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Analysis for ideal regimens of intravenous patient-controlled analgesia according to grade of postoperative pain intensity – a retrospective observation study

조선대학교 대학원

의 학 과

서 종 식

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수술 후 통증 강도 따른 정맥 자가조절진통의 최적 조합을 위한 분석 - 후향적 관찰 연구

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ABSTRACT

수술 후 통증 강도에 따른 정맥 자가조절진통의 최적 조합을 위한 분석 - 후향적 관찰 연구

서 종 식
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목적: 전자 의무 기록 검토를 통해 수술 후 6 시간의 통증 강도 등급에 따라 구조진통제(rescue analgesic) 및 구조항구토제(rescue antiemetics)를 줄이는 최적의 펜타닐 기반 정맥 자가조절진통(patient-controlled analgesia: PCA) 조합을 찾기 위해 조사했다.

대상 및 방법: 단일 3차 병원에서 수술을 받은 4106명의 환자를 대상으로 PCA에 사용된 약물들(마약성 진통제, 보조진통제, 보조항구토제)의 용량, PCA 기기 설정[기저주입속도(background infusion rate: BIR), 일회투여용량(bolus volume), 잠금간격(lockout interval)]을 후향적으로 조사하였다. 마약성 진통제, 보조 진통제 용량은 펜타닐 등가선량으로 전환하여 펜타닐의 용량(DOSE-FEN-OP, DOSE-FEN-NONOP)으로 변환 후, 이 용량은 이용하여 각각의 BIR (BIR-FEN-OP, BIR-FEN-NONOP)를 재산출하였다. 일차 관심 변수들은 구조진통제 및 구조항구토제를 요구하지 않을 PCA 설정값들, DOSE-FEN-OP, DOSE-FEN-NONOP, BIR-FEN-OP, BIR-FEN-NONOP의 컷오프 값을 찾는 것이며, 수신자 조작 특성 곡선(Receiver Operating Characteristic Curve: ROC curve) 분석을 사용하였다. 이차 관심 변수들은 수술 후 48 시간 동안 구조진통제(rescue analgesic) 또는 구조항구토제(rescue antiemetic)를 필요로 하는 독립적인 위험 요인들을 확인하는 것이며, 이들은 다변량 이분형 로지스틱 회귀분석을 이용하여 오즈비(odds ratios: OR)를 분석했다.

결과: 구조진통제 또는 구조항구토제를 요구할 PCA 설정 컷오프 값들은 다음과 같았다. 낮은 PPI 군: BIR은 각각 1.75 mL/h [곡선아래면적(Area Under

the Curve: AUC): 0.515)]와 3.00 mL/h (AUC: 0.494), 일회투여용량은 각각 0.5 mL (AUC: 0.610)과 1.25 mL (AUC: 0.576), 그리고 잠금간격은 각각 12.5 min (AUC: 0.619)과 17.5 min (AUC: 0.583)이었다. 중간 PPI 군: BIR은 각각 1.75 mL/h (AUC: 0.504)와 1.75 mL/h (AUC: 0.523), 일회투여용량은 각각 0.5 mL (AUC: 0.524)과 1.75 mL (AUC: 0.519), 그리고 잠금간격은 각각 5 min (AUC: 0.512) and 25 min (AUC: 0.525)이었다. 높은 PPI 군: BIR은 각각 1.75 mL/h (AUC: 0.508)와 1.75 mL/h (AUC: 0.541), 일회투여용량은 각각0.5 mL (AUC: 0.573)와 0.5 mL (AUC: 0.491), 그리고 잠금간격은 각각 5 min (AUC: 0.605)과 12.5 min (AUC: 0.522)이었다.

PCA에 사용된 DOSE-FEN-OP에 대한 컷오프 값들은 다음과 같았다. 낮은 PPI 군: 각각 950 μg (AUC: 0.559)와 950 μg (AUC: 0.615)이였다. 중간 PPI 군: 각각 950 μg (AUC: 0.612)와 950 μg (AUC: 0.627)이였다. 높은 PPI 군: 각각 950 μg (AUC: 0.660)와 850 μg (AUC: 0.614)이였다.

PCA에 사용된 DOSE-FEN-NONOP에 대한 컷오프 값들은 다음과 같았다. 낮은 PPI 군: 각각 250 μg (AUC: 0.501)와 50 μg (AUC: 0.470)이였다. 중간 PPI 군: 각각 550 μg (AUC: 0.500)와 450 μg (AUC: 0.548)이였다. 높은 PPI 군: 각각 700 μg (AUC: 0.540)와 700 μg (AUC: 0.629)이였다.

BIR-FEN-OP에 대한 컷오프 값들은 다음과 같았다. 낮은 PPI 군: 각각 19 μg/h (AUC: 0.567)와 19 μg/h (AUC: 0.613)이였다. 중간 PPI 군: 각각 19 μg/h (AUC: 0.610)와 19 μg/h (AUC: 0.634)이였다. 높은 PPI 군: 각각 19 μg/h (AUC: 0.662)와 17 μg/h (AUC: 0.641)이였다.

BIR-FEN-NONOP에 대한 컷오프 값들은 다음과 같았다. 낮은 PPI 군: 각각 7 μg/h (AUC: 0.509)와 1 μg/h (AUC: 0.468)이였다. 중간 PPI 군: 각각 11 μg/h (AUC: 0.500)와 8.5 μg/h (AUC: 0.557)이였다. 높은 PPI 군: 각각 14 μg/h (AUC: 0.546)와 14 μg/h (AUC: 0.660)이였다.

구조진통제 요구에 대한 위험 인자들은 성별($p < 0.001$), 마취 시간($p = 0.001$), PCA 설정 중 일회투여용량($p = 0.002$), 마약성 진통제 용량($p < 0.001$)

으로 확인되었다. 여성이 남성보다 약 1.6배 약물 요구 가능성이 높았다 (OR: 1.563). 마취시간 1 시간, 일회투여용량 1 mL, 마약성 진통제 1 μg 증가에 따라 구조진통제 요구 확률을 유의하게 감소시키는 것으로 확인되었다(OR: 각각 0.899, 0.687, 0.998). 여기에 사용된 다변량 로지스틱 회귀분석에 사용된 인자들을 모두 통제한 후 PPI의 정도에 따른 그룹에 대한 분석 결과는 다음과 같았다. 낮은 PPI 군: BIR가 1 mL/h 증가 할수록 구조진통제 요구 확률을 유의하게 감소시킨다(OR: 0.143, p = 0.047). 중간 PPI 군: 여성 환자는 구조진통제 요구 위험도가 남자보다 증가하고, 마취시간 1 시간, 일회투여용량 1 mL, 마약성 진통제 1 μg 증가에 따라 구조진통제 요구 확률을 유의하게 감소시킬 수 있는 인자로 확인되었다(각각, OR: 1.666, p < 0.001 / OR: 0.898, p = 0.014 / OR: 0.469, p < 0.001 / OR: 0.998, p < 0.001). 높은 PPI 군: 흡연자, 잠금간격 1 분 증가, 마약성 진통제 1 μg 증가가 구조진통제 요구 확률을 유의하게 감소하는 인자로 확인되었다(각각, OR: 0.488, p = 0.049 / OR: 0.941, p < 0.001 / OR: 0.998, p < 0.001).

구조항구토제의 요구에 대한 위험인자들은 PCA 설정 중 BIR와 마약성 진통제 용량으로 확인되었다. BIR가 1 mL/h 과 마약성 진통제 1 μg 증가에 따라 구조항구토제 요구 확률을 유의하게 감소시키는 것으로 확인되었다(각각, OR: 0.294, p = 0.034/ OR: 0.999, p = 0.015). PPI의 정도에 따른 분석 결과는 다음과 같다. 낮은 PPI 군: ASA PS Ⅲ이 ASA PS Ⅰ보다 6.8배 높은 구조항구토제 요구 확률을 유의하게 감소하는 인자로 확인되었다 (OR: 6.800, p = 0.041). 중간 PPI 군: 구조항구토제 요구 확률을 유의하게 감소 또는 증가시키는 인자들을 확인할 수 없었다. 높은 PPI 군: 마취시간 1 시간, BIR 1 mL/h, 비마약성 진통제 1 μg 증가에 따라 구조항구토제 요구 확률을 유의하게 감소하는 인자로 확인되었다(각각, OR: 0.479, p = 0.012 / OR: 0.010, p = 0.004 / OR: 0.997, p = 0.006).

결론: 수술 후 통증 강도에 따른 최적의 PCA 설정을 위해서는 1.75 mL/h의 기저주입속도, 0.5 mL의 일회투여용량을 기준으로 조절이 필요하다. 하지만, 잠금간격은 예상 되는 수술 후 통증 정도가 낮은 경우는 12.5 분 이내로

설정하는 것이 최적의 조건을 제공하지만, 중등도 이상의 통증이 예상되는 경우 5 분 이내로 조절이 필요하다. 이에 PCA 설정에서는 기저주입속도와 일회투여용량 보다는 잠금간격 조정이 더 고려되어야 할 부분이다. 약물 조합적인 측면에서는 마약성 진통제의 사용을 950 μg 범위에서 유지하면서, 예상되는 통증의 정도가 증가할수록 비마약성 진통제의 용량을 증가하여 조절하는 것이 최적의 PCA 효과를 제공할 수 있음을 보여주었다. 하지만, 구조진통제 또는 구조항구토제의 요구에 대한 컷오프 값들이 서로 겹쳐 있지 않아, 두 가지 목표를 모두 만족시킬 수 있는 값이 없을 수도 있다는 것을 의미한다. 그러므로 구조진통제의 요구 감소를 위한 PCA를 설정하거나, 구조항구토제의 요구 감소를 위한 PCA를 설정할 것인가에 따라 PCA의 설정과 약물 용량을 조정할 필요가 있다.

구조진통제 또는 구조항구토제의 요구 증가 또는 감소는 여성, 마취 시간, BIR, 일회투여용량, 마약성 및 비마약성 진통제 용량들의 복합적인 영향으로 발생할 수 있음을 알 수 있다. 하지만 오즈비(OR > 0.9)가 매우 낮게 나타나는 일부 인자들은 비록 통계적으로 유의한 결과를 보이더라도 구조약물(rescue drugs)요구 확률에 미치는 효과가 낮다는 것을 고려하여 임상 환경에 적용할 필요성이 있다.

구조진통제 또는 구조항구토제의 요구 확률을 증가 또는 감소시킬 수 있는 위험 인자들과 컷오프 값들을 참고하여 환자의 예상되는 PPI에 따라 PCA의 설정과 약물 용량을 결정하는 것이 최적의 펜타닐 기반 정맥 자가조절진통 조합을 제공할 수 있을 것으로 사료된다.

Ⅰ. INTRODUCTION

Intravenous patient-controlled analgesia (PCA) has become the most common modality for postoperative pain control as standard practice worldwide, with high satisfaction despite the lack of consensus on the appropriate dose of opioids and adjuvants [1, 2]. Opioid-based PCA has been related to postoperative nausea and vomiting (PONV), or insufficient analgesia if the opioid doses are inappropriate. Thus, patients commonly require rescue analgesics or antiemetics for controlling these adverse events.

Recently, the drug combination of opioids, non-opioid analgesics, and antiemetics have been usually adopted for intravenous PCA, considering the reduction of opioid doses, the opioid-sparing effects of non-opioid analgesics, and the reduction of PONV [3]. Most studies have focused on assessing the effects of different opioids, non-opioid adjuvant analgesics, and adjuvant antiemetics on postoperative pain and PCA-related adverse events [1, 4-21]. In addition, ideal PCA regimens have been studied to maximize postoperative analgesia and minimize opioid-related adverse events at the same time [3, 14, 15]. However, there remains difficulties in providing optimal postoperative analgesia without adverse events because of inadequate pain control due to various postoperative pain intensities, individual opioid requirement, and unadjustable risk factors [2, 22].

Previously, morphine was the most commonly used opioid for postoperative analgesia, but it has a significant risk of opioid-related adverse events such as PONV, pruritus, and sedation [18]. Nowadays, among opioids, fentanyl is popularly adopted as more appropriate and suitable opioid than morphine for intravenous PCA due to its rapid onset and short duration of action [1, 23]. Especially, fentanyl has low opioid-related adverse events and high satisfaction

score compared with morphine [18]. Fentanyl-based PCA with background infusion and bolus dosing have been used for several decades. However, there remains hesitations in using the textbook-recommended fentanyl doses for PCA, because it is thought that these fentanyl doses would be a bit much for Koreans to use and that there would be several side effects. Furthermore, the attending anesthesiologist liberally decided PCA regimens by their preference and judgment, with various PCA device setting [background infusion rate (BIR), bolus volume, and lockout interval], and various doses of fentanyl with or without adjuvant analgesics and adjuvant antiemetics. Thus, several patients receiving PCA may require rescue analgesics due to inadequate postoperative analgesia, and rescue antiemetics or discontinuation of PCA due to opioid-related adverse events. This is not only a problem in our hospitals, but in many hospitals. Therefore, it is necessary to develop the ideal recommendable intravenous PCA regimens based on clinical situations. However, there is a relative shortage of evidence regarding proper fentanyl use in PCA because most studies were conducted with morphine-based regimens [1, 14].

The intravenous PCA regimens applied to patients after surgery at Chosun University Hospital were analyzed by reviewing the electronic medical record. The ideal fentanyl-based intravenous PCA regimens that reduce rescue analgesics and rescue antiemetics requirements were investigated, according to grades of postoperative pain intensity (PPI) during the first six postoperative hours, regardless of surgical department and surgical type.

Ⅱ. MATERIALS and METHODS

1. Study Design and Ethical Statement

The Institutional Review Board (IRB) of the Chosun University Hospital approved this retrospective study by electronic medical record review (approval number: CHOSUN 2018-12-008) on January 3, 2019. The IRB also waived the written informed consent from patients because the patient's identification information was anonymized before the analysis, and this study had no more than minimal risk to subjects. This study was prospectively registered with the Clinical Research Information Service (CRIS: https://cris.nih.go.kr/, ref: KCT0003889) on May 7, 2019 and was conducted according to the Declaration of Helsinki of 1964 and all its subsequent revisions.

2. Selection of Study Population

This study enrolled 4151 patients who received intravenous PCA, aged 12–100 years, with an American Society of Anesthesiologists physical status (ASA PS) of I–III, and who were scheduled to undergo any elective surgeries from January 1, 2018 to November 30, 2018. Patients with cognitive disorders (n = 30), unstable hemodynamics requiring administration of intensive care units (n = 15), and who received any type of nerve block or skin infiltration of local anesthetics additionally (n = 0) were excluded from this study. Finally, 4106 patients were enrolled in this study (Fig. 1).

Fig. 1. Flowchart of this study. Group L, NRS > 4 at the 6th postoperative hour; Group M, 4 ≤ NRS < 7 at the 6th postoperative hour; Group H, NRS ≥ 7 at the 6th postoperative hour [24].

3. Anesthetic management

After premedication with intramuscular midazolam or none, the patients were transferred to an operating room. All patients received either general anesthesia (inhaled or balanced anesthesia), total intravenous anesthesia, or regional anesthesia. A 50% oxygen–air or medical air mixture was used during mechanical ventilation. Consistent hypotension was controlled with intermittent bolus volume either of 100 μg phenylephrine or 10 mg ephedrine. Consistent high blood

pressure was controlled with intermittent bolus volume of 1 mg nicardipine. Bradycardia below 50 beats/min was controlled with intermittent bolus volume of 0.5 mg atropine. Tachycardia above 120 beats/min was controlled with intermittent bolus volume of 10 mg esmolol. Intraoperative hypothermia was prevented with application of air-forced blanket warmer. Appropriate neuromuscular blockers for neuromuscular paralysis were used based on patient's underlying diseases, which was fully recovered by sugammadex, glycopyrrolate and pyridostigmine, or both. Persistent opioid-related respiratory nonresponse was stimulated with 0.1 mg naloxone intermittent injection during emergence in patients receiving intraoperative opioids. Persistent sedation with midazolam premedication was reversed with 0.3 mg flumazenil during emergence.

4. Interventions

Every application of PCA were followed by the hospital protocol for postoperative pain management. Anesthesiologists explained how to use PCA devices to all patients, who agreed to use intravenous PCA for postoperative analgesia, on the day before surgery. For PCA device with bolus dosing, the patients were instructed to push the "demand" button of each device whenever they experienced pain of >4 points on the numeric rating scale (Numerical Rating Scale [NRS]: 0 = no pain, 10 = worst pain).

The attending anesthesiologists operated each PCA device at the end of the surgery. A total PCA volume of 100 mL, comprised of normal saline, opioids (fentanyl, sufentanil, or oxycodone), adjuvant analgesics (none, nefopam, or ketorolac), and adjuvant antiemetics (none or ramosetron), was used. Moreover, 200 μg fentanyl was used as the reference dose for PCA regimens, and it was adjusted according to age, underlying diseases such as chronic kidney disease, risk of PONV, and expected PPI. Other opioid doses were decided according to the dose of fentanyl equivalent. Basically, all PCA devices were set with BIR of 2 mL/h, bolus volume of 2 mL, and lockout interval of 30 min. However, the

attending anesthesiologist has liberally decided regimens, settings, and devices for PCA according to their preference and judgment, considering the patient's safety.

In patients receiving PCA, rescue analgesics and antiemetics were administrated only on demand and not routinely. When patients experienced pain of NRS > 4, the patient pushed the "demand" button for administration of a preset bolus volume. When patients required additional rescue analgesics within lockout interval, physicians or nurses injected opioids, nonsteroidal anti-inflammatory drugs, or other analgesics. PONV (NRS > 4) was controlled by intravenous injection of 10 mg metoclopramide or 0.3 mg ramosetron.

The nurses, who were trained in the hospital to assess patients using the NRS, recorded the scores of postoperative pain and PONV, the rescue analgesics and antiemetics, and any adverse events in electronic medical records. The anesthesiologists decided whether to stop the PCA device based on severity of signs and symptoms.

5. Outcomes

The PCA devices (with or without bolus dosing), PCA regimens (kinds and doses of opioids, adjuvant analgesics, adjuvant antiemetics), and PCA device settings (BIR, bolus volume, lockout interval) were investigated. Doses of opioids, non-opioid analgesics, and total analgesics were converted to doses of fentanyl equivalents (in μg; DOSE-FEN-OP, DOSE-FEN-NONOP, and DOSE-FEN-TOTAL, respectively) with ratios of oxycodone (μg) to fentanyl (100:1), sufentanil (μg) to fentanyl (1:10), ketorolac (mg) to fentanyl (25:100), and nefopam (mg) to fentanyl (1:20). Then, their BIRs were recalculated with these converted doses (BIR-FEN-OP, BIR-FEN-NONOP, and BIR-FEN-TOTAL) [25-28]. DOSE-FEN-TOTAL was the total analgesic doses of fentanyl equivalents converted from opioid and non-opioid analgesics.

The NRS at the 6th, 12th, 24th, and 48th postoperative hours were

investigated. Meanwhile, the use of bolus dosing, rescue analgesics, and rescue antiemetics was investigated during the 48th postoperative hour.

Age, sex, weight, body mass index (BMI), ASA PS, surgery department, PPI grades at the 6th postoperative hour, history of previous opioid intake, underlying diseases (diabetic mellitus, hypertension, chronic obstructive pulmonary disease, coronary disease, etc.), PONV risk factors (smoking, motion sickness, and previous PONV), anesthesia duration, anesthesia method, and intraoperative opioid. Age and BMI were categorized at 20-year intervals and by obesity classification, respectively.

6. Analysis

The primary endpoints were the cutoff values of PCA settings, DOSE-FEN-OP, DOSE-FEN-NONOP, BIR-FEN-OP, and BIR-FEN-NONOP that could increase or decrease the probability of requiring rescue analgesic or rescue antiemetics. The secondary endpoints were the independent risk factors that could increase or decrease the requirement for rescue analgesic or rescue antiemetic during the 48 postoperative hours.

All statistical analyses were performed with SPSS Statistics for Windows, ver. 26.0 (IBM Corp., Armonk, NY, USA). All data were presented as means (95% confidence intervals [CI]), means ± standard deviation (SD), or numbers (percentage) of patients (n [%]).

Receiver operating characteristic (ROC) curve analysis was performed to obtain cutoff values of PCA settings (BIR, bolus volume, and lockout interval), DOSE-FEN-OP, DOSE-FEN-NONOP, DOSE-FEN-TOTAL, DOSE-EME (antiemetics dose), BIR-FEN-OP, BIR-FEN-NONOP, BIR-FEN-TOTAL, and BIR-EME (background infusion rate of antiemetics) that would require rescue analgesics or antiemetics. Optimal cutoff values were determined based on the maximum values of the Youden index, calculated by [sensitivity + specificity −

1]. Statistical significance was set at $p < 0.05$.

Descriptive statistics for all patients was performed, and a logistic regression model was conducted to verify the independent predictors of rescue analgesics and antiemetics requirements during the 48th postoperative hour. Potential confounding factors for analysis was selected based on Shin's study [2], which included the following: sex, age, BMI, ASA PS, smoking history, previous opioid intake history, anesthesia duration, PCA settings (BIR, bolus volume, and lockout interval), intraoperative opioid use, and doses of analgesics and antiemetics. First, a univariate logistic regression analysis was performed to identify significant predictors, and a multivariate logistic regression analysis was then conducted using the aforementioned variables. Odds ratios (ORs) and 95% CIs were estimated.

Then, a logistic regression model and ROC curve analysis were performed after all patients were allocated into low, moderate, and high PPI groups (group L, group M, and group H, respectively) according to NRS > 4, 4 ≤ NRS < 7, NRS ≥ 7 at the 6th postoperative hour [24].

Continuous variables were analyzed using the one-way analysis of variance (ANOVA) test, following the Scheffe's Post hoc test, while nominal variables were analyzed with the χ^2 test or Fisher's exact test. For the analysis of time-interval data that passed Mauchly's sphericity test, I used repeated measures ANOVA; for data that did not pass Mauchly's sphericity test, Wilk's lambda multivariate analysis of variance was used. To compare three groups in each time interval, one-way ANOVA test was used. Statistical significance was set at $p < 0.05$.

Ⅲ. RESULTS

1. General Descriptive Analysis of All Patients

1.1. Characteristics of Patients Who Received Intravenous PCA

In this study, 4106 patients were eligible for analysis (Fig. 1). The patients' characteristics are shown in Table 1. Among patients, 50.7% were women. Most patients had ASA PS Ⅰ (44.5%) and Ⅱ (48.2%). In addition, 50% patients had underlying diseases, of which hypertension (32% of all patients) and diabetic mellitus (18% of all patients) were the most common. Among patients, 10.1% had smoking history, 79.1% were opioid naïve, and 83.8% received intraoperative opioid. The mean anesthesia duration was 2.2 h.

Table 1. Characteristics of patients who received intravenous PCA (n = 4106).

Sex (M/F)	2026 (49.3) / 2084 (50.7)
Age (years)	57.4 ± 18.2
Age ≤ 20	148 (3.6)
20 < Age ≤ 40	625 (15.2)
40 < Age ≤ 60	1371 (33.4)
60 < Age ≤ 80	1628 (39.6)
Age ≥ 80	334 (8.1)
Height (cm)	163.3 ± 9.5
Weight (kg)	63.9 ± 12.4
BMI (kg/m^2)	23.9 ± 3.7
BMI < 18.5	229 (5.6)
18.5 ≤ BMI < 23.0	1495 (36.4)
23.0 ≤ BMI < 25.0	915 (22.3)

25.0 ≤ BMI < 30.0	1259 (30.7)
BMI ≥ 30.0	208 (5.1)
ASA PS (Ⅰ/Ⅱ/Ⅲ)	1826 (44.5) / 1978 (48.2) / 302 (7.4)
Underlying disease (No/Yes)	2055 (50) / 2051 (50)
Hypertension (No/Yes)	2794 (68) / 1312 (32)
Diabetic mellitus (No/Yes)	3367 (82) / 739 (18)
COPD (No/Yes)	4024 (98) / 82 (2)
Coronary disease (No/Yes)	4024 (98) / 82 (2)
Others (No/Yes)	3369 (82.1) / 737 (17.9)
Smoking (No/Yes)	3691 (89.9) / 415 (10.1)
Opioid naïve (No/Yes)	857 (20.9) / 3249 (79.1)
Anesthesia duration (h)	2.2 ± 1.4
Intraoperative opioid (No/Yes)	665 (16.2) /3441 (83.8)

The values are expressed as means ± standard deviation, or numbers (percentage) of patients. ASA PS, American Society of Anesthesiologists physical status; BMI, body mass index; COPD, chronic obstructive pulmonary disease; PCA, patient-controlled analgesia. Opioid naïve, patients without history of previous opioid intake.

1.2. Operation Departments and Postoperative Pain Intensity (PPI) Grades

Orthopedic surgery (49.1%), general surgery (22.6%), and neurosurgery (14.3%) were the most common operation departments. Low PPI grade (NRS < 4) was recorded in 15.6% of the patients, while moderate and high PPI grades were recorded in 64.9% and 19.5%, respectively (Table 2).

Table 2. Operation departments and postoperative pain intensity grades (n = 4106).

Operation departments	
Orthopedic surgery	2014 (49.1)

General surgery	926 (22.6)
Neurosurgery	588 (14.3)
Cardiothoracic surgery	235 (5.7)
Obstetric and gynecological surgery	204 (5)
Urology surgery	57 (1.4)
Otorhinolaryngology surgery	55 (1.3)
Oral and maxillofacial surgery	25 (0.6)
Plastic surgery	2 (0)
Grades of PPI	
Low	640 (15.6)
Moderate	2666 (64.9)
High	800 (19.5)

The values are expressed as numbers (percentage) of patients. PPI, postoperative pain intensity. Low PPI, numeric rating scale (NRS) < 4 at the 6th postoperative hour; Moderate PPI, 4 ≤ NRS < 7 at the 6th postoperative hour; High PPI, NRS ≥ 7 at the 6th postoperative hour [24].

1.3. Characteristics of Anesthesia

As shown in Table 3, 84.6% patients received general anesthesia, while 11.3% patients received regional anesthesia. In general anesthesia, balanced anesthesia was most common (72.2% of all patients). Furthermore, 83.8% of patients received intraoperative opioids during general or regional anesthesia, and 81.4% of patients received remifentanil.

Table 3. Characteristics of anesthesia (n = 4106).

Anesthesia method

General Anesthesia	3473 (84.6)
Inhaled Anesthesia	44 (1.1)
Balanced Anesthesia	2963 (72.2)
TIVA	466 (11.3)
Regional Anesthesia	633 (15.4)
Intraoperative opioids (No/Yes)	665 (16.2) /3441 (83.8)
Remifentanil	3341 (81.4)
Sufentanil	100 (2.4)
None	665 (16.2)

The values are expressed as numbers (percentage) of patients. TIVA, total intravenous anesthesia.

1.4. Regimens for Intravenous Patient-Controlled Anesthesia

Table 4 summarizes the regimens for intravenous PCA. Of the 4106 patients, 4001 (97.4%) patients received fentanyl, and the remaining 105 (2.6%) received sufentanil or oxycodone. In addition, 3980 (96.9%) patients received an intravenous PCA containing adjuvant analgesics, of which 88.1% and 8.8% received nefopam and ketorolac, respectively. Ramosetron (5HT3 receptor antagonist) were added as adjuvant antiemetics in 3979 (96.9%) patients.

The mean DOSE-FEN-OP and DOSE-FEN-NONOP were 891.9 μg and 692.2 μg, respectively, while the mean antiemetic dose (DOSE-EME) was 1.2 mg.

The mean BIR, bolus volume, and lockout interval were 1.99 mL/h, 1.68 mL/bolus, and 24.08 min, respectively. The most common BIR, bolus volume, and lockout interval were 2 mL/h (98.7%), 2 mL/bolus (76.3%), and 30 min (72.6%), respectively.

Table 4. Regimens for intravenous PCA (n = 4106).

Drugs	
Opioids (Fentanyl/others)	4001 (97.4) / 105 (2.6)
Fentanyl	4001 (97.4)
Oxycodone	78 (1.9)
Sufentanil	27 (0.7)
Adjuvant analgesics (No/Yes)	126 (3.1) / 3980 (96.9)
None	126 (3.1)
Nefopam	3617 (88.1)
Ketorolac	363 (8.8)
Adjuvant antiemetics (No/Yes)	127 (3.1) / 3979 (96.9)
None	127 (3.1)
Ramosetron	3979 (96.9)
Doses	
DOSE-FEN-TOTAL (μg)*	1584.1 ± 347.7
DOSE-FEN-OP (μg)*	891.9 ± 217.6
DOSE-FEN-NONOP (μg)*	692.2 ± 227.8
DOSE-EME (mg)	1.2 ± 0.1
Settings	
BIR (mL/h)	1.99 ± 0.1
1 /1.5 /2 /3 mL/h	32 (0.8) /22 (0.5)/ 4051 (98.7)/ 1(0)
Bolus volume (mL/bolus)	1.68 ± 0.63
0 /1 /1.5 /2 mL	368 (9.0) /525 (12.8)/79 (1.9)

	/3134 (76.3)
Lockout interval (min)	24.08 ± 10.37
0 /10 /15 /20 / 30 min	480 (11.7) /50 (1.2) /592 (14.4) /4 (0.1) /2980 (72.6)

The values are expressed as means ± standard deviation, or numbers (percentage) of patients. BIR, background infusion rate; PCA, patient-controlled analgesia; DOSE-EME, dose of antiemetics. *, doses of fentanyl equivalents (μg) converted from opioids (DOSE-FEN-OP DOSE-FEN-OP), non-opioid adjuvant analgesics (DOSE-FEN-NONOP), and total analgesics (DOSE-FEN-TOTAL) with ratios of oxycodone (μg) to fentanyl (100:1), ratios of sufentanil (μg) to fentanyl (1:10), ratio of ketorolac (mg) to fentanyl (25:100), and ratio of nefopam (mg) to fentanyl (1:20) [25-28].

1.5. Postoperative Pain Intensity

Of the 4106 patients, 2839 (96.1%) patients showed NRS > 4, with a mean NRS of 5 at the 6th postoperative hours. In addition, 8.8%, 15.0%, and 10.2% of patients showed NRS > 4 at the 12th, 24th, 48th postoperative hours, respectively (Table 5).

Table 5. Postoperative numeric rating scale (n = 4106).

Numeric rating scale (0: lowest, 10: worst)	
6th Postoperative hour	5.0 ± 2.0
12th Postoperative hour	1.9 ± 1.6
24th Postoperative hour	2.0 ± 2.0
48th Postoperative hour	1.3 ± 1.8
Categorized numeric rating scale (Low/more than moderate)*	
6th Postoperative hour	1267 (30.9) / 2839 (69.1)
12th Postoperative hour	3745 (91.2) / 361 (8.8)

24th Postoperative hour	3489 (85.0) / 617 (15.0)
48th Postoperative hour	3686 (89.8) / 420 (10.2)

The values are expressed as means ± standard deviation, or numbers (percentage) of patients. *: Low, numeric rating scale (NRS) < 4 at the 6th postoperative hour; Moderate, 4 ≤ NRS < 7 at the 6th postoperative hour; High, 7 ≤ NRS at the 6th postoperative hour [24].

1.6. Postoperative Rescue Analgesic and Rescue Antiemetic Requirements

Among patients, 852 (20.8%) and 106 (2.6%) required rescue analgesics and antiemetics, respectively, at least once during the 48th postoperative hour (Table 6).

Table 6. Rescue analgesic and rescue antiemetic requirements during PCA (n = 4106).

Rescue analgesic requirement (No/Yes)	3254 (79.2) / 852 (20.8)
Rescue antiemetic requirement (No/Yes)	4000 (97.4) / 106 (2.6)

The values are expressed as numbers (percentage) of patients. PCA, patient-controlled analgesia.

1.7. Background Infusion Rate of Opioids, Non-Opioid Adjuvant Analgesics, and Adjuvant Antiemetics for PCA

The background infusion rates were recalculated with doses of fentanyl equivalents (μg) converted from opioids (BIR-FEN-OP), non-opioid adjuvant analgesics (BIR-FEN-NONOP), and total analgesics (BIR-FEN-TOTAL), with ratios of oxycodone (μg) to fentanyl (100:1), ratios of sufentanil (μg) to fentanyl (1:10), ratio of ketorolac (mg) to fentanyl (25:100), and ratio of nefopam (mg) to fentanyl (1:20) [25-28].

The average values of BIR-FEN-OP, BIR-FEN-NONOP, and BIR-FEN-TOTAL

were 17.8 ± 4.5 μg/h, 13.8 ± 4.6 μg/h, and 31.6 ± 7.2 μg/h, respectively, and they showed wide ranges between 4.0 μg/h and 44.0 μg/h, between 0.0 μg/h and 120.0 μg/h, and between 6.0 μg/h and 140.0 μg/h, respectively. The average value of BIR-EME was 23.4 ± 2.2 μg/h, and it showed a wide range between 0.0 μg/h and 36.0 μg/h (Table 7).

Table 7. Background infusion rate (BIR) of opioids, non-opioid analgesics, and adjuvant antiemetics for PCA (n = 4106).

BIR-FEN-TOTAL (μg/h)*	31.6 ± 7.2
BIR-FEN-OP (μg/h)*	17.8 ± 4.5
BIR-FEN-NONOP (μg/h)*	13.8 ± 4.6
BIR-EME (μg/h)	23.4 ± 2.2

The values are expressed as means ± standard deviation, or numbers (percentage) of patients. BIR, background infusion rate; BIR-EME, BIR for adjuvant antiemetics; PCA, patient-controlled analgesia. *, BIRs recalculated with doses of fentanyl equivalents (μg) converted from opioids (BIR-FEN-OP), non-opioid adjuvant analgesics (BIR-FEN-NONOP), and total analgesics (BIR-FEN-TOTAL) with ratios of oxycodone (μg) to fentanyl (100:1), ratios of sufentanil (μg) to fentanyl (1:10), ratio of ketorolac (mg) to fentanyl (25:100), and ratio of nefopam (mg) to fentanyl (1:20) [25-28].

1.8. Cutoff Value of Potential Variables for Requiring Rescue Analgesics

The cutoff values for BIR, bolus volume, and lockout interval were 1.75 mL/h (area under the curve [AUC]: 0.506), 0.5 mL (AUC: 0.546), and 5 min (AUC: 0.548), respectively. The cutoff values for DOSE-FEN-OP, DOSE-FEN-NONOP, and DOSE-FEN-TOTAL were 950 μg (AUC: 0.615), 550 μg (AUC: 0.508), and 1750 μg (AUC: 0.593), respectively. For BIR-FEN-OP, BIR-FEN-NONOP, BIR-EME, and BIR-FEN-TOTAL, the cutoff values were 19 μg/h (AUC: 0.615),

8.5 μg/h (AUC: 0.511), 21 μg/h (AUC: 0.516), and 35 μg/h (AUC: 0.593), respectively (Table 8).

The cutoff values for PCA settings (bolus volume and lockout time), DOSE-FEN-OP, DOSE-FEN-TOTAL, BIR-FEN-OP, and BIR-FEN-TOTAL were statistically significant.

Table 8. Cutoff value of potential variables for requiring rescue analgesics (n = 4106).

Potential Variables	Cutoff value	AUC	Sens. (%)	Spec. (%)	Youden index	95% CI	p value
PCA setting							
BIR (1 mL/h)	1.75	0.506	99.0	2.3	0.013	0.484, 0.528	0.596
Bolus volume (1 mL)	0.5	0.546	94.2	21.0	0.152	0.523, 0.569	< 0.001*
Lockout interval (min)	5	0.548	91.5	23.7	0.152	0.525, 0.570	< 0.001*
Dose (μg)							
DOSE-FEN-OP†	950	0.615	50.0	71.5	0.215	0.595, 0.635	< 0.001*
DOSE-FEN-NONOP†	550	0.508	89.7	12.8	0.025	0.486, 0.531	0.451
DOSE-FEN-TOTAL†	1750	0.593	36.4	78.3	0.147	0.572, 0.614	< 0.001*
BIR (μg/h)							
BIR-FEN-OP†	19	0.632	46.0	76.4	0.224	0.579, 0.685	< 0.001*
BIR-FEN-NONOP†	8.5	0.565	88.7	22.6	0.113	0.506, 0.624	0.031*
BIR-EME	21	0.525	92.5	12.3	0.048	0.467, 0.582	0.404

BIR-FEN-TOTAL†	31	0.629	62.2	58.5	0.207	0.574, 0.685	< 0.001*

AUC, area under the curve; BIR, background infusion rate; BIR-EME, BIR for adjuvant antiemetics; CI, confidence interval. Sens., Sensitivity; Spec., Specificity. *, statistical significance at $p < 0.05$. †, Potential Variables (Doses and BIRs) were doses of fentanyl equivalents (μg) converted from opioids (DOSE-FEN-OP), non-opioid adjuvant analgesics (DOSE-FEN-NONOP), and total analgesics (DOSE-FEN-TOTAL) with ratios of oxycodone (μg) to fentanyl (100:1), ratios of sufentanil (μg) to fentanyl (1:10), ratio of ketorolac (mg) to fentanyl (25:100), and ratio of nefopam (mg) to fentanyl (1:20), and BIRs recalculated with these converted doses (BIR-FEN-OP, BIR-FEN-NONOP, and BIR-FEN-TOTAL) [25-28].

1.9. Cutoff Value of Potential Variables for Requiring Rescue Antiemetics

The cutoff values for BIR, bolus volume, and lockout interval were 1.75 mL/h (AUC: 0.522), 1.75 mL (AUC: 0.522), and 25 min (AUC: 0.534), respectively. The cutoff values for DOSE-FEN-OP, DOSE-FEN-NONOP, and DOSE-FEN-TOTAL were 950 μg (AUC: 0.622), 450 μg (AUC: 0.553), and 1750 μg (AUC: 0.619), respectively. For BIR-FEN-OP, BIR-FEN-NONOP, BIR-EME, and BIR-FEN-TOTAL, the cutoff values were 19 μg/h (AUC: 0.632), 8.5 μg/h (AUC: 0.565), 21 μg/h (AUC: 0.525), and 31 μg/h (AUC: 0.629), respectively (Table 9).

The cutoff values for DOSE-FEN-OP, DOSE-FEN-TOTAL, BIR-FEN-OP, BIR-FEN-NONOP, and BIR-FEN-TOTAL were statistically significant.

Table 9. Cutoff value of potential variables for requiring rescue antiemetics (n = 4106).

Potential Variables	Cutoff	AUC	Sens.	Spec.	Youden	95%	p

	value		(%)	(%)	index	CI	value
PCA setting							
BIR (1 mL/h)	1.75	0.522	98.8	5.7	0.045	0.465, 0.580	0.448
Bolus volume (1 mL)	1.75	0.522	76.5	29.2	0.057	0.466, 0.577	0.442
Lockout interval (min)	25	0.534	72.8	34.9	0.077	0.478, 0.590	0.240
Dose (μg)							
DOSE-FEN-OP†	950	0.622	46.1	75.5	0.216	0.570, 0.675	<0.001*
DOSE-FEN-NONOP†	450	0.553	89.5	18.9	0.084	0.494, 0.612	0.076
DOSE-FEN-TOTAL†	1750	0.619	62.3	56.6	0.189	0.563, 0.674	<0.001*
BIR (μg/h)							
BIR-FEN-OP†	19	0.632	46.0	76.4	0.224	0.579, 0.685	<0.001*
BIR-FEN-NONOP†	8.5	0.565	88.7	22.6	0.113	0.506, 0.624	0.031*
BIR-EME	21	0.525	92.5	12.3	0.048	0.467, 0.582	0.404
BIR-FEN-TOTAL†	31	0.629	62.2	58.5	0.207	0.574, 0.685	<0.001*

AUC, area under curve; BIR, background infusion rate; BIR-EME, BIR for adjuvant antiemetics; CI, confidence interval. Sens., sensitivity; Spec., specificity. *, statistical significance at $p < 0.05$. †, Potential Variables (Doses and BIRs) were doses of fentanyl equivalents (μg) converted from opioids (DOSE-FEN-OP), non-opioid adjuvant analgesics (DOSE-FEN-NONOP), and total analgesics (DOSE-FEN-TOTAL) with ratios of oxycodone (μg) to fentanyl (100:1), ratios of sufentanil (μg) to fentanyl (1:10), ratio of ketorolac (mg) to fentanyl (25:100), and

ratio of nefopam (mg) to fentanyl (1:20), and BIRs recalculated with these converted doses (BIR-FEN-OP, BIR-FEN-NONOP, and BIR-FEN-TOTAL) [25-28].

1.10. Risk Factors of Rescue Analgesics Requirement According to Logistic Regression Analysis

Upon univariate analysis, female sex, smoking history, anesthesia duration, PCA settings (BIR, bolus volume, and lockout interval), and fentanyl equivalent doses of opioids and non-opioid analgesics were identified as independent risk factors that could increase or decrease the probability of requiring rescue analgesics (Table 10). Female sex was a risk factor that could increase the probability of requiring rescue analgesics by 30.5%, compared with male sex (OR: 1.695, $p < 0.001$). Smoking history was also a risk factor that could increase the probability of requiring rescue analgesics by 25.9% (OR: 0.741, $p = 0.029$). Furthermore, an anesthesia duration that was longer by 1 h could decrease the probability of requiring rescue analgesics by 7.3% (OR: 0.927, $p = 0.009$). In addition, the probability of requiring rescue analgesics was lower when the PCA device was set with faster BIR (OR: 0.408, $p = 0.008$), larger bolus volume (OR: 0.622, $p < 0.001$), and longer lockout interval (OR: 0.974, $p < 0.001$). A 1 μg increase in fentanyl equivalent doses of opioids and non-opioid analgesics could also decrease the probability of requiring rescue analgesics by 0.2% (OR: 0.998, $p < 0.001$) and 0% (OR: 1.000, $p = 0.047$), respectively.

Upon multivariate analysis after adjustment with potential confounding factors, female sex, anesthesia duration, bolus volume of PCA setting, and dose of opioid were identified as independent risk factors (Table 10). Female sex was a risk factor that could increase the probability of requiring rescue analgesics by 56.3%, compared with male sex (OR: 1.563, $p < 0.001$). An anesthesia duration that was longer by 1 h could lower the probability of requiring rescue analgesics by 10.1% (OR: 0.899, $p = 0.001$). The probability of rescue analgesics requirement

was lower when the PCA device was set with larger bolus volume (OR: 0.687, p = 0.002). Furthermore, a 1 μg increase in fentanyl equivalent doses of opioids could lower the probability of rescue analgesics requirement by 0.2% (OR: 0.998, p < 0.001).

Table 10. Odds ratios (ORs) obtained from univariate and multivariate binary logistic regression analyses, estimating the association between potential confounding factors and rescue analgesic requirement (n = 4106).

Confounding factors	Univariate		
	Crude OR	95% CI	p value
Female sex	1.695	1.453, 1.976	<0.001*
Age (years)			
Age ≤ 20	1 (ref.)		
20 < Age ≤ 40	1.330	0.831, 2.130	0.235
40 < Age ≤ 60	1.378	0.880, 2.158	0.161
60 < Age ≤ 80	1.199	0.767, 1.875	0.426
Age ≥ 80	1.425	0.863, 2.351	0.166
BMI (kg/m^2)			
BMI < 18.5	1 (ref.)		
18.5 ≤ BMI < 23.0	1.170	0.816, 1.678	0.392
23.0 ≤ BMI < 25.0	1.210	0.833, 1.758	0.318
25.0 ≤ BMI < 30.0	1.258	0.874, 1.809	0.216
BMI ≥ 30.0	1.266	0.789, 2.030	0.328
ASA PS			
Ⅰ	1 (ref.)		
Ⅱ	0.975	0.834, 1.140	0.753

Ⅲ	0.810	0.591, 1.109	0.189
Smoking (Yes)	0.741	0.565, 0.970	0.029*
Opioid naïve (Yes)	0.914	0.761, 1.097	0.336
Anesthesia duration (per h)	0.927	0.876, 0.982	0.009*
Intraoperative opioid use (Yes)	0.862	0.706, 1.052	0.144
BIR of PCA setting (per 1 mL/h)	0.408	0.210, 0.794	0.008*
Bolus volume of PCA setting (1 mL)	0.622	0.559, 0.694	<0.001*
Lockout interval of PCA setting (per min)	0.974	0.967, 0.980	<0.001*
DOSE-FEN-OP (μg)†	0.998	0.998, 0.999	<0.001*
DOSE-FEN-NONOP (μg)†	1.000	0.999, 1.000	0.047*

Confounding factors	Multivariate		
	Adjusted OR	95% CI	p value
Female sex	1.563	1.319, 1.852	<0.001*
Age (years)			
Age ≤ 20	1 (ref.)		
20 < Age ≤ 40	1.003	0.614, 1.641	0.989
40 < Age ≤ 60	0.965	0.599, 1.554	0.882
60 < Age ≤ 80	0.896	0.544, 1.475	0.665
Age ≥ 80	1.072	0.613, 1.875	0.808
BMI (kg/m^2)			
BMI < 18.5	1 (ref.)		
18.5 ≤ BMI < 23.0	1.204	0.826, 1.755	0.335
23.0 ≤ BMI < 25.0	1.194	0.806, 1.768	0.377
25.0 ≤ BMI < 30.0	1.308	0.892, 1.919	0.169

BMI ≥ 30.0	1.269	0.777, 2.074	0.341
ASA PS			
Ⅰ	1 (ref.)		
Ⅱ	0.997	0.814, 1.221	0.976
Ⅲ	0.822	0.573, 1.177	0.284
Smoking (Yes)	0.951	0.710, 1.274	0.736
Opioid naïve (Yes)	0.867	0.715, 1.050	0.143
Anesthesia duration (per h)	0.899	0.843, 0.959	0.001*
Intraoperative opioid use (Yes)	0.904	0.727, 1.124	0.363
BIR of PCA setting (per 1 mL/h)	0.694	0.346, 1.390	0.303
Bolus volume of PCA setting (1 mL)	0.687	0.539, 0.875	0.002*
Lockout interval of PCA setting (per min)	0.992	0.977, 1.007	0.274
DOSE-FEN-OP (μg)†	0.998	0.998, 0.999	<0.001*
DOSE-FEN-NONOP (μg)†	1.000	1.000, 1.000	0.600

ASA PS, American Society of Anesthesiologists physical status; BIR, background infusion rate; BMI, body mass index; CI, confidence interval; OR, odds ratio; PCA, patient-controlled analgesia. Opioid naïve: patients without history of previous opioid intake. *, statistical significance at $p < 0.05$. †, doses of fentanyl equivalents (μg) converted from opioids (DOSE-FEN-OP) and non-opioid adjuvant analgesics (DOSE-FEN-NONOP) with ratios of oxycodone (μg) to fentanyl (100:1), ratios of sufentanil (μg) to fentanyl (1:10), ratio of ketorolac (mg) to fentanyl (25:100), and ratio of nefopam (mg) to fentanyl (1:20) [25-28].

1.11 Risk Factors of Rescue Antiemetics Requirement According to Logistic Regression Analysis

Upon univariate analysis, the BIR of PCA setting and the fentanyl equivalent doses of analgesics were identified as independent risk factors that could increase or decrease the probability of requiring rescue antiemetics. The probability of requiring rescue antiemetics was lower when the PCA device was set with faster BIR (OR: 0.185, p = 0.001). A 1 μg increase in fentanyl equivalent doses of opioids and non-opioid analgesics could lower the probability of requiring rescue antiemetics by 0.2% (OR: 0.998, p < 0.001) and by 0.1% (OR: 0.999, p = 0.002), respectively (Table 11).

Upon multivariate analysis after adjustment with potential confounding factors, the BIR of PCA setting and the fentanyl equivalent doses of opioids were identified as independent risk factors that could increase or decrease the probability of requiring rescue antiemetics. The probability of requiring rescue antiemetics was lower by 70.6% when the PCA device was set with faster BIR (OR: 0.294, p = 0.034). A 1 μg increase in fentanyl equivalent doses of opioids could also lower the probability of requiring rescue antiemetics by 0.1% (OR: 0.999, p = 0.015) (Table 11).

Table 11. Odds ratios (ORs) obtained from univariate and multivariate binary logistic regression analyses, estimating the association between potential confounding factors and rescue antiemetic requirement (n = 4106).

	Univariate		
Confounding factors	Crude OR	95% CI	p values
Female sex	1.090	0.741, 1.604	0.661
Age (years)			
Age ≤ 20	1 (ref.)		
20 < Age ≤ 40	1.429	0.316, 6.455	0.643
40 < Age ≤ 60	2.025	0.483, 8.487	0.335

60 < Age ≤ 80	1.980	0.475, 8.258	0.348
Age ≥ 80	2.720	0.601, 12.311	0.194
BMI (kg/m^2)			
BMI < 18.5	1 (ref.)		
18.5 ≤ BMI < 23.0	3.361	0.809, 13.971	0.095
23.0 ≤ BMI < 25.0	3.583	0.847, 15.151	0.083
25.0 ≤ BMI < 30.0	2.299	0.541, 9.775	0.259
BMI ≥ 30.0	4.540	0.953, 21.629	0.058
ASA PS	0.000		
Ⅰ	1 (ref.)		
Ⅱ	1.384	0.918, 2.088	0.121
Ⅲ	1.407	0.675, 2.936	0.362
Smoking (Yes)	1.484	0.851, 2.586	0.164
Opioid naïve (Yes)	0.660	0.430, 1.014	0.058
Anesthesia duration (per h)	0.921	0.791, 1.071	0.284
Intraoperative opioid use (Yes)	0.882	0.533, 1.459	0.625
BIR of PCA setting (per 1 mL/h)	0.185	0.065, 0.522	0.001*
Bolus volume of PCA setting (1 mL)	0.943	0.699, 1.272	0.703
Lockout interval of PCA setting (per min)	0.990	0.973, 1.008	0.267
DOSE-FEN-OP (μg)†	0.998	0.997, 0.999	<0.001*
DOSE-FEN-NONOP (μg)†	0.999	0.998, 0.999	0.002*
DOSE-EME (mg)	0.381	0.082, 1.777	0.219

Confounding factors	Multivariate		
	Adjusted OR	95% CI	p value
Female sex	1.109	0.724, 1.699	0.633
Age (years)			
Age ≤ 20	1 (ref.)		
20 < Age ≤ 40	1.188	0.256, 5.515	0.826
40 < Age ≤ 60	1.673	0.382, 7.338	0.495
60 < Age ≤ 80	1.599	0.347, 7.359	0.547
Age ≥ 80	2.079	0.408, 10.594	0.379
BMI (kg/m^2)			
BMI < 18.5	1 (ref.)		
18.5 ≤ BMI < 23.0	3.337	0.793, 14.044	0.100
23.0 ≤ BMI < 25.0	3.389	0.788, 14.566	0.101
25.0 ≤ BMI < 30.0	2.264	0.524, 9.789	0.274
BMI ≥ 30.0	4.385	0.907, 21.186	0.066
ASA PS			
Ⅰ	1 (ref.)		
Ⅱ	1.230	0.737, 2.052	0.429
Ⅲ	1.106	0.479, 2.553	0.813
Smoking (Yes)	1.612	0.874, 2.971	0.126
Opioid naïve (Yes)	0.727	0.468, 1.131	0.157

Anesthesia duration (per h)	0.912	0.770, 1.081	0.287
Intraoperative opioid use (Yes)	0.962	0.559, 1.656	0.889
BIR of PCA setting (per 1 mL/h)	0.294	0.095, 0.910	0.034*
Bolus volume of PCA setting (1 mL)	1.259	0.744, 2.132	0.391
Lockout interval of PCA setting (per min)	0.978	0.948, 1.008	0.150
DOSE-FEN-OP (μg)†	0.999	0.998, 1.000	0.015*
DOSE-FEN-NONOP (μg)†	0.999	0.998, 1.000	0.076
DOSE-EME (mg)	0.787	0.151, 4.096	0.776

ASA PS, American Society of Anesthesiologists physical status; BIR, background infusion rate; BMI, body mass index; CI, confidence interval; OR, odds ratios; PCA, patient-controlled analgesia; Opioid naïve, patients without history of previous opioid intake; DOSE-EME, antiemetics dose; *, statistical significance at $p < 0.05$; †, doses of fentanyl equivalents (μg) converted from opioids (DOSE-FEN-OP) and non-opioid adjuvant analgesics (DOSE-FEN-NONOP) with ratios of oxycodone (μg) to fentanyl (100:1), ratios of sufentanil (μg) to fentanyl (1:10), ratio of ketorolac (mg) to fentanyl (25:100), and ratio of nefopam (mg) to fentanyl (1:20) [25-28].

2. Group Analysis with Grade of PPI

2.1. Characteristics of Patients Who Received Postoperative Intravenous PCA

There were no significant differences in sex, age, height, weight, BMI, ASA PS, and anesthesia duration among the groups. In addition, there were no significant differences in the prevalence of underlying disease, smoking, opioid naïve, and intraoperative opioid use among the groups (Table 12).

Table 12. Characteristics of patients who received intravenous PCA (n = 4106).

	Group L (n = 640)	Group M (n = 2666)	Group H (n = 800)	p value
Female sex	317 (49.5)	1354 (50.8)	412 (51.5)	0.755
Age (years)	58.3 (56.9, 59.7)	57.3 (56.7, 58.0)	57 (55.8, 58.2)	0.367
Height (cm)	163.3 (162.6, 164.1)	163.4 (163, 163.7)	163.1 (162.4, 163.7)	0.748
Weight (kg)	63.5 (62.6, 64.5)	63.9 (63.5, 64.4)	63.9 (63, 64.7)	0.736
BMI (kg/m^2)	23.73 (23.44, 24.01)	23.88 (23.74, 24.02)	23.93 (23.67, 24.18)	0.551
ASA PS (Ⅰ/Ⅱ/Ⅲ)	256 (40) / 334 (52.2) / 50 (7.8)	1206 (45.2) / 1266 (47.5) / 194 (7.3)	364 (45.5) / 378 (47.3) / 58 (7.2)	0.186
Underlying disease (Yes)	324 (50.6)	1311 (49.2)	416 (52)	0.350
Smoking (Yes)	64 (10)	270 (10.1)	81 (10.1)	0.995
Opioid naïve (Yes)	500 (78.1)	2098 (78.7)	651 (81.4)	0.208
Anesthesia duration (h)	2.32 (2.19, 2.45)	2.20 (2.15, 2.26)	2.19 (2.09, 2.28)	0.137
Intraoperative opioid (Yes)	522 (81.6)	2243 (84.1)	676 (84.5)	0.238

The values are expressed as means (95% confidence intervals), or numbers (percentage) of patients. ASA PS, American Society of Anesthesiologists physical status; BMI, body mass index; PCA, patient-controlled analgesia. Opioid naïve: patients without history of previous opioid intake. Group L, NRS > 4 at the 6th postoperative hour; Group M, 4 ≤ NRS < 7 at the 6th postoperative hour; Group H, NRS ≥ 7 at the 6th postoperative hour [24].

2.2. Drugs Consisting of Intravenous PCA

There were no significant differences in opioid, adjuvant analgesic, and adjuvant antiemetics included in PCA regimens among the groups (Table 13).

Table 13. Drugs for intravenous PCA (n = 4106).

	Group L (n = 640)	Group M (n = 2666)	Group H (n = 800)	p value
Opioids				
Fentanyl	627 (98)	2600 (97.5)	774 (96.8)	0.665
Oxycodone	10 (1.6)	49 (1.8)	19 (2.4)	
Sufentanil	3 (0.5)	17 (0.6)	7 (0.9)	
Adjuvant analgesics (Yes)	615 (96.1)	2596 (97.4)	768 (96)	0.081
Adjuvant antiemetics (Yes)	615 (96.1)	2596 (97.4)	768 (96)	0.062

The values are expressed as numbers (percentage) of patients. PCA, patient-controlled analgesia. Group L, NRS > 4 at the 6th postoperative hour; Group M, 4 ≤ NRS < 7 at the 6th postoperative hour; Group H, NRS ≥ 7 at the 6th postoperative hour [24].

2.3. Setting and Drug Doses of Intravenous PCA

Among the PCA settings, there were significant differences in bolus volume and lockout interval among the three groups (p = 0.001 and p = 0.001, respectively) (Table 14). Bolus volume and lockout interval of group M were higher than that of group L (p = 0.002 and p = 0.002), but there were no significant differences between groups M and H.

There was a significant difference in DOSE-EME among the three groups (p < 0.001), while there were no significant differences in DOSE-FEN-OP,

DOSE-FEN-NONOP, and DOSE-FEN-TOTAL (Table 14). DOSE-EME of group M was also higher than that of groups L and H (p = 0.002 and p =0.002, respectively).

Table 14. Setting and drug doses of intravenous PCA (n = 4106).

	Group L (n = 640)	Group M (n = 2666)	Group H (n = 800)	p value
Settings				
BIR (mL/h)	1.99 (1.98, 2.00)	1.99 (1.98, 1.99)	1.99 (1.99, 2.00)	0.409
Bolus volume (mL/bolus)	1.61 (1.55, 1.66)	1.71† (1.68, 1.73)	1.67 (1.62, 1.71)	0.001*
Lockout interval (min)	22.82 (21.93, 23.71)	24.45† (24.08, 24.83)	23.83 (23.08, 24.58)	0.001*
Doses				
DOSE-FEN-TOTAL (μg) §	1595.20 (1556.76, 1633.65)	1579.67 (1567.85, 1591.50)	1590.19 (1568.07, 1612.30)	0.514
DOSE-FEN-OP (μg) §	890.98 (873.49, 908.48)	890.10 (881.93, 898.28)	898.69 (883.49, 913.88)	0.615
DOSE-FEN-NONOP (μg) §	704.22 (672.32, 736.12)	689.57 (683.07, 696.07)	691.50 (678.73, 704.27)	0.343
DOSE-EME (mg)	1.18 (1.18, 1.19)	1.18 † (1.18, 1.18)	1.17 ‡ (1.16, 1.170)	<0.001*

The values are expressed as means (95% confidence intervals). BIR, background infusion rate; DOSE-EME, dose of antiemetics; PCA, patient-controlled analgesia. *, statistical significance at $p < 0.05$ in one-way ANOVA. †, $p < 0.05$ compared with group L. ‡, $p < 0.05$ compared with group M. §, doses of fentanyl equivalents (μg) converted from opioids (DOSE-FEN-OP), non-opioid adjuvant analgesics

(DOSE-FEN-NONOP), and total analgesics (DOSE-FEN-TOTAL) with ratios of oxycodone (μg) to fentanyl (100:1), ratios of sufentanil (μg) to fentanyl (1:10), ratio of ketorolac (mg) to fentanyl (25:100), and ratio of nefopam (mg) to fentanyl (1:20) [25-28]. Group L, NRS > 4 at the 6th postoperative hour; Group M, 4 ≤ NRS < 7 at the 6th postoperative hour; Group H, NRS ≥ 7 at the 6th postoperative hours [24].

2.4. Postoperative Numeric Rating Scale (NRS)

Significant differences in NRS among the three groups were shown in repeated measures ANOVA ($p < 0.001$). The NRS at every time interval were significantly different among the three groups ($p < 0.001$, Table 15). At the 6th postoperative hour, the NRS of group H was significantly higher than that of groups L and M ($p < 0.001$ and $p < 0.001$, respectively), and the NRS of group M was higher than that of group L ($p < 0.001$). At the 12th postoperative hour, the NRS of group H was significantly higher than that of groups L and M ($p < 0.001$ and $p < 0.001$, respectively), and the NRS of group M was higher than that of group L ($p < 0.001$). At the 24th postoperative hour, the NRS of group H was significantly higher than that of groups L and M ($p < 0.001$ and $p < 0.001$, respectively), and the NRS of group M was higher than that of group L ($p < 0.001$). At the 48th postoperative hour, the NRS of group H was significantly higher than that of groups L and M ($p < 0.001$ and $p < 0.001$, respectively), while there was no significant difference between the NRS of groups M and L.

Table 15. Postoperative numeric rating scale (0: lowest, 10: worst) (n = 4106).

	Group L (n = 640)	Group M (n = 2666)	Group H (n = 800)	p value
6th postoperative hour	1.25 (1.16, 1.33)	5.19 † (5.16, 5.22)	7.27 †,‡ (7.23, 7.31)	<0.001*

12th postoperative hour	1.21 (1.08, 1.34)	1.8 † (1.74, 1.86)	2.65 †,‡ (2.52, 2.77)	<0.001*
24th postoperative hour	1.3 (1.17, 1.44)	1.96 † (1.89, 2.04)	2.68 †,‡ (2.53, 2.82)	<0.001*
48th postoperative hour	1.13 (1.00, 1.27)	1.27 (1.20, 1.33)	1.76 †,‡ (1.62, 1.89)	<0.001*

The values are expressed as means (95% confidence intervals). *, statistical significance at $p < 0.05$ in one-way ANOVA. †, $p < 0.05$ compared with group L. ‡, $p < 0.05$ compared with group M. Group L, NRS > 4 at the 6th postoperative hour; Group M, 4 ≤ NRS < 7 at the 6th postoperative hour; Group H, NRS ≥ 7 at the 6th postoperative hour [24].

2.5. Requirement for Rescue Analgesics and Antiemetics during Intravenous PCA

The requirement for rescue analgesics was significantly different among the three groups ($p < 0.001$, Table 16), and it was highest in group H (26.6%), followed by group M (20%) and group L (16.6%, Table 16). On the other hand, rescue antiemetics requirement was not significantly different among the three groups.

Table 16. Requirement for rescue analgesics and antiemetics during intravenous PCA (n = 4106).

	Group L (n = 640)	Group M (n = 2666)	Group H (n = 800)	p value
Rescue analgesic requirement (Yes)	106 (16.6)	533 (20)	213 (26.6)	<0.001*
Rescue antiemetic requirement (Yes)	16 (2.5)	67 (2.5)	23 (2.9)	0.843

The values are expressed as numbers (percentage) of patients. PCA, patient-controlled analgesia. *, statistical significance at $p < 0.05$. Group L, NRS > 4 at the 6th postoperative hour; Group M, 4 ≤ NRS < 7 at the 6th postoperative hour; Group H, NRS ≥ 7 at the 6th postoperative hour [24].

2.6. Background Infusion Rate of Opioids, Non-Opioid Analgesics, and Antiemetics for PCA

There were no significant differences in BIR-FEN-OP, BIR-FEN-TOTAL, and BIR-EME among groups. BIR-FEN-NONOP was significantly different among groups (p = 0.014) and was lower in group H than group L (p = 0.020, Table 17).

In patients with low PPI, BIR-FEN-OP, BIR-FEN-NONOP, and BIR-FEN-TOTAL had wide ranges: between 6.0 μg/h and 41.4 μg/h, between 0.0 μg/h and 120 μg/h, and between 8.0 μg/h and 140 μg/h, respectively. BIR-EME showed a wide range between 0.0 μg/h and 24.0 μg/h.

In patients with moderate PPI, BIR-FEN-OP, BIR-FEN-NONOP, and BIR-FEN-TOTAL had wide ranges: between 4.0 μg/h and 44.0 μg/h, between 0.0 μg/h and 24 μg/h, and between 6.0 μg/h and 60.0 μg/h, respectively. BIR-EME showed a wide range between 0.0 and 36.0 μg/h.

In patients with high PPI, BIR-FEN-OP, BIR-FEN-NONOP, and BIR-FEN-TOTAL had wide ranges between 5.0 μg/h and 43.0 μg/h, between 0.0 μg/h and 20 μg/h, and between 8.0 μg/h and 59.0 μg/h, respectively. BIR-EME showed a wide range between 12.0 μg/h and 24.0 μg/h.

Table 17. Background infusion rates of total analgesics (opioids and adjuvant analgesics) and adjuvant antiemetics for PCA (n = 4106).

	Group L (n = 640)	Group M (n = 2666)	Group H (n = 800)	p value
BIR-FEN-TOTAL (μg/h)‡	17.75 (17.40, 18.11)	17.72 (17.55, 17.89)	17.93 (17.62, 18.24)	0.505
BIR-FEN-OP (μg/h)‡	14.03 (13.38, 14.67)	13.73 (13.59, 13.86)	13.79 (13.53, 14.04)	0.337

BIR-FEN-NONOP (μg/h)‡	23.57 (23.40, 23.74)	23.45 (23.37, 23.53)	23.24† (23.08, 23.41)	0.014*
BIR-EME (μg/h)	31.78 (31.00, 32.56)	31.45 (31.20, 31.69)	31.71 (31.26, 32.17)	0.439

The values are expressed as means (95% confidence intervals). BIR, background infusion rate; BIR-EME, BIR for adjuvant antiemetics; PCA, patient-controlled analgesia. *, statistical significance at $p < 0.05$ in one-way ANOVA. †, $p < 0.05$ compared with group L. ‡, BIRs recalculated with doses of fentanyl equivalents (μg) converted from opioids (BIR-FEN-OP), non-opioid adjuvant analgesics (BIR-FEN-NONOP), and total analgesics (BIR-FEN-TOTAL) with ratios of oxycodone (μg) to fentanyl (100:1), ratios of sufentanil (μg) to fentanyl (1:10), ratio of ketorolac (mg) to fentanyl (25:100), and ratio of nefopam (mg) to fentanyl (1:20) [25-28].

2.7. Cutoff Values of Potential Variables for Requiring Rescue Analgesics

2.7.1. Cutoff Values of Potential Variables for Requiring Rescue Analgesics in Patients with Low PPI Grade

The cutoff values for BIR, bolus volume, and lockout interval were 1.75 mL/h (AUC: 0.515), 0.5 mL (AUC: 0.610), and 12.5 min (AUC: 0.619), respectively (Table 18). The cutoff values for DOSE-FEN-OP, DOSE-FEN-NONOP, and DOSE-FEN-TOTAL were 950 μg (AUC: 0.559), 250 μg (AUC: 0.501), and 1750 μg (AUC: 0.541), respectively (Table 18). For BIR-FEN-OP, BIR-FEN-NONOP, BIR-EME, and BIR-FEN-TOTAL, the cutoff values were 19 μg/h (AUC: 0.567), 7 μg/h (AUC: 0.509), 15 μg/h (AUC: 0.510), and 35 μg/h (AUC: 0.548), respectively (Table 18).

The cutoff values for PCA settings (bolus volume and lockout time),

DOSE-FEN-OP, and BIR-FEN-OP showed statistical significance (Table 18).

Table 18. Cutoff values of potential variables for requiring rescue analgesics in patients with low PPI (n = 640).

Potential Variables	Cutoff value	AUC	Sens. (%)	Spec. (%)	Youden index	95% CI	p value
PCA setting							
BIR (1 mL/h)	1.75	0.515	99.8	3.8	0.036	0.454, 0.577	0.627
Bolus volume (1 mL)	0.5	0.610	90.8	33.0	0.238	0.546, 0.674	0.001*
Lockout interval (min)	12.5	0.619	87.6	36.8	0.244	0.555, 0.682	<0.001*
Dose (μg)							
DOSE-FEN-OP†	950	0.559	48.7	69.8	0.185	0.505, 0.612	0.032*
DOSE-FEN-NONOP†	250	0.501	96.1	4.7	0.008	0.442, 0.561	0.971
DOSE-FEN-TOTAL†	1750	0.541	35.6	78.3	0.139	0.486, 0.597	0.143
BIR (μg/h)							
BIR-FEN-OP†	19	0.567	48.7	69.8	0.185	0.513, 0.622	0.015*
BIR-FEN-NONOP†	7	0.509	95.7	8.5	0.042	0.448, 0.569	0.783
BIR-EME	15	0.510	99.6	4.7	0.043	0.449, 0.571	0.756
BIR-FEN-TOTAL†	35	0.548	35.6	78.3	0.139	0.492, 0.605	0.095

AUC, area under the curve; BIR, background infusion rate; BIR-EME, BIR for adjuvant antiemetics; CI, confidence interval. Sens., Sensitivity; Spec., Specificity. *, statistical significance at $p < 0.05$. †, Potential Variables (Doses and BIRs) were doses of fentanyl equivalents (μg) converted from opioids (DOSE-FEN-OP),

non-opioid adjuvant analgesics (DOSE-FEN-NONOP), and total analgesics (DOSE-FEN-TOTAL) with ratios of oxycodone (μg) to fentanyl (100:1), ratios of sufentanil (μg) to fentanyl (1:10), ratio of ketorolac (mg) to fentanyl (25:100), and ratio of nefopam (mg) to fentanyl (1:20), and BIRs recalculated with these converted doses (BIR-FEN-OP, BIR-FEN-NONOP, and BIR-FEN-TOTAL) [25-28].

2.7.2. Cutoff Values of Potential Variables for Requiring Rescue Analgesics in Patients with Moderate PPI Grade

The cutoff values for BIR, bolus volume, and lockout interval were 1.75 mL/h (AUC: 0.504), 0.5 mL (AUC: 0.524), and 5 min (AUC: 0.512), respectively. The cutoff values for DOSE-FEN-OP, DOSE-FEN-NONOP, and DOSE-FEN-TOTAL were 950 μg (AUC: 0.612), 550 μg (AUC: 0.500), and 1750 μg (AUC: 0.583), respectively. For BIR-FEN-OP, BIR-FEN-NONOP, BIR-EME, and BIR-FEN-TOTAL, the cutoff values were 19 μg/h (AUC: 0.610), 11 μg/h (AUC: 0.500), 21 μg/h (AUC: 0.504), and 35 μg/h (AUC: 0.581), respectively (Table 19).

The cutoff values for PCA settings (bolus volume and lockout time) were not statistically significant, while those of DOSE-FEN-OP, DOSE-FEN-TOTAL, BIR-FEN-OP, and BIR-FEN-TOTAL were statistically significant.

Table 19. Cutoff values of potential variables for requiring rescue analgesics in patients with moderate PPI (n = 2666).

Potential Variables	Cutoff value	AUC	Sens. (%)	Spec. (%)	Youden index	95% CI	p value
PCA setting							
BIR (1 mL/h)	1.75	0.504	98.7	2.3	0.010	0.476, 0.531	0.790
Bolus volume (1 mL)	0.5	0.524	95.1	17.3	0.124	0.495, 0.552	0.104
Lockout interval	5	0.512	92.1	18.4	0.105	0.483,	0.414

(min)						0.540	
Dose (μg)							
DOSE-FEN-OP†	950	0.612	49.1	70.5	0.196	0.587, 0.638	<0.001*
DOSE-FEN-NONOP†	550	0.500	90.0	12.8	0.028	0.472, 0.528	0.986
DOSE-FEN-TOTAL†	1750	0.583	35.2	77.3	0.125	0.557, 0.610	<0.001*
BIR (μg/h)							
BIR-FEN-OP†	19	0.610	48.9	70.4	0.193	0.584, 0.635	<0.001*
BIR-FEN-NONOP†	11	0.500	89.2	13.9	0.031	0.473, 0.528	0.979
BIR-EME	21	0.504	92.7	8.3	0.010	0.477, 0.532	0.762
BIR-FEN-TOTAL†	35	0.581	35.1	77.1	0.122	0.555, 0.608	<0.001*

AUC, area under the curve; BIR, background infusion rate; BIR-EME, BIR for adjuvant antiemetics; CI, confidence interval. Sens., Sensitivity; Spec., Specificity. *, statistical significance at $p < 0.05$. †, Potential Variables (Doses and BIRs) were doses of fentanyl equivalents (μg) converted from opioids (DOSE-FEN-OP), non-opioid adjuvant analgesics (DOSE-FEN-NONOP), and total analgesics (DOSE-FEN-TOTAL) with ratios of oxycodone (μg) to fentanyl (100:1), ratios of sufentanil (μg) to fentanyl (1:10), ratio of ketorolac (mg) to fentanyl (25:100), and ratio of nefopam (mg) to fentanyl (1:20), and BIRs recalculated with these converted doses (BIR-FEN-OP, BIR-FEN-NONOP, and BIR-FEN-TOTAL) [25-28].

2.7.3. Cutoff Values of Potential Variables for Requiring Rescue Analgesics in Patients with High PPI Grade

The cutoff values for PCA settings (BIR, bolus volume, and lockout interval) were 1.75 mL/h or lower (AUC: 0.508), 0.5 mL (AUC: 0.573), and 5 min (AUC: 0.605), respectively. DOSE-FEN-OP, DOSE-FEN-NONOP, and

DOSE-FEN-TOTAL were 950 μg (AUC: 0.660), 700 μg (AUC: 0.540), and 1550 μg (AUC: 0.656), respectively. For BIR-FEN-OP, BIR-FEN-NONOP, BIR-EME, and BIR-FEN-TOTAL, the cutoff values were 19 μg/h (AUC: 0.662), 14 μg/h (AUC: 0.546), 21 μg/h (AUC: 0.545), and 35 μg/h (AUC: 0.658), respectively (Table 20).

The cutoff values for PCA settings (bolus volume and lockout time), DOSE-FEN-OP, DOSE-FEN-TOTAL, BIR-FEN-OP, and BIR-FEN-TOTAL showed statistical significance.

Table 20. Cutoff values of potential variables for requiring rescue analgesics in patients with high PPI grade (n = 800).

Potential Variables	Cutoff value	AUC	Sens. (%)	Spec. (%)	Youden index	95% CI	p value
PCA setting							
BIR (1 mL/h)	1.75	0.508	99.7	1.9	0.016	0.462, 0.553	0.741
Bolus volume (1 mL)	0.5	0.573	93.9	24.4	0.183	0.526, 0.620	0.002*
Lockout interval (min)	5	0.605	91.1	32.4	0.235	0.558, 0.652	<0.001*
Dose (μg)							
DOSE-FEN-OP†	950	0.660	54.2	74.6	0.288	0.617, 0.703	<0.001*
DOSE-FEN-NONOP†	700	0.540	64.4	41.8	0.062	0.494, 0.586	0.088
DOSE-FEN-TOTAL†	1550	0.656	70.9	58.7	0.296	0.612, 0.699	<0.001*
BIR (μg/h)							
BIR-FEN-OP†	19	0.662	54.0	74.6	0.286	0.619, 0.704	<0.001*
BIR-FEN-NONOP†	14	0.546	64.2	42.7	0.069	0.500, 0.592	0.050
BIR-EME	21	0.54	92.0	16.9	0.089	0.499,	0.057

BIR-FEN-TOTAL†	31	5 0.658	70.7	59.2	0.299	0.592 0.615, 0.701	<0.001*

AUC, area under the curve; BIR, background infusion rate; BIR-EME, BIR for adjuvant antiemetics; CI, confidence interval. Sens., Sensitivity; Spec., Specificity. *, statistical significance at $p < 0.05$. †, Potential Variables (Doses and BIRs) were doses of fentanyl equivalents (μg) converted from opioids (DOSE-FEN-OP), non-opioid adjuvant analgesics (DOSE-FEN-NONOP), and total analgesics (DOSE-FEN-TOTAL) with ratios of oxycodone (μg) to fentanyl (100:1), ratios of sufentanil (μg) to fentanyl (1:10), ratio of ketorolac (mg) to fentanyl (25:100), and ratio of nefopam (mg) to fentanyl (1:20), and BIRs recalculated with these converted doses (BIR-FEN-OP, BIR-FEN-NONOP, and BIR-FEN-TOTAL) [25-28].

2.8. Cutoff Values of Potential Variables for Requiring Rescue Antiemetics

2.8.1. Cutoff Values of Potential Variables for Requiring Rescue Antiemetics in Patients with Low PPI Grade

The cutoff values for BIR, bolus volume, and lockout interval were 3 mL/h (AUC: 0.494), 1.25 mL (AUC: 0.576), and 17.5 min (AUC: 0.583), respectively. The cutoff values for DOSE-FEN-OP, DOSE-FEN-NONOP, and DOSE-FEN-TOTAL were 950 μg (AUC: 0.615), 50 μg (AUC: 0.470), and 1350 μg (AUC: 0.543) respectively. The cutoff values for BIR-FEN-OP, BIR-FEN-NONOP, BIR-EME, and BIR-FEN-TOTAL were 19 μg/h (AUC: 0.613), 1 μg/h (AUC: 0.468), 25 μg/h (AUC: 0.474), and 27 μg/h (AUC: 0.541), respectively (Table 21).

The cutoff values for all potential variables were not statistically significant.

Table 21. Cutoff values of potential variables for requiring rescue antiemetics in patients with low PPI (n = 640).

Potential Variables	Cutoff value	AUC	Sens. (%)	Spec. (%)	Youden index	95% CI	p value
PCA setting							
BIR (1 mL/h)	3	0.494	0.0	100.0	0.000	0.352, 0.635	0.929
Bolus volume (1 mL)	1.25	0.576	75.5	43.7	0.192	0.433, 0.720	0.297
Lockout interval (min)	17.5	0.583	69.6	50.0	0.196	0.443, 0.723	0.246
Dose (μg)							
DOSE-FEN-OP†	950	0.615	46.2	75.0	0.212	0.487, 0.744	0.079
DOSE-FEN-NONOP†	50	0.470	96.2	6.2	0.024	0.328, 0.612	0.679
DOSE-FEN-TOTAL†	1350	0.543	79.5	31.2	0.107	0.400, 0.686	0.554
BIR (μg/h)							
BIR-FEN-OP†	19	0.613	46.2	75.0	0.212	0.485, 0.740	0.083
BIR-FEN-NONOP†	1	0.468	96.2	6.2	0.024	0.327, 0.610	0.661
BIR-EME	25	0.474	0.00	100.0	0.000	0.337, 0.610	0.704
BIR-FEN-TOTAL†	27	0.541	79.2	31.2	0.104	0.400, 0.683	0.567

AUC, area under the curve; BIR, background infusion rate; BIR-EME, BIR for adjuvant antiemetics; CI, confidence interval. Sens., Sensitivity; Spec., Specificity. *, statistical significance at $p < 0.05$. †, Potential Variables (Doses and BIRs) were doses of fentanyl equivalents (μg) converted from opioids (DOSE-FEN-OP), non-opioid adjuvant analgesics (DOSE-FEN-NONOP), and total analgesics (DOSE-FEN-TOTAL) with ratios of oxycodone (μg) to fentanyl (100:1), ratios of sufentanil (μg) to fentanyl (1:10), ratio of ketorolac (mg) to fentanyl (25:100), and ratio of nefopam (mg) to fentanyl (1:20), and BIRs recalculated with these converted doses (BIR-FEN-OP, BIR-FEN-NONOP, and BIR-FEN-TOTAL) [25-28].

2.8.2. Cutoff Values of Potential Variables for Requiring Rescue Antiemetics in Patients with Moderate PPI Grade

The cutoff values for BIR, bolus volume, and lockout interval were 1.75 mL/h (AUC: 0.523), 1.75 mL (AUC: 0.519), and 25 min (AUC: 0.525), respectively. The cutoff values for DOSE-FEN-OP, DOSE-FEN-NONOP, and DOSE-FEN-TOTAL were 950 μg (AUC: 0.627), 450 μg (AUC: 0.548), and 1550 μg (AUC: 0.619), respectively. For BIR-FEN-OP, BIR-FEN-NONOP, BIR-EME, and BIR-FEN-TOTAL, the cutoff values were 19 μg/h (AUC: 0.634), 8.5 μg/h (AUC: 0.557), 21 μg/h (AUC: 0.532), and 31 μg/h (AUC: 0.626), respectively (Table 22).

The cutoff values for PCA settings (bolus volume and lockout time) were not statistically significant, while those of DOSE-FEN-OP, DOSE-FEN-TOTAL, BIR-FEN-OP, and BIR-FEN-TOTAL were statistically significant.

Table 22. Cutoff values of potential variables for requiring rescue antiemetics in patients with moderate PPI (n = 2666).

Potential Variables	Cutoff value	AUC	Sens. (%)	Spec. (%)	Youden index	95% CI	p value
PCA setting							
BIR (1 mL/h)	1.75	0.523	98.6	6.0	0.046	0.450, 0.596	0.534
Bolus volume (1 mL)	1.75	0.519	77.1	28.4	0.055	0.45, 0.588	0.592
Lockout interval (min)	25	0.525	73.5	32.8	0.063	0.455, 0.595	0.482
Dose (μg)							
DOSE-FEN-OP †	950	0.627	45.8	77.6	0.234	0.564, 0.690	<0.001*
DOSE-FEN-NONOP†	450	0.548	89.8	20.9	0.107	0.473, 0.623	0.209

DOSE-FEN-TOTAL†	1550	0.619	62.3	55.2	0.175	0.552, 0.687	0.001*
BIR (μg/h)							
BIR-FEN-OP†	19	0.634	45.6	77.6	0.232	0.570, 0.698	<0.001*
BIR-FEN-NONOP†	8.5	0.557	89.1	23.9	0.130	0.481, 0.633	0.139
BIR-EME	21	0.532	92.7	13.4	0.061	0.458, 0.605	0.398
BIR-FEN-TOTAL†	31	0.626	62.1	56.7	0.188	0.558, 0.693	<0.001*

AUC, area under the curve; BIR, background infusion rate; BIR-EME, BIR for adjuvant antiemetics; CI, confidence interval. Sens., Sensitivity; Spec., Specificity. *, statistical significance at $p < 0.05$. †, Potential Variables (Doses and BIRs) were doses of fentanyl equivalents (μg) converted from opioids (DOSE-FEN-OP), non-opioid adjuvant analgesics (DOSE-FEN-NONOP), and total analgesics (DOSE-FEN-TOTAL) with ratios of oxycodone (μg) to fentanyl (100:1), ratios of sufentanil (μg) to fentanyl (1:10), ratio of ketorolac (mg) to fentanyl (25:100), and ratio of nefopam (mg) to fentanyl (1:20), and BIRs recalculated with these converted doses (BIR-FEN-OP, BIR-FEN-NONOP, and BIR-FEN-TOTAL) [25-28].

2.8.3. Cutoff Values of Potential Variables for Requiring Rescue Antiemetics in Patients with High PPI Grade

The cutoff values for BIR, bolus volume, and lockout interval were 1.75 mL/h (AUC: 0.541), 0.5 mL (AUC: 0.491), and 12.5 min (AUC: 0.522), respectively. The cutoff values for DOSE-FEN-OP, DOSE-FEN-NONOP, and DOSE-FEN-TOTAL were 850 μg (AUC: 0.614), 700 μg (AUC: 0.629), and 1450 μg (AUC: 0.670), respectively. For BIR-FEN-OP, BIR-FEN-NONOP, BIR-EME, and BIR-FEN-TOTAL, the cutoff values were 17 μg/h (AUC: 0.641), 14 μg/h (AUC: 0.660), 21 μg/h (AUC: 0.539), and 29 μg/h (AUC: 0.700), respectively

(Table 23).

The cutoff values for PCA settings (bolus volume and lockout time) were not statistically significant, while those of DOSE-FEN-NONOP, DOSE-FEN-TOTAL, BIR-FEN-OP, BIR-FEN-NONOP and BIR-FEN-TOTAL were statistically significant.

Table 23. Cutoff values of potential variables for requiring rescue antiemetics in patients with high PPI grade (n = 800).

Potential Variables	Cutoff value	AUC	Sens. (%)	Spec. (%)	Youden index	95% CI	p value
PCA setting							
BIR (1 mL/h)	1.75	0.541	99.5	8.7	0.082	0.413, 0.668	0.530
Bolus volume (1 mL)	0.5	0.491	89.1	13.0	0.021	0.373, 0.610	0.886
Lockout interval (min)	12.5	0.522	85.1	21.7	0.068	0.399, 0.646	0.721
Dose (μg)							
DOSE-FEN-OP†	850	0.614	61.4	60.9	0.223	0.481, 0.746	0.093
DOSE-FEN-NONOP†	700	0.629	63.4	60.9	0.243	0.510, 0.748	0.033*
DOSE-FEN-TOTAL†	1450	0.670	74.8	60.9	0.357	0.541, 0.798	0.010*
BIR (μg/h)							
BIR-FEN-OP†	17	0.641	61.3	65.2	0.265	0.507, 0.774	0.039*
BIR-FEN-NONOP†	14	0.660	63.2	65.2	0.284	0.541, 0.778	0.008*
BIR-EME	21	0.539	89.8	17.4	0.072	0.412, 0.665	0.549
BIR-FEN-TOTAL†	29	0.700	74.5	65.2	0.397	0.575, 0.826	0.002*

AUC, area under the curve; BIR, background infusion rate; BIR-EM, BIR for

adjuvant antiemetics; CI, confidence interval. Sens., Sensitivity; Spec., Specificity. *, statistical significance at $p < 0.05$. †, Potential Variables (Doses and BIRs) were doses of fentanyl equivalents (μg) converted from opioids (DOSE-FEN-OP), non-opioid adjuvant analgesics (DOSE-FEN-NONOP), and total analgesics (DOSE-FEN-TOTAL) with ratios of oxycodone (μg) to fentanyl (100:1), ratios of sufentanil (μg) to fentanyl (1:10), ratio of ketorolac (mg) to fentanyl (25:100), and ratio of nefopam (mg) to fentanyl (1:20), and BIRs recalculated with these converted doses (BIR-FEN-OP, BIR-FEN-NONOP, and BIR-FEN-TOTAL) [25-28].

2.8.4. Summary of Cutoff Values on Requirement of Rescue Analgesics and Antiemetics According to Postoperative Pain Intensities

For patients low expected PPI, this study showed cutoff values for background infusion rate of 1.75−3 mL/h, bolus volume of 0.5−1.25 mL, and lockout interval of <12.5 min for effective analgesia without side effects (Fig. 2). For patients with moderate expected PPI, this study showed cutoff values for background infusion rate of 1.75 mL/h, bolus volume of 0.5−1.75 mL, and lockout interval of <5 min for effective analgesia without side effects (Fig. 2). For patients with high expected PPI, this study showed cutoff values for background infusion rate of 1.75 mL/h, bolus volume of 0.5 mL, and lockout interval of <5 min for effective analgesia without side effects (Fig. 2).

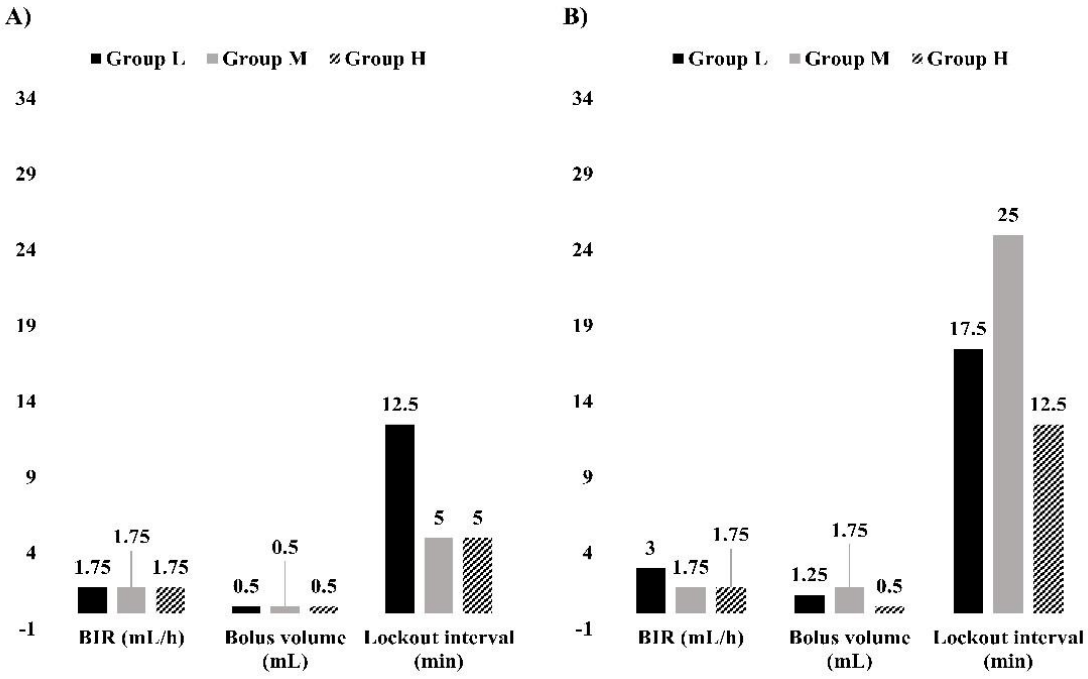

Fig. 2. Cutoff values of PCA settings for the reduction of rescue analgesic requirement (A) and rescue antiemetics (B) according to PPI. Group L: NRS > 4 at the 6th postoperative hour, n = 640; Group M: 4 ≤ NRS < 7 at the 6th postoperative hour, n = 2666; Group H: NRS ≥ 7 at the 6th postoperative hour, n = 800 [24].

For the reduction of the demand for rescue analgesics, cutoff values of opioid dose were >950 μg (19 μg/h) of fentanyl equivalent regardless of PPI (Fig. 3). However, cutoff values of non-opioid dose were increased and were >250 μg (7 μg/h), >550 μg (11 μg/h), >700 μg (14 μg/h) of fentanyl equivalent for patients with low, moderate, and high expected PPI, respectively (Fig. 3). However, for the reduction of the demand for rescue antiemetics, cutoff values of opioid dose were >950 μg (19 μg/h) of fentanyl equivalent in patients with low and moderate expected PPI and >850 μg (17 μg/h) in patients with high expected PPI (Fig. 3). However, cutoff values of non-opioid dose were increased and were >50 μg (1 μg/h), >450 μg (8.5 μg/h), and >700 μg (14 μg/h) of fentanyl equivalent for patients with low, moderate, and high expected PPI, respectively (Fig. 3), which

were less than those for the reduction of the demand for rescue analgesics.

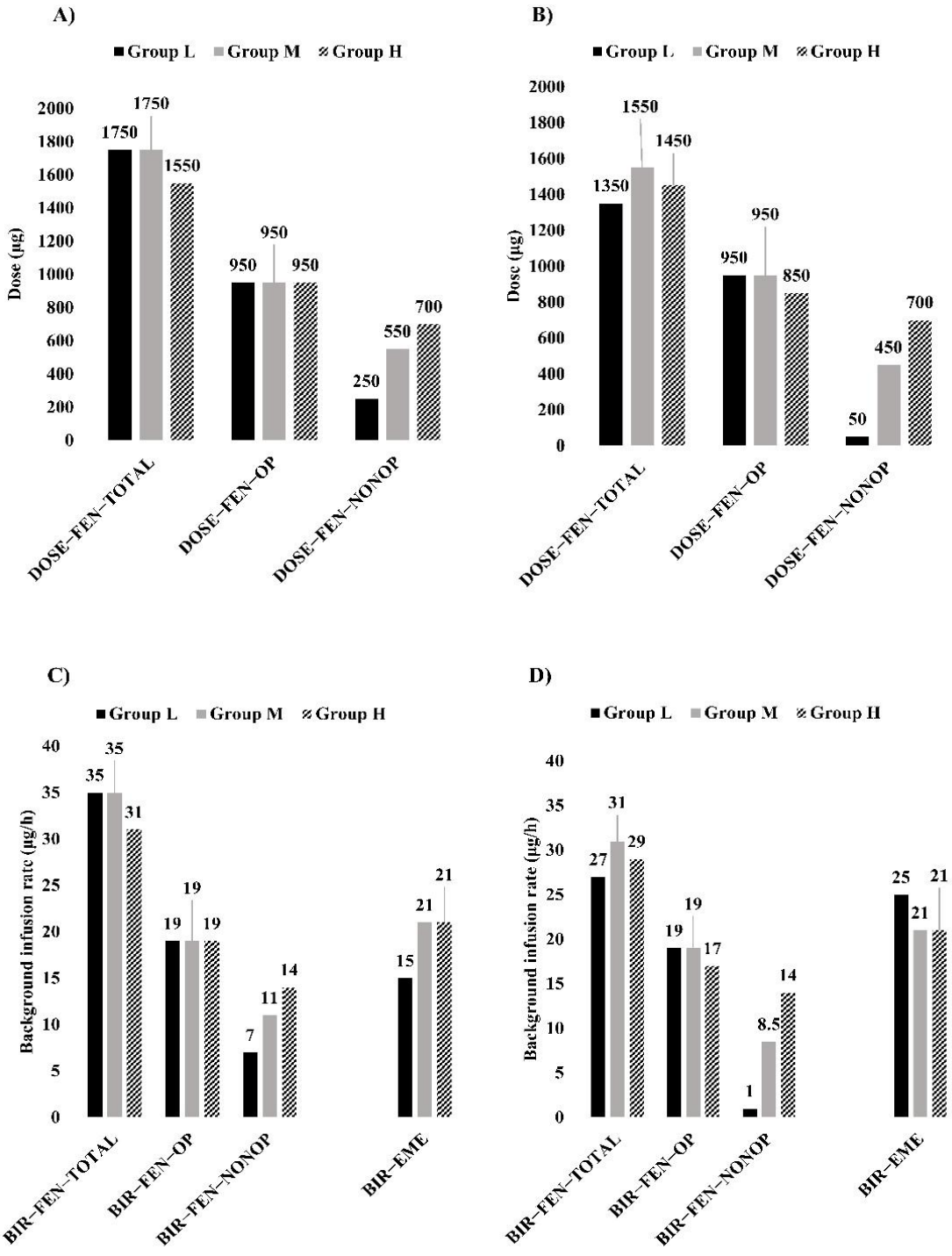

Fig. 3. Cutoff values of doses (A and B) and BIR (C and D) for the reduction of the requirement for rescue analgesic (A and C) and rescue antiemetics (B and

D) according to PPI. BIR, background infusion rate. Group L: NRS > 4 at the 6th postoperative hour, n = 640; Group M, 4 ≤ NRS < 7 at the 6th postoperative hour, n = 2666; Group H: NRS ≥ 7 at the 6th postoperative hour, n = 800 [24].

2.9. Risk Factors of Rescue Analgesics and Rescue Antiemetics Requirement According to PPI

2.9.1. Risk Factors of Rescue Analgesics Requirement

Upon multivariate analysis after adjustment with potential confounding factors, the independent risk factors, which could increase or decrease the probability of requiring rescue analgesics, included ASA PS and BIR of PCA setting in patients with low PPI grade (Table 24). ASA PS Ⅱ was a risk factor that could decrease the probability of requiring rescue analgesics by 56.1%, compared with ASA PS Ⅰ (OR: 0.439, p = 0.007). A BIR that is faster by 1 mL/h could lower the probability of requiring rescue analgesics by 83.7% (OR: 0.143, p = 0.047).

In patients with moderate PPI grade, the risk factors were female sex, anesthesia duration, bolus volume of PCA setting, and fentanyl equivalents dose of opioids. Female sex was a risk factor that could increase the probability of requiring rescue analgesics by 66.6%, compared with male sex (OR: 1.666, p < 0.001). An anesthesia duration that was longer by 1 h could lower the probability of requiring rescue analgesics by 10.2% (OR: 0.898, p = 0.014). The probability of requiring rescue analgesics was also lower when the PCA device was set with larger bolus volume (OR: 0.467, p < 0.001). A 1 μg increase in fentanyl equivalent dose of opioids could lower the probability of requiring rescue analgesics by 0.2% (OR: 0.998, p < 0.001). However, the probability of requiring rescue analgesics with increasing fentanyl equivalent dose of opioids is very small (OR: 0.998); thus, it is greatly influenced by the adjustment of bolus

volume (OR: 0.469).

In patients with high PPI grade, the risk factors were smoking history, lockout interval of PCA setting, and dose of opioid. Smoking history was a risk factor that could increase the probability of requiring rescue analgesics by 51.2%, compared with the absence of smoking history (OR: 0.488). The probability of requiring rescue analgesics was lower when the PCA device was set with longer lockout interval (OR: 0.941, $p < 0.001$). Furthermore, a higher analgesic dose could lower the probability of requiring rescue analgesics by 0.2% (OR: 0.998, $p < 0.001$). However, the difference in rescue analgesics requirements with increasing dose of opioid is very small (OR: 0.998).

Table 24. Odds ratios (ORs) obtained from multivariate binary logistic regression analyses, estimating the association between potential confounding factors and rescue analgesic requirement (n = 4106).

Confounding factors	Crude OR	95% CI	p value
Low PPI grade (n = 640)			
Female sex	1.182	0.727, 1.922	0.499
Age (years)			
Age ≤ 20	1 (ref.)		
20 < Age ≤ 40	0.987	0.218, 4.463	0.987
40 < Age ≤ 60	1.161	0.272, 4.961	0.841
60 < Age ≤ 80	1.855	0.403, 8.546	0.428
Age ≥ 80	1.762	0.316, 9.814	0.518
BMI (kg/m^2)			
BMI < 18.5	1 (ref.)		
18.5 ≤ BMI < 23.0	2.484	0.699, 8.821	0.160

23.0 ≤ BMI < 25.0	2.154	0.580, 8.010	0.252
25.0 ≤ BMI < 30.0	3.374	0.946, 12.036	0.061
BMI ≥ 30.0	2.136	0.416, 10.965	0.363
ASA PS			
Ⅰ	1 (ref.)		
Ⅱ	0.439	0.242, 0.795	0.007*
Ⅲ	0.382	0.131, 1.115	0.078
Smoking (Yes)	1.429	0.661, 3.090	0.364
Opioid naïve (Yes)	0.892	0.513, 1.550	0.686
Anesthesia duration (per h)	0.843	0.709, 1.002	0.053
Intraoperative opioid use (Yes)	0.891	0.491, 1.619	0.705
BIR of PCA setting (per 1 mL/h)	0.143	0.021, 0.976	0.047*
Bolus volume of PCA setting (1 mL)	0.630	0.338, 1.174	0.146
Lockout interval of PCA setting (per min)	0.979	0.942, 1.019	0.299
DOSE-FEN-OP (μg)†	1.000	0.999, 1.001	0.683
DOSE-FEN-NONOP (μg)†	1.000	0.999, 1.000	0.400
Moderate PPI grade (n = 2666)			
Female sex	1.666	1.346, 2.062	<0.001*
Age (years)			
Age ≤ 20	1 (ref.)		
20 < Age ≤ 40	1.206	0.651, 2.237	0.551
40 < Age ≤ 60	1.118	0.613, 2.042	0.716

60 < Age ≤ 80	1.077	0.576, 2.016	0.816
Age ≥ 80	1.477	0.731, 2.984	0.277
BMI (kg/m^2)			
BMI < 18.5	1 (ref.)		
18.5 ≤ BMI < 23.0	1.072	0.652, 1.763	0.785
23.0 ≤ BMI < 25.0	1.175	0.701, 1.968	0.541
25.0 ≤ BMI < 30.0	1.147	0.692, 1.902	0.594
BMI ≥ 30.0	1.290	0.694, 2.399	0.421
ASA PS			
Ⅰ	1 (ref.)		
Ⅱ	0.991	0.765, 1.282	0.943
Ⅲ	0.854	0.546, 1.334	0.488
Smoking (Yes)	1.069	0.742, 1.540	0.720
Opioid naïve (Yes)	0.860	0.678, 1.091	0.213
Anesthesia duration (per h)	0.898	0.824, 0.978	0.014*
Intraoperative opioid use (Yes)	0.906	0.690, 1.191	0.481
BIR of PCA setting (per 1 mL/h)	0.886	0.362, 2.168	0.790
Bolus volume of PCA setting (1 mL)	0.469	0.315, 0.697	<0.001*
Lockout interval of PCA setting (per min)	1.025	0.999, 1.051	0.055
DOSE-FEN-OP (μg)†	0.998	0.998, 0.999	<0.001*
DOSE-FEN-NONOP (μg)†	1.001	1.000, 1.001	0.076
High PPI grade (n = 800)			

Confounding factors	Adjusted OR	95% CI	p value
Female sex	1.392	0.966, 2.006	0.076
Age (years)			
Age ≤ 20	1 (ref.)		
20 < Age ≤ 40	0.647	0.222, 1.882	0.424
40 < Age ≤ 60	0.562	0.201, 1.572	0.272
60 < Age ≤ 80	0.449	0.151, 1.338	0.151
Age ≥ 80	0.369	0.109, 1.249	0.109
BMI (kg/m^2)			
BMI < 18.5	1 (ref.)		
18.5 ≤ BMI < 23.0	1.225	0.595, 2.524	0.581
23.0 ≤ BMI < 25.0	0.854	0.399, 1.827	0.685
25.0 ≤ BMI < 30.0	1.063	0.512, 2.209	0.870
BMI ≥ 30.0	0.809	0.282, 2.321	0.693
ASA PS			
Ⅰ	1 (ref.)		
Ⅱ	1.394	0.902, 2.156	0.135
Ⅲ	0.983	0.444, 2.176	0.966
Smoking (Yes)	0.488	0.239, 0.995	0.049*
Opioid naïve (Yes)	0.767	0.493, 1.191	0.237
Anesthesia duration (per h)	0.963	0.845, 1.097	0.570
Intraoperative opioid use (Yes)	0.829	0.503, 1.366	0.461
BIR of PCA setting (per 1	0.166	0.020, 1.382	0.097

mL/h)			
Bolus volume of PCA setting (1 mL)	1.339	0.826, 2.170	0.236
Lockout interval of PCA setting (per min)	0.941	0.913, 0.970	<0.001*
DOSE-FEN-OP (μg)†	0.998	0.997, 0.998	<0.001*
DOSE-FEN-NONOP (μg)†	1.000	0.999, 1.001	0.653

ASA PS, American Society of Anesthesiologists physical status; BIR, background infusion rate; BMI, body mass index; CI, confidence interval; OR, odds ratio; PCA, patient-controlled analgesia; PPI, postoperative pain intensity. Opioid naïve, patients without history of previous opioid intake. *, statistical significance at $p < 0.05$. †, doses of fentanyl equivalents (μg) converted from opioids (DOSE-FEN-OP) and non-opioid adjuvant analgesics (DOSE-FEN-NONOP) with ratios of oxycodone (μg) to fentanyl (100:1), ratios of sufentanil (μg) to fentanyl (1:10), ratio of ketorolac (mg) to fentanyl (25:100), and ratio of nefopam (mg) to fentanyl (1:20) [25-28].

2.9.2. Risk Factors of Rescue Antiemetics Requirement

Upon multivariate analysis after adjustment with potential confounding factors, the independent risk factor, which could increase or decrease the probability of requiring rescue antiemetics, was the ASA PS in patients with low PPI grade. ASA PS Ⅲ was a risk factor that could increase the probability of requiring rescue antiemetics by 6.8 times, compared with ASA PS Ⅰ (OR: 6.800, $p = 0.041$, Table 25).

In patients with moderate PPI grade, there were no risk factors identified by multivariate analysis (Table 25).

In patients with high PPI grade, the risk factors were anesthesia duration, BIR

of PCA setting, and fentanyl equivalents dose of non-opioid analgesics. An anesthesia duration that was 1 h longer could lower the probability of requiring rescue antiemetics by 52.1% (OR: 0.479, p = 0.012, Table 25). The probability of requiring rescue antiemetics was lower by 99.0% when the PCA device was set with faster BIR (OR: 0.010, p = 0.004, Table 25). Furthermore, a 1 μg increase in fentanyl equivalent doses of non-opioid analgesics could also lower the probability of requiring rescue antiemetics by 0.3% (OR: 0.997, p = 0.006, Table 25).

Table 25. Odds ratios (ORs) obtained from multivariate binary logistic regression analyses, estimating the association between potential confounding factors and rescue antiemetic requirement (n = 4106).

Confounding factors	Crude OR	95% CI	p value
Low PPI grade (n = 640)			
Female sex	1.047	0.332, 3.302	0.938
Age (years)			
Age ≤ 20	1 (ref.)		
20 < Age ≤ 40	8332270.615		0.998
40 < Age ≤ 60	9951586.385		0.998
60 < Age ≤ 80	4664332.561		0.998
Age ≥ 80	3423388.293		0.998
BMI (kg/m^2)			
BMI < 18.5	1 (ref.)		
18.5 ≤ BMI < 23.0	34713312.48		0.997
23.0 ≤ BMI < 25.0	17239035.43		0.998
25.0 ≤ BMI < 30.0	35958336.13		0.997
BMI ≥ 30.0	109827799.4		0.997

ASA PS			
Ⅰ	1 (ref.)		
Ⅱ	2.164	0.558, 8.390	0.264
Ⅲ	6.800	1.081, 42.759	0.041*
Smoking (Yes)	3.066	0.801, 11.742	0.102
Opioid naïve (Yes)	0.603	0.190, 1.914	0.391
Anesthesia duration (per h)	1.061	0.758, 1.485	0.729
Intraoperative opioid use (Yes)	1.090	0.214, 5.557	0.917
BIR of PCA setting (per 1 mL/h)	3.10894E+15		0.998
Bolus volume of PCA setting (1 mL)	1.160	0.330, 4.075	0.816
Lockout interval of PCA setting (per min)	0.968	0.895, 1.046	0.409
DOSE-FEN-OP (μg)†	0.998	0.995, 1.000	0.059
DOSE-FEN-NONOP (μg)†	1.000	0.999, 1.001	0.937
DOSE-EME (mg)	6.89358E+24		0.997
Moderate PPI grade (n = 2666)			
Female sex	1.323	0.771, 2.269	0.310
Age (years)			
Age ≤ 20	1 (ref.)		
20 < Age ≤ 40	0.668	0.126, 3.556	0.636
40 < Age ≤ 60	1.121	0.236, 5.335	0.886
60 < Age ≤ 80	1.527	0.304, 7.673	0.608
Age ≥ 80	3.021	0.528, 17.285	0.214
BMI (kg/m^2)			
BMI < 18.5	1 (ref.)		

18.5 ≤ BMI < 23.0	1.628	0.372, 7.132	0.518
23.0 ≤ BMI < 25.0	2.171	0.485, 9.719	0.311
25.0 ≤ BMI < 30.0	1.344	0.297, 6.082	0.701
BMI ≥ 30.0	3.135	0.609, 16.146	0.172
ASA PS			
Ⅰ	1 (ref.)		
Ⅱ	0.902	0.469, 1.735	0.756
Ⅲ	0.351	0.093, 1.326	0.123
Smoking (Yes)	1.421	0.592, 3.412	0.431
Opioid naïve (Yes)	0.774	0.440, 1.361	0.374
Anesthesia duration (per h)	1.019	0.828, 1.255	0.859
Intraoperative opioid use (Yes)	0.803	0.414, 1.560	0.518
BIR of PCA setting (per 1 mL/h)	0.264	0.066, 1.066	0.062
Bolus volume of PCA setting (1 mL)	1.227	0.593, 2.542	0.581
Lockout interval of PCA setting (per min)	0.986	0.945, 1.028	0.496
DOSE-FEN-OP (μg)†	0.999	0.998, 1.000	0.070
DOSE-FEN-NONOP (μg)†	0.999	0.998, 1.000	0.218
DOSE-EME (mg)	0.382	0.055, 2.646	0.330
High PPI grade (n = 800)			
Confounding factors	Adjusted OR	95% CI	p Value
Female sex	0.667	0.241, 1.846	0.436
Age (years)			
Age ≤ 20	1 (ref.)		
20 < Age ≤ 40	84024268.15		0.998

40 < Age ≤ 60	48695316.61		0.998
60 < Age ≤ 80	28557062.42		0.998
Age ≥ 80	6933255.227		0.998
BMI (kg/m^2)			
BMI < 18.5	1 (ref.)		
18.5 ≤ BMI < 23.0	64687778.79		0.997
23.0 ≤ BMI < 25.0	33574295.16		0.997
25.0 ≤ BMI < 30.0	11589798.34		0.997
BMI ≥ 30.0	0.144		1.000
ASA PS			
Ⅰ	1 (ref.)		
Ⅱ	1.800	0.580, 5.587	0.309
Ⅲ	3.805	0.725, 19.958	0.114
Smoking (Yes)	0.767	0.177, 3.324	0.723
Opioid naïve (Yes)	0.401	0.144, 1.118	0.081
Anesthesia duration (per h)	0.479	0.269, 0.851	0.012*
Intraoperative opioid use (Yes)	1.531	0.374, 6.265	0.554
BIR of PCA setting (per 1 mL/h)	0.010	0.000, 0.240	0.004*
Bolus volume of PCA setting (1 mL)	1.809	0.615, 5.322	0.282
Lockout interval of PCA setting (per min)	0.96	0.902, 1.023	0.207
DOSE-FEN-OP (μg)†	0.999	0.997, 1.001	0.552
DOSE-FEN-NONOP (μg)†	0.997	0.995, 0.999	0.006*
DOSE-EME (mg)	4.579	0.086, 244.539	0.453

ASA PS, American Society of Anesthesiologists physical status; BIR, background infusion rate; BMI, body mass index; CI, confidence interval; OR, odds ratio; PCA, patient-controlled analgesia; PPI, postoperative pain intensity. Opioid naïve, patients without history of previous opioid intake; DOSE-EME, antiemetics dose. *, statistical significance at $p < 0.05$. †, doses of fentanyl equivalents (μg) converted from opioids (DOSE-FEN-OP) and non-opioid adjuvant analgesics (DOSE-FEN-NONOP) with ratios of oxycodone (μg) to fentanyl (100:1), ratios of sufentanil (μg) to fentanyl (1:10), ratio of ketorolac (mg) to fentanyl (25:100), and ratio of nefopam (mg) to fentanyl (1:20) [25-28].

Ⅳ. DISCUSSION

This study is meaningful because it analyzed the cutoff values of PCA parameters that would not require rescue analgesics and antiemetics in patients receiving postoperative PCA.

1. General Information from All Patients

There remains a debate over whether to use background infusions and adjuvant analgesics combination. Some studies suggested that the PCA applying continuous background infusion and bolus dosing provided better postoperative analgesia with lower opioid consumption and adverse effects [29, 30]. On the other hand, other studies also discouraged the application of background infusion for intravenous PCA due to the risk of opioid-induced adverse effects such as respiratory depression, regardless of the sedation level without benefit of analgesic improvement [31]. However, the relative safety of continuous background infusion can be improved when it is applied to patients with known opioid requirements for postoperative analgesia, with opioid tolerance, or with surgeries that are expected to result in severe postoperative pain [31]. In the Chosun University Hospital, anesthesiologists also preferred applying continuous background infusions for PCA to all patients, but with them deciding the settings and drug compositions of PCA devices based on their preference and judgment, regardless of PPI (although 79.1% of patients were opioid naïve) or their previous medical records of PCA regimens.

To provide effective postoperative analgesia, it is important to provide the ideal PCA regimen, considering the predicted PPIs of each patient. This study identified the cutoff values of settings and drug compositions for ideal PCA regimen in all patients and those sub-grouped according to PPI grades at the 6th postoperative hour.

Most patients received PCA set with 2 mL/h of BIR, 2 mL of bolus volume, and 30 min of lockout interval, with mean values of 1.99 mL/h, 1.68 mL, and 24.08 min, respectively. The mean DOSE-FEN-OP, DOSE-FEN-NONOP, and DOSE-FEN-TOTAL were 892 μg, 692 μg, and 1584 μg, respectively. The mean BIR-FEN-OP, BIR-FEN-NONOP, and BIR-FEN-TOTAL were 17.80 μg/h, 23.40 μg/h, and 31.60 μg/h, respectively, while BIR-EME was 23.4 ± 2.2 μg/h. In these settings, 69.1% of patients experienced a postoperative pain of NRS > 4 at the 6th postoperative hour, and 20.8% and 2.6% of patients required rescue analgesics and rescue antiemetics, respectively, postoperatively.

2. Cutoff Values of Potential Variables for Requiring Rescue Analgesics and Antiemetics

A previous study analyzed the cutoff values that would not require rescue analgesics and rescue antiemetics in patients receiving fentanyl-based postoperative PCA [2]. This study suggested only the cutoff values for BIRs in general, and in situations with or without the addition of adjuvant analgesics and adjuvant antiemetics. However, the study did not show a more detailed cutoff values for PCA setting, drug doses, and each BIR of opioids, non-opioid analgesic, and antiemetics. Thus, the present study calculated the cutoff values for these potential variables to reduce the requirement for rescue analgesia and rescue antiemetics in most patients.

2.1. PCA Settings

As a basic concept, to reduce the requirement for rescue analgesia, the PCA device should be set with values greater than the cutoff values of background infusion rate and bolus volume and less than the cutoff value of lockout interval. On the other hand, to reduce the requirement for rescue antiemetics, the PCA device should be set with values less than the cutoff values of background infusion rate, bolus volume, and lockout interval. A shorter lockout interval may

increase the administration of opioid, which could increase the risk of opioid-induced adverse effects. However, in cases that use a PCA regimen with pre-mixed antiemetics as adjuvant, it can also provide a counteracting effect that offsets side effects by increasing their administrated dosage. Thus, setting the lockout interval below the cutoff value can reduce the demand for rescue antiemetics.

For general patients, the present study showed that the cutoff values of BIRs that would require rescue analgesics and rescue antiemetics were similar at 1.75 mL/h. However, the cutoff values that will require rescue analgesics and rescue antiemetics were 0.5 mL and 1.75 mL, respectively, for bolus volume and 5 min and 25 min, respectively, for lockout time. These findings suggest that in patients receiving PCA premixed with analgesics and antiemetics, the effective PCA would be provided with at least 1.75 mL/h of BIR, less than 5 min of lockout intervals, and adjustment of bolus dose within 0.5 mL and 1.75 mL, considering the effective postoperative analgesia without requiring rescue analgesics and rescue antiemetics.

PCA settings may be changed according to PPI grades. For patients with low expected PPI, this study showed cutoff values of 1.75–3 mL/h for background infusion rate, 0.5–1.25 mL for bolus volume, and <12.5 min for lockout interval, which could lead to effective analgesia without requirement for rescue analgesics and antiemetics. For patients with moderate expected PPI, this study showed cutoff values of 1.75 mL/h for background infusion rate, 0.5–1.75 mL for bolus volume, and <5 min for lockout interval. For patients with high expected PPI, this study showed cutoff values of 1.75 mL/h for background infusion rate, 0.5 mL for bolus volume, and <5 min for lockout interval. These findings suggest that the effective PCA can be provided by adjusting the lockout interval and bolus volume rather than BIR, and by applying smaller bolus dose and shorter lockout interval according to increasing PPI grade.

2.2. DOSE−FENs and BIR−FENs of Analgesics and Antiemetics

The doses of opioid and adjuvants (non-opioid analgesics and antiemetics) should be adjusted because controlling PCA settings alone is not enough to achieve sufficient analgesia without adverse effects.

For general patients, this study showed that the cutoff values of DOSE-FEN-OP and DOSE-FEN-TOTAL, at 950 μg and 1750 μg, respectively, were similar for requiring rescue analgesics (BIR-FEN-TOTAL: 19 μg/h) and rescue antiemetics (BIR-FEN-TOTAL: 31 μg/h). However, the cutoff values of DOSE-FEN-NONOP were 550 μg and 450 to require rescue analgesics and rescue antiemetics, respectively, but the cutoff values of BIR-FEN-NONOP were the same at 8.5 μg/h. Shin et al. [2] suggested that a fentanyl BIR should be at least 0.38 μg/kg/h to provide effective postoperative analgesia without administration of rescue analgesics and a fentanyl BIR of over 0.36 μg/kg/h to administer rescue antiemetic. However, compared to Shin's study [2], the present study showed higher BIR-FEN-TOTAL of at least 0.58 μg/kg/h for rescue analgesics requirement and over 0.41 μg/kg/h for rescue antiemetics requirement based on the patient's body weight. This discrepancy can be explained by the difference in the type of surgery included in the statistical analysis; the present study included many surgeries with various PPIs and PONV, while Shin's study included only a single operation (laparoscopic abdominal surgery).

Doses and BIR can also be changed according to PPI grades. For reducing the demand of rescue analgesics, this study showed that cutoff values of opioid dose were similar with that of fentanyl equivalent regardless of PPI, but cutoff values of non-opioid dose were increased. However, for reducing the demand of rescue antiemetics, the cutoff values of opioid dose were >950 μg (19 μg/h) of fentanyl equivalent regardless of PPI. On the other hand, the cutoff values of non-opioid dose were increased and were >50 μg (1 μg/h), >450 μg (8.5 μg/h), and >700 μg (14 μg/h) of fentanyl equivalent for patients with low, moderate, and high

expected PPI, respectively. These cutoff values were less than those for reducing the demand for rescue analgesics. Moreover, the results also showed that to reduce the requirement for rescue analgesics, the cutoff values of doses and BIRs for total analgesics were less in patients with high expected PPI than those with low expected PPI. The cutoff values of doses and BIR also showed similar pattern, but they were lower than those for reducing the requirement for rescue analgesics. This suggests that there is no optimal dose and BIR of analgesics for reducing the demand for rescue analgesics and rescue antiemetics, and we should consider that, if the dose or BIR of PCA drugs is set between those cutoff values to reduce the demand for rescue analgesics and rescue antiemetics, the patients may suffer from uncontrolled postoperative pain, PONV, or both.

The sum of cutoff values of opioids and non-opioid analgesics were not equal to doses and BIRs for total analgesic, respectively. This can be explained by the variation in PCA settings collected in this study and the effect of these settings on the calculated cutoff values for opioids and non-opioid analgesics, despite the conversion of all analgesics to opioid dose of fentanyl equivalent. This indicates that effective PCA can be provided in patients with high expected PPIs, when the PCA device is set with fewer bolus dose and shorter lockout interval rather than increasing dose and BIR of total analgesic.

The cutoff values for the BIR of antiemetics was increased according to PPI grade, and it was higher in patients with low expected PPI but was similar in patients with moderate and high expected PPIs for reducing the demand for rescue analgesics. However, to reduce the demand for rescue antiemetics, the cutoff value for the BIR of antiemetics was higher (25 μg/h) than that (15 μg/h) for reducing the demand for rescue analgesics in patients with low expected PPI but were similar (21 μg/h) in patients with moderate and high PPIs. Thus, we can set the BIR of antiemetics between 15 μg/h to 25 μg/h considering the risk of benefit between effective analgesia and less adverse events.

Therefore, it is necessary to adjust the PCA settings and doses of analgesics to provide effective analgesia without adverse events, and PCA should be prepared whether to provide effective analgesia or to minimize opioid-induced adverse events.

3. Risk Factors of Requirements for Rescue Analgesics and Rescue Antiemetics

Female sex, anesthesia duration, bolus volume of PCA setting, and dose of opioid were identified as independent risk factors of rescue analgesic requirement.

The present study showed that female sex was a risk factor that could require rescue analgesics rather than male sex. Female patients experienced more postoperative pain than male patients, and female sex was a risk factor for postoperative pain [32]. Female patients may also require more rescue analgesics than male patients if we use the same regimens for PCA regardless of sex. However, it was not a risk factor for the rescue antiemetics requirement. Thus, for female patients, the focus was on determining the kinds of analgesics, their dose, and the setting of PCA device. However, unlike these studies, Shine et al. [2] reported that female sex was a risk factor for requiring rescue antiemetics, but not the risk factor for requiring rescue analgesics. This discrepancy can be explained by the sufficiency in adjuvant antiemetic doses. While Shine et al. [2] did not specify how much antiemetics doses were used in patients enrolled in their study, the patients in the present study received an average of 1.2 mg of ramosetron (antiemetics). It is assumed that this dose might be sufficient to offset the PCA-related nausea and vomiting. The longer anesthesia durations were revealed as a risk factor for the reducing rescue analgesic requirement with small OR (0.927). However, Bakan et al. [33] showed that the intraoperative opioid was related with higher rescue analgesic requirements compared with the opioid-free anesthesia. Kim et al. [34] also suggested that total intravenous anesthesia (TIVA) influenced the reduction of postoperative opioid consumption compared to balanced anesthesia. Therefore, this discrepancy can be explained by

uneven patient enrollments, in which patients without intraoperative opioid were smaller (16.5%) than those receiving intraoperative opioids, and patients undergoing balanced anesthesia was less (11.3%) than those undergoing TIVA (72.2%).

The present study showed that higher bolus volume of PCA setting and larger premixed opioid dose were related to the decreased demand for rescue analgesics. However, the effect of increased premixed opioid dose was very low with small OR (0.998). Thus, bolus volume of PCA setting is more related to the decreased demand for rescue analgesics (OR: 0.687). This study also revealed that faster BIR of PCA setting and larger premixed opioid dose were independent risk factors of rescue antiemetics requirement. Similar with the risk factor for rescue analgesic requirement, the effect of increased premixed opioid dose was very low with small OR (0.999). Thus, BIR of PCA setting seems to be more related to the decreased demand for rescue antiemetics (OR: 0.294). However, in general, if the premixed analgesic dose is constant, faster BIR settings can predict the risk of more side effects due to an increase in the analgesic dose administered to patients. Shin et al. [2] also identified the lower BIR of fentanyl as a risk factor of rescue analgesics, and the higher BIRs of fentanyl as a risk factor of rescue antiemetics. Particularly, the higher BIR of fentanyl is a double-edged sword that could decrease the demand for rescue analgesics and increase the demand for rescue antiemetics [2]. Therefore, the demand for rescue analgesics and rescue antiemetics could be decreased by reducing the infused fentanyl dose through the combination of non-opioid analgesics and antiemetics. Considering the routine co-premixed antiemetics, the results can be supported by a faster BIR settings that can also increase the antiemetics dose administered to patients and provide an offsetting effect on side effects, thereby becoming a factor that can reduce rescue antiemetics requirement.

4. Limitations of This Study

This study has some limitations. First, the AUCs of the cutoff values were relatively low due to the uneven distribution and low incidence of parameters. A randomized controlled trial using data with normal distribution is necessary to support this result. Second, the patients receiving various opioids and non-opioid analgesics during PCA were enrolled, and all analgesics were converted into opioid dose of fentanyl equivalents with conversion ratios reported in previous literatures. However, the conversion ratios between opioids have been well known and validated, but conversion ratios between opioids and non-opioid analgesics were not. Therefore, careful interpretation of the findings of this study is necessary to provide fentanyl-based PCA for effective postoperative analgesia, and further research will be required with the dosages and settings presented in this study. Third, Apfel score has been commonly used to identify risk factors for PONV, and it is the sum score of risk factors such as female sex, history of motion sickness or PONV, history of smoking, and planned/expected postoperative opioid use [35]. It is also an important variable for determining the risk factor of rescue antiemetics requirement. However, the data for history of motion sickness or PONV could not be accessed because of the lack of data recorded in their medical record. Fourth, the subgroup analysis with the types of surgery was not performed, despite this study including many surgeries with various PPIs and PONV. A well designed randomized controlled trial or a retrospective study is necessary to confirm the effective procedure-specific regimens in the future.

Ⅴ. CONCLUSIONS

For the optimal or ideal regimens of PCA depending on PPI, adjustment is needed based on a BIR of 1.75 mL/h and bolus volume of 0.5 mL. The lockout interval is recommended to be adjusted within 12.5 min for the low expected PPI, and within 5 min for the moderate and high expected PPI. Therefore, the adjustment of the lockout interval should be considered more than those of BIR and bolus volume for the PCA setting.

For optimal or ideal regimens of PCA, drug combinations should also be considered depending on the degree of PPI. Basically, while maintaining 950 μg of fentanyl, increasing the dosage of non-opioid analgesics (with doses of fentanyl equivalent) could provide effective PCA, considering the expected increase in PPI.

However, as the degree of PPI increased, we found that there were some parameters of which the cutoff values did not overlap with the probability of requiring rescue analgesics or rescue antiemetics. This suggests that patients receiving a PCA with settings and drug doses between the cutoff values for rescue antiemetics and those for rescue analgesics may suffer from uncontrolled postoperative pain or PONV, which is the worst-case scenario [2]. Therefore, it is necessary to decide first whether to minimize the possibility of a rescue analgesics requirement or to minimize the possibility of a rescue antiemetics requirement. Based on this decision, the PCA setting and drug dosage should be determined carefully.

Female sex, anesthesia duration, BIR, bolus volume, and fentanyl equivalent doses of opioids or non-opioid analgesics were found as factors that could increase or decrease the probability of requiring rescue analgesics or rescue antiemetics. However, although they are statistically significant, some of these

factors are unlikely to reduce or increase the probability of both drugs or for each requirement, as odds ratio approaches 1.0. Considering this, it is necessary to apply these factors to clinical patients based on careful interpretation.

Finally, the optimal fentanyl-based PCA could be provided by determining the setting and drug dosage of PCA, considering the cutoff values and risk/benefit factors calculated according to the expected degree of PPI. In addition, further research will need to find optimal regimens that can maximize PCA analgesic effects and minimize adverse events such as PONV.

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Legends for Figure

Fig. 1. Flowchart of this study. Group L, NRS > 4 at the 6th postoperative hour; Group M, 4 ≤ NRS < 7 at the 6th postoperative hour; Group H, NRS ≥ 7 at the 6th postoperative hours.

Fig. 2. Cutoff values of PCA settings for the reduction of rescue analgesic requirement (A) and rescue antiemetics (B) according to PPI. Group L (n = 640), NRS > 4 at the 6th postoperative hour; Group M (n = 2666), 4 ≤ NRS < 7 at the 6th postoperative hour; Group H (n = 800), NRS ≥ 7 at the 6th postoperative hours.

Fig. 3. Cutoff values of doses (A and B) and BIR (C and D) for the reduction of rescue analgesic requirement (A and C) and rescue antiemetics (B and D) according to PPI. BIR, background infusion rate. Group L (n = 640), NRS > 4 at the 6th postoperative hour; Group M (n = 2666), 4 ≤ NRS < 7 at the 6th postoperative hour; Group H (n = 800), NRS ≥ 7 at the 6th postoperative hour.