



ORIGINAL ARTICLE

Relationship between the incidence and risk factors of postoperative nausea and vomiting in patients with intravenous patient-controlled analgesia



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Summary *Objective:* This study aims to evaluate retrospectively the electronic medical records of surgical patients who received intravenous patient-controlled analgesia, to identify potential relationships between the incidence and risk factors of postoperative nausea and vomiting (PONV).

Methods: Records of 6773 adult patients who received fentanyl-based intravenous patient-controlled analgesia after surgery at Chung-Ang University Hospital between January 1, 2010 and December 31, 2015 were reviewed. Multiple logistic regressions were used to identify risk factors for PONV.

Results: Of 6773 patients, 1216 (18.0%) were recorded to have PONV. In multiple logistic regression analysis, female gender, nonsmoking status, history of motion sickness or PONV, use of desflurane and nitrous oxide, and preintubation use of opioid analgesia were independent risk factors for PONV.

Conclusions: Despite the use of antiemetic prophylaxis, 18.0% of patients with intravenous patient-controlled analgesia had PONV. Use of desflurane and nitrous oxide, in addition to risk factors included in the Apfel score (female gender, nonsmoking status, history of PONV or motion sickness, and use of postoperative opioids) were identified as independent risk factors. As the incidence of PONV was 2.8%, 6.0%, 11.7%, 15.2%, 21.1%, 50.0%, and 100% for patients who

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had 0, 1, 2, 3, 4, 5, and all these risk factors, respectively, risk-adapted, multimodal, or combination therapy should be applied for patients receiving general anesthesia.

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1. Introduction

Postoperative nausea and vomiting (PONV) is one of the most common complications after general anesthesia and surgery. It can be very unpleasant for patients, who may even consider it the most troublesome experience in addition to postoperative pain.^{1,2} Various factors, such as patient characteristics, the method of anesthesia, and the type of surgery can affect the incidence of PONV.

Opioids have an important role in routine postoperative analgesic therapy.³ A previous study showed that up to 75% of patients might suffer from postoperative pain, with up to 30% of them experiencing moderate or severe postoperative pain.⁴ Therefore, proper management of postoperative pain is required to improve the quality of outcomes for patients and to prevent postoperative complications.

Patient-controlled analgesia (PCA) allows patients to self-administer medications to relieve pain and is an effective method of postoperative pain control.⁵ However, postoperative opioid usage was reported to be a risk factor for PONV.⁶ Therefore, patients receiving intravenous patient-controlled analgesia (IV-PCA) have at least one risk factor for PONV, suggesting that effective evaluation of PONV and prophylactic treatment must be considered to reduce or prevent the incidence of PONV.

In this retrospective study, we evaluated the incidence and identified the risk factors of PONV in patients who received IV-PCA treatment and a single dose of prophylactic antiemetic.

2. Methods

The present study was approved by the Institutional Review Board of Chung-Ang University Hospital (Seoul, Korea) in August 2016 (C2016173[1916]), and because the study involved the evaluation of pre-existing de-identified electronic medical records of patients, the requirement for informed consent was waived. The manuscript was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.⁷

This was a retrospective cohort study involving the evaluation of prospectively collected medical records of 6773 patients who received fentanyl-based IV-PCA after surgery at Chung-Ang University Hospital between January 1, 2010 and December 31, 2015. The exclusion criteria for this study were patient age below 19 years and patient refusal of PCA.

Data were collected by a nurse who had been working in our hospital for more than 10 years and as a PCA specialist for more than 5 years. She only undertakes tasks related to IV-PCA and makes rounds of patients who have had IV-PCA at least once daily to collect information regarding PONV, pain scores, and other postoperative complications such as

headache, dizziness, or requirement of rescue antiemetic. Data were collected only by this nurse, who had received training regarding standardized scoring variables [pain visual analog scale and nausea numerical rating scale (NRS)] before the commencement of this study. Data collected by the nurse during the first 2 years (2008–2009) were not included in the analysis.

The data included 21 demographic characteristics, as well as anesthetic, surgical, or PCA-related factors closely related with the incidence of PONV. Specifically, we collected data on age, gender, body mass index, smoking status, history of PONV or motion sickness, type of anesthetic agent used (propofol, desflurane, or sevoflurane), and use of nitrous oxide (N₂O) or remifentanyl. Additionally, data were also collected on the use of anticholinergics (glycopyrrolate) as premedication, preintubation opioid or intraoperative opioid, nefopam, ketorolac, ramosetron, palonosetron or granisetron in IV-PCA, and reversal agents; the dosage of fentanyl in IV-PCA; laparoscopic surgery; and the duration of surgery. In addition, the severity of pain and nausea, frequency of vomiting (expulsion of stomach contents or involuntary retching not productive of stomach contents), incidence of headache and dizziness, discontinuation of PCA, and administration of rescue antiemetics on Postoperative Days 0 and 1 were analyzed.

The severity of nausea was rated using a five-point NRS as follows. If the patient felt absolutely no sensation of nausea, the score was 0; mild sensation, 1; moderate sensation, 2; and severe sensation, 3; and if the patient felt as if he/she was about to vomit, the score was 4. Use of a "rescue antiemetic" indicated that an additional antiemetic treatment was given during the postoperative period. According to our hospital protocol, antiemetics were administered by patient request or when the degree of nausea was 3 or greater on the NRS. Metoclopramide was given as a first-line drug, and if the nauseating sensation persisted, ramosetron or palonosetron was administered via the IV route. PONV cases were defined by the presence of nausea (NRS ≥ 1), vomiting, or requirement of rescue antiemetic medication during Postoperative Days 0 and 1.

According to our hospital protocol, general anesthesia was maintained at an average of 1.5 ± 1 minimal alveolar concentration of desflurane or sevoflurane. Either 0.05–0.10 $\mu\text{g}/\text{kg}/\text{min}$ of remifentanyl was administered throughout surgery or a 2 $\mu\text{g}/\text{kg}$ bolus of fentanyl was administered 2 minutes before the intubation with 50% N₂O and the volatile anesthetic given thereafter. If the patient felt pain during anesthesia, the anesthesiologist administered a 1 $\mu\text{g}/\text{kg}$ bolus of fentanyl for pain control.

We used the standardized IV-PCA protocol of the Department of Anesthesiology and Pain Medicine in our institution, which was a continuous infusion of 1 mL/h, as well as a bolus of 1 mL with a 15-minute lockout interval. The 100-mL IV-PCA solution contained fentanyl, ketorolac

or nefopam, and ramosetron, palonosetron, or granisetron. The correct dosage of fentanyl, ketorolac, or nefopam was established according to individual surgery departments, as well as the expected intensity of pain (mild, moderate, or severe) after each type of surgery.

The demographic and clinical characteristics were summarized using descriptive statistics. Continuous variables were expressed as the mean value $\pm$ standard deviation and categorical variables as an absolute number (percentage).

Univariate analysis using logistic regression was performed to calculate the relative risk estimates as odds ratios (ORs) with 95% confidence intervals (CIs) with a two-sided p value of 0.05 for the identification of the independent risk factors for PONV. Multivariate analysis with backward selection was performed with factors that had univariate p values of <0.10 upon logistic regression. Multicollinearity diagnostics indicated no multicollinearity issues (condition indices <30 and variance influence factor values <10) between the chosen independent variables in this study. The incidence of PONV was calculated for the number of independent risk factors per patient. In addition, a chi-square test for linear trends was used to assess changes in the incidence of PONV over the number of independent risk factors.

A p value of <0.05 was considered statistically significant. All statistical analyses were performed using Statistical Package for Social Sciences software, version 23.0 (IBM Corp., Armonk, NY, USA).

3. Results

This study included 6773 patients who received opioid-based IV-PCA after various surgeries at our hospital. The demographic characteristics and perioperative factors of the patients included in this study are summarized in Table 1.

Of 6773 patients, 4068 (60.1%) were women. The mean age was 50.21 ± 17.91 years, and 6553 patients (96.7%) received volatile anesthesia with either sevoflurane or desflurane. N_2O was used in 4305 patients (63.6%), and continuous infusion of remifentanyl was used in 1639 patients (24.2%). In 3320 patients (49.0%), 0.05 mg of palonosetron was administered intravenously at the end of the surgery and was included in PCA for prophylaxis of PONV, while 3055 patients (45%) received 0.3 mg of ramosetron in the same manner. Granisetron (5.9%) was used in other cases. PONV occurred in 1216 patients (18.0%; Table 1) and PCA was discontinued in 416 patients (6.1%), mostly because of PONV.

In univariate analysis for PONV, young age; female gender; a low body mass index; nonsmoking status; history of PONV or motion sickness; use of preintubation opioid, desflurane, N_2O , or intraoperative opioid; laparoscopic surgery; duration of surgery; and dosage of fentanyl in PCA were risk factors. However, the use of total intravenous anesthesia reduced the risk for PONV (Table 2).

By multivariate analysis with logistic regression, female gender (OR, 2.900; 95% CI, 2.391–3.518; $p < 0.001$), nonsmoking status (OR, 1.348; 95% CI, 1.042–1.745; $p = 0.023$), history of PONV or motion sickness (OR, 17.548;

95% CI, 13.053–12.950; $p < 0.001$), and use of preintubation opioid (OR, 1.303; 95% CI, 1.086–1.564; $p = 0.004$), desflurane (OR, 2.209; 95% CI, 1.196–4.083; $p = 0.011$), and N_2O (OR, 1.536; 95% CI, 1.262–1.868; $p < 0.001$; Table 3) were statistically significant risk factors for PONV. Chi-square test results for linear trend indicated a significant increase in the incidence of PONV associated with the number of independent risk factors evaluated (0 = 2.8%, 1 = 6.0%, 2 = 11.7%, 3 = 15.2%, 4 = 21.1%, 5 = 50.0%, and 6 = 100.0%; p for trend <0.001 ; Figure 1).

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

Variables	<i>n</i> = 6773
Patient characteristics	
Age (y)	50.21 $\pm$ 17.91
Gender M:F (<i>n</i>)	2705 (39.9):4068 (60.1)
BMI (kg/m ²)	23.83 $\pm$ 4.04
Smoking (<i>n</i>)	1239 (18.3)
History of PONV or motion sickness (<i>n</i>)	254 (3.8)
Anesthetic factor	
Premedication (anticholinergic) (<i>n</i>)	1922 (28.4)
Preintubation opioid (<i>n</i>)	3889 (57.4)
Sevoflurane (<i>n</i>)	2690 (39.7)
Desflurane (<i>n</i>)	3863 (57.0)
TIVA (<i>n</i>)	220 (3.2)
N_2O (<i>n</i>)	4305 (63.6)
Remifentanyl (<i>n</i>)	1639 (24.2)
Intraoperative opioid (<i>n</i>)	3901 (57.6)
Surgical factor	
Laparoscopy (<i>n</i>)	2037 (30.1)
Duration of surgery (min)	161.17 $\pm$ 108.63
PCA-related factor	
PCA fentanyl (100 μ g)	12.73 $\pm$ 3.07
Ketorolac (<i>n</i>)	2039 (30.1)
Nefopam (<i>n</i>)	3824 (56.5)
Antiemetic (<i>n</i>)	
Ramosetron	3055 (45.1)
Palonosetron	3320 (49.0)
Granisetron	398 (5.9)
Postoperative complication	
Nausea, retching, and vomiting (<i>n</i>)	1216 (18.0)
Headache (<i>n</i>)	44 (0.6)
Dizziness (<i>n</i>)	150 (2.2)
Discontinuation of PCA (<i>n</i>)	416 (6.1)
Requirement of rescue antiemetic including routine order (<i>n</i>)	1661 (24.5)

BMI = body mass index; F = female; M = male; *n* = number; N_2O = nitrous oxide; PCA = patient-controlled analgesia; PONV = postoperative nausea and vomiting; TIVA = total intravenous anesthesia.

Table 2 Univariate analysis of risk factors for postoperative nausea and vomiting.

Variables	OR	95% CI	<i>p</i>
Patient characteristics			
Younger age (y)	1.005	1.001–1.009	0.011
Female (<i>n</i>)	3.319	2.805–3.927	<0.001
BMI (kg/m ²)	0.962	0.944–0.980	<0.001
Nonsmoking (<i>n</i>)	2.387	1.908–2.994	<0.001
History of PONV or motion sickness (<i>n</i>)	17.339	13.097–22.955	<0.001
Anesthetic factor			
Premedication (anticholinergic) (<i>n</i>)	1.008	0.868–1.171	0.919
Preintubation opioid (<i>n</i>)	1.419	1.233–1.634	<0.001
Anesthetics (<i>n</i>)			
Sevoflurane	1		
Desflurane	1.341	1.180–1.523	<0.001
TIVA	0.577	0.379–0.879	<0.001
N ₂ O (<i>n</i>)	1.851	1.588–2.159	<0.001
Remifentanyl (<i>n</i>)	0.567	0.474–0.679	<0.001
Intraoperative opioid (<i>n</i>)	1.024	1.001–1.046	0.043
Surgical factor			
Laparoscopy (<i>n</i>)	1.215	1.043–1.414	0.012
Duration of surgery (min)	1.001	1.000–1.002	0.026
PCA-related factor			
PCA fentanyl (100 µg)	1.024	1.001–1.046	0.043
Ketorolac (<i>n</i>)	0.930	0.802–1.080	0.342
Nefopam (<i>n</i>)	1.027	0.896–1.178	0.698
Antiemetic (<i>n</i>)			
Granisetron	1		
Ramosestron	0.973	0.842–1.124	0.532
Palonosetron	0.945	0.791–1.129	0.645

BMI = body mass index; CI = confidence interval; *n* = number; N₂O = nitrous oxide; OR = odds ratio; PCA = patient-controlled analgesia; PONV = postoperative nausea and vomiting; TIVA = total intravenous anesthesia.

Table 3 Multivariate analysis of risk factors for postoperative nausea and vomiting.

Variables	OR	95% CI	<i>p</i>
Female	2.900	2.391–3.518	<0.001
Nonsmoking	1.348	1.042–1.745	0.023
History of PONV or motion sickness	17.548	13.053–22.590	<0.001
Preintubation opioid	1.303	1.086–1.564	0.004
Desflurane	2.209	1.196–4.083	0.011
N ₂ O	1.536	1.262–1.868	<0.001

CI = confidence interval; N₂O = nitrous oxide; OR = odds ratio; PONV = postoperative nausea and vomiting.

4. Discussion

PONV is one of the most common and undesirable complications after anesthesia and surgery. It is influenced by

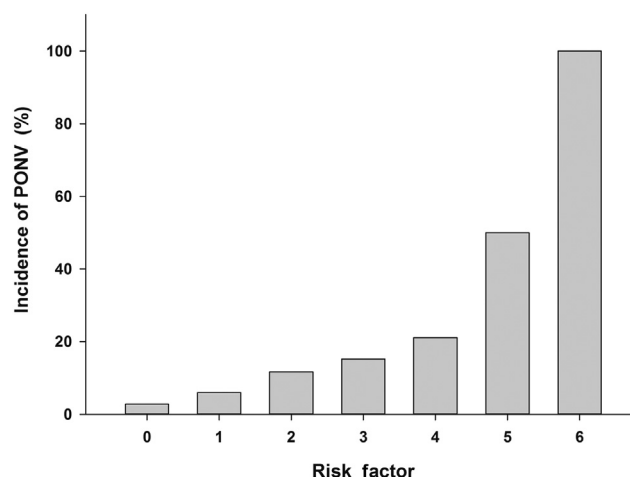


Figure 1 Incidence of PONV per number of risk factors. Incidence of PONV as a percentage per number of independent risk factors, evaluated using chi-square test for linear trend (0 = 2.8%, 1 = 6.0%, 2 = 11.7%, 3 = 15.2%, 4 = 21.1%, 5 = 50.0%, 6 = 100.0%, *p* for trend <0.001). POD = postoperative day; PONV = postoperative nausea and vomiting.

various factors including the administration of volatile anesthetics, use of postoperative opioids for pain, type of surgery, and patient characteristics.⁸ In this retrospective study evaluating prospectively collected medical records, the incidence of PONV in patients receiving fentanyl-based IV-PCA was 18.0%. Risk factors for PONV were female gender, nonsmoking status, history of PONV or motion sickness, and use of preintubation opioid, desflurane, or N₂O. Of these results, female gender, nonsmoking status, and history of PONV or motion sickness correlated with the results of other previous studies. According to Apfel et al,⁹ female gender, nonsmoking status, history of PONV or motion sickness, young age, duration of anesthesia, and postoperative opioids were risk factors for PONV. Additionally, Koivuranta et al¹⁰ suggested a risk score model of PONV that included female gender, history of PONV, duration of surgery over 60 minutes, nonsmoking status, and history of motion sickness as risk factors of PONV.

Postoperative opioid use as a part of PCA is also a known risk factor. As we included patients who were treated only with opioid-based IV-PCA, every participant of this study exhibited at least one risk factor for PONV (postoperative opioid treatment for pain). In addition, over 60% of the patients were female and 81.7% nonsmokers. In line with previous studies, these patients were expected to have a significantly high risk for PONV.

Despite the use of opioid-based IV-PCA, the overall incidence of PONV was lower than in a previous study.⁶ According to the Apfel et al's⁶ simplified risk score, the estimated probability of PONV was 10%, 21%, 39%, 61%, and 78% if 0, 1, 2, 3, and 4 risk factors were present, respectively. In this study, with postoperative use of opioid-based IV-PCA as a baseline risk factor, the incidence of PONV was 18%, which was lower than the expected probability according to Apfel et al. This may be explained by the routine use of prophylactic antiemetics. Furthermore, second-generation antiemetics such as ramosetron and palonosetron were

mainly used, which demonstrate greater effectiveness compared with first-generation antiemetics. In our analysis, the effectiveness of palonosetron and ramosetron was compared, but no significant difference was found between them, consistent with the results of a previous study.¹¹

Similar to the results of previous studies, nonsmoking status was an independent risk factor for PONV. Apfel et al¹² showed that volatile anesthetics are responsible for PONV during the early postoperative period, when the pharmacokinetic effects have a marked role in any perceived differences. Volatile anesthetic agents are metabolized by cytochrome P450 2E1, which can be induced by nicotine and polycyclic aromatic hydrocarbons from smoking.¹³ Thus, the increased induction of liver enzymes in patients who smoke might contribute to a higher rate of metabolism and to faster recovery from general anesthesia. Furthermore, nicotine inhibits the function of 5HT₃ receptors,¹⁴ which would also affect the outcome of PONV.

Interestingly, desflurane, N₂O, and preintubation use of opioid were also identified as statistically significant risk factors for PONV. Although desflurane was a risk factor for PONV in this study, there is still an unresolved controversy regarding the effect of desflurane and sevoflurane on PONV. Several studies reported significant differences between sevoflurane and desflurane in terms of severity of nausea and incidence of vomiting. One study reported the incidences of PONV during 24 hours after breast surgery as 22% with isoflurane, 36% with sevoflurane, and 67% with desflurane. Late PONV (PONV in the surgical ward in that study) was significantly more common with desflurane than with sevoflurane.¹⁵ In another study, administration of desflurane was also a risk factor for PONV.³

Owing to its low blood/gas partition coefficient, the washout time of desflurane is faster than that of other volatile agents, and consequently, enables faster recovery and re-establishment of cognitive function. In addition, desflurane causes more airway irritation compared with other inhalant agents. Faster emergence from anesthesia, combined with airway irritation, may contribute to the patient's early recognition of discomfort and increase the incidence of reported PONV.

In contrast, a meta-analysis by Macario et al¹⁶ showed no difference in the incidence of PONV between desflurane and sevoflurane. Furthermore, Wallenborn et al¹⁷ reported no difference between isoflurane, desflurane, and sevoflurane with respect to frequency or severity of postoperative nausea, vomiting, or both.

The use of N₂O also contributed to the incidence of PONV as reported by previous studies.^{18–21} Apfel et al²² also showed that substituting N₂O with nitrogen reduced the risk of PONV by 12%. A meta-analysis by Fernández-Guisasola et al²³ concluded that avoiding nitrous oxide reduced the risk of PONV. The mechanisms by which nitrous oxide causes PONV are not yet clearly defined, but some possible mechanisms have been suggested. Certain actions of nitrous oxide on central opioid and dopaminergic receptors,^{24,25} changes of middle ear pressure by the diffusion of nitrous oxide into the middle ear cavity,²⁶ and bowel distention²⁷ may all contribute to PONV.

The use of preintubation opioid was also shown to increase the incidence of PONV significantly. Laryngoscopy during the induction of general anesthesia and intubation

itself may increase the blood pressure and heart rate of patients by stimulating the sympathoadrenal response.^{28,29} Preintubation opioids can be used to minimize hemodynamic changes during the induction. A 2 µg/kg bolus of fentanyl was used in our hospital to minimize the pain stimulus during laryngoscopy. This use of preintubation opioid analgesia was shown to be a significant risk factor for PONV.

Additionally, laparoscopic surgery itself has been reported to increase the incidence of PONV.³⁰ However, in this study, although laparoscopy was considered a risk factor for PONV in univariate analysis, it proved to be statistically insignificant.

Of note, PONV can still occur after the use of a single dose of antiemetic in patients who undergo general anesthesia. In this retrospective study, 14.5% of the patients showed PONV and 24.5% required additional rescue antiemetic despite the use of an antiemetic for prophylaxis of PONV. PCA was discontinued in 6.1% of the patients because of PONV. Appropriate action must be taken to reduce or prevent the incidence of PONV and provide better quality of postsurgery outcomes for patients.

The present study had some limitations. First, we evaluated postoperative conditions associated with IV-PCA once daily for each patient. The patients answered our questions regarding the NRS scores for nausea, frequency of vomiting per day, and visual analog scale scores for pain and other complications including headache, dizziness, and drowsiness. This method of evaluation might have caused a recall bias, which could have led to underestimation of the incidence of PONV.⁹ Second, because of the retrospective nature of the study, it was difficult to relate effects to causation because of the possibility of unevaluated confounding factors. Third, because this was a single-center study, it might not be possible to generalize the results of this study to a wider population.

5. Conclusions

In conclusion, female gender, nonsmoking status, history of PONV or motion sickness, use of preintubation opioids, use of desflurane, and use of N₂O were all identified as independent risk factors for PONV. The results of our study suggest that combination therapy should be considered to control PONV.

Conflicts of interest

The authors have no conflicts of interest to declare.

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