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Factors Associated with Postoperative Nausea and Vomiting after Breast Cancer Surgery with Inhalation Anesthesia

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Background: The incidence and risk factors of postoperative nausea and vomiting (PONV) and early PONV (ePONV) were evaluated in patients who underwent breast surgery with volatile anesthesia.

Methods: In this retrospective study, multivariate logistic regression was used to determine incidence and identify risk factors for PONV.

Results: Among 928 patients, 166 (18%) and 220 (24%) had ePONV and PONV, respectively. In multivariate analysis, anesthesia duration and use of desflurane were independent risk factors for ePONV. For PONV, anesthesia duration and Apfel score were independent risk factors.

Conclusions: Our results indicate that desflurane was the main cause of ePONV. However, during the delayed phase, a higher Apfel score was the strongest predictor. In the early and delayed phases, long anesthesia duration was associated with high risk of PONV. Thus, prolonged anesthesia and desflurane use should be avoided for patients at high risk of PONV, particularly those with high Apfel scores.

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Key words: PONV, sevoflurane, desflurane, anesthesia

Introduction

Postoperative nausea and vomiting (PONV) is a frequent complication after general anesthesia. Estimated incidence is 25% to 30% in the general population but can reach 70% to 80% among high-risk patients[1]. Although often self-limiting, PONV has been reported to be more uncomfortable than postoperative pain[2]. Moreover, PONV is associated with postoperative complications such as increased intracranial pressure, fluid and electrolyte imbalance, suture tension, abdominal wound dehiscence, and esophageal tear[3]. Multiple factors have been reported to be associated with PONV incidence, including female sex, history of smoking and motion sickness, opioid use, method used for anesthesia, and surgery type[4].

A previous study reported that PONV is 2 to 3 times less frequent in males than in females[5]. Thus, surgical procedures performed for women (e.g., gynecological surgery) are associated with a high PONV incidence[6]. Previous studies reported extremely high rates of PONV (60% to 84%) after breast surgery performed with general anesthesia[7–9]. Furthermore, strong evidence indicates that volatile anesthetics are emetogenic and associated with PONV, especially early PONV (ePONV), which is defined as PONV that occurs within 4 hours after anesthesia[10,11]. In our center, ≥90% of patients received inhalation anesthesia consisting of desflurane and sevoflurane. Although desflurane and sevoflurane are widely used in clinical practice and are strongly associated with PONV, no large study has investigated this association. Thus, we analyzed incidence and risk factors for PONV and ePONV in patients after breast cancer surgery with inhalation anesthesia.

Materials and Methods

The Ethics Committees of Nippon Medical School approved the study (approval no. R1-10-1209), and the electronic medical records of 972 adults who had received general anesthesia at our university hospital between April 2014 and March 2019 were reviewed. Patients who

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had undergone breast surgery were enrolled in this study. To eliminate any effects attributable to the type of anesthesia used, we excluded men, patients who had an American Society of Anesthesiologists classification of 3 or higher, and those who had received total intravenous anesthesia.

Demographic and perioperative variables that are potentially related to PONV were recorded, including age, smoking history, body mass index, history of motion sickness or PONV, and Apfel score. Variables related to the anesthesia and procedure were duration of anesthesia, administration of volatile anesthetics and intra-/postoperative opioid infusion, intraoperative bleeding, and infusion volume. Postoperative variables consisted of use of the Numerical Rating Scale (NRS; 0-10: 0 = no symptoms, 10 = worst) for pain; incidence of nausea, retching, or vomiting; and need for a rescue analgesic or antiemetic. In routine practice, PONV and pain intensity were recorded by a nurse upon leaving the operating room.

Anesthetic Technique

General anesthesia was administered using standardized techniques and induced via intravenous administration of 1.5 mg/kg propofol, 0.6 to 1 mg/kg rocuronium, and 1 to 2 μg/kg fentanyl after insertion of an endotracheal tube into the trachea. On the basis of the patient's condition and the preference of the anesthesiologist, inhaled anesthesia was maintained with both inhalation anesthetics (5% to 7% desflurane and 1.5% to 3% sevoflurane). Similar minimum alveolar concentration values were achieved by using the circulatory index and general guidelines for administering anesthesia.

Statistical Analysis

Patient demographic and clinical characteristics were summarized using descriptive statistics. The mean (SD) was used to express continuous variables, and absolute number (percentage) was used to express categorical variables. Relative risk estimates expressed as odds ratios (ORs) with 95% confidence intervals (CIs) were calculated by univariate analysis with logistic regression. A two-sided p value of 0.05 was used to identify independent risk factors for PONV. Factors with univariate p values of <0.10 on logistic regression were subjected to multivariate analysis with backward selection. Multicollinearity diagnostics showed no multicollinearity issues (condition indices <30 and variance influence factor values <10) between the selected independent variables in this study. PONV incidence was calculated for the number of independent risk factors per patient. A threshold p value of <0.05 was considered to indicate statistical significance. Statistical Package for Social Sciences software was used for all statistical analyses.

Table 1 Patient, anesthetic, and operative characteristics and postoperative conditions

Variables	N = 928
Patient characteristics	
Age (y)	58.61 ± 14.31
BMI (kg/m²)	22.57 ± 3.86
Smoking (n)	117
History of PONV or motion sickness (n)	30
Apfel score	2.04 ± 0.49
Anesthesia-related factors	
Sevoflurane (n)	811
Desflurane (n)	117
Duration of anesthesia (min)	226.86 ± 79.51
Intraoperative opioid dose (μg)	263.19 ± 155.38
Postoperative opioid infusion (n)	98
NRS	3.28 ± 3.11
Operative factors	
Intraoperative bleeding (mL)	85.88 ± 94.94
Infusion volume (mL)	1,177.42 ± 558.04

Data are presented as mean ± SD, absolute number (%), or mean (95% confidence interval)
BMI: Body Mass Index, PONV: Postoperative nausea and vomiting, NRS: Numerical Rating Scale

Results

A scatterplot of the variables showed no obvious linear relationship. Multiple logistic regression analysis was performed by using the forward selection method with the likelihood ratio method, and the results are shown below. The model chi-square test ($p < 0.01$) results and all variables were significant ($p < 0.01$). The result of the Hosmer-Lemeshow test was good (0.085), and the discriminant median was 82.1%, which is relatively good. There were no outliers (i.e., where the predicted value exceeded ±3 SD relative to the measured value).

This study included 928 patients who underwent surgery for breast cancer at our hospital. Patient demographic characteristics and perioperative factors are shown in **Table 1**.

The mean age of the patients was 22.57 ± 3.86 years, and the mean body mass index was 22.25 ± 3.86 kg/m^2. Of the patients, 117 (12.6%) had a history of smoking, 30 (3.2%) reported a history of PONV/motion sickness, and the mean Apfel score was 2.04 ± 0.49. A total of 811 patients (87.4%) received volatile anesthesia with sevoflurane; 98 patients (10.5%) received postoperative opioids, and the mean dose of intraoperative opioid was 263.2 ±

155.4 μg. The mean duration of anesthesia was 226.86 ± 79.51 minutes. Regarding operative factors, mean intraoperative blood loss was 85.88 ± 94.94 mL and mean infusion volume was 1,177.42 ± 558.04 mL. On multivariate analysis with logistic regression, desflurane use (OR, 1.003; 95% CI, 1.001-1.006; $p < 0.01$) and duration of anesthesia (OR, 1.792; 95% CI, 1.128-2.847; $p = 0.014$; **Table 2**) were significant risk factors for ePONV. In addition, Apfel score (OR, 1.398; 95% CI, 1.013-1.928; $p = 0.041$) and duration of anesthesia (OR, 1.004; 95% CI, 1.002-1.006; $p < 0.01$; **Table 2**) were significant risk factors for PONV (**Table 2**).

To further investigate the effect of anesthesia type on ePONV, the timing of PONV development was compared between the sevoflurane and desflurane groups. Sevoflurane was associated with less PONV in the early phase, as shown by the Kaplan-Meier curves (**Fig. 1**; $P > 0.05$ for comparisons); however, the differences were small in the late phase.

Table 2 Multivariate analysis of postoperative nausea and vomiting risk factors

Variables	OR	95% CI	*p*
PONV			
Apfer score	1.398	1.013–1.928	0.041
Duration of anesthesia	1.004	1.002–1.006	<0.001
Early PONV			
Duration of anesthesia	1.003	1.001–1.006	0.003
Anesthetic agent	1.792	1.128–2.847	0.014

OR: Odds ratio, CI: confidence interval, PONV: Postoperative nausea and vomiting

Discussion

Our results suggest that ePONV was primarily induced by perioperative administration of emetogenic stimuli (i.e., type of volatile anesthesia, prolonged duration of anesthesia). In particular, anesthesia maintenance with sevoflurane resulted in lower risk of ePONV, as compared with desflurane (OR, 1.79), and shorter duration of anesthesia was more effective for reducing both early and late PONV. In addition, patient factors and Apfel score were associated with PONV. The strongest risk factor for PONV was use of volatile anesthetics, as compared with intravenous anesthesia. The OR for volatile anesthesia was 2.3 to 2.4, and the effect was limited to the early postoperative period[12].

Desflurane and sevoflurane are characterized by low solubility in blood, resulting in its rapid activity and emergence from anesthesia[13,14]. However, their use is associated with a dose-dependent increase in PONV[15]. Studies of the effects of desflurane and sevoflurane on PONV have yielded conflicting findings. A study by Wallenborn et al. reported no difference between isoflurane, desflurane, and sevoflurane in the frequency and severity of postoperative nausea, vomiting, or both[14], and a recent meta-analysis by Macario et al. found no difference in

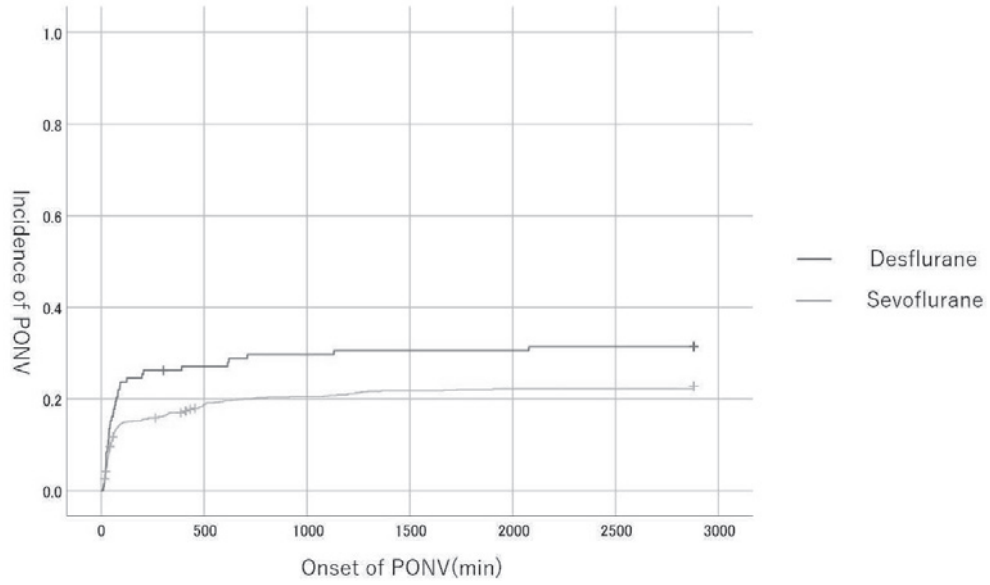

Fig. 1 Kaplan–Meier curves showing proportions of patients with nausea and vomiting over time, by type of maintenance anesthesia.
Note: The difference between sevoflurane and desflurane is only significant during the early postoperative period.

the frequency of PONV between desflurane and sevoflurane. The authors reported that patients who received desflurane had a high rate of ePONV onset, although the difference was not significant[11].

In contrast, some studies reported that ePONV incidence was higher for desflurane than for sevoflurane[16]. A study of patients administered intravenous, fentanyl-based, patient-controlled analgesia reported that PONV was higher after desflurane (OR, 1.42) than after sevoflurane[17]. Similarly, another study showed that desflurane administration was a risk factor for PONV[14]. In the present study, desflurane was only associated with ePONV incidence, not with late PONV. The rates of ePONV for desflurane and sevoflurane significantly differed: 26.49% and 16.62%, respectively (P <0.05). However, in a comparison of the total rate of PONV between these anesthetics, this difference was small. In addition, as revealed by the Kaplan-Meier curves, the difference between sevoflurane and desflurane was greatest during the first 4 hours, when pharmacologic kinetic effects are most likely to account for such differences (**Fig. 1**). A previous study reported that use of volatile anesthetics was the strongest risk factor for PONV development, which was limited to the early postoperative period[12].

Because of the low blood/gas partition coefficient of desflurane, its washout time is more rapid than that of other volatile agents. Therefore, desflurane use promotes rapid recovery and reestablishment of cognitive function. Moreover, airway irritation is worse with desflurane than with other inhaled agents. Thus, quicker emergence from anesthesia, combined with increased airway irritation, may hasten recognition of discomfort and increase the likelihood of patient-reported PONV.

In this study, longer duration of anesthesia was identified as a risk factor for PONV, as in a previous study[18,19]. However, the cutoff values used were different. The present cutoff value (i.e., 180 minutes) was considerably longer than those used in previous studies. Fero et al. suggested that prolonged exposure to volatile anesthetics and administration of larger quantities of opioids, which occurs in conjunction with longer duration of anesthesia and surgery, may be associated with PONV[20]. However, it is unclear whether longer use of volatile anesthetics with low solubility affects PONV in a dose-related manner.

In this study, the patient groups did not significantly differ in relation to smoking rate, history of motion sickness, or history of PONV; however, Apfel score was significantly different. Apfel's simplified risk score is used for patients receiving volatile anesthetics without antiemetics. The predicted incidence of PONV was 10%, 20%, 40%, 60%, and 80% for 0, 1, 2, 3, and 4 risk factors, respectively, based on Apfel's simplified risk score[1]. In our study, the predicted incidence of PONV was lower than that reported in Apfel's study, likely because of our shorter operating time. Therefore, we believe that PONV incidence was low because anesthesia time was short. Surprisingly, no significant interactions between antiemetics and surgical variables were observed.

This study has several limitations: 1) the patients' postoperative symptoms were evaluated only once per day, when the nurse visited the patients. Patients were asked to rate their symptoms by using the NRS for nausea, the number of vomiting episodes, and the NRS for pain. This may have introduced recall bias and led to underestimation of PONV incidence; 2) the retrospective nature of the study makes it difficult to evaluate causation, because of potential unevaluated confounding factors; and 3) this was a single-center study conducted in Japan. A multicenter study would yield results of greater accuracy and reliability.

Although PONV is a multifactorial event, our findings suggest that a difference in volatile anesthetics is the primary cause of ePONV. However, this difference had no effect on delayed PONV, for which a higher Apfel score was the main predictor. In addition, long duration of anesthesia was associated with high risk of PONV during the early and delayed phases. Thus, prolonged anesthesia and desflurane use should be avoided for patients at high risk for PONV, especially those with high Apfel scores.

Conflict of Interest: The authors declare no conflicts of interest.

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