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ORIGINAL RESEARCH

Intraoperative Sufentanil Consumption and the Risk of Postoperative Nausea and/or Vomiting: A Retrospective Observational Study

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ABSTRACT

Introduction: Post-operative nausea and/or vomiting (PONV) is a common post-operative adverse reaction and has been associated with post-operative sufentanil injection. The assessment of the relationship between intraoperative opioid consumption and PONV has been understudied. This study examined the relationship between intraoperative sufentanil administration and PONV.

Methods: This was a single-center retrospective observational study. Patients who underwent video-assisted thoracoscopic surgery under general anesthesia with the preoperative thoracic paravertebral block between January 2017 and June 2020 at the Peking University People's Hospital were recruited for this study. Patients were grouped into two groups according to whether or not PONV occurred on postoperative day 1 (POD1). The factors associated with PONV were analyzed using logistic regression.

Results: A total of 2733 patients, 1510 males and 1223 females, were included in this study. Among them, 143 patients developed PONV, a 5.2% (143/2733) PONV incidence. Logistic regression analysis showed that female, non-smoking, sufentanil patient-controlled intravenous analgesia (PCIA), POD1 opioids consumption, and a time-weighted average of intraoperative sufentanil (twSuf) were associated with PONV. All patients were further divided into four subgroups based on intraoperative twSuf. Logistic regression analysis revealed that twSuf higher than 0.21 $\mu g\,kg^{-1}\,h^{-1}$ was an independent risk factor for PONV.

Conclusions: Intraoperative sufentanil injection with a twSuf higher than 0.21 $\mu g\,kg^{-1}\,h^{-1}$ increased the risk of PONV in patients undergoing thoracoscopic surgery under general anesthesia after a preoperative thoracic paravertebral block.

Keywords: Post-operative nausea and/or vomiting (PONV); Video-assisted thoracoscopic surgery (VATS); Sufentanil; General anesthesia

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Key Summary Points

Post-operative nausea and/or vomiting (PONV) is a common post-operative adverse reaction. Previous research on PONV has focused mostly on postoperative opioid consumption, with less research on the relationship between opioid consumption and PONV in the book.

Sufentanil is the most commonly used opioid in thoracoscopic lung surgery in China. Therefore, this retrospective study investigated the relationship between intraoperative sufentanil consumption and PONV.

Intraoperative sufentanil injection with a twSuf higher than 0.21 μg kg^{-1} h^{-1} increased the risk of PONV in patients undergoing thoracoscopic surgery under general anesthesia after a preoperative thoracic paravertebral block.

INTRODUCTION

Post-operative nausea and/or vomiting (PONV) is a common post-operative adverse reaction [1]. Patients often rate PONV worse than post-operative pain, and this feeling is also linked to a decline in patient satisfaction [2, 3]. Apfel score has been used to predict PONV using four variables: gender, history of motion sickness and/or PONV, smoking status, and post-operative opioid consumption [4]. For several years, anesthesiologists have used propofol maintenance, post-operative multimodal analgesia, and prophylactic antiemetic medications in patients at risk of PONV. However, the incidences remain at around 15–30% [5–7]. Therefore, there is a need to examine other factors that increase the risk of PONV.

In a systematic review of 22 studies, which included 95,154 patients, Apfel and colleagues found that post-operative use of opioids increased PONV incidence (OR 1.39, $P < 0.001$), while no significant effect was observed when using intraoperative opioids (OR 1.03, $P = 0.47$) [1]. However, further analysis of the literature included in the above study showed that intraoperative opioid consumption differed less between the PONV and non-PONV groups, which may have masked the relationship between intraoperative opioid consumption and PONV.

Several regional block techniques have been combined with general anesthesia over the past few years, particularly in the thoracic paravertebral block (PVB) in thoracoscopic surgery [8]. The implementation of preoperative PVB for thoracoscopic surgery reduces intraoperative opioid administration [9]. Many anesthesiologists have also changed the amount and type of opioids used for anaesthetization. However, using large doses of opioids during anesthesia induction remains a common practice [10, 11]. This has resulted in differences in opioid consumption during thoracoscopy. Therefore, there is a need to examine the relationship between intraoperative opioid consumption and PONV. Sufentanil is the most commonly used opioid in thoracoscopic lung surgery in our center. Therefore, this retrospective study investigated the relationship between intraoperative sufentanil consumption and PONV.

METHODS

Study Design

This was a single-center retrospective observational study that investigated the relationship between intraoperative opioid consumption and PONV using binary logistic regression analysis. The study protocol was reviewed and approved by the Academic Committee of Peking University People's Hospital (approval No. 2020PHB308-01). Because this study was retrospective, the ethics committee considered informed consent unnecessary and therefore waived the requirement to obtain informed consent. Patient data were handled with extreme confidentiality.

Patients

Data for patients of all ages and all genders who underwent thoracoscopic surgery at the Peking University People's Hospital between January 2017 and June 2020 were obtained from the electronic medical record system. Patients who did not receive a preoperative thoracic paravertebral block or had previously undergone thoracic surgery, open or intermediate open thoracic surgery, esophageal or cardiac surgery, main airway surgery, emergency surgery and post-operative admission to the intensive care unit were excluded. Patients who did not receive postoperative patient-controlled intravenous analgesia (PCIA) and those who did not receive analgesic follow-up on postoperative day 1 (POD1) were also excluded.

Primary Outcome

The primary outcome of this study was the PONV on POD 1. All the study participants were followed up by professionally trained anesthesia nurses, and the data were captured in an electronic database. Patients with missing PONV data were excluded from the study.

Nausea was defined as any unpleasant sensation with the urge to vomit, whereas vomiting was defined as successful or unsuccessful (retching) expulsion of gastric contents. PONV was defined as nausea, vomiting, or both. All patients administered with post-operative antiemetic drugs were also recorded as PONV (+). The incidence of PONV between the end of surgery and the POD 1 follow-up time point was recorded in the POD 1 post-operative analgesic follow-up record.

Anesthesia and Pain Management

Intraoperative sufentanil consumption was defined as the time-weighted average of intraoperative sufentanil (twSuf): (total intraoperative sufentanil administration)/(body weight)/(anesthesia time) ($\mu g\ kg^{-1}\ h^{-1}$).

Patients were treated with a thoracic paravertebral block before thoracoscopic surgery followed by double-lumen tracheal intubation under general anesthesia. Anesthesia was induced using propofol 1.5–2 $mg\ kg^{-1}$ or etomidate 0.2–0.3 $mg\ kg^{-1}$, cisatracurium 0.3–-0.4 $mg\ kg^{-1}$ or rocuronium 0.5–0.6 $mg\ kg^{-1}$, and sufentanil 0.2–0.4 $\mu g\ kg^{-1}$ and/or remifentanil 0.5–2 $\mu g\ kg^{-1}$. Anesthetization was maintained using propofol and remifentanil. The propofol dosage was adjusted during the procedure to maintain the electroencephalographic bispectral index (BIS) between 40–60, and muscle relaxants were applied according to the muscle relaxation interval. The remifentanil dose was adjusted to maintain blood pressure and heart rate between 80 and 120% of basal blood pressure and heart rate. At the same time, additional sufentanil was administered in appropriate doses according to the changes in the heart rate and blood pressure during surgery. Before the end of the procedure, patients aged $\geq$ 18 years were intravenously administered 8 mg of ondansetron or 5 mg of tropisetron. Patients aged $<$ 18 years were intravenously injected with 0.15 $mg\ kg^{-1}$–8 mg of ondansetron.

All patients received post-operative sufentanil patient-controlled intravenous analgesia (PCIA) or oxycodone PCIA. Patients receiving a sufentanil PCIA who were older than 65 years or younger than 16 years with a body mass index lower than 18 $kg\ m^{-2}$ had a background infusion setting of 0.5 $\mu g\ h^{-1}$ and a single dose of 1.5 μg with a 15-min interval between each compression. The rest of the patients had a background infusion setting of 1.5 $\mu g\ h^{-1}$, a single compression dose setting of 1.5 μg, and a 15-min interval between each compression. Patients receiving oxycodone PCIA had a background infusion set to 0 $mg\ h^{-1}$, a single compression dose set to 1 mg, and a 5-min interval set between each compression. Fentanyl (0.02–0.05 mg IV/IM) or sufentanil (2–5 μg IV/IM) or morphine (2–5 mg IV/IM), or oral Tylenol 1 tablet (5 mg oxycodone plus 375 mg paracetamol) was administered if the post-operative numerical rating scale of pain (NRS) was $>$ 3 points and PCIA did not resolve with two compressions.

Data Collection

The demographic and clinical data, including the patient demographics (sex, age, height, weight), comorbidities (hypertension, diabetes, coronary artery disease), smoking history, ASA score, surgery types, surgery times, opioids consumption (sufentanil and remifentanil), blood loss, fluid volume, urine volume, postoperative analgesic pump types, pain scores (NRS at rest and NRS during activity) on POD1, and opioid administration on POD1 of the patients were retrieved from the electronic record system of the hospital.

The consumption of opioids was converted to equivalent morphine dosage using the following formulae [12]: 5 mg oral oxycodone was equivalent to 2 mg IV morphine; 0.1 mg IV/IM fentanyl was equivalent to 10 mg IV morphine; 5 μg IV sufentanil was equivalent to 5 mg IV morphine.

Statistical Analysis

The relationship between intraoperative opioid consumption and PONV was assessed using binary logistic regression analysis. Sample size estimation was based on Events Per Variable criterion (EPV) > 10. Based on previous studies and actual data, ten variables, including sex, age, smoking history, type of surgery, duration of surgery, intraoperative fluid volume, intraoperative sufentanil consumption, intraoperative remifentanil consumption, postoperative opioid consumption, and type of PCIA, were assessed. Therefore, at least 100 PONV (+) patients were needed for the study. Previous studies have shown that the incidence of PONV in patients undergoing thoracoscopic surgery with preoperative PVB administration was about 25% [10]. Therefore, 400 patients were required for the assessment.

Categorical data were expressed as percentages, and differences between the two patient groups were compared using the chi-square test. Normally distributed data were expressed as $X \pm SD$. Differences between groups of normally distributed data were evaluated by *t* test. Non-normally distributed data were expressed with median [25% quartile, 75% quartile] and were analyzed using the Mann–Whitney *U* test or the Kruskal–Wallis test.

Patients who developed PONV were in the PONV (+) group, while those who did not were in the PONV (–) group. The twSuf between the two groups was compared. The demographic characteristics and intraoperative conditions of patients were also compared. The relationship between twSuf and PONV was evaluated by logistic regression analysis at a 95% confidence interval (CI) (inclusion criteria were $P < 0.2$). Patients were classified into four subgroups by median and quartiles of twSuf since the relationship between twSuf and PONV may not be linear. Logistic regression analysis of the four subgroups was then performed.

Data were analyzed using SPSS 25.0 (IBM Corp., Armonk, NY, USA), and $P < 0.05$ (two-sided) was considered statistically significant.

RESULTS

A total of 4630 patients underwent thoracic surgery between January 2017 and June 2020 at Peking University People's Hospital. Among them, 726 did not receive preoperative PVB, 132 underwent esophageal or cardiac surgery, 63 had open or intermediate open chest surgery, five underwent main airway surgery, 12 were admitted to the intensive care unit after surgery, 27 underwent emergency surgery, and 102 underwent previous thoracic surgery. Additionally, 830 had incomplete POD1PONV follow-up data. Finally, 2733 patients were included in the final analysis. Of these, 143 (5.2%) had PONV, while 2590 (94.8%) had no PONV (Fig. 1).

There was no statistical difference in BMI, ASA grade, comorbidities, types of antiemetic drugs, intraoperative remifentanil consumption, and intraoperative fluid infusion between the two groups ($P > 0.05$). The patients in the PONV (+) group were younger ($P = 0.026$), mainly females ($P < 0.001$), mainly non-smokers ($P < 0.001$), more likely to undergo pulmonary wedge resection ($P = 0.002$), and had shorter wake-up time from the anesthesia ($P = 0.003$), less intraoperative blood loss

($P = 0.030$), required lower twSuf injection ($P < 0.001$), required frequent sufentanil PCIA ($P < 0.001$), and required higher opioid consumption on POD 1 ($P = 0.01$) (Table 1).

The results of binary logistic regression for the incidence of PONV on POD 1 are shown in Table 2. The results show that female gender, non-smoking, sufentanil PCIA, twSuf, and opioid consumption on POD 1 were associated with PONV.

The quartiles and twSuf medians for all patients were 0.14, 0.21, and 0.29 $\mu g\ kg^{-1}\ h^{-1}$. Patients were divided into four groups based on twSuf levels: G1 (twSuf $\leq 0.14\ \mu g\ kg^{-1}\ h^{-1}$), G2 ($0.14\ \mu g\ kg^{-1}\ h^{-1} <$ twSuf $\leq 0.21\ \mu g\ kg^{-1}\ h^{-1}$), G3 ($0.21\ \mu g\ kg^{-1}\ h^{-1} <$ twSuf $\leq 0.29\ \mu g\ kg^{-1}\ h^{-1}$), G4 (twSuf $> 0.29\ \mu g\ kg^{-1}\ h^{-1}$). The G1 group had 673 patients (24.6%), G2 had 702 patients (25.7%), G3 had 659 patients (24.1%), and G4 had 699 patients (25.6%).

Logistic analysis performed on the four subgroups of twSuf revealed that high sufentanil consumption was an independent risk factor for PONV (Table 3).

Table 4 shows the postoperative pain in both groups. PONV (+) patients had higher NRS scores in both resting and activating states ($P = 0.010$, $P = 0.004$) than PONV (–) patients. In addition, the PONV (+) group had more post-operative analgesic pump compressions than the PONV (–) group ($P = 0.011$).

DISCUSSION

This study revealed that intraoperative sufentanil consumption is an independent risk factor for PONV. Other risk factors included female, non-smoking, sufentanil PCIA, and POD1 opioid consumption. The incidence of PONV in patients receiving thoracoscopic surgery under

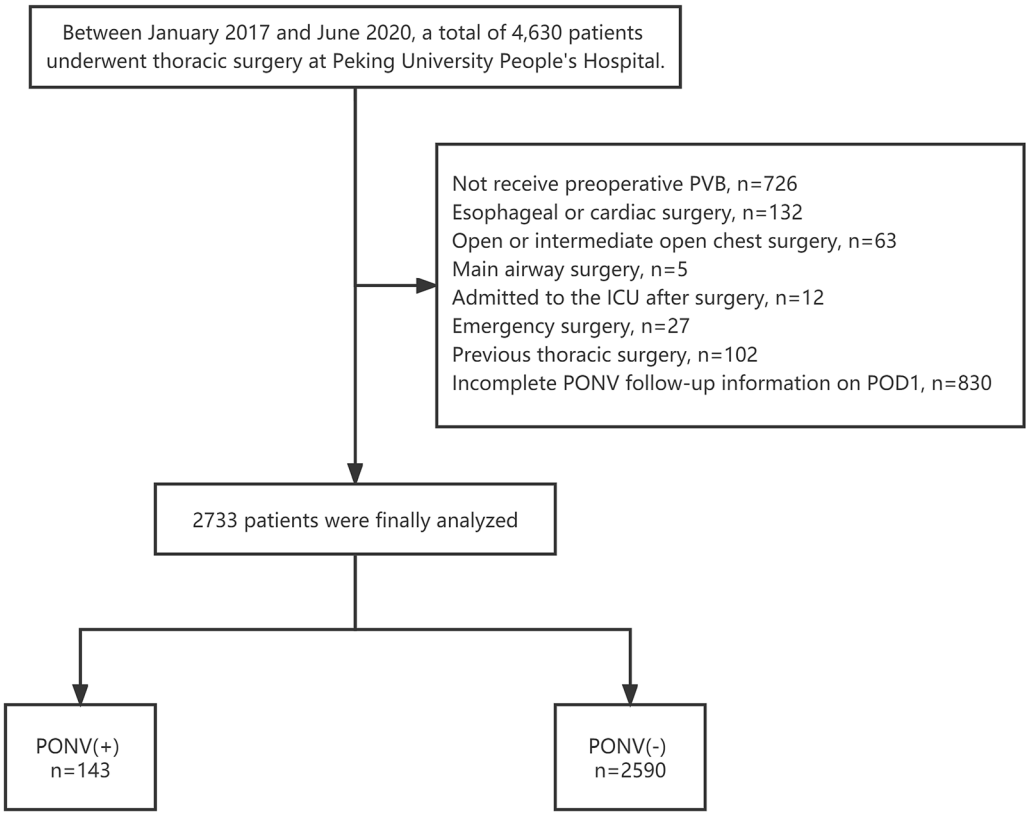

Fig. 1 The study flowchart. *PVB* paravertebral block, *ICU* Intensive Care Unit, *POD 1* postoperative day 1; *PONV* postoperative nausea and/or vomiting

Table 1 Comparison of demographics of patients with and those without PONV

Variable	PONV (–) $n = 2590$	PONV (+) $n = 143$	*P*
Age (years)	57 (13–87)	55 (8–81)	0.026
Gender (male/female), *n*	1396/1194	114/29	< 0.001
BMI (kg m^{-2}), mean (SD)	24.2 (3.2)	23.8 (3.1)	0.121
ASA (1/2/3), *n*	440/1981/149	31/105/7	0.475
Comorbidities, *n* (%)			
Hypertension	740 (28.6)	40 (28.0)	0.924
Diabetes	287 (11.1)	13 (9.1)	0.497
Coronary heart disease	125 (4.8)	9 (6.3)	0.423
Smoking history, *n* (%)	670 (25.9)	8 (5.6)	< 0.001
Type of operation, *n* (%)			0.002
Pulmonary wedge resection	801(30.9)	66 (46.2)	
Segmental pneumonectomy	118 (4.6)	3 (2.1)	
Lobectomy	1408 (54.4)	56 (39.2)	
Sleeve lobectomy	9(0.3)	0(0)	
Pneumonectomy	11 (0.4)	1 (0.7)	
Mediastinal surgery	243 (9.4)	17 (11.9)	
Antiemetic (tropisetron/ondansetron), n	2454/136	134/9	0.564
Operation time (min), mean (SD)	116 (50)	103 (45)	0.003
Intraoperative blood loss (ml), median [IQR]	20 [20 to 50]	20 [20 to 40]	0.030
Intraoperative urine output (ml), mean (SD)	432 (324)	432 (331)	0.984
Intraoperative infusion volume (ml), mean (SD)	1259 (430)	1269 (393)	0.776
Intraoperative remifentanil consumption (μg kg^{-1} min^{-1}), median [IQR]	0.04 [0.04 to 0.06]	0.05 [0.04 to 0.06]	0.109
Intraoperative sufentanil consumption (μg kg^{-1} h^{-1}), median [IQR]	0.21 [0.14 to 0.29]	0.28 [0.21 to 0.42]	< 0.001
Type of patient-controlled analgesia pump (sufentanil/oxycodone)	636/1954	84/59	< 0.001
Equivalent morphine dose on POD1 (mg), median [IQR]	4.6 [1.5 to 19.8]	25.0 [6.0 to 36.5]	< 0.001

twSuf time-weighted average of sufentanil dose, *POD1* postoperative day

general anesthesia following preoperative thoracic paravertebral block was 5.2%.

The association between intraoperative opioid consumption and PONV has been investigated in previous studies. Hozumi and colleagues demonstrated a dose-dependent association between intraoperative remifentanil administration and PONV in 433 female

Table 2 Logistic regression analysis for incidence of PONV

Variable	Odds ratio	95% confidence interval of exp (b)		*P*
		Lower limit	Upper limit	
Female	2.018	1.252	3.253	0.004
No smoking	3.958	1.74	9.002	0.001
Sufentanil analgesia pump	1.728	1.004	2.977	0.048
Intraoperative sufentanil consumption	58.13	18.867	179.102	< 0.001
Equivalent morphine dose on POD1	1.028	1.015	1.041	< 0.001

twSuf time-weighted average of sufentanil dose, *POD1* postoperative day

Table 3 Logistic regression analysis based on categories of time-weighted doses of intraoperative sufentanil (twSuf) for the incidence of PONV

Variable	Odds ratio	95% confidence interval of exp (b)		*P*
		Lower limit	Upper limit	
Female	1.981	1.229	3.193	0.005
No smoking	3.756	1.675	8.421	0.001
Sufentanil analgesia pump	1.739	1.015	2.979	0.044
Categories of intraoperative sufentanil consumption				
G2 (vs. G1)	1.298	0.63	2.676	0.480
G3 (vs. G1)	2.225	1.131	4.376	0.020
G4 (vs. G1)	3.659	1.919	6.977	< 0.001
Equivalent morphine dose on POD1	1.739	1.015	2.979	< 0.001

G1, twSuf $\leq$ 0.14 μg kg^{-1} h^{-1}); G2, 0.14 μg kg^{-1} h^{-1} < twSuf $\leq$ 0.21 μg kg^{-1} h^{-1}; G3, 0.21 μg kg^{-1} h^{-1}- < twSuf $\leq$ 0.29 μg kg^{-1} h^{-1}; G4, twSuf > 0.29 μg kg^{-1} h^{-1})
POD1 postoperative day 1

Table 4 Analgesia on postoperative day 1

Variable	PONV (–) *n* = 2590	PONV (+) *n* = 143	*P*
Press times of analgesic pump, median [IQR]	1 [0 to 2]	1 [0 to 2]	0.011
NRS score on POD 1, median [IQR]			
NRS resting	1.0 [0.0 to 2.0]	1.0 [0.0 to 2.0]	0.010
NRS activity	3.0 [2.0 to 4.0]	3.0 [3.0 to 4.0]	0.004

POD1 postoperative day 1, *NRS* numerical rating scale of pain

patients [13]. Choi and colleagues also found that remifentanil administration was associated with PONV after surgery [14]. A prospective cohort study by Mauermann and colleagues showed that intraoperative fentanyl consumption was associated with PONV [15]. However, Apfel and colleagues found no relationship between intraoperative opioid consumption and PONV [1]. Thus, the relationship between intraoperative opioid consumption and PONV remains controversial. These controversies could result from the different intraoperative opioids and the anesthetic protocols used in the relevant studies. Herein, all patients received preoperative PVB, which entailed switching from sufentanil-only to a combination of sufentanil remifentanil or remifentanil only. These alterations were mainly responsible for the variations in intraoperative sufentanil administration in this study, which also revealed an association between intraoperative sufentanil administration and PONV. These findings support the opioid-sparing anesthesia protocol and provide ideas for adjusting and optimizing the anesthesia protocol.

This study also found that patient sex, smoking history, post-operative analgesic pump drug formulation, and post-operative opioid consumption were associated with PONV. Previous studies have revealed that several factors, including female sex, smoking history, and postoperative opioid administration, are associated with PONV [4, 7]. The PONV incidence was lower in patients with oxycodone PCIA than in patients with sufentanil PCIA. These findings could be due to the unique mechanism underlying oxycodone action [16, 17]. Opioids induce nausea and vomiting mainly by acting directly on μ-receptors in the brainstem and the anterior cingulate cortex while slowing gastrointestinal motility and delaying gastric emptying by acting on μ-receptors in the gastrointestinal tract, and these effects are produced in a dose-dependent manner [3, 18]. Sufentanil is a μ-receptor agonist that provides effective analgesia for patients. However, the effect of sufentanil is only short-lived. Therefore, patients need frequent sufentanil administration after the blood levels have decreased to maintain good analgesia. Oxycodone is a dual agonist of μ and κ receptors [16]. The κ receptors relieve not only physical pain but also visceral pain. Therefore, its analgesic effect is more comprehensive than that of sufentanil. In addition, oxycodone is a long-acting opioid. Therefore, the equivalent dose of oxycodone per unit of time is less than that of sufentanil. We found that lower opioid administration reduces the incidence of adverse effects, consistent with Tao [19] and Han findings [20].

This study found no association between surgery time and PONV. However, the surgery time of the PONV (+) group was shorter than that of the PONV (–) group, which could be because more patients in the PONV (+) group underwent pulmonary wedge resection. However, this result contradicts the previous studies [21]. Previous studies have shown that long surgery duration is one of the risk factors for PONV. The reason for this may be due to differences in anesthesia protocols. The previous studies included general anesthesia patients, with some not receiving regional blocks. Therefore, the long surgery time may represent a more complex procedure, surgical trauma, and post-operative opioid consumption, thus increasing the PONV incidence. However, in this study, all patients received preoperative thoracic paravertebral block, which is effective in relieving postoperative pain after thoracoscopic surgery, and its effect can last for about 20 h after surgery [22]. Therefore, the post-operative pain was effectively controlled by the thoracic paravertebral block despite PONV (–) patients having a longer operative time. As a result, the longer operative time did not significantly increase postoperative opioid consumption.

This study had a 5.2% PONV incidence, significantly lower than the 25% PONV incidence in the study by Okajima and his colleagues [10]. These findings could be due to: (1) in this study, patients consumed fewer intraoperative opioids; (2) many patients used oxycodone PCIA, thus reducing post-operative opioid consumption; and (3) all patients received 5-HT3 receptor antagonists at the end of surgery as prophylactic antiemetic medication. Apfel and colleagues found that 5-HT3 receptor antagonists reduce the PONV incidence by

approximately 25% [7]. Routine application of 5-HT3 receptor antagonists may also be one of the reasons for the low overall PONV incidence in this study.

In this study, the post-operative NRS scores were higher in the PONV (+) group than in PONV (-) group. However, both groups had lower NRS scores with unrealistic differences. Previous studies have shown hyperalgesia with remifentanil dosage above 0.1 $\mu g\,kg^{-1}\,min^{-1}$ for more than 30 min [23]. A study by Mauermann with colleagues on 21 healthy volunteers showed that high fentanyl dosage reduces pain intensity and causes hyperalgesia, and the effects lasted until 4–6 h [24]. Sufentanil, a member of the fentanyl family, may also cause hyperalgesia in patients. However, no studies directly show that sufentanil has these characteristics. Hyperalgesia increases postoperative pain and, thus, postoperative opioid requirements, increasing the PONV incidence.

This study had several limitations. First, this was a retrospective observational study that showed the association between sufentanil consumption and PONV risk, but it did not explore the causal association. Second, the generalizability of the findings is limited since this study was a single-center study. Third, although the PONV assessment is one of the standardized assessments for post-operative patients in our center, the assessment quality may still be poor compared to prospective studies. In addition, the severity or frequency of PONV was not determined. Finally, we obtained information on prophylactic antiemetic medications and the patient's smoking history. However, information on other risk factors, including PONV history and motion sickness history, was not obtained, which may have influenced our findings. Thus, the actual relationship between sufentanil and PONV risk was not established. Because of these limitations, this is only a hypothesis-generating study. Further studies are needed to refute or confirm our findings.

CONCLUSIONS

In this retrospective observational study, intraoperative sufentanil administration increased the risk of PONV in patients who received a preoperative thoracic paravertebral block and underwent thoracoscopic surgery under general anesthesia. A time-weighted average of sufentanil higher than 0.21 $\mu g\,kg^{-1}\,h^{-1}$ was an independent risk for PONV.

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Author Contribution. All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Ran Zhang, Wei Xin Zhang, and Xiao Ran Ma. The first draft of the manuscript was written by Ran Zhang and all authors commented on previous versions of the manuscript. Yi Feng helped design, review, and modify the study design. All authors read and approved the final manuscript.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval. The study protocol was reviewed and approved by the Academic Committee of Peking University People's Hospital (approval No. 2020PHB308-01). Because this study was retrospective, the ethics committee considered informed consent unnecessary and

therefore waived the requirement to obtain informed consent.

Conflict of Interest. The authors declare no conflicts of interest.

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