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ORIGINAL ARTICLE

Associations between ondansetron and the incidence of postoperative nausea and vomiting and food intake in Japanese female undergoing laparoscopic gynecological surgery: a retrospective study

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Abstract

Purpose Prevention of postoperative nausea and vomiting (PONV) is important to achieve DREAM (drinking, eating, mobilization). Ondansetron inhibits PONV, but its effects on postoperative food intake have not been investigated. This study aimed to examine associations between ondansetron and PONV incidence, and postoperative food intake.

Methods This retrospective study included adult patients ($n=632$) who underwent laparoscopic gynecological surgery at Kyushu University Hospital between January 2017 and June 2023. Outcomes were PONV on the day of surgery, PONV up to the day after surgery, and food intake, which was assessed for breakfast and lunch on the day after surgery. Odds ratios (ORs) for PONV incidence and postoperative no-food intake were calculated between those with and without ondansetron during surgery. Multivariable-adjusted analysis was performed using possible confounding factors for PONV. Synergistic effects of combining ondansetron with dexamethasone or total intravenous anesthesia (TIVA) were assessed.

Results Multivariable-adjusted ORs for PONV on the day of surgery and up to the day after surgery were 0.56 (95% confidence interval, 0.32–0.99, $p=0.04$) and 0.52 (0.30–0.93, $p=0.03$), respectively, in the ondansetron group ($n=84$) compared with the non-ondansetron group ($n=548$). In contrast, multivariable-adjusted ORs for no-food intake of breakfast and lunch the day after surgery in the ondansetron group compared with the non-ondansetron group were not significant. Analysis of synergistic effects on PONV showed no significant interaction between ondansetron and dexamethasone or ondansetron and TIVA combinations.

Conclusion Ondansetron administration during surgery was significantly associated with decreased PONV risk but was not associated with food intake the day after surgery.

Keywords Ondansetron · Food intake · PONV

Introduction

The Enhanced Recovery After Surgery (ERAS) protocol aims to improve patient safety, reduce postoperative complications, shorten hospital stays, and save costs [1]. Specifically, achievement of DREAM (Drinking, Eating, Mobilization) goals within 24 h after surgery has been proposed as a core component for the ERAS protocol [2]. Postoperative nausea and vomiting (PONV), pain, surgical technique, and gastrointestinal dysfunction are factors that hinder the achievement of DREAM goals, and anesthesiologists are primarily involved in postoperative pain management and PONV control.

Metoclopramide, droperidol, and related drugs have been used to prevent PONV; ondansetron, a 5-HT_3 antagonist, has been used to treat postoperative gastrointestinal

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symptoms in Japan since August 2021. Ondansetron exerts its antiemetic effect by acting on 5-HT_3 receptors located in the vagal nerve terminals of the gastrointestinal tract and the chemoreceptor trigger zone (CTZ) in the fourth ventricle. Its antiemetic effect has been observed in gastrointestinal symptoms and in nausea and vomiting associated with anti-cancer drugs [3]. Ondansetron is generally used to minimize the incidence of nausea in patients undergoing chemotherapy or PONV in patients undergoing surgery [4]. The efficacy of ondansetron against PONV has been reported in many cases, and the use of ondansetron is expected to make a significant contribution to the achievement of DREAM.

Although the effects of ondansetron are reported to differ between racial groups [5], there are few associated reports on the Japanese population and there are no reports of comparisons with Asian populations. In addition, few studies have examined the effect of ondansetron on early postoperative food intake [6]. In the present study, we hypothesized that ondansetron reduces PONV incidence and contributes to adequate food intake in the early postoperative period in patients undergoing laparoscopic gynecological surgery under general anesthesia. Primarily, this study aimed to examine the associations of ondansetron with PONV incidence and food intake. Our secondary aim was to determine whether ondansetron-dexamethasone co-administration and ondansetron-total intravenous anesthesia (TIVA) combination have a synergistic effect on PONV incidence and food intake.

Methods

Patients and study design

This observational, nonrandomized, retrospective study was approved by the Institutional Clinical Research Ethics Committee of Kyushu University, Fukuoka, Japan (IRB: Clinical Research number #23055-01). All study protocols complied with the Declaration of Helsinki (2013). We enrolled 1108 Japanese patients undergoing laparoscopic gynecological surgery at our university hospital from January 2017 to June 2023. All patients were Japanese, with no other Asian, White, Black, or Hispanic patients included. Patients who underwent surgery in the afternoon, who received continuous fentanyl for postoperative analgesia, who had no information on food intake, or who had incomplete information were excluded. Data were extracted using a data warehouse (DWH) mining tool (Nihon Kohden, Tokyo, Japan). Data on patient age, height, body weight, body mass index (BMI), operation and anesthesia time, anesthetic technique (TIVA or volatile anesthesia), administration of dexamethasone or ondansetron during surgery, history of smoking and motion sickness, amount of bleeding and urine, incidence of PONV, and food intake were obtained. Incidence of PONV was defined as the administration of metoclopramide, which was the most commonly used drug in our hospital for PONV. Confirmation of metoclopramide administration in the ward till the day after surgery and amount of food intake in the morning or at lunch on the day after surgery was extracted from electronic medical records.

Anesthesia

Anesthesia was induced by the intravenous administration of fentanyl, propofol, and rocuronium. It was maintained with desflurane (4–5%), sevoflurane (1.5–2%) or propofol (target-controlled infusion of 3–4 μg/mL), remifentanil, and a 40–50% oxygen–air mixture. Additional bolus infusions of fentanyl and rocuronium were administered, as required. No epidural catheter insertion was performed. To manage postoperative pain, anesthesiologists administered acetaminophen or fentanyl before the end of surgery. Ondansetron and dexamethasone were administered alone or in combination at the discretion of the anesthesiologist. TIVA or inhalation anesthesia was also chosen at the anesthesiologist's discretion. No antiemetics other than ondansetron and dexamethasone were used for PONV prophylaxis.

Statistical analysis

Data were presented as median (interquartile ranges) for continuous variables and percentages for categorical variables. Baseline characteristics were compared using the Mann–Whitney U test for continuous variables and the chi-square test for categorical variables. Logistic regression analysis was performed to estimate the odds ratios (ORs) with 95% confidence intervals (CIs) for PONV incidence and no-food intake. In the multivariable-adjusted analysis, patient age, BMI, operation time, anesthesia technique (TIVA or volatile anesthesia), amount of bleeding, fentanyl/anesthesia time (h)/body weight (μg/hour/kg), dexamethasone administration, and smoking and motion sickness history were included in the model. ORs for PONV and no-food intake were compared between the groups that did and did not receive ondansetron during surgery. We also performed sensitivity analysis using propensity score (PS) matching. PS was calculated for all covariates used in the multivariable-adjusted analysis. The nearest neighbor matching method with 1:1 matching was performed.

In addition, we examined whether intraoperative ondansetron in combination with dexamethasone and ondansetron in combination with TIVA were associated with PONV and food intake. The patients were categorized into four groups, depending on whether they received ondansetron and dexamethasone or TIVA or not. ORs were calculated for each

group, and a model was created with an interaction term to determine if there were any synergistic effects.

SAS software package (version 9.4; SAS Institute, Cary, NC, USA) was used for all statistical analyses. Two-sided values of $p < 0.05$ were considered statistically significant.

Results

Baseline characteristics of participants

Among 1108 patients, 632 were analyzed; 429 patients who underwent surgery in the afternoon and an additional 47 patients were excluded (Fig. 1). Patients who received intraoperative ondansetron were younger and more likely to have motion sickness. Anesthesia time and operation time were longer in patients who did not receive ondansetron. TIVA, dexamethasone, and fentanyl were more likely to be used in patients who received ondansetron. (Table 1).

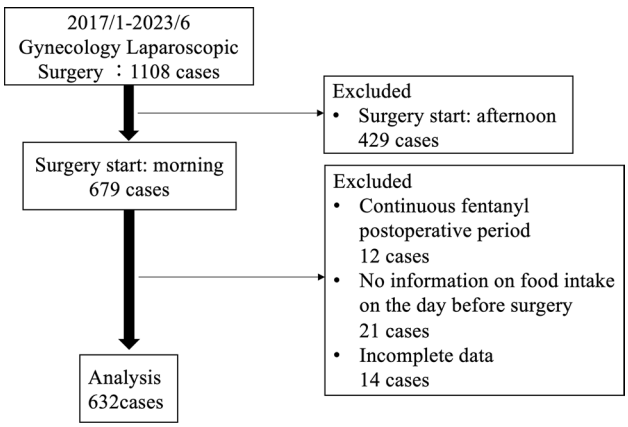

Fig. 1 Flow diagram

Association between ondansetron and incidence of PONV and food intake

Crude ORs for PONV on the day of surgery and up to the day after surgery was significantly lower (No. events/patients: 25/84 vs. 246/548, 25/84 vs. 259/548, respectively) in patients who received ondansetron (OR: 0.52, 95% CI: 0.32–0.86, OR: 0.47, 95% CI: 0.29–0.78, respectively). In the multivariable-adjusted analysis, this association remained significant even after adjusting for potential confounding factors. (Table 2). ORs for no-breakfast and no-lunch intake the day after surgery in patients who received ondansetron were not significant (No. events/patients: 50/84 vs. 330/548, 27/84 vs. 240/548, respectively) in the crude and multivariable-adjusted model (Table 2). The results of sensitivity analysis using propensity score matching was similar to those of the main analysis (Online Resource 1).

Association between ondansetron-dexamethasone co-administration on incidence of PONV

Forty-six patients were administered both ondansetron and dexamethasone (Table 3). Multivariable-adjusted ORs for PONV on the day of surgery (OR:0.36, 95% CI 0.18–0.76) and up to the day after surgery (OR:0.31, 95% CI 0.15–0.65) were significantly lower in patients who received ondansetron-dexamethasone co-administration than in those who received neither ondansetron and dexamethasone, whereas no significant interactions

Table 1 Comparison of baseline characteristics of patients

	Ondansetron		P value
	−	+	
No. of patients	548	84	
Age (years)	48 (39–59)	47 (36–54)	0.01
Body mass index (kg/m^2)	22.6 (20.2–26.2)	21.7 (19.7–25.6)	0.27
Operation time (min)	204 (134–293)	178 (120–243)	0.01
Anesthesia time (min)	284 (201–378)	244 (191–316)	0.01
Amount of fentanyl (μg)	250 (200–300)	300 (200–350)	0.31
Fentanyl/anesthesia time (h) /weight (μg/h/kg)	0.95 (0.68–1.28)	1.12 (0.84–1.44)	0.002
Total intravenous anesthesia (%)	26.8	40.5	0.01
Dexamethasone (%)	8.8	54.8	< 0.001
Smoking (%)	23.0	21.4	0.75
Motion sickness (%)	23.0	45.2	< 0.001

Data are presented as medians (interquartile range) or percentages

PONV postoperative nausea and vomiting

Table 2 Crude and multivariable-adjusted odds ratios for PONV and food intake

	Ondansetron	No. of patients	No. of events	Crude OR (95%CI)	P value	Multivariable-Adjusted OR (95% CI)	P value
PONV on the day of surgery	+	84	25	0.52 (0.32–0.86)	0.01	0.56 (0.32–0.99)	0.04
	–	548	246	1.00 (Reference)		1.00 (Reference)	
PONV up to the day after surgery	+	84	25	0.47 (0.29–0.78)	0.003	0.52 (0.30–0.93)	0.03
	–	548	259	1.00 (Reference)		1.00 (Reference)	
No-breakfast intake the day after surgery	+	84	50	0.97 (0.61–1.55)	0.90	1.60 (0.90–2.86)	0.11
	–	548	330	1.00 (Reference)		1.00 (Reference)	
No-lunch intake the day after surgery	+	84	27	0.61 (0.37–0.99)	0.04	1.02 (0.53–1.94)	0.96
	–	548	240	1.00 (Reference)		1.00 (Reference)	

Multivariable adjustment was performed with age, body mass index, operation time, fentanyl/anesthesia time (h)/weight, total intravenous anesthesia, dexamethasone, smoking, and motion sickness

CI confidence interval; *OR* odds ratio; *PONV* postoperative nausea and vomiting

Table 3 Crude and multivariable-adjusted odds ratios of PONV for ondansetron and dexamethasone combination

	Ondansetron	Dexamethason	No. of patients	No. of events	Crude OR (95% CI)	P value for interaction	Multivariable-Adjusted OR (95% CI)	P value for interaction
PONV on the day of surgery	–	–	500	225	1.00 (Reference)	0.55	1.00 (Reference)	0.46
	–	+	48	21	0.95 (0.52–1.73)		0.85 (0.45–1.59)	
	+	–	38	13	0.64 (0.32–1.27)		0.67 (0.32–1.39)	
	+	+	46	12	0.43 (0.22–0.85)		0.36 (0.18–0.76)	
PONV up to the day after surgery	–	–	500	238	1.00 (Reference)	0.68	1.00 (Reference)	0.58
	–	+	48	21	0.86 (0.47–1.56)		0.73 (0.39–1.37)	
	+	–	38	13	0.57 (0.29–1.14)		0.60 (0.29–1.24)	
	+	+	46	12	0.39 (0.20–0.77)		0.31 (0.15–0.65)	

Multivariable adjustment was performed with age, body mass index, operation time, fentanyl/anesthesia time (h)/weight, total intravenous anesthesia, smoking, and motion sickness

CI confidence interval; *OR* odds ratio; *PONV* postoperative nausea and vomiting

were observed between ondansetron and dexamethasone administration (P for interaction: 0.46 for PONV on the day of surgery, and 0.58 for PONV up to the day after surgery) (Table 3).

Association between ondansetron-TIVA combination on incidence of PONV

Thirty-four patients received ondansetron and were managed with TIVA (Table 4). Multivariable-adjusted ORs for PONV on the day of surgery (OR: 0.19, 95% CI 0.08–0.47) and up to the day after surgery (OR:0.17, 95% CI 0.07–0.42) were significantly lower in patients who received both ondansetron and TIVA, whereas no significant interactions were observed between ondansetron and TIVA (P for interaction: 0.99 for PONV on the day of surgery, and 0.97 for PONV up to the day after surgery) (Table 4).

Discussion

In the present study, we examined the association of administering 4 mg of ondansetron at the end of surgery with PONV incidence and food intake. To our knowledge, only a few studies have examined the effects of ondansetron on postoperative food intake. Furthermore, this study was the first report of ondansetron on PONV for Japanese patients. In a comparison between fosaprepitant, a neurokinn-1 receptor antagonist, and ondansetron for PONV prophylaxis in Japanese patients undergoing lower extremity surgery, authors found that ondansetron was no more effective than fosaprepitant in reducing PONV [7]. However, they did not directly compare the impact of ondansetron on PONV. This study revealed that reduction of PONV was expected to contribute to the achievement of DREAM in terms of drinking and mobility. On the other hand, the positive effect on food intake was not evident in this study.

Table 4 Crude and multivariable-adjusted odds ratios of PONV for ondansetron and TIVA combination

	Ondansetron	TIVA	No. of patients	No. of events	Crude OR (95% CI)	P value for interaction	Multivariable-Adjusted OR (95% CI)	P value for interaction
PONV on the day of surgery	–	–	401	196	1.00 (Reference)	0.78	1.00 (Reference)	0.99
	–	+	147	50	0.54 (0.36–0.80)		0.40 (0.25–0.63)	
	+	–	50	18	0.59 (0.32–1.08)		0.50 (0.27–0.96)	
	+	+	34	7	0.27 (0.12–0.64)		0.19 (0.08–0.47)	
PONV up to the day after surgery	–	–	401	206	1.00 (Reference)	0.79	1.00 (ref)	0.97
	–	+	147	53	0.53 (0.36–0.79)		0.39 (0.25–0.62)	
	+	–	50	18	0.53 (0.29–0.98)		0.45 (0.24–0.86)	
	+	+	34	18	0.25 (0.10–0.58)		0.17 (0.07–0.42)	

Multivariable adjustment was performed with age, body mass index, operation time, fentanyl/anesthesia time (h)/weight, dexamethasone, smoking, and motion sickness

CI confidence interval; *OR* odds ratio; *PONV* postoperative nausea and vomiting; *TIVA* total intravenous anesthesia

Effect of ondansetron in preventing PONV is widely known, and combination therapy is more effective than administration of ondansetron only. Combination therapy (ondansetron + droperidol) significantly reduced PONV at 30 min, 3 h, and 6 h after laparoscopic cholecystectomy compared with administration of droperidol or ondansetron only and required less use of rescue antiemetic treatment [8]. Additionally, different combinations of drugs have different effects. Administration of ondansetron with droperidol or dexamethasone is more effective in preventing PONV than administration of dexamethasone with droperidol [9]. The nausea incidence rates at 2 h after surgery were 7%, 30%, and 33% in group 1 (TIVA with propofol, droperidol, and ondansetron), group 2 (droperidol and ondansetron with isoflurane and nitrous oxide), and group 3 (TIVA with propofol), respectively ($P < 0.05$, group 1 versus group 2 and 3) [10]. Consensus guidelines recommend evaluation of the risk of PONV and the use of two or more antiemetic agents in high-risk cases [3]. The results of the present study support this consensus (Tables 3 and 4).

On examining the associations between sociodemographic factors and PONV incidence, Black patients were less likely to experience PONV compared to White patients and Hispanic patients were more likely to experience PONV than White patients [5]. Ondansetron is metabolized by hepatic cytochrome P-450 (CYP3A4, CYP2D6 and CYP1A2) [11]. The mean metabolic ratios of these enzymes were different among Japanese, Korean, and Chinese patients [12]. On the other hand, few comparison studies have been conducted on Japanese patients. PONV incidence was 32% (0–2 h after surgery) and 37% (0–24 h after surgery) in patients who received ondansetron before general anesthesia with inhalation agents [7]. Consistent with our study, PONV incidence was reduced by ondansetron administration, but not in all cases.

A previous telephone survey of outpatients undergoing day surgery reported that ondansetron suppressed PONV, and more patients were able to start eating normally on the day after discharge than those in the placebo group [6]. Therefore, antiemetic agents may improve postoperative food intake. However, all the patients in this study skipped meals on the day of surgery at the request of their physicians. Thus, it is possible that if meals had been adapted to the patient's wishes on the day of surgery, the outcomes would have been different. Additionally, PONV mostly developed on the day of surgery, and very few cases of PONV developed on the day after surgery.

Furthermore, the half-life of ondansetron is approximately 5 h, which may be one reason why it did not affect food intake on the day after surgery. Postoperative pain may play a significant role in PONV and food intake on the day after surgery. In the present study, the postoperative administration of analgesics and fentanyl during surgery was similar in both groups.

Limitation

The limitations of this study are as follows. First, we were unable to compare food intake on the day of surgery, where the effect of ondansetron could best be assessed. However, considering that about 60% of the patients were not able to eat at all on the morning of the day after surgery, it is expected that most of them would not be able to eat even if they were offered food on the night of surgery, making it difficult to verify the effect of ondansetron in any case. Second, no clear criteria were established for PONV because this was a retrospective observational study. Hence, there may have been some missed cases of PONV, but their incidence was similar to that reported in the past. On the other hand, cases wherein metoclopramide was administered after extubation

were considered to have PONV, but it is possible that the metoclopramide was administered prophylactically and PONV incidence was overestimated. Third, the sample size of the study was small. Then, we cannot determine whether the results are decisive due to the very wide 95% confidence interval. Fourth, residual confounders may exist, although the risk estimates were adjusted for possible confounding factors. Fifth, as this was an observational study, we could not address causation. Further studies, such as randomized controlled trials, are required to prove a causal relationship.

Conclusion

Ondansetron administration was significantly associated with a decreased risk of PONV but not with food intake on the day after surgery. Ondansetron-dexamethasone co-administration and ondansetron-TIVA combination were associated with a lower risk of PONV, although no synergistic effect on PONV was noted. Randomized controlled trials or larger studies are needed to further clarify the associations between ondansetron and food intake.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00540-023-03295-0.

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Author contributions KS: methodology, formal analysis, writing—original draft, writing—review and editing. ST, ST and KU: data curation, data analysis, and writing—review. KY: writing—review and editing, supervision.

Data availability The data generated during and/or analyzed during the current study are available within the manuscript and its supplementary file.

Declarations

Conflict of interest No external funding and no competing interests declared.

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