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ORIGINAL ARTICLE

Oral administration of aprepitant to prevent postoperative nausea in highly susceptible patients after gynecological laparoscopy

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Abstract
Purpose The use of opioids following surgery is associated with a high incidence of postoperative nausea and vomiting (PONV). We conducted a prospective, randomized, double-blind, placebo-controlled study to investigate the effect of orally administered aprepitant, a neurokinin-1 receptor antagonist, for reducing PONV in patients with fentanyl-based, patient-controlled analgesia (PCA) given intravenously after gynecological laparoscopy.
Methods One hundred and twenty female patients (ages 21–60) undergoing laparoscopic hysterectomy were randomly allocated to receive 80 mg (A80 group, $n = 40$) or 125 mg aprepitant (A125 group, $n = 40$) or placebo (control group, $n = 40$) orally 2 h before anesthesia induction. Anesthesia was maintained with isoflurane and remifentanil, and PCA IV using fentanyl and ketorolac were provided for 48 h after surgery. Incidences of nausea, vomiting/retching, and use of rescue antiemetics were recorded at 2, 24, and 48 h after surgery. Complete response was defined as no PONV and no need for rescue treatment.
Results The incidence of complete response was significantly lower in the A80 and A125 groups than in controls, 56 % and 63 %, vs. 28 %, respectively, $P = 0.007$ and $P = 0.003$, respectively, during the first 48 h, and 65 % and 65 % vs. 38 %, respectively, both $P = 0.025$, during the first 2 h. However, there were no statistically significant differences between A80 and A125 groups in the incidences of complete response and PONV during the study period.
Conclusions Aprepitant 80 mg orally was effective in lowering the incidence of PONV in the first 48 h after anesthesia in patients receiving fentanyl-based PCA after gynecological laparoscopy.

Keywords Aprepitant · Gynecological laparoscopy · Neurokinin-1 receptor antagonists · Postoperative nausea and vomiting

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Introduction

Postoperative nausea and vomiting (PONV) is one of the most common distressing symptoms after general anesthesia and can lead to significant clinical problems, such as postoperative pain, dehydration, electrolyte imbalance, dehiscence of surgical wounds, hemorrhage, and aspiration pneumonia [1]. Interestingly, the incidence of PONV after gynecological laparoscopy is reported to be nearly 80 % [2]. After surgery, opioids-based patient-controlled analgesia (PCA) intravenously (IV) is an effective and safe alternative to invasive regional analgesia [3]. In addition, PCA IV with a basal infusion has been reported to be more effective in lowering the resting pain score than boluses only [4], but it may result in greater risk of PONV. Despite mixing an antiemetic agent into the PCA regimen, fentanyl-based PCA IV has nearly a 60 % incidence of PONV [5]. Thus, in highly susceptible patients, fentanyl-based PCA IV should be accompanied by effective prevention for PONV.

Aprepitant is a highly selective, centrally active neurokinin-1 (NK_1) receptor antagonist with a half-life of 9–12 h [6, 7]. The drug is effective for reducing opioid-induced emesis and PONV [7, 8]. NK_1 receptor antagonists are known to be highly effective for preventing both acute and delayed emesis and should thus have particular benefits in patients undergoing abdominal surgery for whom preventing vomiting is a high priority [9]. However, the effect of aprepitant on PONV associated with opioid-based PCA after surgery has not been previously studied. Therefore, we conducted a prospective, randomized, double-blind, placebo-controlled study to compare the efficacy of two different oral dosages of aprepitant for preventing PONV in patients receiving fentanyl-based PCA IV after gynecological laparoscopy.

Methods

After obtaining Institutional Review Board approval and written informed consent from each study participant, 123 patients [American Society of Anesthesiologists (ASA) physical status I or II; age 21–60 years] who were scheduled for elective laparoscopic total hysterectomy were enrolled in this double-blind, randomized controlled trial. The Apfel simplified risk score indicated that our patient population and the anesthesia techniques used would lead to a high risk of PONV in all treatment groups [10]. Exclusion criteria were liver, neurologic, and active pulmonary disease; cardiac arrhythmia; and/or allergies to any perioperative medications used in this study. A randomization list was generated using Microsoft Excel's random function, after which 40 patients were assigned to one of three groups: no prophylactic antiemetics (control group) preoperatively oral administration of 80 mg (A80 group), or 125 mg (A125 group) of aprepitant. To achieve blinding, an independent researcher prepared the study solutions, which consisted of a drinking cup wrapped in foil containing 10 ml saline in the control group and a cup containing dissolved aprepitant tablets in the treatment groups. The test drug was administered orally 2 h before anesthesia induction.

Patients received no premedication, and standard anesthetic monitoring was used throughout the surgery. Anesthesia was induced with Sodium Pentothal (4–5 mg/kg), remifentanil (starting at 1 μg/kg/h), and rocuronium (1 mg/kg) to facilitate tracheal intubation. Anesthesia was maintained with 1–2 % volume isoflurane in fractional inspiratory oxygen (FiO_2) of 0.5 without nitrous oxide (N_2O), with positive pressure ventilation adjusted to maintain end-tidal carbon dioxide tension of 30–35 mmHg throughout the procedure. Neuromuscular blockade was achieved with rocuronium as required. At the completion of surgery and onset of spontaneous breathing, residual muscle paralysis was reversed with glycopyrrolate (0.4 mg) and pyridostigmine (0.2 mg/kg). Esophageal temperature was maintained at 36.0 ± 1 °C by air warming (Bair Hugger warming unit Model 505; Arizant Healthcare Inc., MN, USA). Postoperative analgesia was provided IV using a mixture of ketorolac (180 mg) and fentanyl (15 μg/kg) in normal saline (total 100 ml) using a controlled ambulatory infusion system (Ambix Anaplus; Ewha Fresenius Kabi Korea, Seoul, Korea). Postsurgical analgesia was first administered at a rate of 2 ml/h, after which patients could receive a 0.5-ml bolus every 15 min using the patient-controlled pump. For patients who reported a verbal rating scale (VRS) >4 from postanesthesia care unit (PACU) to 2 days postoperatively, first-line analgesic treatment was a single dose of 30 mg ketorolac (IV), and 50 μg fentanyl (IV) as a second-line treatment.

All intraoperative medications and the anesthesia duration were recorded. The end of the procedure was the start of the observational period (0 h). Patients were monitored continuously in the PACU, and the incidences of nausea, vomiting, retching, and use of rescue therapy were recorded throughout the hospital stay by specially trained personnel blinded to all patient treatments. Assessments were made at 2 h, 24 h, and 48 h postoperatively at any time at which a patient complained of symptoms and immediately before administration of rescue medication. Patients rated nausea on an 11-point VRS, with 0 representing no nausea and 10 representing worst possible nausea. Complete response was defined as no nausea, retching, or vomiting and no need for rescue therapy. Rescue medication was provided if a patient had more than one episode of vomiting or retching, nausea lasting >15 min, or requested medication for nausea or vomiting. Rescue was done with dexamethasone (5 mg IV) as the first-line treatment. If the patient did not respond to the initial treatment, metoclopramide (10 mg IV) was administered as the second-line treatment. Safety assessments included awakening time (interval between the end of surgery and the patient's ability to obey commands) and duration of recovery from anesthesia [11]. Any other adverse effects were also recorded.

Statistical analyses were performed using the statistical package SPSS 11.0 for Windows (SPSS, Chicago, IL, USA). Sample size was predetermined using a power analysis based on the assumptions that the incidence of PONV in the control group would be 60 %, an improvement from 60 % to 22.5 % was considered clinically important, and $\alpha = 0.05$ with a power $(1 - \beta)$ of 0.8 [12]. This analysis indicated that 40 patients per group would allow detection of an antiemetic effect. All values are expressed as mean ± standard deviation (SD), median (interquartile range), or number (%) of patients. Analysis

Table 1 Patient characteristics

	A80 ($n = 40$)	A125 ($n = 40$)	Control ($n = 40$)
Age (year)	46 ± 5	46 ± 5	46 ± 6
Weight (kg)	58 ± 9	59 ± 7	59 ± 8
Height (cm)	157 ± 4	159 ± 5	159 ± 6
Apfel's simplified risk score	3 (2–4)	3 (2–4)	3 (2–4)
History of PONV	1	1	0
History of motion sickness	3	4	2
Nonsmoking	38	38	37
Operation time (min)	102 ± 33	96 ± 38	102 ± 54
Anesthesia time (min)	123 ± 37	122 ± 38	126 ± 53
Pneumoperitoneum time (min)	94 ± 33	87 ± 38	93 ± 54

All values are mean ± standard deviation (SD), number of patients, or median (interquartile ranges)

Control placebo, *A80* aprepitant 80 mg orally, *A125* aprepitant 125 mg orally, *PONV* postoperative nausea and vomiting, *Apfel's simplified risk score* PONV risk assessment scoring system using major independent predictors (female gender, nonsmoking, use of postoperative opioids, prior history of motion sickness or PONV) corresponding to approximately 10 %, 20 %, 40 %, 60 %, and 80 % risks of PONV

of variance (ANOVA) with Bonferroni's correction, Fisher's exact test, or Mann–Whitney *U* test was performed, as appropriate. A P value <0.05 was considered statistically significant.

Results

The three groups of patients did not differ in characteristics, surgery or anesthesia duration, or and Apfel's simplified risk score (Table 1). The Apfel's simplified risk score indicated that all patients were at moderate to high risk of PONV, and patients' risks according to the scores did not significantly differ between groups (Table 1).

Figure 1 illustrates the incidence of complete responses during the study: in controls, A80, and A125 groups 28 %, 56 %, and 63 %, respectively, during the first 48 h; 38 %, 65 %, and 65 %, respectively, during the first 2 h. The incidence of complete responses was higher in the A80 and A125 groups than in the control group during the first 48 h ($P = 0.007$ and $P = 0.003$, respectively), and during the first 2 h (both $P = 0.0025$). Table 2 lists the incidence of retching, vomiting, and rescue treatment. The incidence of nausea was significantly lower in the A80 and A125 groups than in controls (35 %, 35 % vs. 63 %, respectively; both $P = 0.0025$), during the first 2 h, and the incidence of vomiting was significantly lower in A80 and A125 groups than in controls (0 %, 0 % vs. 20 %, respectively; both $P = 0.005$) for 2–24 h after anesthesia. However, differences in the incidences of complete response, nausea, and vomiting between A80 and A125 groups were not statistically significant during the study period. The peak VRS scores of nausea [median (range)] were 6 (0–10), 4 (0–10), and 4 (0–10) in control, A80, and A125 groups, respectively, during the 48 after anesthesia and not significantly differ between groups.

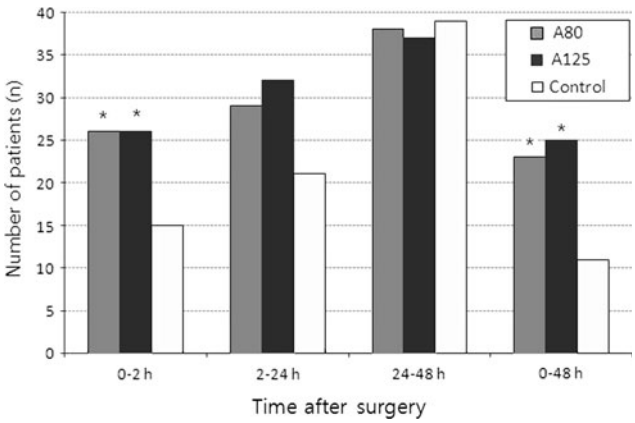

Fig. 1 Incidence of complete response (no nausea, no vomiting, no rescue) during first 48 h after gynecological laparoscopy. The incidence of complete response was higher in both aprepitant (A) 80-mg and A 125-mg groups compared with the control (placebo) group during the first 2 and 48 h after surgery. *P value: < 0.05, compared with the control group

Table 3 lists the incidences of adverse effects. There was no statistically significant difference in the incidence of adverse effects among the three groups. All adverse events, including dizziness, headache, dyspepsia, and abdominal distension, were mild and did not require treatment. There was no statistically significant difference in the use of analgesics postoperatively among groups.

Discussion

This study demonstrates that aprepitant 80 mg orally could reduce PONV in patients with fentanyl-based PCA IV after

gynecological laparoscopy. However, increasing the dose to 125 mg had no further beneficial effect.

The etiology of PONV is not entirely understood but is probably related to multiple factors, including surgical procedures such as laparoscopy or thyroidectomy, the use of volatile anesthetics and N_2O, female gender, postoperative pain, and the use of opioids postoperatively [13]. Apfel's simplified risk score for PONV in adult patients undergoing general anesthesia comprises four risk factors: female gender, nonsmoking, history of motion sickness or PONV, and the use of opioids postoperatively [10]. A simplified risk score of 2–3 for PONV indicates high risk, and a score >3 is considered very high risk [10]. The Apfel scores indicated that nearly all patients in this study had a very high risk of PONV. Although a previous study by Kakuta et al. [14] reported that the incidence of PONV was only 27 % at delayed phase (2–24 h after anesthesia) in patients undergoing gynecological laparoscopy without fentanyl-based PCA IV, 47 % of patients in our control group had PONV in the delayed phase. This high incidence may be due to the use of the PCA IV regimen using fentanyl. Despite the importance of PCA-IV-related PONV prophylaxis, its result is not satisfactory. Ondansetron, which is a frequently used 5-hydroxytryptamine receptor 3 ($5\text{-}HT_3$) antagonist, was effective in reducing the incidence of PONV [15]. However, ondansetron has been shown to have no beneficial effect in reducing incidence or severity of PCA-IV-related PONV [16, 17]. These results suggest that more effective antiemetic therapy is needed to prevent PCA-IV-related PONV.

Aprepitant is a potent and highly selective nonpeptide NK_1 receptor antagonist capable of crossing the blood–brain barrier and exerts antiemetic action by blocking substance P at central emetic pathways, such as the dorsal vagal complex and area postrema [6, 18]. In a previous study [19], aprepitant 40 mg or 125 mg orally were more effective than ondansetron 4 mg IV in reducing the severity of nausea during the first 48 h after surgery and preventing vomiting 24–48 h after surgery in patients undergoing open abdominal surgery with various anesthesia techniques. In addition, another study investigating the effect of aprepitant in patients undergoing gynecological laparoscopy without PCA IV reported that aprepitant 80 mg orally can effectively diminish PONV and also increase pain tolerance [14]. This study showed that aprepitant 80 and 125 mg orally seemed to be promising as a prophylactic antiemetic in patients with high susceptibility for developing PONV when administering opioid-based IV PCA. Meanwhile, we hypothesized that a larger dose of aprepitant might be more effective on PCA-IV-related PONV in patients after gynecological laparoscopy. However, although we found a trend toward a greater complete response in the A125 group to reduce PONV 2–24 h after anesthesia, the incidence of PONV was not statistically significantly different between A80 and A125 groups during the study period. Previous randomized controlled trials show that NK_1 receptor antagonists are particularly effective for preventing postoperative vomiting, even more so than other classes of antiemetics [9]. This is consistent with our results. In our study, no patient in either treatment group experienced vomiting during the study period, and the incidence of vomiting at 2–24 h after surgery was significantly lower in the treatment groups than in the control group.

As the half-life of aprepitant is 9–13 h, its antiemetic efficacy is reported to be longer than that of ondansetron [8]. In our study, we hypothesized that aprepitant might be effective in reducing late PONV (2–48 h after anesthesia). However, statistically significant differences did not exist among the groups at 2–48 h after anesthesia, except

Table 2 Incidence of postoperative nausea and vomiting

	Control ($n = 40$)	A80 ($n = 40$)	A125 ($n = 40$)
Nausea			
0–2 h after anesthesia	25 (63)	14 (35)*	14 (35)*
2–24 h after anesthesia	16 (40)	11 (28)	8 (20)
24–48 h after anesthesia	1 (3)	2 (5)	3 (8)
Retching			
0–2 h after anesthesia	3 (8)	0 (0)	1 (3)
2–24 h after anesthesia	3 (8)	0 (0)	0 (0)
24–48 h after anesthesia	0 (0)	0 (0)	0 (0)
Vomiting			
0–2 h after anesthesia	3 (8)	0 (0)	0 (0)
2–24 h after anesthesia	8 (20)	0 (0)*	0 (0)*
24–48 h after anesthesia	0 (0)	0 (0)	0 (0)
Rescue			
0–48 h after anesthesia	8 (20)	3 (8)	4 (10)

Values are expressed as number of patients (%)

Control placebo, *A80* aprepitant 80 mg orally, *A125* aprepitant 125 mg orally

* P value: < 0.05 compared with control group

Table 3 Incidences of adverse events and the use of analgesics postoperatively

	Control ($n = 40$)	A80 ($n = 40$)	A125 ($n = 40$)
Adverse events			
Dizziness	1	1	3
Headache	3	1	1
Dyspepsia	0	2	0
Abdominal distension	0	0	1
Analgesics used postoperatively			
Ketorolac 30 mg IV	5	4	4
Fentanyl 50 μg IV	2	3	2

Values are expressed as numbers of patients

Control placebo, *A80* aprepitant 80 mg orally *A125* aprepitant 125 mg orally,

between control and A125 groups, 2–24 h after anesthesia. This is likely because sensitivity assay of treatment efficacy could not be performed due to the low incidence of PONV, which was only 3 % in the control group at 24–48 h after anesthesia. Adverse events of dizziness, headache, dyspepsia, and abdominal distension were observed but were well tolerated without particular treatment. Diemunsch et al. [8] reported that clinical studies generally indicate that NK_1 receptor antagonists are safe, well-tolerated, and nontoxic.

This study has some limitations: In particular, doses <80 mg were not studied. Diemunsch et al. [20] reported that the efficacy profile of aprepitant 40 mg was clinically similar to that of aprepitant 125 mg in patients undergoing major abdominal surgery with various anesthetic techniques, although their study was not a placebo-controlled trial. Therefore, further study is needed to characterize the clinical efficacy of lower doses of aprepitant (<80 mg) on opioid-based PCA-associated PONV. Another limitation is that we did not conduct a cost-effectiveness analysis of orally administered aprepitant for prophylactic use. In Korea, the prices of aprepitant for oral administration (US $18 and $22 for 80 mg and 125 mg, respectively) are similar or cheaper than those of the 5-HT_3 antagonists, such as ondansetron (US $26 for 8 mg) and ramosetron (US $38 for 0.3 mg). Meanwhile, they are much more expensive than other commonly used antiemetics, such as metoclopramide (US $0.48 for 10 mg), which are administered as rescue antiemetics. However, the use of traditional antiemetics is limited by their side effects, which include sedative, dysphoric, and extrapyramidal symptoms. As the decision for or against specific antiemetics should be based on medical reasoning, anesthesiologists should make an informed choice regarding the antiemetic used. Even though previous publications of analysis of patients' willingness to pay suggest that they are prepared to pay around US $17–56 for an antiemetic that would completely prevent PONV [21–23], aprepitant orally to prevent PONV may not be cost effective for routine prophylactic use. Thus, we suggest it should be limited to patients with known hyperreaction to opioids or anesthetics, or past history of severe PONV not treated successfully with low-cost antiemetics, such as metoclopramide and droperidols.

In conclusion, aprepitant orally is effective in lowering the incidences of PONV in the first 48 h after anesthesia. Because the efficacy profile of aprepitant 80 mg is clinically different from that of aprepitant 125 mg, the 80-mg dose is adequate to provide improved prophylaxis against fentanyl-based PCA-IV-related PONV in patients undergoing gynecological laparoscopy with isoflurane anesthesia.

References

1. Madej TH, Simpson KH. Comparison of the use of domperidone, droperidol and metoclopramide in the prevention of nausea and vomiting following gynaecological surgery in day cases. Br J Anaesth. 1986;58:879–83.
2. Eriksson H, Korttila K. Recovery profile after desflurane with or without ondansetron compared with propofol in patients undergoing outpatient gynecological laparoscopy. Anesth Analg. 1996;82:533–8.
3. Kim JA, Kim TH, Yang M, Gwak MS, Kim GS, Kim MJ, Cho HS, Sim WS. Is intravenous patient controlled analgesia enough for pain control in patients who underwent thoracoscopy? J Korean Med Sci. 2009;24:930–5.
4. Sinatra R, Chung KS, Silverman DG, Brull SJ, Chung J, Harrison DM, Donielson D, Weinstock A. An evaluation of morphine and oxymorphone administered via patient-controlled analgesia (PCA) or PCA plus basal infusion in postcesarean-delivery patients. Anesthesiology. 1989;71:502–7.
5. Choi YS, Shim JK, Yoon do H, Jeon DH, Lee JY, Kwak YL. Effect of ramosetron on patient-controlled analgesia related nausea and vomiting after spine surgery in highly susceptible patients: comparison with ondansetron. Spine (Phila Pa 1976). 2008;33:E602–6.
6. Tattersall FD, Rycroft W, Francis B, Pearce D, Merchant K, MacLeod AM, Ladduwahetty T, Keown L, Swain C, Baker R, Cascieri M, Ber E, Metzger J, MacIntyre DE, Hill RG, Hargreaves RJ. Tachykinin NK1 receptor antagonists act centrally to inhibit emesis induced by the chemotherapeutic agent cisplatin in ferrets. Neuropharmacology. 1996;35:1121–9.
7. Tattersall FD, Rycroft W, Hill RG, Hargreaves RJ. Enantioselective inhibition of apomorphine-induced emesis in the ferret by

the neurokinin1 receptor antagonist CP-99,994. Neuropharmacology. 1994;33:259–60.
8. Diemunsch P, Gan TJ, Philip BK, Girao MJ, Eberhart L, Irwin MG, Pueyo J, Chelly JE, Carides AD, Reiss T, Evans JK. Aprepitant-PONV Protocol 091 International Study Group. Single-dose aprepitant vs ondansetron for the prevention of postoperative nausea and vomiting: a randomized, double-blind phase III trial in patients undergoing open abdominal surgery. Br J Anaesth. 2007;99:202–11.
9. Apfel CC, Malhotra A, Leslie JB. The role of neurokinin-1 receptor antagonists for the management of postoperative nausea and vomiting. Curr Opin Anaesthesiol. 2008;21:427–32.
10. Apfel CC, Läärä E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. Anesthesiology. 1999;91:693–700.
11. Aldrete JA, Kroulik D. A postanesthetic recovery score. Anesth Analg. 1970;49:924–34.
12. White H, Black RJ, Jones M, Mar Fan GC. Randomized comparison of two anti-emetic strategies in high-risk patients undergoing day-case gynaecological surgery. Br J Anaesth. 2007;98:470–6.
13. Gan TJ, Meyer T, Apfel CC, Chung F, Davis PJ, Eubanks S, Kovac A, Philip BK, Sessler DI, Temo J, Tramèr MR. Department of Anesthesiology, Duke University Medical Center. Consensus guidelines for managing postoperative nausea and vomiting. Anesth Analg. 2003;97:62–71.
14. Kakuta N, Tsutsumi YM, Horikawa YT, Kawano H, Kinoshita M, Tanaka K, Oshita S. Neurokinin-1 receptor antagonism, aprepitant, effectively diminishes post-operative nausea and vomiting while increasing analgesic tolerance in laparoscopic gynecological procedures. J Med Invest. 2011;58:246–51.
15. Tramer MR, Reynolds DJ, Moore RA, McQuay HJ. Efficacy, dose-response, and safety of ondansetron in prevention of postoperative nausea and vomiting: a quantitative systematic review of randomized placebo-controlled trials. Anesthesiology. 1997;87:1277–89.
16. Millo J, Siddons M, Innes R, Laurie PS. Randomised double-blind comparison of ondansetron and droperidol to prevent postoperative nausea and vomiting associated with patient-controlled analgesia. Anaesthesia. 2001;56:60–5.
17. Cherian VT, Smith I. Prophylactic ondansetron does not improve patient satisfaction in women using PCA after caesarean section. Br J Anaesth. 2001;87:502–4.
18. Ariumi H, Saito R, Nago S, Hyakusoku M, Takano Y, Kamiya H. The role of tachykinin NK-1 receptors in the area postrema of ferrets in emesis. Neurosci Lett. 2000;286:123–6.
19. Gan TJ, Apfel CC, Kovac A, Philip BK, Singla N, Minkowitz H, Habib AS, Knighton J, Carides AD, Zhang H, Horgan KJ, Evans JK. Aprepitant-PONV Study Group. A randomized, double-blind comparison of the NK1 antagonist, aprepitant, versus ondansetron for the prevention of postoperative nausea and vomiting. Anesth Analg. 2007;104:1082–9.
20. Diemunsch P, Apfel C, Gan TJ, Candiotti K, Philip BK, Chelly J, Carides AD, Evans JK, Ho TW, Reiss T. Preventing postoperative nausea and vomiting: post hoc analysis of pooled data from two randomized active-controlled trials of aprepitant. Curr Med Res Opin. 2007;23:2559–65.
21. van den Bosch JE, Bonsel GJ, Moons KG, Kalkman CJ. Effect of postoperative experiences on willingness to pay to avoid postoperative pain, nausea, and vomiting. Anesthesiology. 2006;104:1033–9.
22. 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.
23. Chung S, Kim KO, Lee JH, Lee K. How much are patients willing to pay for prevention of postoperative nausea and vomiting? Korean J Anesthesiol. 2009;57:151–4.