | 173 ± 45 vs 180 ± 59 | IV pentozone | 35 ± 11 vs 38 ± 13 | F30 vs F30 | No |
| Habib, 201124  | 7              | Craniotomy | Sevoflurane/fentanyl1 | Ondan 4 mg vs Ap 40 mg | 180 ± 179 | N/A | IV fentanyl | 48 ± 13 vs 51 ± 13 | 28/23 vs 30/23 | No |
| Gan, 201123   | 7              | Open ABD | Sevoflurane/isoflurane/desflurane/N2O | Rola 200 mg vs Rola 70 mg vs Rola 20 mg vs Rola 5 mg vs placebo | 120 ± 54 vs 126 ± 54 vs 132 ± 66 vs 132 ± 60 | 132 ± 60 | IV fentanyl | 47.4 ± 10.9 vs 44.1 ± 10.1 vs 47.1 ± 12.6 | F104 vs F103 vs F102 vs F103 vs F103 | Yes |
| Altorjay, 201122 | 4              | Mixed   | Volatile anesthetics | Caso 50 mg + Ondan 4 mg placebo + Ondan 4 mg | 87.7 ± 50.4 vs 92.1 ± 76.4 | N/A | N/A | 11.2 vs 13.2 | 44.6 ± 10.1 vs 45.8 ± 10.1 | F23 vs F235 | Yes |
| Singh, 201022  | 6              | GYN and ABD | Sevoflurane/desflurane/N2O | Caso 150 mg + placebo vs Caso 150 mg + Ondan 4 mg vs Caso 100 mg + Ondan 4 mg vs Caso 50 mg + Ondan 4 mg vs Ondan 4 mg | 79.1 ± 51.8 vs 80.5 ± 47.9 vs 77.2 ± 49.9 | 77.2 ± 43.3 | IV fentanyl | 38.5 ± 8.33 vs 39 ± 3.74 vs 39.5 ± 8.58 vs 38.1 ± 8.24 vs 39.3 ± 8.15 | F142 vs F140 vs F140 vs F140 vs F140 | Yes |
| Gan, 20074     | 8              | Open ABD | Volatile anesthetics/N2O | Ap 125 mg + Ap 40 mg vs Ondan 4 mg vs Ondan 4 mg | N/A | 120 ± 60 vs 120 ± 60 vs 120 ± 60 | N/A | 120 ± 60 vs 120 ± 60 vs 120 ± 60 | 238/14 vs 245/16 vs 245/16 | Yes |
| Dimoussis, 200729  | 8              | Open ABD | Volatile anesthetics/N2O | Ap 125 mg + Ap 40 mg vs Ondan 4 mg vs Ondan 4 mg | N/A | 114 ± 60 vs 120 ± 60 vs 108 ± 54 | Multiple drugs | 46 ± 11 vs 46 ± 11 vs 46 ± 11 | 274/30 vs 273/30 vs 273/30 | Yes |
| Geszeni, 20005   | 6              | GYN     | Isoflurane/morphone/N2O | CP 200 mg vs placebo | 108 ± 64 vs 81 ± 34 | N/A | PCA | 42 ± 8 vs 43 ± 7 | F20 vs F24 | No |

ABD = abdominal, AP = aperient, Caso = caesiont, Endo = endoscopic, GYN = gynecological, IV = intravenous, N/A = not available, Ondan = ondansetron, OTORI = otorhinolaryngological, PCA = patient-controlled analgesia, Rama = ramelmodron, Rola = rolapitant, SD = standard deviation.
| Study          | Intervention (I1 vs I2) | Time Points | Nausea | Vomiting | Rescue Drug | CR | Time to First Vomiting, h | Adverse Events/Other Outcomes | Authors’ Conclusions |
|---------------|-------------------------|-------------|--------|----------|-------------|----|--------------------------|-------------------------------|----------------------|
| Vallejo, 2012 | Ap 40 mg vs Placebo    | 0–48 h      | Severity scale was lower in Ap group \( (P = 0.014) \) | 7/75 vs 22/75 \( (P = 0.003) \) | 32/75 vs 33/75 \( (P = 0.869) \) | 26/75 vs 20/74 \( (P = 0.288) \) | N/A | N/A | The addition of 40 mg of aprepitant to ondansetron significantly decreases postoperative vomiting rates and nausea severity. |
| Habib, 2011   | Ap 40 mg vs Placebo    | 0–2 h       | 3/75 vs 13/75 \( (P = 0.026) \) | 20/75 vs 24/75 \( (P = 0.531) \) | 14/75 vs 21/75 \( (P = 0.189) \) | 44.4 ± 11.7 vs 34.1 ± 20.0 \( (P = 0.008) \) | N/A | N/A | When combined with dexamethasone (10 mg), Ap 40 mg was more effective than ondansetron 4 mg in preventing postoperative vomiting, but not the incidence or severity of nausea, need for rescue antiemetics, or CR rates. |
| Ondan 4 mg    | Ap 80 mg vs Placebo    | 0–24 h      | 1/75 vs 3/75 \( (P = 0.353) \) | 1/75 vs 3/75 \( (P = 0.353) \) | 14/75 vs 21/75 \( (P = 0.189) \) | N/A | N/A | The amount of pain medication used by patients in the Ap group was significantly less for diclofenac and pentazocine compared with placebo. |
| Kakuta, 2011  | Ap 80 mg vs Placebo    | 0–2 h       | 1/75 vs 3/75 \( (P = 0.353) \) | 1/75 vs 3/75 \( (P = 0.353) \) | 14/75 vs 21/75 \( (P = 0.189) \) | N/A | N/A | Ap (80 mg) lowered the incidence of PONV, decreased pain medication requirements, and promoted recovery in patients undergoing laparoscopic gynecological surgery compared with placebo. |
| Lee, 2012    | Ap 80 mg vs Placebo    | 0–6 h       | 1/75 vs 3/75 \( (P = 0.353) \) | 1/75 vs 3/75 \( (P = 0.353) \) | 14/75 vs 21/75 \( (P = 0.189) \) | N/A | N/A | Dizziness: 8/42 vs 10/42 \( (P = 0.595) \); Headache: 5/42 vs 6/42 \( (P = 0.746) \); Sedation: 1/42 vs 2/42 \( (P = 0.557) \); Ap (80 mg) combined with 0.3 mg of ramosetron decreased the incidence of PONV, the use of rescue antiemetics and nausea severity as compared to 0.3 mg of ramosetron alone. |
| Study                     | Intervention (H vs L) | Time Points | Nausea                        | Vomiting                      | Rescue Drug | CR     | Time to First Vomiting, h | Adverse Events/Other Outcomes                                                                 |
|--------------------------|----------------------|-------------|-------------------------------|-------------------------------|-------------|--------|--------------------------|------------------------------------------------------------------------------------------------|
| Sinha, 2014²⁹            | Ap 80 mg vs placebo  | 0–30 min;   | Nausea VRS did not show       | 0.2                           |             |        | 6.5 ± 0.1 vs 3.2 ± 0.2   | Additional 80 mg of Ap to ondansetron could delay the latency to vomiting and reduce the incidence of vomiting in morbidly obese patients undergoing laparoscopic bariatric surgery. |
|                          |                      | 0–1 h;      |                               |                               |             |        | (P = 0.019)               |                                                                                                 |
|                          |                      | 0–2 h;      |                               |                               |             |        |                          |                                                                                                 |
|                          |                      | 0–48 h;     |                               |                               |             |        |                          |                                                                                                 |
|                          |                      | 0–72 h;     |                               |                               |             |        |                          |                                                                                                 |
|                          |                      | 0–6 h;      |                               |                               | N/A         |        |                          |                                                                                                 |
|                          |                      | 6–24 h      |                               |                               |             |        |                          |                                                                                                 |
|                          |                      | 0–24 h      |                               |                               |             |        |                          |                                                                                                 |
| Alonso-Dumian, 2012²⁹   | Ap 80 mg vs Ondan 4 mg| 0–6 h;      | 0/30 vs 0/30 (P = 0.002)      | N/A                           |             |        |                          | Sleepiness: 0/30 vs 1/30 (P = 0.313); Constipation: 0/30 vs 1/30 (P = 0.313); QT intervals elongation: 0/30 vs 6/30 (P = 0.031) |
|                          |                      | 2–24 h      |                               |                               |             |        |                          |                                                                                                 |
|                          |                      | 0–24 h      |                               |                               |             |        |                          |                                                                                                 |
| Jung, 2013²⁹            | Ap 125 mg vs Ap 80 mg | 0–2 h;      | 0.40 ± 0.40 vs 3.40 (P = 0.017) | 26/40 vs 26/40 vs 15/40 (P = 0.007) |             |        |                          | 80 mg of Ap was able to lower the incidence of PONV during the rst 48h after gynecological laparoscopy. |
|                          |                      | 2–24 h      | 8/40 vs 11/40 vs 16/40 (P = 0.139) | 29/40 vs 32/40 vs 21/40 (P = 0.004) |             |        |                          |                                                                                                 |
|                          |                      | 0–24 h      | 16/40 vs 17/40 vs 29/40 (P = 0.005) | 26/40 vs 25/40 vs 12/40 (P = 0.002) |             |        |                          |                                                                                                 |
|                          |                      | 24–48 h     | 3/40 vs 2/40 vs 1/40 (P = 0.591) | 38/40 vs 37/40 vs 39/40 (P = 0.591) |             |        |                          |                                                                                                 |
|                          |                      | 0–48 h      | 0/40 vs 0/40 (P = 1)           | 24/50 vs 22/40 vs 11/40 (P = 0.004) |             |        |                          |                                                                                                 |
| Lim, 2015²⁵             | Ap 125 mg vs Ap 80 mg | 0–6 h;      | No difference was found among groups in the RINVR scale. | 0/26 vs 2/28 vs 6/24 (P = 0.011) |             |        | N/A                       | No obvious adverse effect was found in 3 groups. Oral 125mg but not 80 mg of Ap was effective in preventing PONV. |
|                          |                      | 0–24 h      | PONV: 1/26 vs 5/28 vs 7/24 (P = 0.055) | 103/293 vs 97/293 vs 104/280 (P = 0.599) |             |        |                          |                                                                                                 |
| Diemunsch, 2007²⁹       | Ap 125 mg vs Ap 40 mg | 0–24 h;     | Peak nausea scores were lower in both aprepitant groups compared with ondansetron. | 41/293 vs 47/293 vs 81/280 (P < 0.001) |             |        | 42.5 ± 13.7 vs 41.3 ± 15.1 vs 36.3 ± 17.7 (P < 0.001) | The rates of adverse events were similar across groups 40 mg and 125 mg of Ap were more effective than 4 mg of ondansetron for preventing vomiting at 24 and 48 h after open abdominal surgery. |
|                          |                      | 0–48 h      | 44/290 vs 53/292 vs 95/279 (P < 0.001) | 185/293 vs 188/293 vs 154/280 (P = 0.049) |             |        |                          |                                                                                                 |
| Study          | Intervention (I1 vs I2) | Time Points | Nausea | Vomiting | Rescue Drug | CR       | Time to First Vomiting, h | Adverse Events/Other Outcomes | Authors’ Conclusions |
|---------------|-------------------------|-------------|--------|----------|-------------|---------|--------------------------|------------------------------|----------------------|
| Gan, 20071^4  | Ap 125 mg vs Ap 40 mg   | 0–2 h; 0–6 h; 0–24 h; 0–48 h; 0–72 h; 0–96 h; 0–120 h | Peak nausea scores showed no difference among groups. | 12/239 vs 25/248 vs 63/246 (P < 0.001) vs 14/239 vs 16/239 vs 69/235 (P < 0.001) | 134/239 vs 136/248 vs 133/246 (P = 0.905) vs 103/239 vs 112/248 vs 103/246 (P = 0.757) | 45.7 ± 9.3 vs 43.4 ± 12.2 vs 36.3 ± 17.8 (P < 0.001) | No differences were found in the incidences of serious adverse events across the groups. | 40 mg and 125 mg of Ap were superior to 4 mg of ondansetron for preventing vomiting in the first 24 and 48 h, but not nausea control, the use of rescue drugs, or CR. |
|               | Ondan 4 mg              |             |        |          |             |         |                          |                              |                      |
|               |                         |             |        |          |             |         |                          |                              |                      |
| Singla, 2010^21 | Caso 150 mg vs Caso 100 mg vs Caso 50 mg vs Caso placebo | 0–24 h; 0–48 h; 0–72 h; 0–96 h; 0–120 h | N/A | 93/140 vs 89/140 vs 49/140 vs 94/140 (P = 0.591) vs 101/40 vs 61/40 vs 13/140 vs 40/140 (P < 0.001) | 80/140 vs 84/140 vs 78/140 vs 53/140 (P < 0.001) | 110.1 ± 30.3 vs 113.2 ± 25.2 vs 107.1 ± 33.9 vs 83.3 ± 50.9 (P < 0.005) | 68/131 vs | Additional casopitant to ondansetron produced better emesis prevention than ondansetron alone in the first postoperative 24 h. |
|               |                         |             |        |          |             |         |                          |                              |                      |
| Alterjay, 2011^22 | Caso 50 mg vs placebo | 0–24 h; 0–48 h; 0–72 h; 0–96 h; 0–120 h | N/A | 24/233 vs 59/235 (P = 0.013) vs 24/233 vs 73/235 (P < 0.001) | 60/233 vs 73/235 (P = 0.203) vs 160/233 vs 138/235 (P < 0.025) | 44.0 ± 12 vs 11.7 ± 12 vs 11.7 ± 12 vs 83.3 ± 50.9 (P < 0.005) | 95/235 vs 87/237 (P < 0.007) | The combination of 50 mg of casopitant and 4 mg of ondansetron was superior to ondansetron only in preventing postoperative emesis in patients at high risk for PONV. |
|               |                         |             |        |          |             |         |                          |                              |                      |
|               |                         |             |        |          |             |         |                          |                              |                      |
| Gan, 2011^23  | Rola 200 mg vs Rola 70 mg vs Rola 5 mg vs Ondan 4 mg vs Placebo | 0–24 h; 0–48 h; 0–72 h; 0–120 h | N/A | 85/104 vs 14/104 vs 38/103 vs 21/103 vs 38/103 vs 23/104 vs 43/103 (P < 0.001) | 107/233 vs 110/233 vs 103/233 vs 90/233 (P = 0.049) vs 37/103 (P = 0.472) vs 38/104 vs 27.4 ± 2.6 | 28.3 ± 33.5 vs 28.3 ± 33.5 vs 28.3 ± 33.5 vs 28.3 ± 33.5 vs 28.3 ± 33.5 vs 28.3 ± 33.5 vs 28.3 ± 33.5 | The incidence of adverse events was not significantly different across all groups. Rolapitant (70 mg and 200 mg) reduces the incidence of emetic episodes up to 120 h after surgery. |                      |
| Study          | Intervention (I1 vs I2) | Time Points | Nausea | Vomiting | Rescue Drug | CR          | Time to First Vomiting, h | Adverse Events/Other Outcomes | Authors’ Conclusions |
|----------------|-------------------------|-------------|--------|----------|-------------|-------------|--------------------------|-------------------------------|----------------------|
| CP 200 mg vs placebo | 0–0.5 h; N/A             | 21/104 vs 22/104 vs | 0–8 h: 2/20 vs | 0–8 h: 5/20 vs | 36/104 vs 39/104 vs | 33/103 vs 32/103 vs | 18/103 (P = 0.131) | 23.7 ± 0.3 vs | Patients receiving CP experienced more headaches compared with placebo. |
| CP 100 mg vs placebo | 0–1 h; 0–1.5 h; N/A      | 12/24 (P = 0.008) 11/24 (P = 0.026) | 0–72 h: 10/20 vs 11/24 (P = 0.026) | 0–72 h: 8/20 vs 11/24 (P = 0.026) | 18/1 ± 17 (P > 0.05) | N/A | N/A | N/A | N/A |
| CP 200 mg vs Ondan 4 mg | 0–12 h; 0–72 h; N/A     | 0–72 h: 9/21 vs 14/21 (P = 0.215) | 0–72 h: 16/21 vs 17/21 (P = 1) | 0–72 h: 16/21 vs 17/21 (P = 1) | N/A | N/A | N/A | N/A | N/A |
|                | 0–8 h: 42/52 vs          | 0–24 h: 3/52 vs 12/24 (P = 0.012) | 0–24 h: 3/52 vs 12/24 (P = 0.012) | 0–24 h: 3/52 vs 12/24 (P = 0.012) | 30/52 (P = 0.169) | 31/52 (P = 0.169) | N/A | N/A | N/A |
| Gesztoki, 2000 | CP 200 mg vs placebo     | 0–103 (P = 0.295) | 50/103 (P < 0.001) | 21/103 (P = 0.266) | 32/104 vs 32/104 vs | 32/103 vs 34/103 vs | 0–8 h: 2/20 vs | 0–8 h: 5/20 vs | N/A |
| Liu et al, 2015 | CP 200 mg vs Ondan 4 mg  | 91/104 (P = 0.295) | 50/103 (P < 0.001) | 21/103 (P = 0.266) | 32/104 vs 32/104 vs | 32/103 vs 34/103 vs | 0–8 h: 2/20 vs | 0–8 h: 5/20 vs | N/A |

AP = aprepitant, Caso = casopitant, CR = complete response, N/A = not available, Ondan = ondansetron, RINVR = Rhodes Index of nausea, vomiting, and retching, Rola = rolapitant, VRS = verbal rating scale.
15% to 50% in these studies. When the anti-vomiting role of aprepitant was compared with placebo, meta-analysis of 3 studies recruiting 224 patients found that 80 mg of aprepitant could lower the proportions of patients suffering from postoperative vomiting compared with placebo (\(P < 0.001\), Figure 3A). The pooled incidence was 3.8% (95% CI = 1.1 to 12.8) for 80 mg of aprepitant and was 21.1% (95% CI = 8.2 to 54.0) for placebo. Sinha et al reported that the incidence of vomiting at 72 hours after surgery was significantly lower in patients receiving additional 80 mg of aprepitant (3.1% vs 15%; \(P = 0.021\)).

For other doses of aprepitant tested, Vallejo et al reported that 40 mg of aprepitant was more effective in preventing vomiting than placebo (RR = 0.31; 95% CI = 0.14 to 0.69; \(P = 0.003\)). Jung et al found that none of the 40 patients receiving 125 mg of aprepitant developed vomiting while 11 of the 40 patients receiving placebo were diagnosed with post-operative vomiting (\(P = 0.03\)).

Three studies with 1171 patients compared the roles of 40 mg of aprepitant and 4 mg ondansetron in reducing post-operative vomiting. Meta-analysis using the fixed-effects model revealed that 40 mg of aprepitant was more effective than 4 mg of ondansetron in preventing vomiting (\(P < 0.001\), Figure 3B). The pooled incidence was 13.3% (95% CI = 9.5 to 18.4) for 40 mg of aprepitant and was 28.4% (95% CI = 24.6 to 32.9) for 4 mg of ondansetron.

Alonso-Damian et al did not find a superior role of 80 mg of aprepitant in preventing postoperative vomiting in patients accepting open abdominal surgery compared with 4 mg of ondansetron. The study recruited only 30 patients for each group and the reported incidences of vomiting were low (0/30 vs 1/30; 80 mg aprepitant vs 4 mg ondansetron). Based on their reported incidences of vomiting, 311 patients per group were needed to get a significant difference.

Meta-analysis of the 2 studies recruiting 1058 patients found that 125 mg of aprepitant was more effective in reducing the incidence of vomiting compared with 4 mg of ondansetron (\(P = 0.01\), Figure 3C). The pooled incidence was 8.7% (95% CI = 3.2 to 23.6) for 125 mg of aprepitant and was 27.5% (95% CI = 23.8 to 31.7) for ondansetron.

In terms of other NK-1R antagonists, synthesized data from 2 studies suggested that 50 mg of casopitant could further decrease the incidences of vomiting by 65.1% compared with placebo (pooled incidences, 9.9% vs 25.5%) (Figure 3D).

Gan et al found that patients assigned to 20, 70, and 200 mg of rolapitant had lower incidences of emesis (27%, 20%, and 13%, respectively) compared with patients taking placebo (42%). There was a linear relationship between the incidence of vomiting and the dose of rolapitant. Gesztesi et al performed a dose-ranging and interaction study of CP122721 to test its antiemetic effects. In their dose-ranging study, 10% (2/20) of the patients that received 200 mg of CP122721 experienced vomiting within the first 8 hours after surgery in comparison with that 50% (12/24) of the patients in the placebo group were found to experience vomiting (\(P = 0.008\)). In the interaction study, the effects of 4 mg of ondansetron and 200 mg of CP122721 alone, and their combinational effects on preventing PONV were tested. The incidences of PONV within the first 2-hour post-surgical period were 6% in patients treated with 200 mg of CP122721, 17% in patients taking 4 mg of ondansetron and 2% in patients receiving both CP122721 and ondansetron (\(P < 0.05\)).

The incidence of nausea: aprepitant (Ap) 80mg vs. placebo

| Study          | Ap 80mg Events | Placebo Events | Weight | Risk Ratio | Risk Ratio |
|----------------|---------------|----------------|--------|------------|------------|
|                | Total         | Total          |        | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Kakuta 2011    | 12            | 21             | 25.0%  | 0.57 [0.35, 0.94] |           |
| Jung 2013      | 17            | 29             | 34.5%  | 0.59 [0.39, 0.88] |           |
| Lee 2012       | 21            | 42             | 40.5%  | 0.62 [0.44, 0.86] |           |
| Total (95% CI) | 50            | 84             | 112    | 100.0%     | 0.60 [0.47, 0.75] |

Heterogeneity: \(X^2 = 0.08, df = 2 (P = 0.96); I^2 = 0\%

Test for overall effect: \(Z = 4.39 (P < 0.0001)\)

FIGURE 2. Summarized risk ratios (RRs) for the incidences of nausea.
Secondary Outcomes

Use of Rescue Drugs

A total of 11 studies8,13–15,20,22,24,25,27–29 reported the incidence of using rescue drugs in treating post-surgical nausea and vomiting. Meta-analysis of 2 studies8,25 recruiting 144 patients showed that patients receiving 80 mg of aprepitant were less likely to take rescue drugs compared with those taking placebo (pooled RR = 0.45; 95% CI = 0.26 to 0.77; P = 0.004). Vallejo et al27 tested the comparative effects of 40 mg of aprepitant with placebo on reducing the use of rescue drugs and did not find a significant difference between 40 mg of aprepitant and placebo.

When aprepitant was compared with 4 mg of ondansetron,14,20,24 no significant difference was found between 40 mg of aprepitant and ondansetron (n = 3; pooled RR = 0.97; 95% CI = 0.86 to 1.10; P = 0.65); or between 125 mg of aprepitant and ondansetron (n = 2; pooled RR = 1; 95% CI = 0.87 to 1.14; P = 0.96) in the incidences of using rescue drugs.14,20

In the trial by Gesztesi et al,15 200 mg but not 100 mg of CP122721 was found to be effective in decreasing the use of rescue drugs.
rescue drugs compared with placebo during the first 72 hours after surgery (P = 0.019 for 200 mg CP122721 vs placebo; and P = 1 for 100 mg CP122721 vs placebo). Moreover, there was no difference in the incidence of using rescue drugs between 200 mg of CP122721 and 4 mg of ondansetron (P = 0.169). Based on their reported incidences, 290 patients per group were needed for 200 mg of CP122721 and 4 mg of ondansetron to get a significant difference.

**Complete Response**

There were 8 studies\(^{14,20–24,27–29}\) that reported the CR values of NK-1R antagonists. The effects of aprepitant (40 mg) against ondansetron (4 mg) were tested in 3 studies.\(^{14,20,24}\) Meta-analysis using the random-effect model found no significant difference between 40 mg of aprepitant and ondansetron (pooled RR = 1.08; 95% CI = 0.91 to 1.29; P = 0.36). The pooled incidence was 46.3% (95% CI = 32.5 to 65.7) for patients receiving 40 mg of aprepitant and 46.3% (95% CI = 36.9 to 58.0) for patients taking 4 mg of ondansetron. There was no difference in CR rates between 125 mg of aprepitant and 4 mg of ondansetron (N = 2; pooled RR = 1.10, 95% CI = 0.98 to 1.24; P = 0.1).\(^{14,20}\)

When the effects of NK-1R antagonists on CR rates were compared with placebo, Vallejo et al\(^{27}\) found no beneficial effect of 40 mg of aprepitant (37.3% vs 26.7%; P = 0.288). Based on these incidences, 405 patients per group were needed to get a difference between 40 mg of aprepitant and placebo whereas study by Vallejo et al\(^{27}\) recruited only 75 patients per group.

When additional 50 mg of casopitant was used besides 4 mg of ondansetron, meta-analysis from 2 studies\(^{21,22}\) recruiting 748 patients supported that patients receiving additional casopitant were more likely to be diagnosed with CR than those taking placebo (pooled RR = 1.26; 95% CI = 1.12 to 1.42; P < 0.001). In addition, Gan et al\(^{22}\) found that there was an increase in CR rates in the rolapitant group (70 and 200 mg) compared with that in the placebo group during the postoperative 48-to-72-hour period.

**Time to First Vomiting Episode**

Eight studies\(^{14,15,20–24,29}\) reported the time to first vomiting episode after surgery. We identified 3 studies\(^{14,20,24}\) with 1171 patients that compared the effects of 40 mg aprepitant with 4 mg of ondansetron on the time to first vomiting. Meta-analysis using the fixed effects model showed that 40 mg aprepitant could delay the time to first vomiting compared with ondansetron (pooled SMD = 0.40; 95% CI = 0.28 to 0.51; P < 0.001).

Another 2 studies\(^{14,20}\) recruiting 1058 patients evaluated the effects of 125 mg of apreipitant and 4 mg of ondansetron on the time to first vomiting. The synthesized results using a random-effect model suggested that 125 mg of aprepitant was more effective in delaying the vomiting latency compared with 4 mg of ondansetron (pooled SMD = 0.52; 95% CI = 0.26 to 0.78; P < 0.001).

Altorjay et al\(^{22}\) found a postponement of first vomiting by 50 mg of casopitant compared with placebo and the relative hazard ratio for the risk of emesis was 0.414 (95% CI = 0.265 to 0.646). Singla et al\(^{21}\) reported a superior effect of 50 mg of casopitant on the delay of time to the first vomiting. We did not synthesize the data because of huge heterogeneity.

Gan et al\(^{23}\) found that the median time to first vomiting episode was longer in patients receiving 200 mg of rolapitant and shorter in patients receiving 70 mg of rolapitant compared with patients receiving placebo. Gesztesi et al\(^{15}\) reported that 200 mg of CP122721 could delay the onset of emesis compared with placebo.

**NMA for the Incidences of Vomiting**

NMA was performed to further compare the effects of placebo, ondansetron, and different doses of apreipitant on postoperative vomiting occurrences. A total of 7 studies\(^{8,14,20,24–26,28}\) were included in the present NMA. As shown in Figure 4, higher doses of apreipitant (80 and 120 mg) but not 40 mg of apreipitant was effective in preventing post-surgical vomiting compared with placebo. No significant difference was found among different doses of apreipitant. Meanwhile, 125 mg
of aprepitant bears significant superiority in the prevention of vomiting in comparison with 4 mg of ondansetron.

**DISCUSSION**

Our current systematic review and meta-analysis supported the following findings. Firstly, drugs and dosages of NK-1R antagonists used for preventing PONV are still being explored and differ a lot among the 14 identified trials. Secondly, based on the synthesized and individual data as well as the trial quality, higher doses of aprepitant (80 and 125 mg), casopitant (100 and 150 mg), rolapitant (20, 70, and 200 mg), and CP122721 (200 mg) were effective in preventing PONV compared with placebo (Table 4). However, the effects of NK-1R antagonists against ondansetron in reducing PONV occurrence were uncertain. Last but not the least, available data did not find a dose-related effect of aprepitant in preventing PONV. More large high-quality trials are needed to clarify this question.

As the first NK-1R antiemetic approved by the FDA, aprepitant was the mostly tested agent in our identified trials. As the meta-analysis found that all dosages of aprepitant (40, 80, and 125 mg) were effective in reducing the incidence of postoperative vomiting but not the rates of nausea. The dissociative effect on nausea and vomiting was also seen in casopitant, rolapitant, and CP122721 (Table 4). These results supported the hypothesis that nausea and vomiting were 2 biologically different phenomena that occur due to common but differentiated etiologies. Moreover, our current findings were similar to previous reports. Albany et al found that when combined with a 5-HT3 receptor antagonist and dexamethasone, aprepitant could more effectively suppress nausea but not vomiting in tumor patients receiving cisplatin and dexamethasone, aprepitant could more effectively suppress nausea and vomiting also in casopitant, rolapitant, and CP122721 (200 mg). This finding suggested that problem.

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Our NMA including both direct and indirect data did not find a difference in preventing vomiting among different dosages of aprepitant (Figure 4). This finding suggested that aprepitant was a powerful antiemetic drug and low-to-moderate dose of aprepitant might be sufficient to control PONV with minimal adverse effects. However, we suggested that the finding should be taken with caution. As there were only 7 studies included in the NMA, a great bias was likely to be evident. Furthermore, the NMA results suggested that 80 and 125 mg but not 40 mg of aprepitant were superior to ondansetron in controlling postoperative vomiting. Considering these data, more clinical trials with high quality were needed to test the most appropriate dosage of NK-1R antagonists in preventing PONV.

Another conclusion that could be drawn from our study was that NK-1R antagonists, especially rolapitant and casopitant could delay the time to first vomiting episode, compared with ondansetron. This might be mainly due to their longer acting time compared with ondansetron. One alternative explanation was the different acting mechanisms of NK-1R and 5-HT3 receptor antagonists, as studies had suggested that vomiting at early phase and late phase might be caused by different drugs used in the perioperative settings.
| Comparisons                  | Incidence of nausea | Incidence of vomiting | Incidence of using rescue drug | Complete response rates | Time to fist vomiting |
|------------------------------|---------------------|-----------------------|-------------------------------|-------------------------|-----------------------|
|                              | Efficacy            | Conclusions based on | Efficacy                      | Conclusions based on   | Efficacy              | Conclusions based on |
| Ap 40 mg vs placebo          | N/A                 | N/A                   | > Single                       | = Single                | = Single              | N/A                   |
| Ap 80 mg vs placebo          | > Single, META      | > Single, META, NMA   | > Single, Meta                 | UC                     | Single, Meta         | > Single              |
| Ap 125 mg vs placebo         | > Single, NMA       | > Single, NMA         | > Single, Meta                 | UC                     | Single, Meta         | > Single              |
| Ap 40 mg vs Ap 80 mg         | N/A                 | N/A                   | N/A                           | N/A                    | N/A                   | N/A                   |
| Ap 40 mg vs Ap 125 mg        | N/A                 | N/A                   | Single, NMA                   | = Single, single        | = Single              | N/A                   |
| Ap 80 mg vs Ap 125 mg        | = Single, NMA       | = Single, NMA         | = Single, NMA                 | = Single, single        | = Single              | N/A                   |
| Ap 40 mg vs Ondan 4 mg       | = Single, NMA       | = Single, NMA         | = Single, NMA                 | = Single, single        | = Single              | N/A                   |
| Ap 40 mg vs Ondan 4 mg       | = Single, META      | = Single, META        | = Single, META                | = Single, META         | > Single, META       | > Single, META       |
| Ap 80 mg vs Ondan 4 mg       | UC                  | Single, NMA           | = Single, META, NMA           | = Single, META         | = Single, META       | > Single, META       |
| Ap 125 mg vs Ondan 4 mg      | N/A                 | N/A                   | N/A                           | N/A                    | N/A                   | N/A                   |
| Caso 50 mg vs placebo        | N/A                 | > Single, META, NMA   | > Single, Meta                | > Meta                 | > Meta               | > Meta               |
| Caso 100 mg vs placebo       | = Single, NMA       | = Single, NMA         | = Single, NMA                 | = Single, single        | = Single              | = Single             |
| Caso 150 mg vs placebo       | = Single, NMA       | = Single, NMA         | = Single, NMA                 | = Single, single        | = Single              | = Single             |
| Rola 5 mg vs placebo         | = Single, NMA       | = Single, NMA         | = Single, NMA                 | = Single, single        | = Single              | = Single             |
| Rola 20, 70, 200 mg vs Caso 500 mg | = Single, NMA      | = Single, NMA         | = Single, NMA                 | = Single, single        | = Single              | = Single             |
| Rola 20, 70, 200 mg vs Ondan 4 mg | = Single, NMA     | = Single, NMA         | = Single, NMA                 | = Single, single        | = Single              | = Single             |
| CPI 00 mg vs placebo         | N/A                 | N/A                   | > Single, NMA                 | > Single, single        | = Single              | = Single             |
| CPI 100 mg vs placebo        | N/A                 | N/A                   | > Single, NMA                 | > Single, single        | = Single              | = Single             |
| CPI 200 mg vs Ondan 4 mg     | = Single, NMA       | = Single, NMA         | = Single, NMA                 | = Single, single        | = Single              | = Single             |

AP = aprepitant, Caso = casopitant, N/A = not available, NMA = network meta-analysis, Ondan = ondansetron, Rola = rolapitant, UC = uncertain defined as that there was no direct comparison between the 2 drugs or the trial quality was low with a score of <3 or inadequate number of participants.
comprehensive evaluation of related adverse events were needed before a recommendation of using NK-1R antagonists to prevent PONV could be made.

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