A Korean Predictive Model for Postoperative Nausea and Vomiting

Postoperative nausea and vomiting (PONV) is one of the most common and distressing complications after surgery. An identification of risk factors associated with PONV would make it easier to select specific patients for effective antiemetic therapy. We designed a case-controlled study to identify the risk factors for PONV in 5,272 surgical patients. At postoperative 2 and 24 hr, patients were visited and interviewed on the presence and severity of PONV. Thirty nine percent of patients experienced one or more episodes of nausea or vomiting. Five risk factors were highly predictive of PONV: 1) female, 2) history of previous PONV or motion sickness, 3) duration of anesthesia more than 1 hour, 4) non-smoking status, and 5) use of opioid in the form of patient controlled analgesia (PCA), in the order of relevance. The formula to calculate the probability of PONV using the multiple regression analysis was as follows: P (probability of PONV)=$1/1+e^{-z}$, Z=-1.885+0.894 (gender)+0.661 (history)+0.584 (duration of anesthesia)+0.196 (smoking status) +0.186 (use of PCA-based opioid) where gender: female=1, male=0; history of previous PONV or motion sickness: yes=1, no=0; duration of anesthesia:more than 1 hr=1, less than or 1 hr=0; smoking status: no=1, yes=0; use of PCA-based opioid: yes=1, no=0.

Key Words : *Models, Statistical; Postoperative Nausea and Vomiting; Risk Factors*

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INTRODUCTION

Postoperative nausea and vomiting (PONV) is generally known to affect patients undergoing all types of anesthesia and has been characterized as the "big little problem" (1). In the past, it had been mostly underestimated because it is self-limited and rarely causes serious medical problems. However, clinicians' awareness about the clinical relevance of PONV has gradually increased and PONV is now recognized as one of the most distressing side effects to the postoperative patients, with an incidence between 20% and 80% (2-5). This undesirable postoperative symptom, thus, has been an important reason for poor patient satisfaction in the postoperative period (6). Patients often consider PONV as worse than postoperative pain (7, 8) and are willing to pay substantially in order to avoid PONV (9).

Additionally, PONV has been associated with serious complications after surgery. PONV has been reported to induce, if rare, incisional pain, hematoma, wound dehiscence, esophageal rupture, and bilateral pneumothorax and to increase the risk of aspiration (10). Furthermore, the discharge from the postanesthesia care unit (PACU) may be delayed, and hospital admission (or readmission) in ambulatory patients often occurs due to PONV, which have been known to increase the medical cost (11).

Routine antiemetic prophylaxis to all surgical patients has not been recommended, because it may impose unnecessary side effects related to the antiemetic drugs as well as the economic burden. Rather, selective prophylaxis in patients who are likely to have PONV, after identifying most predictive risk factors, would offer much benefit resulting in improved satisfaction (3, 12).

Several studies have been performed to identify presumed risk factors for PONV and develop risk models to calculate the probability of PONV (7, 10, 13). Many factors have been traditionally known to cause PONV, but some of them have turned out to be indifferent to the occurrence of PONV. In addition, smoking status has newly emerged as a powerful risk factor (2). Moreover, the probability and the major risk factors of PONV may seem to be different according to the races. In this context, predictive risk factors that would be unique in a Korean population need to be recognized. Moreover, the quantification of the relative impact of the risk factors on PONV could lead to the development of risk models to stratify risk categories and identify those patients at higher risk for PONV.

In this study, our objective was to identify the predictive risk factors of PONV by assessing various factors including patient-, surgery- and anesthesia-related variables and to develop a predictive model to calculate the probability of PONV by using the multiple regression analysis.

MATERIALS AND METHODS

With approval of the Institutional Review Board, we enrolled 5,272 inpatients over 15 yr old from 20 April to 10 August 2004 in this case-controlled study. Patients who were transferred to intensive care unit, discharged on the same day, received local anesthesia or had communication difficulties were excluded

Perioperative anesthetic techniques whether general or regional anesthesia and anesthetic drugs administered to the patients were at the discretion of the anesthesiologists.

At two hours after the surgery in the PACU, the presence and severity of PONV, history of previous PONV and motion sickness, and smoking status were interviewed by one of the researchers. Additionally, at 24 hr after the surgery, the presence and severity of PONV and post-operative opioid use with patient-controlled analgesia (PCA) device were recorded at ward by one of our investigators. PCA regimens varied according to the type of surgeries but all included opioids such as morphine and fentanyl in their components. Preoperative patient characteristics and intra-operative variables were recorded on specifically designed, standardized study forms. Each patient was regarded as having PONV when he or she experienced any nausea and/or vomiting within the first 24 post-operative periods.

Descriptive statistics on characteristics of patients, surgery, and anesthesia were denoted in characteristics and their frequencies. For categorical variables, the chi-square analysis was performed to estimate the statistical differences. For continuous variables, the Student t test was used to compare their mean values between PONV and non-PONV groups.

To identify independent predictors for PONV, we used a multiple logistic regression using a forward selection procedure ($p \leq 0.000$ to enter). In this model, the estimated probability of PONV, denoted by P, depends on the score Z according to the formula $p = 1/1 + e^{-Z}$:

in which, $Z = b_0 + b_1 x_1 + ... + b_K x_K$ is a weighted sum of the values $x_1, ..., x_K$ of K risk factor or predictor, coded as 1 if present and 0 if absent, with $b_1, ..., b_K$ as the weight or estimated regression coefficient, and each described as the log odds-ratio associated with the corresponding factor (so that the corresponding odds ratio is obtained from $OR_j = \exp(b_j)$ for factor j). The intercept b_0 means the baseline log odds of PONV, that is, $P_0 = 1/1 + e^{-b_0}$ is the estimated baseline risk of PONV in a patient without any risk factors.

RESULTS

Overall, thirty nine percent of patients (2,063 out of 5,272 patients) experienced PONV either in the PACU or at ward. The incidence of PONV in the PACU was higher than at ward (27% vs. 21%, $p \leq 0.001$). Among 2,063 patients with PONV, 946 patients (42%) in the PACU only, 625 patients

Table 1. Incidences of PONV

	PACU	Ward	PACU+Ward
PONV (−)	3,834 (72.72)	4,155 (78.81)	3,209 (60.87)
PONV (+)	1,438 (27.28)	1,117 (21.19)	2,063 (39.13)
Nausea	1,160 (22.00)	829 (15.73)	1,526 (28.95)
Retching	112 (2.13)	29 (0.55)	132 (2.50)
Vomiting	166 (3.15)	259 (4.91)	405 (7.68)

Values are numbers of patients (%); PACU, post-anesthesia care unit.

Table 2. Risk factors for PONV

		Number	%	OR	CI	p
Gender	Male	2,344	26	2.9	2.61-3.31	0.000
	Female	2,928	50			
History	No	3,964	34	2.4	2.11-2.73	0.000
	Yes	1,308	55			
Non-smoking	No	1,055	27	2.0	1.75-2.36	0.000
	Yes	4,217	42			
OP duration	≤1 hr	645	27	1.9	1.55-2.23	0.000
	>1 hr	4,627	40			
PCA use	No	3,260	37	1.28	1.14-1.43	0.000
	Yes	2,012	43			
Anesthetic agent	Volatile	5,317	27	1.96	1.21-3.25	0.002
	Propofol	135	16			
BMI (kg/m²)	<25	3,252	40	1.18	1.03-1.33	0.004
	≥25	2,000	36			
ASA class	I	3,309	40			0.063
	Others	1,963	37			
N₂O	No	2,059	40			0.120
	Yes	3,213	38			
PCA mode	IV	1,840	39			0.779
	Epidural	182	41			
Intra-OP opioid	No	3,139	39			0.770
	Yes	2,135	39			
PACU opioid	No	868	39			0.999
	Yes	4,404	39			

Number, number of patients; OR, odds ratio; CI, confidence interval; History, history of PONV or motion sickness; OP, operation; PCA, patient-controlled analgesia; BMI, body mass index; N₂O, use of N₂O during anesthesia; PACU, post anesthesia care unit.

(28%) newly at ward, and 492 patients (22%) had PONV at the two places together. Nausea was more frequently observed in the PACU, whereas the incidence of vomiting was higher at ward ($p < 0.001$) (Table 1).

Using a multiple logistic regression analysis with a forward selection, we found that female, history of previous PONV or motion sickness, duration of anesthesia more than one hour, non-smoking status, and the use of PCA-based opioid were high risk factors of PONV in the order of relevance (Table 2).

As less relevant risk factors of PONV, the use of propofol was related to lower occurrence of PONV in the PACU than inhalational agents. Low body mass index (BMI) (<25) was associated with PONV than high BMI (≥25). The American Society of Anesthesiologists (ASA) physical status, the use of N₂O, and the use of opioids in the operating room or in the PACU were not significant predictors of PONV. The

Table 3. Distribution of the patients with PONV according to type of surgery

	PONV (−)	PONV (+)
Laparotomy (n=1,334)	840 (63)	494 (37)
Laparoscopy (n=523)	293 (56)	230 (44)
Orthopedic (n=603)	456 (58)	336 (42)
Neurosurgery (n=163)	126 (59)	88 (41)
Vascular (n=47)	51 (83)	11 (17)
Maxillofacial (n=56)	34 (46)	40 (54)
Gynecology (n=555)	362 (50)	368 (50)
Urology (n=238)	225 (72)	87 (28)
Plastic (n=128)	92 (55)	76 (45)
Otolaryngology (n=511)	424 (63)	249 (37)
Abdominal (n=569)	460 (62)	288 (38)
Stomatology (n=326)	311 (72)	119 (28)
Major breast (n=244)	200 (62)	121 (38)
Thyroid (n=168)	100 (45)	121 (55)
Thoracic (n=307)	287 (71)	117 (29)
OPH (n=75)	54 (55)	45 (45)
Other surgery (n=18)	20 (83)	4 (17)

Values are number of patients (%). OPH, ophthalmic surgery.

mode of PCA whether intravenous or epidural, did not show any difference in the frequency of PONV (Table 2). The type of anesthesia (general vs. regional) was not associated with the risk of PONV (39% vs. 41%). There was no statistical correlation between age and PONV (the incidences of PONV were 30, 42, 43, 40, 36, 37, 42%, and 36% at every 10 yr interval until 80 yr old).

There was a wide variation in the incidence of PONV according to the type of surgery. The frequency of PONV was significantly higher in the patients undergoing laparoscopic procedure than laparotomy (44% vs. 37%, OR 1.33, p=0.007). Certain type of operations such as maxillofacial, gynecologic, and thyroid operations showed high incidence of PONV (>50%) (Table 3).

Based on the above results, we developed a predictive model to calculate the probability of PONV:

$$P \text{ (probability of PONV)} = 1/1 + e^{-z}$$

where Z=−1.885+0.894 (gender)+0.661 (history)+0.584 (duration of anesthesia)+0.196 (smoking status)+0.186 (use of PCA-based opioid).

[gender: female=1, male=0; history of previous PONV or motion sickness: yes=1, no=0; duration of anesthesia: more than 1 hr=1, less than or 1 hr=0; smoking status: no=1, yes= 0; use of PCA-based opioid: yes=1, no=0] (Table 4).

DISCUSSION

This study was conducted in a large population of 5,272 patients undergoing various operations, and 39% of patients experienced PONV either in the PACU or at ward. We ana-

Table 4. Variables required in the equation

	B	S.E.	df	p	OR	CI (95%)
Gender	0.894	0.068	1	0.000	2.445	2.105-2.868
History	0.661	0.068	1	0.000	1.936	1.665-2.265
OP duration	0.584	0.099	1	0.000	1.793	1.385-2.204
Non-smoking	0.196	0.086	1	0.023	1.217	1.068-1.578
PCA	0.186	0.062	1	0.003	1.204	1.046-1.381
Constant	−1.885	0.116	1	0.000		

CI, confidence interval; History, history of PONV or motion sickness; PCA, patient-controlled analgesia.

lyzed the characteristics of each patient and the type of operations and anesthesia to reveal the relationship of every aspect of those factors with PONV.

Overall incidence of PONV was higher in the PACU than at ward. However, the incidence of vomiting was higher at ward (Table 1). The influence of remaining anesthetic agents might have affected the occurrence of nausea in the PACU and the movement or ambulation of patients at ward might have contributed to the occurrence of vomiting. Contrary to our study, both nausea and vomiting were more frequent at ward than in the PACU in other studies (2, 7, 12).

In this study, gender, history of previous PONV or motion sickness, duration of anesthesia, smoking status, and use of PCA-based opioid were identified as independent predictors of PONV. The correlation of female gender has been well demonstrated and appeared as the most important predictor of PONV (2, 7, 12-16). Likewise, female gender was the most influential risk factor for PONV in our study with an odds ratio of 2.9. The gender difference was not noted in the preadolescent age group or in patients beyond the 8th decade of life, suggesting that variations in serum gonadotropin levels might be a contributing factor in the higher incidence of emesis in women (12, 17).

Another predictor of PONV was history of previous PONV or motion sickness, and it was the second strongest predictor of PONV in this study (odds ratio of 2.4). Tramer et al. (3) have outlined a decision tree for PONV prophylaxis in adults that a positive history of PONV is sufficient to justify the use of prophylactic antiemetics.

The duration of anesthesia was also a predictor of PONV, and the odds ratio was 1.9 for the anesthesia time longer than 1 hr. Pre-medication, volatile anesthetics with nitrous oxide, prolonged fasting, and pain may contribute to the increased incidence of PONV in longer procedures (12, 17).

Another predictor of PONV was smoking status. Non-smoking showed an odds ratio of 2.0 in this study. Chronic exposure to toxic gas (tobacco) may desensitize a patient's reaction to anesthetic gas. As another possible etiology, one of chemicals within cigarette smoke may have anti-emetic effect (18). In addition, chronic consumption of cigarette induces enzyme cytochrome P450 in liver, and high P450 enzyme induction in smokers decomposes anesthetic agents more quickly than in non-smoker resulting in less PONV (19).

The final major risk factor was the use of PCA-based opioid. Opioids are well known emetogenic agents and opioid-induced nausea and vomiting are frequently triggered by movement (17). In our study, the use of opioids in the operating room or in the PACU was not related to PONV, whereas postoperative use of opioids via PCA at ward was. The occurrence of PONV in patients at ward might be partly attributed by the patient's movement. Sudden motion, changes in position, or even transport from the PACU to the ward can precipitate nausea and vomiting in patients who have received opioid compounds. Kamath et al. also demonstrated that 66% of PONV was related to movement (20).

Among other risk factors not included in this risk model, intravenous anesthesia using propofol has generally been known to have anti-emetic effect and reduce the incidence of PONV by half compared to inhalational anesthesia, though the antiemetic effect has been reported to be short-lived (21, 22). Likewise, in our study, the propofol's antiemetic effect was noted only in the PACU (16% vs. 27%, $p=0.002$, OR 1.96).

High BMI is assumed to be related to higher occurrence of PONV. However, in our study, low BMI (<25) showed higher incidence of PONV (40% vs. 36%, $p=0.004$, OR 1.18). It might be due to the fact that female patients had lower BMI than male patients (BMI <25, M:F=965:1,940 versus BMI ≥25, M:F=1,024:1,304, $p<0.001$). Therefore, it could be presumed that gender has greater influence on PONV than BMI itself. Some other studies have reported that obesity has no effect or only minor effect on PONV (2, 12, 21).

The ASA physical status has been reported to be associated with the occurrence of PONV. Cohen et al. and others have demonstrated that a good physical condition as reflected by the low ASA physical status was one of the main risk factors of PONV (2, 23). However, our study showed that there was no significant correlation between the ASA physical status and the occurrence of PONV.

The relevance between the use of N_2O and likelihood of PONV has been debated. The studies, in which N_2O was omitted in an attempt to decrease the incidence of PONV, demonstrated only marginal reduction of PONV (21, 24). Our results revealed that N_2O had no effect on PONV.

General anesthesia has been considered to be more emetogenic than regional anesthesia (7, 15, 16, 25), but this was not evident in our study. In our study, the number of cases of regional anesthesia was too small (182 cases, 3.4%) and was performed mostly in total knee arthroplasty surgeries. During or after the surgery, the considerable amounts of opioids were used. Therefore, we speculate that this might be the reason for statistical indifference in the incidence of PONV between two anesthetic techniques.

It is commonly stated that age has a nonlinear impact on PONV (5, 6, 8). The occurrence of postoperative vomiting is the highest in young adults (12). However, age has not been known to affect strongly to be incorporated in the risk model (7, 13). In our study, patients in their thirties showed the highest incidence of PONV. Maybe the female predominance in this age group might explain the high PONV (M:F=295:533 in thirties and 2,049:2,395 in other age groups, $p<0.001$).

Previously, operations like strabismus surgery, gynecologic surgery, cholecystectomy, craniotomy, otolaryngology, and laparoscopy were considered to be the risk factors of PONV (2, 7, 17). In our study, maxillofacial ($p=0.038$), gynecologic ($p=0.001$), and thyroid ($p≤0.001$) operations had highest incidence of PONV (>50%), and these results are in close agreement with above studies. However, general consensus is that the types of surgeries do not affect PONV (7, 13, 14, 22).

There have been continuous efforts to develop risk models to determine the probability of the PONV (7, 10, 13, 22). Among them, the predictive models suggested by Apfel et al. (22) and Koivuranta et al. (7) have been known to have strong discriminating power and correlation between the predicted and actual incidences of PONV (14).

Apfel: Z=1.27 (female)+0.72 (non-smoking)+0.65 (history of PONV or motion sickness)+0.78 (post-operative opioids)

Koivuranta: Z=0.93 (female)+0.82 (history of PONV)+0.75 (duration of surgery over 60 min)+0.61 (non-smoking)+0.59 (history of motion sickness)

Several studies have demonstrated that putting only a few major risk factors into their predictive models showed better results than the models including a longer list of factors (7, 13, 14, 26). Therefore, in accordance with those studies, we selected five major risk factors ($p≤0.000$) to develop a predictive model. With this risk model, we can readily predict the probability of PONV of individual patient. As an example, if a non-smoking female patient who has a history of motion sickness undergoes a subtotal gastrectomy for 3 hr and receives PCA -based opioid, her probability of PONV would be 65%.

In conclusion, we identified the major predictive risk factors for PONV through this large-scaled study in a Korean population and developed a Korean predictive model for PONV. In addition, this model can be used to calculate the probability of PONV in order to administer prophylactic antiemetics in selected high-risk patients.

REFERENCES

1. Kapur PA. *The big "little problem." Anesth anlag* 1991; 73: 243-5.
2. Cohen MM, Duncan PG, DeBoer DP, Tweed WA. *The postoperative interview: assessing risk factors for nausea and vomiting. Anesth Analg* 1994; 78: 7-16.
3. Tramer MR. *Strategies for postoperative nausea and vomiting. Best Pract Res Clin Anaesthesiol* 2004; 18: 693-701.
4. Gan TJ, Collis R, Hetreed M. *Double-blind comparison of ondansetron, droperidol and saline in the prevention of postoperative nau-*

sea and vomiting. *Br J Anaesth 1994; 72: 544-7.*

5. Gan TJ, Ginsberg B, Grant AP, Glass PS. *Double-blind, randomized comparison of ondansetron and intraoperative propofol to prevent postoperative nausea and vomiting. Anesthesiology 1996; 85: 1036-42.*

6. Myles PS, Williams DL, Hendrata M, Anderson H, Weeks AM. *Patient satisfaction after anaesthesia and surgery: results of a prospective survey of 10811 patients. Br J anaesth 2000; 84: 6-10.*

7. Koivuranta M, Laara E, Snare L, Alahuhta S. *A survey of postoperative nausea and vomiting. Anaesthesia 1997; 52: 443-9.*

8. Macario A, Weinger M, Carney S, Kim A. *Which clinical anesthesia outcomes are important to avoid? The perspective of patients. Anesth Anal 1999; 89: 652-8.*

9. Gan T, Sloan F, Dear GL, El-Moalem HE, Lubarsky DA. *How much are patients willing to pay to avoid postoperative nausea and vomiting? Anesth Analg 2001; 92: 393-400.*

10. Palazzo M, Evans R. *Logistic regression analysis of fixed patient factors for postoperative sickness: a model for risk assessment. Br J Anaesth 1993; 70: 135-40.*

11. Gold BS, Kitz DS, Lecky JH, Neuhaus JM. *Unanticitpated admission to the hospital following ambulatory surgery. JAMA 1989; 262: 3008-10.*

12. Lerman J. *Surgical and patient factors involved in postoperative nausea and vomiting. Br J Anaesth 1992; 69 (Suppl 1): 24S-32S.*

13. Apfel CC, Laara E, Koivuranta M, Greim CA, Roewer N. *A simplified risk score for predicting postoperative nausea and vomiting. Anesthesiology 1999; 91: 693-700.*

14. Apfel CC, Kranke P, Eberhart LH, Roos A, Roewer N. *Comparison of predictive models for postoperative nausea and vomiting. Br J Anaesth 2002; 88: 234-40.*

15. Watcha MF, White PF. *Postoperative nausea and vomiting. Anesthesiology 1992; 77: 162-84.*

16. Quinn AC, Brown JH, Wallace PG, Asbury AJ. *Studies in postoperative sequelae. Nausea and vomiting-still a problem. Anaesthesia 1994; 49: 62-5.*

17. Kovac AL. *Prevention and treatment of postoperative nausea and vomiting. Drugs 2000; 59: 213-43.*

18. Hough M, Sweeney B. *The influence of smoking on postoperative nausea and vomiting. Anaesthesia 1998; 53: 932-3.*

19. Chimbira W, Sweeney BP. *The effect of smoking on postoperative nausea and vomiting. Anaesthesia 2000; 55: 540-4.*

20. Kamath B, Curran J, Hawkey C, Beattie A, Gorbutt N, Guiblin H, Kong A. *Anaesthesia, movement and emesis. Br J Anaesth 1990; 64: 728-30.*

21. Apfel CC, Roewer N. *Risk assessment of postoperative nausea and vomiting. Int Anesthesiol Clin 2003; 41: 13-32.*

22. Apfel CC, Greim CA, Haubitz I, Goepfert C, Usadel J, Sefrin P, Roewer N. *A risk score to predict the probability of postoperative vomiting in adults. Acta Anaesthesiol Scand 1998; 42: 495-501.*

23. Sinclair DR, Chung F, Mezei G. *Can postoperative nausea and vomiting be predicted? Anesthesiology 1999; 91: 109-18.*

24. Divatia JV, Vaidya JS, Badwe RA, Hawaldar RW. *Omission of nitrous oxide during anesthesia reduces the incidence of postoperative nausea and vomiting. A meta-analysis. Anesthesiology 1996; 85: 1055-62.*

25. Apfel CC, Kranke P, Katz MH, Goepfert C, Papenfuss T, Rauch S, Heineck R, Greim CA, Roewer N. *Volatile anaesthetics may be the main cause for early but not delayed postoperative vomiting: a randomized controlled trial of factorial design. Br J Anaesth 2002; 88: 659-68.*

26. Pierre S, Benais H, Pouymayou J. *Apfel's simplified score may favourably predict the risk of postoperative nausea and vomiting. Can J Anaesth 2002; 49: 237-42.*