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Comparison of ondansetron, tropisetron, and palonosetron for the prevention of postoperative nausea and vomiting after middle ear surgery

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ABSTRACT

Background: Postoperative nausea and vomiting (PONV) are 2 of the most frequent adverse effects of anesthesia. PONV prolongs hospital stays and also delays the recovery of patients.
Objective: In this study, the effects of ondansetron, tropisetron, and palonosetron on PONV in patients who had undergone middle ear surgeries such as mastoidectomy or tympanoplasty were compared.
Methods: The study included 165 American Society of Anesthesiologists grade 1 and 2 patients aged 18 to 65 years. Patients were randomized into 3 groups by a closed envelope method. Neither the patients nor the nurses administering the treatments knew which patient belonged to which group. The anesthetic technique was standardized for all groups. During skin closure, 0.075 mg palonosetron, 5 mg tropisetron, and 8 mg ondansetron were administered intravenously to the palonosetron, tropisetron, and ondansetron groups, respectively. After completion of the surgery, the patients were followed for 48 hours. Diclofenac sodium (100 mg IM) was administered to patients experiencing pain and metoclopramide chloride (10 mg IM) was administered to patients with nausea or vomiting. Potential side effects such as headache and constipation were recorded in the postanesthesia care unit and ear, nose, and throat clinic.
Results: There was no significant difference in the effects of all 3 antiemetic agents on the severity of PONV ($P=0.081$). At 48 hours postoperatively, the incidence of PONV was significantly lower in the palonosteron group (38.2%) than the ondansetron group (63.6%) and tropisetron group (61.8%) ($P=0.011$). At 48 hours postoperatively, the incidence of postoperative nausea was significantly lower in the palonosetron group (32.7%) than in the ondansetron group (63.6%) and the tropisetron group (56.4%) ($P=.003$). The incidence of PONV between hours 12 and 24 postoperatively was significantly higher in the ondansetron group (27.3%) than in the palonosetron group (9.1%) ($P=0.013$). The antiemetic requirement in the first hour after surgery was significantly higher in the tropisetron group (25.5%) than in the palonosetron group (7.3%) ($P=.019$).
Conclusions: The results of the current study support those of earlier studies that suggest that palonosetron was statistically more effective than the other 2 formulations in the prevention of PONV in patients who have undergone middle ear surgery. (*Curr Ther Res Clin Exp.* 2019; 80:XXXXXX).

Introduction

Postoperative nausea and vomiting (PONV) is an undesirable clinical condition that increases the likelihood of dehiscence, bleeding, pulmonary aspiration of gastric contents, and electrolyte loss that lead to increased costs, prolonged hospital stays, and delayed recovery. Despite advances in the treatment of nausea and vomiting, PONV has been reported in up to 20% to 30% of all patients undergoing surgery.[1,2] Postoperative vomiting (POV) can be a life-threatening condition by increasing the likelihood of pulmonary aspiration because airway reflexes are not fully recovered after surgery due to the effects of anesthetic and analgesic drugs.

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Persistent vomiting can also cause dehydration and electrolyte imbalance. Moreover, PONV is the most frequent and troublesome complication in the early postoperative period.[3]

In recent years, selective serotonin 5-hydroxytryptamine subtype 3 (5-HT3) receptor antagonists such as ondansetron, tropisetron, dolasetron, granisetron, and palonosetron have been introduced because they are effective in the prevention and treatment of PONV. The 5-HT3 receptor antagonists are more effective and safer agents with a better side effect profile than the traditional drugs.[4,5] Ondansetron, which was developed for the treatment of chemotherapy-induced nausea and vomiting (CINV), was the first introduced. Subsequently, it was shown that ondansetron is also effective in the management of PONV.[6] Palonosetron, which is the most recently introduced agent for the treatment of CINV, has greater receptor affinity and a longer half-life than the other 5-HT3 receptor antagonists.[7] To the best of our knowledge, no single study has investigated the effects of palonosetron, tropisetron, and ondansetron on PONV in patients undergoing middle ear surgery. In this study, our aim was to investigate whether ondansetron, tropisetron, or palonosetron is more effective in reducing the incidence and severity of postoperative nausea (PON) and PONV in patients who have undergone middle ear surgeries like mastoidectomy or tympanoplasty.

Materials and Methods

After receiving approval from the Human Research Ethics Committee Of Erciyes University in Turkey, we began our study with the recruitment of 165 patients aged 18 to 65 years, in American Society of Anesthesiologists grades 1 and 2, and scheduled to undergo middle ear surgery. The study was also conducted according to the Helsinki Declaration Guidelines. All patients received a detailed explanation of the study design and signed an informed consent form. Patients who were: using antiemetic drugs; had a history of motion sickness, mental retardation, vomiting, or allergy to 5-HT3 receptor antagonists; pregnant; morbidly obese; or had known cardiac, neurologic, or psychiatric disorders, were excluded from the study. The patients were randomly assigned to 1 of the 3 following groups according to the number (from 1–3) written inside the closed envelope they picked and given the relevant medication. In the ondansetron group (n = 55), 8 mg ondansetron (5 mL) was administered to each patient; in the tropisetron group (n = 55), 5 mg tropisetron (5 mL) was administered to each patient; and in the palonosetron group (n = 55), 0.075 mg palonosetron (1.5 mL) was administered to each patient (all 3 products were made up to 5 mL with normal saline). No control group was used in this study due to ethical considerations as all the patients were at risk of experiencing PONV.[8–10]

All of the drugs used in this study were prepared for administration by the same researcher who was not involved in the intraoperative or postoperative treatment of the patients. The ondansetron, tropisetron, and palonosetron dosages were identical in volume and the medications were similar in appearance with respect to color and viscosity. In addition, the syringes were similar in appearance. Also, neither the anesthesiologist nor the surgeon was able to see the composition of the solution injected in the operating theatre. The overall blinding process was implemented until all data had been entered into the database and their accuracy confirmed.

Oral intake was stopped 8 hours before surgery to empty the gastric contents. Standard monitoring, including echocardiogram, pulse oximeter, noninvasive blood pressure measurements, and end-tidal carbon dioxide testing, was performed in the operating room. Anesthesia induction was achieved by using pentothal (5 mg/kg) and fentanyl (2 μg/kg) intravenously. Neuromuscular blockade was achieved by using rocuronium bromide (0.6 mg/kg IV) and endotracheal intubation was performed by inserting an orotracheal tube after sufficient muscular relaxation had been achieved. Anesthesia was maintained by using 4% to 6% desflurane in a 50%:50% nitric oxide:oxygen mixture at a flow rate of 3 L/min.[11] Nitric oxide was withdrawn before closure of the tympanic membrane to minimize the potential for nitric oxide diffusion into the middle ear, which can cause nausea and vomiting.[12] After the completion of surgery, patients with sufficient spontaneous respiration were extubated after antagonizing neuromuscular blockade with 0.02 mg/kg atropine and 0.04 mg/kg neostigmine. The patients were then transferred to the postoperative anesthesia care unit where they were monitored for at least an hour. After that, the patients were transferred to the ear, nose, and throat clinic where they were followed over a 48-hour period. Diclofenac sodium (100 mg IM) was given to patients experiencing pain and metoclopramide chloride (10 mg IM) was given to patients with nausea or vomiting. Events of nausea and vomiting, antiemetic drugs given and adverse effects such as headache and constipation were recorded during the time periods 0 to 1, 1 to 6, 6 to 12, 12 to 24, and 24 to 48 hours after surgery in the postoperative anesthesia care unit and the ear, nose, and throat clinic.[13] Nausea and vomiting after surgery were scored as follows: 0 for no nausea and vomiting, 1 for only nausea, 2 for a single nausea episode or gagging within 30 minutes, and 3 for >1 nausea or gagging episode within 30 minutes[14] (Table 1).

Table 1
Postoperative nausea and vomiting scoring system.

Score 0	No nausea and vomiting
Score 1	Only nausea
Score 2	One vomiting within 30 min
Score 3	>1 vomiting within 30 min

Statistical analysis

Statistical analysis was performed by using the Statistical Package for Social Sciences version 15.0 (IBM-SPSS Inc, Armonk, NY). The Kolmogorov-Smirnov test was used to assess normal distribution of parametric data. One-way ANOVA with post-hoc Bonferroni correction was used to compare the groups. The Repeated Measurements ANOVA test was used to compare repeated measurements within the groups. Normally distributed data are expressed as mean (SD) in the tables. The χ^2 test was used to analyze nonparametric data. Nonparametric data in the tables are expressed as n (%). A probability level of $P < 0.05$ was considered to be statistically significant.

Results

There were no significant differences in age, height, weight, gender, and ASA grade classification between the ondansetron, palonosetron, and tropisetron groups ($P > 0.05$) (Table 2). During hours 0 to 48 postsurgery, there was no statictically significant difference in the severity of PONV among the groups ($P > .05$) (Table 3). When the incidences of PON, POV, and PONV during the first 48 hours after surgery were compared among groups, the incidences of PON and PONV were significantly lower in the palonosetron group than in the other 2 groups ($P < 0.05$) (Table 4). The PONV incidence during the 12 to 24 hours postsurgery was significantly higher in the ondansetron group than in the palonosetron group ($P = 0.013$) (Table 5). During the first hour after surgery, the need for an antiemetic agent was significantly greater in the tropisetron group than in the palonosetron group

Table 2
Age, weight, height, American Society of Anesthesiologists (ASA) score, and sex characteristics of groups.

Characteristic	Ondansetron (n = 55)	Tropisetron (n = 55)	Palonosetron (n = 55)	*P* value
mean (SD)				
Age (y)	33.1 (12.3)	34.3 (11.8)	33.4 (12.3)	0.855
Height (cm)	169.5 (8.0)	167.4 (8.5)	167.0 (8.3)	0.253
Weight (kg)	74.7 (12.1)	73.2 (12.7)	70.3 (13.8)	0.191
n (%)				
ASA score				0.588
1	48 (87.3)	46 (83.6)	44 (80)	
2	7 (12.7)	9 (16.4)	11 (20)	
Sex				0.976
Female	25 (45.5)	25 (45.5)	26 (42.3)	
Male	30 (54.5)	30 (54.5)	29 (52.7)	

Table 3
Severity of postoperative nausea, postoperative vomiting, and postoperative nausea and vomiting during 0 to 48 hours after surgery.

Condition	Ondansetron	Tropisetron	Palonosetron	*P* value
n (%)				
No nausea or vomiting	20 (36.4)	21 (38.2)	34 (61.8)	0.081
Only nausea (Score = 1)	27 (49.1)	25 (45.5)	13 (23.6)	0.081
1 vomiting (Score = 2)	8 (14.5)	8 (14.5)	7 (12.8)	0.081
>1 vomiting in 30 min (Score = 3)	0 (0.00)	1 (1.8)	1 (1.8)	0.081

$P > 0.05$ was no significant difference.

Table 4
Incidences of postoperative nausea, postoperative vomiting, and postoperative nausea and vomiting.

Condition	Ondansetron (n = 55)	Tropisetron (n = 55)	Palonosetron (n = 55)	*P* value
n (%)				
Postoperative nausea	35 (63.6)*	31 (56.4)*	18 (32.7)	0.003
Postoperative vomiting	8 (14.5)	9 (16.4)	8 (14.5)	0.954
Postoperative nausea and vomiting	35 (63.6)*	34 (61.8)*	21 (38.2)	0.011

* $P < 0.05$ was considered significant.

Table 5
Distribution of postoperative nausea and vomiting according to time intervals.

Hour	Ondansetron	Tropisetron	Palonosetron	*P* value
n (%)				
0-1	25 (45.5)	21 (38.2)	13 (23.6)	0.052
1-6	17 (30.9)	18 (32.7)	15 (27.3)	0.818
6-12	10 (18.2)	8 (14.5)	7 (12.7)	0.719
12-24	15 (27.3)*	7 (12.7)	5 (9.1)	0.024
24-48	8 (14.5)	5 (9.1)	3 (5.5)	0.268

* $P < 0.05$ was considered significant.

Table 7
Distribution of adverse effect according to groups.

Adverse effect	Ondansetron	Tropisetron	Palonosetron	*P* value*
n (%)				
Headache	10 (18.2)	9 (16.4)	11 (20.0)	0.754
Constipation	4 (7.3)	7 (12.7)	7 (12.7)	0.754
Diarrhea	0 (0.00)	1 (1.80)	0 (0.00)	0.754

* $P < 0.05$ was considered significant

($P = 0.019$) (Table 6). In addition, no significant differences were observed between the groups in adverse effects such as headache, constipation, or diarrhea during the first 48 hours after surgery ($P = .0754$) (Table 7).

Discussion

Many agents, including anxiolytics, dopamine receptor antagonists, antihistamines, anticholinergic agents, corticosteroids, and 5-HT3 receptor antagonists, have been compared for the treatment of nausea and vomiting in patients in medical and surgical settings.[15,16]

Table 6
Need for postoperative antiemetic agent.

Hour	Ondansetron (n = 55)	Tropisetron (n = 5)	Palonosetron (n = 55)	*P* value
n (%)				
0-1	10 (18.2)	14 (25.5)	4 (7.3)*	0.038
1-6	13 (23.6)	20 (36.4)	13 (23.6)	0.228
6-12	5 (9.1)	5 (9.1)	8 (14.5)	0.583
12-24	8 (14.5)	7 (12.7)	3 (5.5)	0.270
24-48	5 (9.1)	3 (5.5)	3 (5.5)	0.677
0-48	27 (49.1)	32 (58.2)	20 (36.4)	0.071

* $P < 0.05$ was considered significant.

Carlisle et al[17] published a systematic review that included 737 randomized, controlled studies that involved 103,237 patients and reported that 8 agents, namely droperidol, metoclopramide, ondansetron, tropisetron, dolasetron, dexamethasone, cyclizine, and granisetron, are effective in the treatment of PONV when compared with a placebo. The highest PONV incidence reported was 80% and 72% of treated patients did not experience any improvement.[17]

In the current study, the PON incidence during the first 48 hours postsurgery was 32.7% in the palonosetron group, 56.4% in the tropisetron group, and 63.6% in the ondansetron group. Preventive effect against PON for palonosetron was found to be statistically higher than the other two formulations ($P < 0.05$). The POV incidence during the same period was 14.4% in the palonosetron group, 16.4% in the tropisetron group, and 14.5% in the ondansetron group, with no statistically significant difference between the groups ($P > 0.05$).

During the study period, the incidence of PONV was 38.2% in the palonosetron group, 61.8% in the tropisetron group, and 63.6% in the ondansetron group, with the PONV incidence significantly lower in the palonosetron group than in other groups ($P < 0.05$). The incidence of adverse effects (ie, headache and constipation) related to the 5-HT3 receptor antagonists was 32.7% in the palonosetron group, 30.8% in the tropisetron group, and 25.5% in the ondansetron group, with no statistically significant differences among them ($P > 0.05$).[18]

In a study of 120 patients, Jellish et al[11] compared the effects of ondansetron (4 mg IV), droperidol (25 μg/kg IV), and a placebo during the first 24 hours after surgery on patients who had undergone middle ear procedures. The incidences of PON and POV were 35% and 18%, respectively, during the first 24 hours after surgery in the ondansetron group, whereas additional antiemetic agents were needed by 23% of patients. These rates were reported as 50%, 32%, and 30%, respectively, in the placebo group.

Jellish et al[11] stated that ondansetron prevented POV more effectively than PON. In addition, the POV incidence was significantly lower in the ondansetron group than the placebo group. The POV incidence in that study was comparable with our data (18% vs 14% in our study). However, the PON incidence (63.6%) was significantly higher than in our study. Jellish et al[11] further reported that the difference in PON incidence could be due to causes such as insufficient use of nitric oxide in the maintenance of anesthesia, use of orogastric decompression before surgery, preoperative midazolam administration, use of anticholinesterase after anesthesia, and a higher number of male patients in the ondansetron group. In addition, the shorter follow-up period (24 hours) in the study of Jellish et al[11] explains the higher level of antiemetic agent use reported in our study.

In a placebo-controlled study of 87 patients who underwent middle ear surgery, Khalil et al[25] administered ondansetron (intravenously) to the study group and normal saline to the control group. In the follow-up period of 24 hours, the PON incidence was 42% in the placebo group and 24% in the ondansetron group, whereas the POV incidence was 63% in the placebo group and 38% in the ondansetron group. Moreover, the PONV incidence was 74% in the placebo group and 48% in the ondansetron group. No significant differences were detected between the ondansetron and placebo groups regarding the incidences of PON, POV, and PONV.[19] In our study, the incidences of PON and PONV in the ondansetron group were higher and the POV incidence was lower than reported by Khalil et al.[25] The lower POV incidence can probably be explained by the higher dose (double) of ondansetron administered in our study. In addition, the lower PON incidence in that study could be due to midazolam being used in premedication.

The finding by Madenoglu et al[20] in a randomized, double-blinded, placebo-controlled study that tropisetron reduced PON more effectively than POV is supported by our findings. However, our finding that POV was lower by 16.3% than reported by Madenoglu et al,[20] despite the longer follow-up period (48 hours) in our study, could be due to the higher tropisetron dose (5 mg) used in our study. In addition, dexamethasone use for surgical reasons in all patient groups in the study by Madenoglu et al[20] could explain the lower PON incidence in our tropisetron group. Separately, in our study, the need for additional antiemetic agents in the palonosetron group appears comparable to that reported in the study of Madenoglu et al[20] in which 0.075 mg palonosetron was also administered.

Although 5-HT3 receptor antagonists were first used in the treatment of CINV, they were later proven to be effective in PONV treatment. However, it has been reported that 5-HT3 receptor antagonists are not as effective for the treatment of PONV. Nausea or vomiting episodes occur more frequently than expected in some cases when 5-HT3 receptor antagonists are used for the treatment of nausea or vomiting. This finding has been attributed to genetic variations in cytochrome P450 enzymes that reduce the effects of 5-HT3 receptor antagonists.[21]

In a Phase III study of 564 patients who underwent chemotherapy, Gralla et al[22] investigated the effects of palonosetron (0.025 and 0.075 mg) and ondansetron (32 mg) on CINV during a period of 120 hours. The authors showed that both doses of palonosetron were as effective as ondansetron in CINV treatment. In the same study, the rates of adverse effects such as headache, constipation, or dizziness were 10.1% in the ondansetron group and 6.9% and 8.5% for the palonosetron doses of 0.025 and 0.075 mg, respectively.[22] In our study, palonosetron was found to be statistically more effective than ondansetron for the treatment of PONV. However, the rate of adverse effects in our study was higher than observed by Gralla et al.[22] This difference is probably due to the different type of surgical intervention; that is, the likelihood of headache as surgery-related in patients who had undergone middle ear surgery as opposed to general anesthesia.

In a review of 34 articles that included 1267 patients, Kazemi-Kjellberg et al[23] evaluated 10 antiemetic agents that included ondansetron, tropisetron, dolasetron, and granisetron. The authors concluded that 5-HT3 receptor antagonists are effective in preventing PONV but more effective in preventing vomiting than nausea.[23] Palonosetron, a novel 5-HT3 receptor antagonist, was not included in the review.[23] In a molecular study by Rojas et al[24] the interaction between palonosetron and 5-HT3 receptors was evaluated. The authors concluded that palonosetron interacts with 5-HT3 receptors in a different manner to the other 5-HT3 receptor antagonists because it has a specific molecular structure.[24] In our study, the higher receptor affinity of the novel agent palonosetron and the allosteric characteristic of serotonin antagonism appear to have played a role in the finding that palonosetron was statistically more effective in the prevention of PONV than the other 2 formulations.

According to Sing et al,[25] palonosetron had a higher efficacy for the control of early-term PONV than a placebo, granisetron, and ondansetron. They concluded that palonosetron is only as reliable and effective as a placebo, ramosetron, granisetron, and ondansetron in terms of preventing late PONV.[25]

The results of a meta-analysis performed by Li et al[26] suggested that because there was no increase in the risk of side effects with palonosetron, intravenous palonosetron would be better as a prophylactic antiemetic 5-HT3 receptor antagonist for preventing PONV than a placebo or first-generation 5-HT3 receptor antagonist.[26]

In our study, amongst the 5-HT3 receptor antagonists compared, palonosetron was statistically found to be as effective as the other 2 formulations in the prevention of POV. In addition, it was statistically found to be more effective than the other 2 formulations in the prevention of PON. Furthermore, our study supports

the results of earlier studies that suggest that palonosetron is statistically more effective in the prevention of PONV than the other 2 formulations.

Currently, the improvement of patient satisfaction, as well as reducing the length of hospital stay and costs, are considered the most important criteria in the assessment of health care professionals and facilities.[27] Among the factors that may influence the assessment of these criteria is the success rate in the prevention of PONV. From that perspective, the treatment of PONV should be done with effective agents that achieve a low level of adverse effects and lower costs.

When compared with conventional antiemetic agents, 5-HT3 receptor antagonists are superior agents for the treatment of PONV in terms of safety and adverse effect profiles. However, PONV prophylaxis should not be recommended routinely for all patients. It is more appropriate to give prophylaxis to high-risk patients by analyzing risk factors that can result from the anesthesia technique and surgical procedure employed.[28]

Conclusions

There were no statistically significant differences in the effectiveness of palonosetron, ondansetron, and tropisetron on the severity of POV. However, palonosetron was found to be more effective in reducing PON and PONV than the other 2 formulations compared.

CRediT authorship contribution statement

Ahmet Aydin: Writing - review & editing, Data curation, Conceptualization, Resources. **Mustafa Kaçmaz:** Writing - review & editing, Data curation, Conceptualization, Resources, Writing - original draft. **Adem Boyaci:** Data curation, Writing - original draft.

Conflicts of Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

References

1. Watcha MF, White PF. Postoperative nausea and vomiting. Its etiology, treatment, and prevention. *Anesthesiology*. 1992;77:162–184.
2. Murphy MJ, Hooper VD, Sullivan E, Clifford T, Apfel CC. Identification of risk factors for postoperative nausea and vomiting in the perianesthesia adult patient. *Journal of perianesthesia Nursing*. 2006;21:377–384.
3. Kovac AL. Prophylaxis of postoperative nausea and vomiting: controversies in the use of serotonin 5-hydroxytryptamine subtype 3 receptor antagonists. *Journal of clinical anesthesia*. 2006;18:304–318.
4. Lipp A, Kaliappan A. Focus on quality: managing pain and PONV in day surgery. *Current Anaesthesia & Critical Care*. 2007;18:200–207.
5. Ho K-Y, Gan TJ. Pharmacology, pharmacogenetics, and clinical efficacy of 5-hydroxytryptamine type 3 receptor antagonists for postoperative nausea and vomiting. *Current Opinion in Anesthesiology*. 2006;19:606–611.
6. Gan TJ, Meyer T, Apfel CC, Chung F, Davis PJ, Eubanks S, Kovac A, Philip BK, Sessler DI, Temo J. Consensus guidelines for managing postoperative nausea and vomiting. *Anesthesia & Analgesia*. 2003;97:62–71.
7. Leon AD. *Palonosetron (Aloxi): a second-generation 5-HT3 receptor antagonist for chemotherapy-induced nausea and vomiting, Baylor University Medical Center Proceedings* Taylor & Francis; 2006:413–416.
8. Tramer M. A rational approach to the control of postoperative nausea and vomiting: evidence from systematic reviews. Part I. Efficacy and harm of antiemetic interventions, and methodological issues. *Acta Anaesthesiologica Scandinavica*. 2001;45:4–13.
9. Aspinall RL, Goodman NW. Denial of effective treatment and poor quality of clinical information in placebo controlled trials of ondansetron for postoperative nausea and vomiting: a review of published trials. *Bmj*. 1995;311:844–846.
10. Apfel C, Roewer N, Korttila K. How to study postoperative nausea and vomiting. *Acta Anaesthesiologica Scandinavica*. 2002;46:921–928.
11. Jellish WS, Thalji Z, Fluter E, Leonetti JP. Ondansetron versus droperidol or placebo when given prophylactically for the prevention of postoperative nausea and vomiting in patients undergoing middle ear procedures. *Journal of clinical anesthesia*. 1997;9:451–456.
12. Fujii Y, Saitoh Y, Tanaka H, Toyooka H. *RETRACTED: Combination of granisetron and droperidol in the prevention of nausea and vomiting after middle ear surgery*. Elsevier; 1999.
13. Hasan RA, LaRouere MJ, Kartush J, Bojrab D. Ambulatory tympanomastoid surgery in children: factors affecting hospital admission. *Archives of Otolaryngology–Head & Neck Surgery*. 2004;130:1158–1162.
14. Sadhasivam S, Shende D, Madan R. Prophylactic Ondansetron in Prevention of Postoperative Nausea and Vomiting following Pediatric Strabismus SurgeryA Dose–Response Study. *Anesthesiology: The Journal of the American Society of Anesthesiologists*. 2000;92:1035–1042.
15. Golembiewski J, Tokumaru S. Pharmacological prophylaxis and management of adult postoperative/postdischarge nausea and vomiting. *Journal of PeriAnesthesia Nursing*. 2006;21:385–397.
16. Jordan K, Schmoll HJ, Aapro MS. Comparative activity of antiemetic drugs. *Critical reviews in oncology/hematology*. 2007;61:162–175.
17. Carlisle J, Stevenson CA. Drugs for preventing postoperative nausea and vomiting. *Cochrane database of systematic reviews*. 2006.
18. Fujii Y, Toyooka H, Tanaka H. Granisetron in the prevention of nausea and vomiting after middle-ear surgery: a dose-ranging study. *British journal of anaesthesia*. 1998;80:764–766.
19. Khalil S, Philbrook L, Rabb M, Wells L, Aves T, Villanueva G, Amhan M, Chuang AZ, Lemak NA. Ondansetron/promethazine combination or promethazine alone reduces nausea and vomiting after middle ear surgery. *Journal of clinical anesthesia*. 1999;11:596–600.
20. Madenoglu H, Yildiz K, Dogru K, Kurtsoy A, Güler G, Boyaci A. Randomized, double-blinded comparison of tropisetron and placebo for prevention of postoperative nausea and vomiting after supratentorial craniotomy. *Journal of neurosurgical anesthesiology*. 2003;15:82–86.
21. Hsu ES. A review of granisetron, 5-hydroxytryptamine3 receptor antagonists, and other antiemetics. *American journal of therapeutics*. 2010;17:476–486.
22. Gralla R, Lichinitser M, Van Der Vegt S, Sleeboom H, Mezger J, Peschel C, Tonini G, Labianca R, Macciocchi A, Aapro M. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. *Annals of Oncology*. 2003;14:1570–1577.
23. Kazemi-Kjellberg F, Henzi I, Tramèr MR. Treatment of established postoperative nausea and vomiting: a quantitative systematic review. *BMC anesthesiology*. 2001;1:2.
24. Rojas C, Stathis M, Thomas AG, Massuda EB, Alt J, Zhang J, Rubenstein E, Sebastiani S, Cantoreggi S, Snyder SH. Palonosetron exhibits unique molecular interactions with the 5-HT3 receptor. *Anesthesia & Analgesia*. 2008;107:469–478.
25. Singh PM, Borle A, Gouda D, Makkar JK, Arora MK, Trikha A, Sinha A, Goudra B. Efficacy of palonosetron in postoperative nausea and vomiting (PONV)—a meta–analysis. *Journal of clinical anesthesia*. 2016;34:459–482.
26. Li Y, Wei X, Zhang S, Zhou L, Zhang J. A meta-analysis of palonosetron for the prevention of postoperative nausea and vomiting in adults. *Journal of PeriAnesthesia Nursing*. 2015;30:398–405.
27. Myles P, Williams D, Hendrata M, Anderson H, Weeks A. Patient satisfaction after anaesthesia and surgery: results of a prospective survey of 10,811 patients. *British journal of anaesthesia*. 2000;84:6–10.
28. Gan TJ, Diemunsch P, Habib AS, Kovac A, Kranke P, Meyer TA, Watcha M, Chung F, Angus S, Apfel CC. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesthesia & Analgesia*. 2014;118:85–113.