



SYSTEMATIC REVIEW

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



Chiaki Murakami^a, Nami Kakuta^a, Shiho Satomi^b, Ryuji Nakamura^c, Hirotsugu Miyoshi^c, Atsushi Morio^c, Noboru Saeki^c, Takahiro Kato^c, Naohiro Ohshita^d, Katsuya Tanaka^a, Yasuo M. Tsutsumi^{id} ^{c,*}

^a Tokushima University, Department of Anesthesiology, Kumamoto, Japan

^b University of California, Department of Anesthesiology, San Diego, USA

^c Hiroshima University, Department of Anesthesiology and Critical Care, Minami, Japan

^d Osaka Dental University, Department of Anesthesiology, Chuo, Japan

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KEYWORDS

Postoperative nausea and vomiting;
Prophylaxis;
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NK-1 receptor antagonists

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; $p < 0.001$).

* Corresponding author.

E-mail: yasuo223@hiroshima-u.ac.jp (Y.M. Tsutsumi).

PALAVRAS-CHAVE

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

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-operatório: 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-Hidroxitriptamina₃ (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).

Crterios 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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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 pre-

vent 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,^{12,14} and it is suggested that NK-1 receptor antagonists, especially aprepitant, can decrease the incidence of postoperative vomiting.^{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.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.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,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 -values < 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

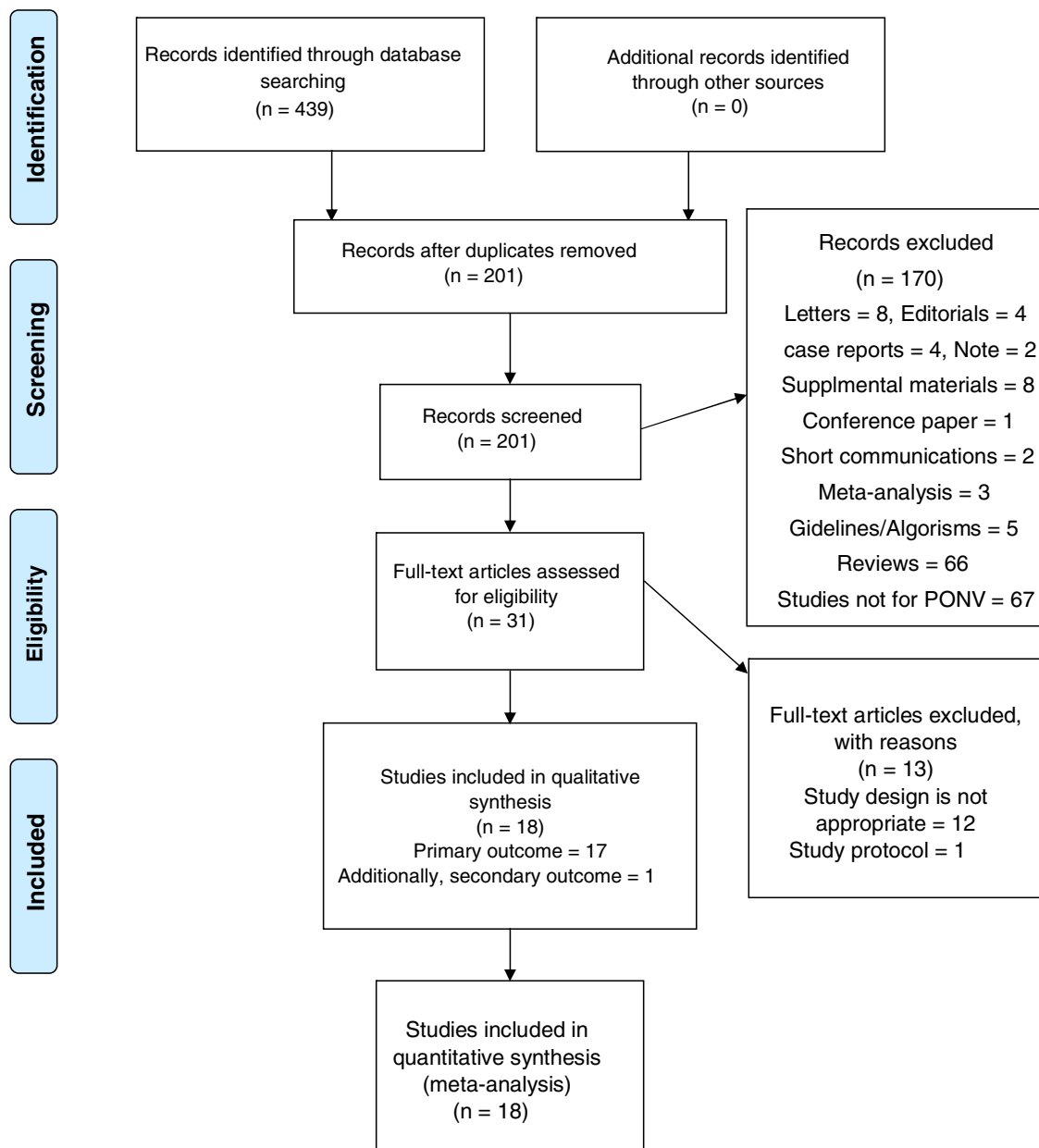


Figure 1 PRISMA 2009 flow diagram.

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^{4,5,8-10,18-30} (Fig. 1). 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 abdo-

minal surgeries, two involved craniotomies, and one each involved lower limb surgery, bariatric surgery, rhinolaryngological 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

Table 1 Characteristics of the included studies.

Author, year, country	Participants	Surgery	Anesthesia	Antiemetic prophylaxis	Patients	Female	Age (y, Mean \pm SD or median)	Surgical Time (min, Mean \pm SD or median)	Anesthesia time (min, Mean \pm SD or median)	Postoperative analgesia	Multicenter study
Yoo et al. ¹⁸ 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 \pm 11.4 vs. 52.1 \pm 12.0	86.2 \pm 56.1 vs. 89.1 \pm 60.0	128.5 \pm 56.1 vs. 131.5 \pm 65.9	Fentanyl-based IV-PCA	No
De Morais et al. ¹⁹ 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. ²⁰ 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. ¹⁰ 2015 Japan	38	Lower limb surgery	Sevoflurane or desflurane	Fosaprepitant 150 mg vs. Ondan 4 mg	19 vs. 19	11 vs. 13	61 \pm 11 vs. 56 \pm 16	171 \pm 47 vs. 183 \pm 67	242 \pm 55 vs. 264 \pm 72	Diclofenac sodium 25 mg pentazocine 15mg loxoprofen 60mg celecoxib 100 mg	No
Soga et al. ⁹ 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 \pm 11 vs. 52 \pm 11	209 \pm 96 vs. 198 \pm 82	246 \pm 94 vs. 239 \pm 86	Epidural anesthesia with fentanyl	No
Long et al. ²¹ 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 \pm 12 vs. 53 \pm 12	153 \pm 64 vs. 159 \pm 81	N/A	N/A	No

Table 1 (Continued)

Author, year, country	Participants	Surgery	Anesthesia	Antiemetic prophylaxis	Patients	Female	Age (y, Mean \pm SD or median)	Surgical Time (min, Mean \pm SD or median)	Anesthesia time (min, Mean \pm SD or median)	Postoperative analgesia	Multicenter study
Sinha et al. ²² 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 \pm 12.45 vs. 43.20 \pm 12.70	153.05 \pm 43.82 vs. 141.97 \pm 41.80	N/A	Fentanyl IV or morphine IV	No
Tsutsumi et al. ⁸ 2014 Japan	64	Elective craniotomy	Propofol	fosaprepitant 150 mg vs. ondansetron 4 mg	32 vs. 32	17 vs. 21	62 \pm 10 vs. 58 \pm 14	366 \pm 137 vs. 403 \pm 197	460 \pm 138 vs. 513 \pm 166	Diclofenac sodium 25 mg pentazocine 15 mg loxoprofen 60mg	No
Moon et al. ²³ 2014 Korea	93	Laparoscopic gynecologic surgery	Desflurane	Ap 40 mg vs. Palono 0.075 mg	46 vs. 47	46 vs. 47	37.9 \pm 11.1 vs. 37.6 \pm 8.0	71.5 \pm 37.7 vs. 79.2 \pm 42.2	N/A	Nefopam 20 mg and automated IV-PCA with fentanyl 20 μ g.kg ⁻¹	No
Lim et al. ²⁴ 2013 Korea	90	Elective rhinolaryngological surgery	Desflurane	Ap 125 mg + Ondan 4 mg vs. Ap 80 mg + Ondan 4 mg vs. Ondan 4mg	26 vs. 28 vs. 24	6 vs. 10 vs. 6	41 \pm 12 vs. 45 \pm 12 vs. 42 \pm 12	55 \pm 32 vs. 83 \pm 72 vs. 62 \pm 32	77 \pm 31 vs. 105 \pm 73 vs. 84 \pm 33	Ketorolac 30 mg	No
Vallejo et al. ²⁵ 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 \pm 73.3 vs. 117.4 \pm 65.4	164.3 \pm 80.1 vs. 153.2 \pm 70.1	Fentanyl, morphine hydromorhine, oxycodone ketorolac, meperidine acetaminophen, ibuprofen	No
Altorjay et al. ²⁶ 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 \pm 12.19 vs. 44.8 \pm 12.44	87.7 \pm 50.39 vs. 92.1 \pm 56.96	N/A	N/A	Yes

Table 1 (Continued)

Author, year, country	Participants	Surgery	Anesthesia	Antiemetic prophylaxis	Patients	Female	Age (y, Mean \pm SD or median)	Surgical Time (min, Mean \pm SD or median)	Anesthesia time (min, Mean \pm SD or median)	Postoperative analgesia	Multicenter study
Lee et al. ²⁷ 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 \pm 8.2 vs. 43.6 \pm 10.4	113.4 \pm 61.6 vs. 124.1 \pm 48.7	145.0 \pm 62.3 vs. 158.8 \pm 48.9	IV-PCA with fentanyl 21 μ g.h ⁻¹	No
Gan et al. ²⁸ 2011 USA	619	Elective open abdominal surgery	Sevoflurane or desflurane or isoflurane	Placebo vs. Rola 5 mg vs. Rola 20 mg vs. Rola 70 mg vs. Rola 200 mg vs. Ondan 4 mg	103 vs. 103 vs. 102 vs. 104 vs. 104	103 vs. 103 vs. 102 vs. 104 vs. 104	45.8 \pm 10.1 vs. 44.6 \pm 10.1 vs. 47.1 \pm 12.8 vs. 44.1 \pm 10.1 vs. 47.4 \pm 10.9 vs. 47.9 \pm 12.6	209 \pm 96 vs. 198 \pm 82	2.2 \pm 1.0 vs. 2.2 \pm 1.1 vs. 2.1 \pm 1.9 vs. 2.0 \pm 0.9 vs. 2.3 \pm 1.1	N/A	Yes
Habib et al. ²⁹ 2011 USA	104	Craniotomy	Isoflurane	Ap 40 mg + dexamethasone 10 mg vs. Ondan 4 mg + dexamethasone 10 mg	51 vs. 53	28 vs. 30	51 \pm 13 vs. 48 \pm 13	180 (130, 223) vs. 179 (128, 213)	N/A	Fentanyl IVoral oxycodone oral acetaminophen	No
Singla et al. ³⁰ 2010 USA	702	Laparotomic gynecologic surgical procedure or laparoscopic cholecystectomy	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. 142	140 vs. 140 vs. 140 vs. 142	39.3 \pm 8.15 vs. 38.1 \pm 8.24 vs. 39.5 \pm 8.58 vs. 39.3 \pm 7.84 vs. 38.5 \pm 8.33	77.2 \pm 43.28 vs. 77.0 \pm 49.87 vs. 80.5 \pm 47.92 vs. 77.8 \pm 43.74 vs. 79.1 \pm 51.76	N/A	N/A	Yes
Diemunsch et al. ⁴ 2007 USA	866	Open abdominal surgery	Volatile anesthesia	Ap 40 mg vs. Ap 125 mg vs. Ondan 4 mg	303 vs. 304 vs. 285	273 vs. 274 vs. 257	46 \pm 11 vs. 46 \pm 11 vs. 45 \pm 11	N/A	2.0 \pm 1.0 vs. 1.9 \pm 1.0 vs. 1.8 \pm 0.9 (h)	N/A	Yes
Gan et al. ⁵ 2007 USA	766	Open abdominal surgery	Volatile anesthesia	Ap 40 mg vs. Ap 125 mg vs. Ondan 4 mg	261 vs. 252 vs. 253	245 vs. 238 vs. 239	46 \pm 11.2 vs. 44 \pm 9.4 vs. 45 \pm 11.2	N/A	2.0 \pm 1.0 vs. 2.0 \pm 1.0 vs. 2.2 \pm 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.

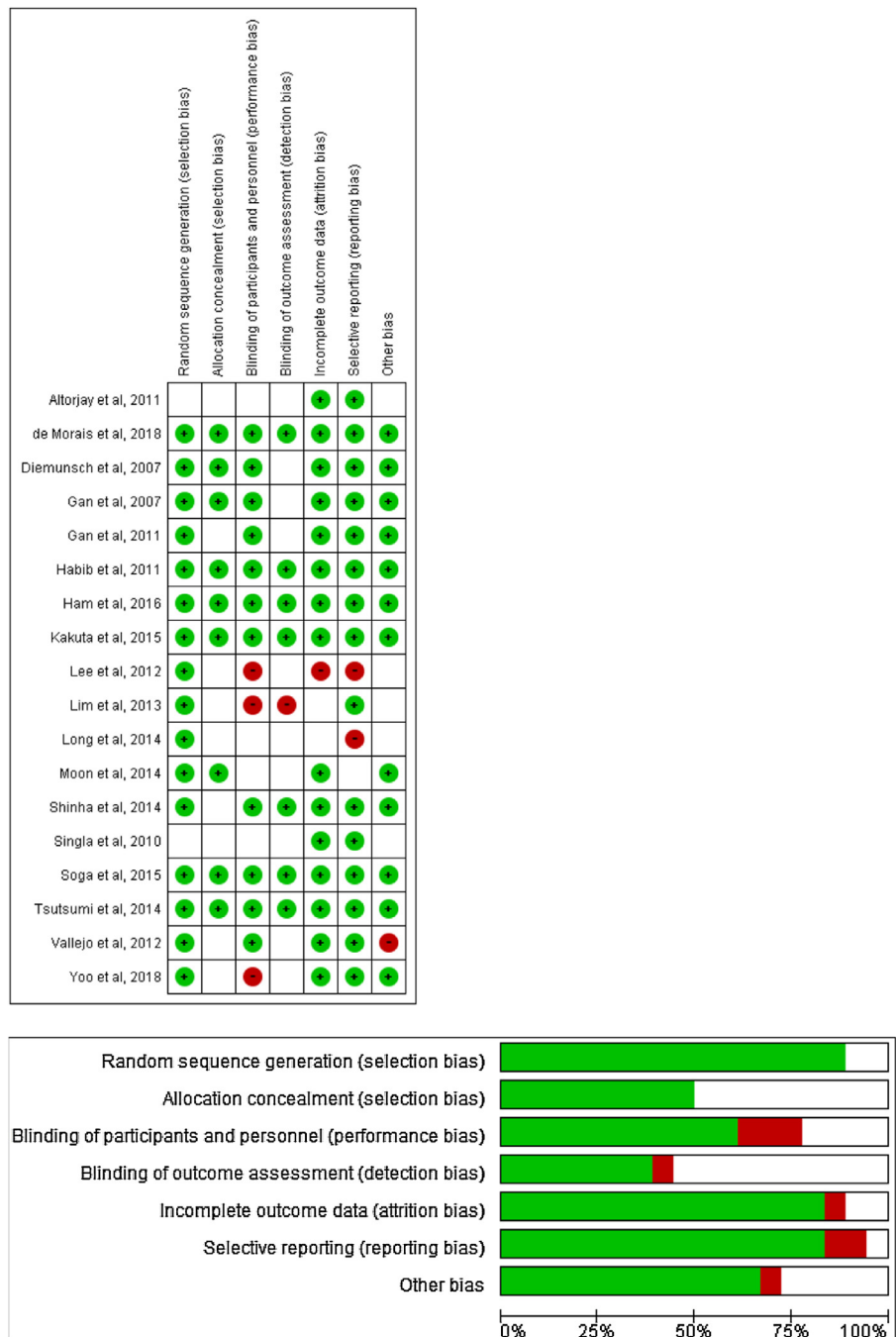


Figure 2 Risk of bias summary of all included studies by Review Manager Version 5 (the Cochrane Collaboration recommendations).

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 studies^{4,5,8–10,27–30} 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,^{4,5,21,29} 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

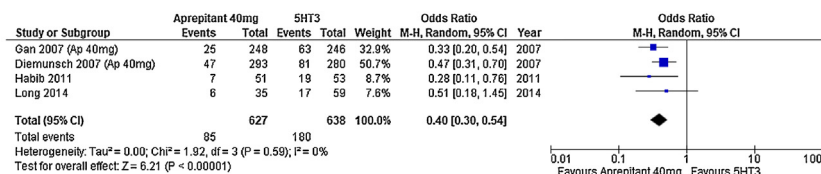


Figure 3 Summarized Odds Ratio (OR) for the incidence of postoperative vomiting in a comparison of aprepitant 40 mg to 5-HT3 receptor antagonists over 0–24 h postoperatively.

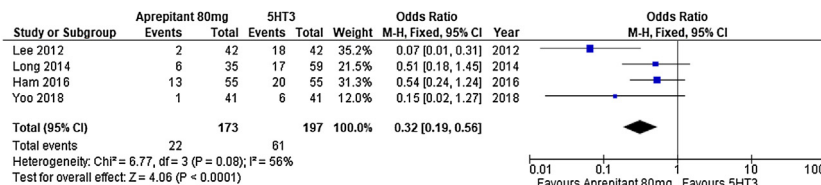


Figure 4 Summarized Odds Ratio (OR) for the incidence of postoperative vomiting in a comparison of aprepitant 80 mg to 5-HT3 receptor antagonists over 0–24 h postoperatively.

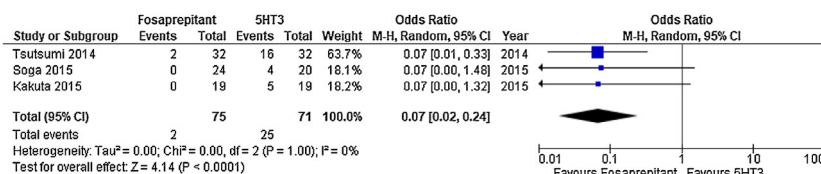


Figure 5 Summarized Odds Ratio (OR) for the incidence of postoperative vomiting in a comparison of fosaprepitant to 5-HT3 receptor antagonists over 0–24 h postoperatively.

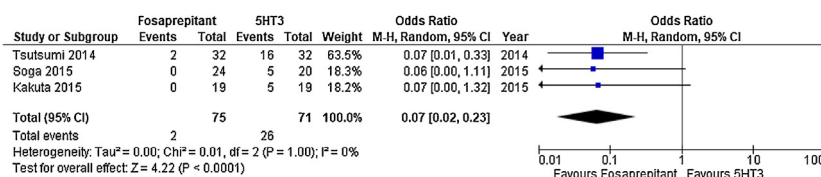


Figure 6 Summarized Odds Ratio (OR) for the incidence of postoperative vomiting in a comparison of fosaprepitant to 5-HT3 receptor antagonists over 0–48 h postoperatively.

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.

Incidence of PONV

Five studies reported the incidence of PONV 0–24 hours after surgery,^{8–10,19,29} 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.^{8–10} 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.^{8–10,20,26,28–30} The pooled Mantel-Haenszel odds ratio was 1.35 (95% CI 1.12–1.63, $p = 0.002$, $I^2 = 55%$) and 1.42 (95% CI 1.09–1.84, $p = 0.009$, $I^2 = 54%$), respectively. Sinha et al. demonstrated the number of patients with CR 0–72 hours postoperatively,²² and Gan et al. also demonstrated CR 0–72 and 0–120 hours postoperatively.²⁸ 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, $p = 0.27$, $I^2 = 29%$).

Five studies also reported the use of rescue drugs 0–48 hours postoperatively.^{8,10,20,27,29} 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.^{4,5,8–10,26,29,30} 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.^{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, aprepitant 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, aprepitant 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 aprepitant, to PONV.^{12–14} Although we could not conduct separate analyses based on the dose of aprepitant 0–48 hours postoperatively because of insufficient data, it may be more beneficial to investigate the dose-dependency of the efficacy of aprepitant over longer postoperative periods. Further studies are needed to establish the efficacy of aprepitant.

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 aprepitant, is a highly selective NK-1 receptor antagonist and has a longer half-life time.⁷ Both aprepitant and fosaprepitant are

considered to be effective for chemotherapy-induced nausea and vomiting (CINV),³¹ and their use has been approved for the prevention CINV by the US Food and Drug Administration (FDA). The use of aprepitant 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 aprepitant. Although higher cost is one of the disadvantages of fosaprepitant, it may be an alternative to aprepitant 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 aprepitant 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.² 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 of 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. Shiho 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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