SYSTEMATIC REVIEW

Neurokinin-1 receptor antagonists for postoperative nausea and vomiting: a systematic review and meta-analysis

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KEYWORDS
Postoperative nausea and vomiting;
Prophylaxis;
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Abstract
Background: Postoperative Nausea and Vomiting (PONV) is a common complication of general anesthesia. Several kinds of antiemetics, including 5-Hydroxytryptamine3 (5-HT3) receptor antagonists, and Neurokinin-1 (NK-1) receptor antagonists have been used to treat PONV.
Objectives: To compare the antiemetic effect of NK-1 receptor antagonists, including fosaprepitant.
Data sources: Online databases (PubMed, MEDLINE, Scopus, The Cochrane Library databases) were used.
Study eligibility criteria, participants, and interventions: Randomized Controlled Trials (RCTs) performed in patients over 18 years with ASA-PS of I–III, aimed to assess the efficacy of antiemetics including NK-1 receptor antagonists and 5-HT3 receptor antagonists, and compared the incidence of PONV were included.
Study appraisal and synthesis methods: All statistical assessments were conducted by a random effect approach, and odds ratios and 95% Confidence Intervals were calculated.
Results: Aprepitant 40 mg and 80 mg significantly reduced the incidence of vomiting 0–24 hours postoperatively (Odds Ratio [OR] = 0.40; 95% Confidence Interval [95% CI 0.30–0.54]; p < 0.001, and OR = 0.32; 95% CI 0.19–0.56; p < 0.001). Fosaprepitant could also reduce the incidence of vomiting significantly both 0–24 and 0–48 hours postoperatively (OR = 0.07; 95% CI 0.02–0.24; p < 0.001 and OR = 0.07; 95% CI 0.02–0.23; p < 0.001).

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Limitations: Risk factors for PONV are not considered, RCTs using multiple antiemetics are included, RCTs for fosaprepitant is small, and some bias may be present.

Conclusions and implications of key findings: Aprepitant and fosaprepitant can be effective prophylactic antiemetics for postoperative vomiting. However, more studies are required for higher-quality meta-analyses.

Systematic review registration number: CRD42019120188.

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Antagonistas do receptor da neurocinina-1 no tratamento de náusea e vômito no pós-operatorário: revisão sistemática e meta-análise

Resumo

Histórico: Náusea e Vômito no Pós-Operatório (NVPO) é um evento adverso frequente da anestesia geral. Várias classes de antieméticos, incluindo antagonistas do receptor 5-Hidroxitriptamina 3 (5-HT3) e antagonistas do receptor da Neurocinina-1 (NK-1), têm sido utilizados para tratar a NVPO.

Objetivo: Comparar o efeito antiemético dos antagonistas do receptor NK-1, incluindo o fosaprepitanto.

Fontes de dados: Foram utilizadas bases de dados on-line (PubMed, MEDLINE, Scopus, The Cochrane Library).

Critérios de elegibilidade do estudo, participantes e intervenções: Foram incluídos Estudos Clínicos Randomizados (ECR) realizados em pacientes acima de 18 anos classificação ASA I a III, com o objetivo de avaliar a eficácia de antieméticos que incluíssem antagonistas do receptor NK-1 e antagonistas do receptor 5-HT3, e que comparassem a incidência de NVPO.

Métodos de avaliação e síntese do estudo: Todas as avaliações estatísticas foram realizadas por abordagem de efeito aleatório e foram calculadas razões de chances e Intervalos de Confiança de 95%.

Resultados: As doses de 40 mg e 80 mg de aprepitanto reduziram significativamente a incidência de vômito no período de 0 a 24 horas pós-operatórias (razão de chances [OR = 0,40]; Intervalo de Confiança de 95% [95% IC] 0,30–0,54; p < 0,001 e OR = 0,32; 95% IC 0,19–0,56; p < 0,001). O fosaprepitanto pode também reduzir significativamente a incidência de vômito tanto de 0–24 horas como no período de 0–48 horas pós-operatórias (OR = 0,07; 95% IC 0,02–0,24; p < 0,001 e OR = 0,07; 95% IC 0,02–0,23; p < 0,001).

Limitações: Os fatores de risco para NVPO não foram analisados, ECRs usando múltiplos antieméticos foram incluídos, ECRs para fosaprepitanto tinham amostras pequenas, podendo haver algum viés.

Conclusões e implicações dos principais achados: Aprepitanto e fosaprepitanto podem ser drogas antieméticas profiláticas efetivas para vômito no pós-operatório. No entanto, são necessários mais estudos para a elaboração de meta-análises de melhor qualidade.

Número de registro da revisão sistemática: CRD42019120188.

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PALAVRAS-CHAVE
Náusea e vômito no pós-operatório; Profilaxia; Tratamento; Antagonistas do receptor NK-1

Introduction

Postoperative Nausea and Vomiting (PONV) occurs in 30–50% of patients receiving general anesthesia, and its incidence can be as high as 80% in high-risk patients who show multiple risk factors such as female gender, non-smoker, history of motion sickness and/or PONV, and postoperative opioid use.1-3 Ondansetron, a selective 5-Hydroxytryptamine 3 (5-HT3) receptor antagonist, is commonly used to prevent PONV,2 but it is difficult to prevent PONV completely.4 Aprepitant, a Neurokinin-1 (NK-1) receptor antagonist with a long half-life of 9–12 hours, has received attention as an effective prophylactic antiemetic for PONV, and several randomized controlled trials have suggested the superior efficacy of aprepitant over other antiemetics in preventing PONV.4-6 Recently, fosaprepitant, one of NK-1 antagonist and a prodrug of aprepitant,7 has also been reported as an effective antiemetic for preventing postoperative vomiting.8-11
Several systematic reviews and meta-analyses on the effects of NK-1 receptor antagonists in preventing PONV, based on the randomized controlled trials published before 2015, have been reported,\textsuperscript{13,14} and it is suggested that NK-1 receptor antagonists, especially aprepitant, can decrease the incidence of postoperative vomiting.\textsuperscript{13,14} However, fosaprepitant was not included in these studies and its efficacy was not evaluated. In addition, no systematic review nor meta-analysis on PONV has compared the efficacy of NK-1 receptor antagonists to that of 5-HT3 receptor antagonists.

Therefore, the objective of this study is to investigate whether NK-1 receptor antagonists including fosaprepitant reduce the incidence of PONV compared to 5-HT3 receptor antagonists. We searched Randomized Controlled Trials (RCTs) of PONV that were conducted for patients undergoing general anesthesia with American Society of Anesthesiologists physical status (ASA) I–III (participants), used both NK-1 receptor antagonists and 5-HT3 receptor antagonists as antiemetics (interventions), compared the efficacy of the antiemetics (comparators), and assessed the incidence of PONV (outcomes), and performed the current systematic review and meta-analysis.

Methods

This systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement.\textsuperscript{15} The approval of the ethics committee was not required since this study was performed by analyzing literature databases and did not involve patients. A protocol for the study was registered with the International Prospective Register of Systematic Reviews (PROSPERO; https://www.crd.york.ac.uk/PROSPERO/) (registration number CRD42019120188).

Eligibility criteria

We included RCTs performed in patients over 18 years-old with ASA-PS of I–III, aimed to assess the efficacy of antiemetics including NK-1 receptor antagonists and 5-HT3 receptor antagonists, and compared the incidence of PONV. We did not impose restrictions on the regions or languages and did not include ongoing studies. Reviews, commentaries, case reports, editorials, letters and duplicated studies were excluded.

Information sources and search strategy

We searched online databases (PubMed, MEDLINE, Scopus, and The Cochrane Library databases) and collected literature published from the inception of each database to February 2019. We used the following terms: Postoperative Nausea and Vomiting (PONV), Neurokinin-1 receptor antagonist (NK-1 receptor antagonist, NK-1R antagonist, NK-1RA, aprepitant, fosaprepitant, casopitant, and rolapitant), and 5-Hydroxytryptamine 3 receptor antagonist (5-HT3 receptor antagonist, ondansetron, palonosetron, granisetron, and ramosetron). Details of search strategy used for PubMed are included in Supplementary Material 1.

Outcomes

The primary outcome was the incidence of nausea and vomiting over 0–24 and 0–48 hours postoperatively as defined in the included studies. The secondary outcome was the incidence of complete response (no vomiting and no rescue antiemetic use), the use of rescue antiemetic, time to the first vomiting episode and adverse effects. Publishing year of included studies, multi-center trials or not, surgery types, the characteristics of participants, types and doses of antiemetics are also assessed.

Study selection and data collection

Two authors (CM and SS) searched online databases, read the titles and abstracts and identified studies meeting the eligibility criteria noted above. Studies that met the exclusion criteria were excluded. Then, two other authors (NK and YMT) read the full texts of the selected studies and evaluated the quality of each study, and decided which studies should be finally included in this meta-analysis.

Study quality assessment

Three authors (CM, SS, and TK) evaluated the quality of the included studies using the Cochrane Collaboration’s tool for assessing risk of bias in randomized trials.\textsuperscript{16} Each study was evaluated on the basis of the following indicators: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective reporting). The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, which provides a transparent and structured process for rating the quality of evidence in systematic reviews and guidelines,\textsuperscript{17} was also used. We categorized the risk of bias of the selected studies into three classes (low risk, unclear risk, or high risk). The publication bias was evaluated by funnel plots visually.

Statistical analysis

Review Manager Version 5 software (Cochrane Collaboration) was used for this meta-analysis. All statistical assessments were conducted by a random effect approach. Odds ratios and 95% Confidence Intervals (95% CIs) were calculated; \( p < 0.05 \) were considered statistically significant. The \( I^2 \) statistic value was used for evaluating heterogeneity between trials. \( I^2 < 40\% \) was considered no significant difference, \( I^2 \) between 40%–60% was considered to have moderate heterogeneity, and \( I^2 > 60\% \) was considered to have high heterogeneity. Subgroup analyses were conducted according to types and doses of study drugs.

Results

A total of 439 articles were initially identified from the databases. After the elimination of duplicates (238 articles) by each reviewer, 170 articles were excluded after assessing
their abstracts, because they did not meet the eligibility criteria. The remaining 31 full-text articles were evaluated, and finally 18 studies related to either primary or secondary outcome in this study were included\(^5\). The results of quality assessment of the included studies are shown in Figure 2.

**Study characteristics**

The characteristics of the included studies are shown in Table 1. They were all prospective randomized trials and were published in English. Five studies were multi-center trials,\(^4,5,26,28,30\) and the other 13 were single-center trials. The earliest trial was published in 2007 and the latest trial was in 2018. Of the 18 included studies, 12 involved abdominal surgeries, two involved craniotomies, and one each involved lower limb surgery, bariatric surgery, rhinolaryngeal surgery, and ambulatory plastic surgery.

Of the 18 included studies, propofol was used for maintaining general anesthesia in two studies by Tsutsumi et al.\(^8\) and Morais et al.,\(^19\) and in the other 16 studies, volatile anesthetics (sevoflurane or desflurane or isoflurane) were used. Two studies by Soga et al.\(^9\) and Morais et al.\(^19\) were performed under combined general anesthesia and epidural anesthesia. Two trials by Lee et al.\(^27\) and Yoo et al.\(^18\) were performed under general and fentanyl Intravenous Patient-Controlled Analgesia (IV-PCA) to manage postoperative analgesia. The remaining 14 studies were performed under general anesthesia only. Three different doses of aprepitant (40, 80 or 120 mg) were used. The doses of
| Author, year, country | Participants | Surgery | Anesthesia | Antiemetic prophylaxis | Patients | Female | Age (y, Mean ± SD or median) | Surgical Time (min, Mean ± SD or median) | Anesthesia time (min, Mean ± SD or median) | Postoperative analgesia | Multicenter study |
|-----------------------|--------------|---------|------------|-----------------------|----------|--------|-----------------------------|---------------------------------------------|---------------------------------------------|-------------------------------|---------------------|
| Yoo et al. 2018 Korea  | 100          | Elective surgery | Sevoflurane or desflurane | Ap 80 mg + Palono. 0.075 mg vs. Palono 0.075 mg | 41 vs. 44 | 41 vs. 44 | 52.4 ± 11.4 vs. 52.1 ± 12.0 | 86.2 ± 56.1 vs. 89.1 ± 60.0 | 128.5 ± 56.1 vs. 131.5 ± 65.9 | Fentanyl-based IV-PCA | No |
| De Morais et al. 2018 Brazil | 66 | Laparoscopic intermediate procedures to abdominal or pelvic cancer | Propofol epidural anesthesia | Ap 80 mg + Ondan 4–8 mg + dexamethasone 4–8 mg vs placebo + Ondan 4–8 mg + dexamethasone 4–8 mg | 34 vs. 32 | 34 vs. 32 | 60.5 (31.87) vs. 50.5 (19.77) | 437.5 (131, 610) vs. 367.5 (145, 600) | N/A | Tramadol 50 mg + dipyrone 2g | No |
| Ham et al. 2016 Korea | 110 | Laparoscopic gynecological surgery | Sevoflurane | Ap 80 mg + Ondan 4 mg vs placebo + Ondan 4 mg | 55 vs. 55 | 55 vs .55 | 40 (22–55) vs. 42 (23–61) | N/A | N/A | Fentanyl IV | No |
| Kakuta et al. 2015 Japan | 38 | Lower limb surgery | Sevoflurane or desflurane | Fosaprepitant 150 mg vs. Ondan 4 mg | 19 vs. 19 | 11 vs. 13 | 61 ± 11 vs. 56 ± 16 | 171 ± 47 vs. 183 ± 67 | 242 ± 55 vs. 264 ± 72 | Diclofenac sodium 25 mg pentazocine 15mg toloxaprofen 60mg celecoxib 100 mg Epidural anesthesia with fentanyl | No |
| Soga et al. 2015 Japan | 44 | Gynecologic abdominal surgery | Sevoflurane, epidural anesthesia with fentanyl | Fosaprepitant 150 mg vs. Ondan 4 mg | 24 vs. 20 | 24 vs. 20 | 52 ± 11 vs. 52 ± 11 | 209 ± 96 vs. 198 ± 82 | 246 ± 94 vs. 239 ± 86 | Epidural anesthesia with fentanyl | No |
| Long et al. 2014 USA | 94 | Elective hysterectomy | Sevoflurane | Ap 40 mg + dexamethasone 8 mg + Ondan 4 mg vs. placebo + dexamethasone 8 mg + Ondan 4 mg | 35 vs. 59 | 35 vs. 59 | 60 ± 12 vs. 53 ± 12 | 153 ± 64 vs. 159 ± 81 | N/A | N/A | No |
Table 1 (Continued)

| Author, year, country | Participants | Surgery | Anesthesia | Antiemetic prophylaxis | Patients | Female | Age (y, Mean ± SD or median) | Surgical Time (min, Mean ± SD or median) | Anesthesia time (min, Mean ± SD or median) | Postoperative analgesia | Multicenter study |
|-----------------------|--------------|---------|------------|-----------------------|----------|--------|-----------------------------|-----------------------------------------------|---------------------------------------------|------------------------|------------------|
| Sinha et al. 2014 USA | 124 Bariatric surgery | Sevoflurane or desflurane | Ap 80 mg + Ondan 4 mg vs. placebo + Ondan 4 mg | 64 vs. 60 | 42 vs. 39 | 43.09 ± 12.45 vs. 43.20 ± 12.70 | 153.05 ± 43.82N/A vs. 141.97 ± 41.80 | Fentanyl IV or morphine IV | No |
| Tsutsumi et al. 2014 Japan | 64 Elective craniotomy | Propofol | fosaprepitant 150 mg vs. ondansetron 4 mg | 32 vs. 32 | 17 vs. 21 | 62 ± 10 vs. 58 ± 14 | 366 ± 137 vs. 403 ± 197 | 460 ± 138 vs. 513 ± 166 | Diclofenac sodium 25 mg pentazocine 15 mg loxoprofen 60 mg | No |
| Moon et al. 2014 Korea | 93 Laparoscopic gynecologic surgery | Desflurane | Ap 40 mg vs. Palon 0.075 mg | 46 vs. 47 | 46 vs. 47 | 37.9 ± 11.1 vs. 37.6 ± 8.0 | 71.5 ± 37.7 vs. 79.2 ± 42.2 | N/A | |
| Lim et al. 2013 Korea | 90 Elective rhinolaryngological surgery | Desflurane | Ap 125 mg + Ondan 4 mg vs. Ap 80 mg + Ondan 4 mg vs. Ondan 4 mg | 26 vs. 28 vs. 24 | 6 vs. 10 vs. 6 | 41 ± 12 vs. 45 ± 12 vs. 42 ± 12 | 55 ± 32 vs. 83 ± 72 vs. 62 ± 32 | 77 ± 31 vs. 105 ± 73 vs. 84 ± 33 | Ketorolac 30 mg | No |
| Vallejo et al. 2012 USA | 150 Ambulatory plastic surgery | Sevoflurane | Ap 40 mg + Ondan 4 mg vs. placebo + Ondan 4 mg | 75 vs. 75 | 70 vs. 70 | 60.5 (31.87) vs. 50.5 (19.77) | 122.9 ± 73.3 vs. 117.4 ± 65.4 | 164.3 ± 80.1 vs. 153.2 ± 70.1 | Fentanyl, morphine hydromorphone, oxycodone ketorolac, meperidine acetaminophen, ibuprofen | No |
| Altorjay et al. 2011 USA | 456 Laparoscopic gynecological surgery | Sevoflurane | Caso 50 mg + Ondan 4 mg vs. placebo + Ondan 4 mg | 227 vs. 229 | 227 vs. 229 | 44.4 ± 12.19 vs. 44.8 ± 12.44 | 87.7 ± 50.39 vs. 92.1 ± 56.96 | N/A | Yes |
| Author, year, country | Participants | Surgery | Anesthesia | Antiemetic prophylaxis | Patients | Female | Age (y. Mean ± SD or median) | Surgical Time (min, Mean ± SD or median) | Anesthesia time (min, Mean ± SD or median) | Postoperative analgesia | Multicenter study |
|------------------------|-------------|---------|------------|-----------------------|----------|--------|-----------------------------|--------------------------------------------|-------------------------------------------|------------------------|-----------------|
| Lee et al. 2012 Korea | 84          | Gynecological surgery | Desflurane | Ap 80 mg + Ramo 0.3 mg vs. Ramo 0.3 mg | 42 vs. 42 | 42 vs. 42 | 43.8 ± 8.2 vs. 43.6 ± 10.4 | 113.4 ± 61.6 vs. 124.1 ± 48.7 | 145.0 ± 62.3 vs. 158.8 ± 48.9 | IV-PCA with fentanyl 21 µg.h⁻¹ | No |
| Gan et al. 2011 USA | 619         | Elective open abdominal surgery | Sevoflurane or desflurane or isoflurane | Placebo vs. Rola 5 mg vs. Rola 20 mg vs. Rola 200 mg vs. Ondan 4 mg | 103 vs. 103 vs. 103 vs. 104 vs. 104 | 103 vs. 103 vs. 103 vs. 103 vs. 104 vs. 104 | 45.8 ± 10.1 ± 10.1 ± 10.1 ± 10.1 ± 10.1 | 209 ± 96 vs. 198 ± 82 | 2.2 ± 1.0 vs. 2.2 ± 1.0 vs. 2.2 ± 1.1 vs. 2.1 ± 1.9 vs. 2.0 ± 0.9 vs. 2.3 ± 1.1 | N/A | Yes |
| Habib et al. 2011 USA | 104         | Craniotomy | Isoflurane | Ap 40 mg + dexamethasone 10 mg vs. Ondan 4 mg + dexamethasone 10 mg | 51 vs. 53 vs. 51 vs. 13 | 28 vs. 30 vs. 48 ± 13 | 180 (130, 223) vs. 179 (128, 213) | N/A | Fentanyl IV oral oxycodone oral acetaminophen N/A | N/A | Yes |
| Singla et al. 2010 USA | 702         | Laparotomic gynecologic surgical procedure or laparoscopic cholecyst-ectomy | Sevoflurane or desflurane | Caso 0 mg + Ondan 4 mg vs. Caso 50 mg + Ondan 4 mg vs. Caso 100 mg + Ondan 4 mg vs. Caso 150 mg + Ondan 4 mg vs. Caso 150 mg | 140 vs. 140 vs. 140 vs. 140 vs. 140 vs. 142 vs. 140 vs. 140 vs. 140 vs. 140 vs. 140 vs. 142 | 140 vs. 140 vs. 140 vs. 140 vs. 140 vs. 142 vs. 140 vs. 140 vs. 140 vs. 140 vs. 140 vs. 142 | 39.3 ± 8.15 vs. 38.1 ± 8.24 vs. 39.5 ± 8.58 vs. 39.3 ± 7.84 vs. 38.5 ± 8.33 | 77.2 ± 43.28 vs. 77.0 ± 49.87 vs. 80.5 ± 47.92 vs. 77.8 ± 43.74 vs. 79.1 ± 51.76 | N/A | N/A |
| Diemunsch et al. 2007 USA | 866         | Open abdominal surgery | Volatile anesthesia | Ap 40 mg vs. Ap 125 mg vs. Ondan 4 mg | 303 vs. 304 vs. 304 | 273 vs. 273 vs. 273 | 46 ± 11 vs. 46 ± 11 vs. 45 ± 11 | N/A | 2.0 ± 1.0 vs. 1.9 ± 1.0 vs. 1.8 ± 0.9 (h) | N/A | Yes |
| Gan et al. 2007 USA | 766         | Open abdominal surgery | Volatile anesthesia | Ap 40 mg vs. Ap 125 mg vs. Ondan 4 mg | 261 vs. 261 vs. 253 | 245 vs. 245 vs. 239 | 46 ± 11 vs. 46 ± 11 vs. 45 ± 11 | N/A | 2.0 ± 1.0 vs. 2.0 ± 1.0 vs. 2.2 ± 1.2 (h) | N/A | Yes |

Ap, Aprepitant; Ondan, Ondansetron; Palono, Palonosetron; Caso, Casopitant; Rola, Rolapitant; Ramo, Ramosetron; IV, intravenous; IV-PCA, Intravenous Patient-Controlled Analgesia; SD, Standard Deviation, N/A, Not Available.
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Figure 2 Risk of bias summary of all included studies by Review Manager Version 5 (the Cochrane Collaboration recommendations).

Fosaprepitant, ondansetron, and palonosetron were 150 mg, 4 mg and 0.075 mg.kg⁻¹ respectively. No major side effects were observed in all included studies.

Primary outcome

Incidence of vomiting

Fourteen studies reported the incidence of vomiting 0–24 hours after surgery,⁴,⁵,⁸–¹⁰,¹⁸–²¹,²⁶–³⁰ and the data of 21 subgroups were available. The pooled Mantel-Haenszel Odds Ratio was 0.33 (95% CI 0.24–0.47, p < 0.00001) and the heterogeneity was 75% (Supplementary Material 2). Ten studies⁴,⁵,⁸–¹⁰,¹⁸–²⁰ reported the incidence of vomiting 0–48 hours after surgery, and the data for 17 subgroups were available. The pooled Mantel-Haenszel Odds Ratio was 0.37 (95% CI 0.25–0.53, p < 0.00001) and the heterogeneity was 80% (Supplementary Material 3). Subgroup analyses were conducted according to types and doses of study drugs. Aprepitant 40 mg was used as an NK1 receptor antagonist in four of the included 14 studies reporting the incidence of vomiting 0–24 hours after surgery,⁴,⁵,¹⁸,²⁰ and aprepitant 80 mg was also used in four studies.¹⁸,²⁰,²¹,²⁷ The pooled Mantel-Haenszel odds ratio was 0.40 (95% CI
Incidence of PONV
Five studies reported the incidence of PONV 0–24 hours after surgery,9,10,19,21 and the data for eight subgroups were available. The pooled Mantel-Haenszel odds ratio was 0.82 (95% CI 0.56–1.19, p = 0.61) and the heterogeneity of this analysis was 47% (Supplementary Material 5). Three studies reported the incidence of PONV 0–48 hours after surgery.9,10,19 The pooled Mantel-Haenszel odds ratio was 1.13 (95% CI 0.42–3.06, p = 0.81) and the heterogeneity was 54% (Supplementary Material 6).

Secondary outcomes

Complete response
Thirteen studies reported the number of patients with no vomiting and no use of rescue drugs (Complete Response – CR) over 0–24 hours postoperatively.4,5,8–10,20,21,24–26,28–30 and eight studies reported these findings for the period 0–48 hours postoperatively.4,5,8–10,20,21,24–26,28–30 The pooled Mantel-Haenszel odds ratio was 1.35 (95% CI 1.12–1.63, p = 0.002, I² = 55%) and 1.42 (95% CI 1.09–1.84, p = 0.009, I² = 54%), respectively. Sinha et al. demonstrated the number of patients CR 0–72 hours postoperatively,22 and Gan et al. also demonstrated CR 0–72 and 0–120 hours postoperatively.23 There were no significant differences between the NK-1 and 5-HT3 groups in both studies.

Use of rescue drugs
Twelve studies reported the use of rescue drugs 0–24 hours postoperatively.4,5,8,10,18,19,23–27,29 Rescue drugs were metoclopramide or dexamethasone. The pooled Mantel-Haenszel odds ratio was 0.90 (95% CI 0.74–1.09, p = 0.27, I² = 29%).

Figure 3 Summarized Odds Ratio (OR) for the incidence of postoperative vomiting in a comparison of aprepitant 40 mg to 5-HT3 receptor antagonists over 0–24 h postoperatively.

Figure 4 Summarized Odds Ratio (OR) for the incidence of postoperative vomiting in a comparison of aprepitant 80 mg to 5-HT3 receptor antagonists over 0–24 h postoperatively.

Figure 5 Summarized Odds Ratio (OR) for the incidence of postoperative vomiting in a comparison of fosaprepitant to 5-HT3 receptor antagonists over 0–24 h postoperatively.

Figure 6 Summarized Odds Ratio (OR) for the incidence of postoperative vomiting in a comparison of fosaprepitant to 5-HT3 receptor antagonists over 0–48 h postoperatively.

0.30–0.54, p < 0.00001) and 0.32 (95% CI 0.19–0.56, p < 0.00001), and the heterogeneity was 0% and 56%, respectively (Figs. 3 and 4). Fosaprepitant was used in three studies.8–10 The pooled Mantel-Haenszel odds ratio for the incidence of vomiting 0–24 and 0–48 hours after surgery was 0.07 (95% CI 0.02–0.24, p < 0.0001) and 0.07 (95% CI 0.02–0.23, p < 0.0001), respectively, and the heterogeneity was both 0% (Figs. 5 and 6). Funnel plots for Figures 3, 4, 5 and 6 are shown in Supplementary Material 4.
Five studies also reported the use of rescue drugs 0–48 hours postoperatively,\textsuperscript{5,10,20,27,28} There were no significant differences between the groups in these studies.

**Time to first vomiting episode**

Nine studies reported the time-to-event analysis for the time to first vomiting 0–24 hours and 0–48 hours postoperatively.\textsuperscript{5,5,6,10,16,26,29,30} All these studies demonstrated that the time was significantly longer in the NK-1 group than in the 5-HT3 group.

**Adverse effects**

Of the included 18 studies, twelve studies reported adverse effects related to the study drugs.\textsuperscript{4,5,18–21,24,25,27–30} There were no significant differences between the NK-1 and 5-HT3 groups in all studies. The common adverse effects were headache, dizziness, and sedation. However, no studies reported any serious events related to the study drugs (Supplementary Material 7).

**Discussion**

The findings of this systematic review and meta-analysis suggest that NK-1 receptor antagonists, alone or in combination with other drugs, are superior to 5-HT3 receptor antagonists in preventing vomiting 0–24 and 0–48 hours postoperatively. Although no significant intergroup differences were observed in PONV during both periods, the percentage of patients with CR 0–24 hours postoperatively was higher in the NK-1 group, and the time to first vomiting was significantly longer in the NK-1 group. These results suggest that NK-1 receptor antagonists were superior in preventing postoperative vomiting.

The NK-1 receptor antagonists included in this meta-analysis are aprepitant, fosaprepitant, rolapitant and casopitant. Rolapitant and casopitant were assessed in only one study each; therefore, subgroup analyses were conducted in the aprepitant or fosaprepitant groups. During both 0–24 and 0–48 hours postoperative periods, aprepiant tends to show superior efficacy for preventing vomiting in comparison with 5-HT3 receptor antagonists. Moreover, in a subgroup analysis comparing aprepitant 40 mg or 80 mg to 5-HT3 receptor antagonists, aprepiant shows significantly stronger effects on postoperative vomiting, although with mild to moderate heterogeneity. Aprepitant has a longer half-life than ondansetron, which may ensure better effects in preventing postoperative vomiting and a longer time to first vomiting. These results are consistent with the findings of some previous meta-analyses, which reported the superiority of NK-1 receptor antagonists, especially aprepiant, to PONV.\textsuperscript{12–14} Although we could not conduct separate analyses based on the dose of aprepiant 0–48 hours postoperatively because of insufficient data, it may be more beneficial to investigate the dose-dependency of the efficacy of aprepiant over longer postoperative periods. Further studies are needed to establish the efficacy of aprepiant.

This meta-analysis included studies in which fosaprepitant was used as a study drug, and this is one of the novel points of the study. Fosaprepitant, a prodrug of aprepiant, is a highly selective NK-1 receptor antagonist and has a longer half-life time.\textsuperscript{7} Both aprepiant and fosaprepitant are considered to be effective for chemotherapy-induced nausea and vomiting (CINV),\textsuperscript{21} and their use has been approved for the prevention CINV by the US Food and Drug Administration (FDA). The use of aprepiant for the prevention of PONV has also been approved by the FDA, but fosaprepitant has not yet gained this approval. There are not so many randomized controlled trials that have compared the efficacy of fosaprepitant and other antiemetics to PONV, and no systematic review and meta-analysis for PONV has been conducted with fosaprepitant. In the above-mentioned databases, three studies met the eligibility criteria of this analysis, and subgroup analysis comparing fosaprepitant to 5-HT3 was conducted. In these three studies, ondansetron was used as a 5-HT3 receptor antagonist. Fosaprepitant showed significantly superior effects against 0–24 and 0–48 hours postoperative vomiting with low heterogeneity, and the time to first vomiting was longer than that with ondansetron. No serious adverse effects of fosaprepitant were reported in the included three studies. This suggests that fosaprepitant shows efficacy in preventing postoperative vomiting similar to aprepiant. Although higher cost is one of the disadvantages of fosaprepitant, it may be an alternative to aprepiant in cases where intravenous administration, not oral intake, is more helpful.

The 5-HT3 receptor antagonist used the most in the included studies was ondansetron. Ramosetron was used in one study and palonosetron was used in two studies. In a subgroup analysis of aprepiant 80 mg compared to 5-HT3 receptor antagonists, ramosetron and palonosetron were included as the study drugs. The heterogeneity of this analysis was slightly high (56%) because the 5-HT3 receptor antagonists are different in the four included studies.

There are several limitations in this meta-analysis. First, we did not consider the risk factors for PONV. Apfel et al. suggested that female gender, opioid use, non-smoker, and motion sickness are the factors influencing the incidence of PONV.\textsuperscript{7} In this meta-analysis, both females and males are included, and epidural anesthesia and IV-PCA with fentanyl were used postoperatively for the management of analgesia in three studies. In addition, the included studies also covered different types of surgeries. These factors may have been responsible for heterogeneity. Second, this meta-analysis included some studies in which NK-1 receptor antagonists or 5-HT3 receptor antagonists were not used alone but in combination with other antiemetics. Dexamethasone and/or droperidol are used in both NK-1 groups and 5-HT3 groups in three studies. These drugs are often used as antiemetics, and their use may influence the incidence of PONV. Therefore, it may be better to exclude these three studies to evaluate the efficacy of NK-1 receptor antagonists or 5-HT3 receptor antagonists alone in PONV. Third, we focused on comparing the efficacy of NK-1 receptor antagonists and 5-HT3 receptor antagonists, but there were only three randomized controlled trials of PONV including fosaprepitant and 5-HT3 receptor antagonists. In a subgroup analysis of the fosaprepitant and 5-HT3 groups, the total number of the included patients was 75 and 71, respectively. This number may be small for evaluating the efficacy of fosaprepitant, so more studies are needed for high-quality meta-analyses. Fourth, we did not contact trial authors for any missing data or outcome data and the assessment of risk of bias of included studies was insufficient. This would
be the most important limitation to evaluate the results of the present study.

Conclusions

This study demonstrated that NK-1 receptor antagonists, especially aprepitant and fosaprepitant, were more effective than 5-HT3 receptor antagonists for preventing postoperative vomiting and delaying the time to first vomiting. However, more data are needed for higher-quality meta-analyses with little heterogeneity.

Author contributions

Chiaki Murakami and Nami Kakuta designed the study, conducted study selection and data extraction, analyzed the data, and wrote the manuscript. Shioh Satomi conducted study selection and data extraction and assessed the methodological quality. Ryuji Nakamura, Hirotsugu Miyoshi, Atsushi Morio, and Naohiro Ohshita performed analysis of the findings and supported to write the manuscript. Katsuya Tanaka helped to analyze the data and write the manuscript. Yasuo M. Tsutsumi designed the study, conducted study selection and data extraction, and helped to assess the methodological quality and write the manuscript. All authors discussed the findings, edited and approved the manuscript. Noboru Saeki and Takahiro Kato helped to rewrite our manuscript and gave us a good suggestion.

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Conflicts of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: https://doi.org/10.1016/j.bjane.2020.06.015.

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