What are the factors affecting postoperative nausea and vomiting following breast cancer surgery with inhalation anesthesia?

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Running title: Postoperative nausea & vomiting factors
Abstract

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

Methods: In this retrospective study, we used a multivariate logistic regression to investigate the incidence and risk factors of PONV.

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

Conclusions: Although many previous studies have shown that PONV is a multifactorial event, our results indicate that desflurane use can be considered a main cause of ePONV. However, in the delayed phase, a higher Apfel score was the main predictor. In the early and delayed phases, a long duration of anesthesia was related to a high risk of PONV. Accordingly, avoiding a long duration of anesthesia and desflurane use is recommended for patients at a high risk of developing PONV, particularly for those with high Apfel scores.

Keywords: PONV, sevoflurane, desflurane, anesthesia
Introduction

One of the most frequently-occurring complications following general anesthesia is postoperative nausea and vomiting (PONV). The estimated incidence in the general population is 25%-30%, which can reach 70%-80% among high risk patients. Although often self-limiting, PONV has been reported to be more uncomfortable than postoperative pain. Moreover, PONV has been associated with various postoperative complications, including increased intracranial pressure, fluid and electrolyte imbalance, suture tension, abdominal wound dehiscence, and esophageal tear. Multiple factors have been reported as being related to the induction of PONV (e.g., sex, history of smoking and motion sickness, opioid use, method used for anesthesia, and surgery type).

A previous study demonstrated that males experience PONV approximately two to three times less frequently compared to females. Because of this, surgical procedures that are performed only for women (e.g., gynecological surgery), associated with a high PONV incidence. Previous studies have identified extremely high rates of PONV (60%-84%) following breast surgery performed with general anesthesia. Furthermore, strong evidence supports volatile anesthetics as emetogenic and being associated with PONV, especially early PONV (ePONV), which is defined as PONV that occurs more than four hours after anesthesia. In our institution, ≥90% of patients received inhalation anesthesia consisting of desflurane and sevoflurane. Although desflurane and sevoflurane are widely used in clinical practice and are highly involved in PONV, there have been no large
studies on this association.

This study aims to elucidate the incidence and risk factors of PONV and ePONV in patients after breast cancer surgery with inhalation anesthesia.

Materials and Methods

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

Patients who had undergone breast surgery were enrolled in this study, whereas patients who were male, had an American Society of Anesthesiologists classification of 3 or higher, or received total intravenous anesthesia were excluded to eliminate any impact that the type of anesthetic may have on the data.

Both demographic and perioperative variables established to be potentially related to PONV were recorded. Such demographic variables consisted of age; history of smoking; body mass index; history of motion sickness or PONV; and Apfel score. The anesthesia- and operation-related variables comprised the duration of anesthesia, administration of volatile anesthetics and intra-/postoperative opioid infusion, intraoperative bleeding, and infusion volume. Postoperative variables consisted of the use of the Numerical Rating Scale (NRS, 0–10; 0 = no symptoms; 10 = worst) for
pain; incidence of nausea, retching, or vomiting; and requirement of rescue analgesic or antiemetic.

In routine practice, PONV and pain intensity were recorded by a nurse upon leaving the operation room.

Anesthetic Technique

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

Statistical analysis

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

Results

We observed a scatter plot of the variables and determined that none of variables displayed a remarkable linear relationship. The multiple logistic regression analysis was performed according to forward selection method with the likelihood ratio method, and the results are shown below. The model chi-square test \( p < 0.01 \) results and each variable \( p < 0.01 \) were significant. The result of the Hosmer–Lemeshow test was good \( 0.085 \), and the discriminant median was 82.1%, which was 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. The demographic characteristics and perioperative factors of the included patients are listed 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/m². 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. Ninety-eight patients (10.5%) received postoperative opioids, and the mean intraoperative opioid use was 263.2 ± 155.4 µg. The mean duration of anesthesia was 226.86 ± 79.51 minutes. In terms of operation factors, the mean intraoperative blood loss was 85.88 ± 94.94 and the mean infusion volume was 1177.42 ± 558.04. 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 statistically 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 statistically significant risk factors for PONV (Table 2).

Here, Table 2 describes the factors that influence the development of PONV. To further investigate the influence of anesthesia type on ePONV, the time of the development of PONV was compared between the sevoflurane and desflurane groups. Sevoflurane was found to be associated with reduced PONV in the early phase as shown by the Kaplan-Meier curves (Fig. 1; \( P > 0.05 \) for comparisons; however, the differences became small in the late phase.
Discussion

Our study shows that ePONV is primarily induced by the perioperative administration of emetogenic stimuli (i.e., type of volatile anesthesia, prolonged duration of anesthesia). In particular, anesthesia maintenance with sevoflurane resulted in a reduced risk of ePONV compared to that of desflurane (OR, 1.79), and shorter anesthesia time was more effective for reducing both early and late PONV. In addition, patient factors and Apfel score had an effect on PONV.

The present research shows that the greatest risk factor for PONV was using volatile anesthetics as compared with intravenous anesthesia. The OR for volatile anesthesia ranged from 2.3 to 2.4, and the effect was limited to the early postoperative period.\textsuperscript{12}

Desflurane and sevoflurane are characterized by low solubility in the blood, resulting in its rapid activity and emergence from anesthesia.\textsuperscript{13,14} However, their use is associated with a dose-dependent increase in PONV.\textsuperscript{15} Several reports have compared the effect of desflurane and sevoflurane on PONV, resulting in conflicting data. The study by Wallenborn et al. reported that there was no difference between isoflurane, desflurane, and sevoflurane regarding the frequency and severity of postoperative nausea, vomiting, or both.\textsuperscript{14}

A recent meta-analysis by Macario et al. demonstrated that there was no difference in the frequency of PONV between desflurane and sevoflurane; the authors reported that patients who received desflurane had a high rate of ePONV onset, albeit without statistical significance.\textsuperscript{11} On the other
hand, some reports have described an increased incidence of ePONV associated with desflurane compared with that observed in patients receiving sevoflurane.\textsuperscript{16}

One study investigated patients administered fentanyl-based intravenous patient-controlled analgesia and reported that PONV increased following desflurane as compared with sevoflurane (OR, 1.42).\textsuperscript{17}

Similarly, another study showed that desflurane administration was a risk factor for PONV.\textsuperscript{14}

In this study, desflurane only had an influence on the incidence of ePONV, but not late PONV. The rates of ePONV for desflurane and sevoflurane were significantly different at 26.49\% and 16.62\%, respectively ($P < 0.05$). However, when comparing the total rate of PONV between these two anesthetic agents, this difference became small. In addition, the major difference between sevoflurane and desflurane was found to occur within the first 4 h, when the pharmacologic kinetic effects are most likely to account for such differences, as revealed by the Kaplan-Meier curve (Fig. 1).

A previous study demonstrated that the use of volatile anesthetics represented the greatest risk factor for the development of PONV, which was limited to the early postoperative period.\textsuperscript{12}

Due to the low blood/gas partition coefficient of desflurane, its washout time occurs more rapidly than that of other volatile agents. As a consequence, desflurane use promotes rapid recovery and reestablishment of cognitive function. Moreover, greater airway irritation occurs following desflurane compared to other inhalant agents. Thus, quicker emergence from anesthesia, combined
with increased airway irritation, may promote the early recognition of discomfort and increase the
likelihood of patients reporting PONV.

In this study, we identified one risk factor for PONV to be a longer duration of anesthesia, similar to
the findings reported in a previous study. However, the cutoff values used by the studies were
different, and our cutoff value (i.e., 180 minutes) was quite long as compared with other research.
Fero et al. considered that prolonged exposure to volatile anesthetics and the administration of a
larger quantities of opioids, which occurs in conjunction with a longer duration of anesthesia or
surgery, may be associated with PONV. However, it remains unknown whether a longer use of
volatile anesthetics with low solubility affects PONV in a dose-related manner.

In this study, the groups did not exhibit any significant differences regarding the smoking rate,
history of motion sickness, or history of PONV; however, the Apfel score was significantly different.

The Apfel’s simplified risk score is based on patients receiving volatile anesthetics without
antiemetics. The predicted incidence of PONV was found to be 10%, 20%, 40%, 60%, or 80% if 0,
1, 2, 3, or 4 risk factors were present, respectively, based on the Apfel’s simplified risk score. 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 considered that the PONV occurrence rate itself was
low because the anesthesia time was short. Surprisingly, no statistically significant interactions were
observed for antiemetics with surgical variables.
There are several limitations associated with the present study: 1) the patients’ postoperative symptoms were only evaluated once per day while the nurse visited the patients. Patients were asked to rate their symptoms using the NRS for nausea, the number of vomiting episodes, and the NRS for pain. Thus, this may have introduced recall bias, and may underestimate the incidence of PONV; 2) the retrospective nature of the study resulted in difficulty relating effects to causation because of potential unevaluated confounding factors; and 3) this was a single-center study conducted in Japan. More accurate and reliable results could be achieved using a multicenter study.

Despite PONV being a multifactorial event, our data indicate that a difference in volatile anesthetics should be considered as a primary cause of this complication for ePONV. However, the difference had no effect on delayed PONV, and a higher Apfel score was the main predictor. In addition, long anesthesia time was associated with a high risk of PONV during the early and delayed phases. Accordingly, avoiding a long duration of anesthesia and desflurane use makes more sense for patients at a high risk for PONV, especially those with high Apfel scores.

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

Fig 1 Kaplan-Meier curves representing the proportion of patients who experienced nausea and vomiting over time according to the type of maintenance anesthesia.

Note: the difference between sevoflurane and desflurane is only related to the early postoperative period.
Fig. 1

![Graph showing the incidence of PONV over time for Desflurane and Sevoflurane](image-url)
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 |
| **Anesthetic factor**                               |        |
| Sevoflurane (n)                                     | 811    |
| Desflurane (n)                                      | 117    |
| Duration of anesthesia (min)                        | 226.86 ± 79.51 |
| Intraoperative opioid (µg)                          | 263.19 ± 155.38 |
| Postoperative opioid infusion (n)                   | 98     |
| NRS                                                 | 3.28 ± 3.11 |
| **Operation factor**                                |        |
| Intraoperative bleeding (mL)                        | 85.88 ± 94.94 |
| **Infusion volume (mL)**                            | 1177.42 ± 558.04 |

Data are presented as the mean ± standard deviation, absolute number (%), or mean (95% confidence
interval)

BMI: Body Mass Index, PONV: Postoperative nausea and vomiting, NRS: Numerical Rating Scale
Table 2 Multivariate analysis 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