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Effect-site concentrations of remifentanil for smooth emergence from combined epidural–general anesthesia or general anesthesia in patients using video double-lumen tube: A randomized trial

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ABSTRACT

Objective: The present study aimed to determine the effect-site concentration of remifentanil of 90% (EC_{90}) for smooth emergence in patients with a video DLT (VDLT) under sevoflurane-maintained general anesthesia and to investigate whether the EC_{90} was affected by epidural anesthesia.

Methods: One hundred and twenty patients who underwent video-assisted thoracic surgery (VATS) were enrolled. Patients received either general anesthesia combined with epidural anesthesia (PEA group, n = 60) or general anesthesia (GA group, n = 60). The primary outcome was the EC_{90} for smooth emergence in both groups. The secondary outcomes were intraoperative emergence, smooth emergence, recovery, and hemodynamic profiles in both groups.

Result: The EC_{90} values for smooth emergence in patients using VDLT were 3.5 ng/ml (95% confidence interval [CI], 3.3–4.4 ng/ml) in the PEA group and 2.7 ng/ml (95% CI, 2.5–3.2 ng/ml) in the GA group. The total amount of remifentanil infusion during emergency was significantly higher in the PEA group (164.6 ± 47.9 μg) than in the GA group (127.1 ± 30.4 μg) ($P < 0.001$). The number of patients who experienced hypotension during emergency in the PEA group was higher than that in the GA group (46.7% versus 13.3%, $P < 0.001$).

Conclusion: The EC_{90} of remifentanil for smooth emergence in patients with VDLT under general anesthesia combined with epidural anesthesia (3.5 ng/ml) was higher than that under general anesthesia (2.7 ng/ml).

Trial registration: Chinese Clinical Trial Registry, ChiCTR2100054230.

1. Introduction

During emergence from general anesthesia, coughing caused by the endotracheal tube is thought to be associated with laryngeal injury (sore throat, hoarseness, pharyngeal edema, or laryngospasm), circulatory fluctuations, bleeding, wound dehiscence, or tear of

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the surgical site anastomosis [1,2]. Many methods have been used to prevent coughing (i.e., smooth emergence [extubation without coughing]) [3–5], such as intravenous opioids [6,7], dexmedetomidine [8,9], lidocaine [10,11], application of lidocaine/prilocaine cream on the surface of the tracheal tube cuff [12] and extubation under deep anesthesia [13]. Among these, remifentanil is ranked highest for smooth emergence [14], and remifentanil target-controlled infusion (TCI) is commonly used for this purpose [7,15–17].

Previous studies have determined the effect-site concentrations (Ces) of remifentanil of 50% and 95% (EC_{50} and EC_{95}, respectively) for smooth emergence using a single-lumen tube (SLT) [15,16,18]. The double-lumen tube (DLT) is widely used in thoracic surgery for lung isolation. The DLT has a larger outer diameter, and its bronchial end needs to be placed into the bronchia, which may cause more irritation to the airway [19]. Therefore, the Ce of remifentanil for smooth emergence in patients with a DLT may be different from that in patients with an SLT. In propofol-maintained general anesthesia, the EC_{50} values for smooth emergence were 3.76 ng/ml in patients with a DLT [20] and 1.67 ng/ml in sevoflurane-maintained female patients with a DLT [7]. These limited reports provide preliminary information and reference for clinical practice, but there are still issues that need to be addressed. One important concern is that regional anesthesia (epidural anesthesia, paravertebral block, erector spinae plane block) combined with general anesthesia is commonly performed in thoracic surgery, even in popular video-assisted thoracic surgery (VATS). Opioid requirements [21,22] and maintenance concentrations of propofol [22] or sevoflurane [21,23] in general anesthesia are significantly reduced by these regional blocks. Therefore, it is possible that the Ce of remifentanil for smooth emergence under general anesthesia combined with regional block is different from that under general anesthesia. Additionally, video DLT (VDLT) has become increasingly popular recently, and compared to a DLT, the VDLT offers a reduced intubation time and need for fiberoptic bronchoscopy, constant visualization of the airways, and easier use than the DLT [24]. However, the configuration of the outer diameter measured at the proximal edge of the tracheal cuff of the VDLT was larger than that of the DLT, which may cause more irritation to the airway [25] and thus impact the dose of remifentanil for smooth emergence. To address these concerns, it is imperative to determine the Ce of remifentanil for smooth emergence from general anesthesia combined with regional block or general anesthesia in patients with a VDLT.

In the present study, the first biased-coin design up-and-down sequential method (BCD-UDM) was used to determine the EC_{90} for smooth emergence using a VDLT in patients under sevoflurane-maintained general anesthesia, and we investigated whether this EC_{90} was affected by epidural anesthesia to provide a dosing regimen of remifentanil for the prevention of emergence coughing in thoracic surgery.

2. Methods

2.1. Study design

This was a prospective, randomized, controlled, patient- and assessor-blinded, single-center clinical study. Ethical approval for this study (B2021-783) was provided by the Ethical Committee of Zhongshan Hospital, Fudan University, Shanghai, China (Chairperson Prof Jia Fan) on November 30, 2021. This study was registered in the Chinese Clinical Trial Registry (identifier number: ChiCTR2100054230) on December 11, 2021. The authors adhered to the Consolidated Standards of Reporting Trials statement and Declaration of Helsinki for reporting randomized controlled trials. Informed consent was obtained from all patients before enrollment.

2.2. Study population

A total of 120 patients aged between 18 and 65 years, with American Society of Anesthesiologists classifications I–II, who underwent elective lung resection with a VDLT from December 2021 to March 2022 at Zhongshan Hospital, Fudan University were recruited. Exclusion criteria were patients with severe respiratory disease, chronic obstructive pulmonary disease, asthma, airway hyperreactivity, history of upper respiratory tract infection or recent tracheobronchitis (during the last 2 weeks), decompensated cardiac disease such as coronary artery disease, severe valvular disease, contraindication to epidural block, history of antitussive drug use, long-term opioid exposure due to chronic pain, history of remifentanil allergy, women during pregnancy or lactation, and participation in any drug clinical trial within 30 days prior to the start of the study. The withdrawal criterion was an unexpected midway change to open surgery. Patients were assigned and randomized according to computer-generated random numbers that were concealed in envelopes, and patients who received either general anesthesia combined with epidural block (PEA group, n = 60) or general anesthesia (GA group, n = 60) were analyzed separately.

2.3. Anesthesia protocol

No premedication was administered before induction. Epidural puncture and catheterization were performed in the PEA group at T_6-T_7, with a dose of 3 ml of 2% lidocaine administered to ensure a successful epidural block. An 18-gauge indwelling needle was used to establish the upper limb and lactated Ringer's solution was administered at 6–10 ml/kg/h in the operating room. Electrocardiography, heart rate (HR), noninvasive blood pressure, oxygen saturation (SpO_2), and bispectral index (BIS) were monitored, and general anesthesia was induced via effect-site TCIs of 4–5 μg/ml of propofol (TCI device; Cardinal Health, Basingstoke, United Kingdom) based on a three-compartment population pharmacokinetic model defined by Schnider et al. [26]. and 3–4 ng/ml of remifentanil (commercial TCI pump; Orchestra Base Primea, Fresinus Vial, France); the pumps were operated using the Minto pharmacokinetic model for remifentanil [27]. Rocuronium (0.6 mg/kg) was administered after the patient lost consciousness. A VDLT (Well Lead Medical Co., Ltd., Guangzhou, China) was used for all patients. The size of the VDLT was selected according to the left main bronchial internal diameter and patient's height, and a smaller tube was selected if necessary in the Asian population [28–30]. A

35–37-French (Fr) DLT was selected for male patients, whereas a 32–35-Fr DLT was selected for female patients. After intubation, radial artery catheterization was performed to measure invasive blood pressure.

During one-lung ventilation, the ventilation parameters of the two groups were set as follows: fraction of inspired oxygen, 70–100%; tidal volume, 5–7 ml/kg; respiratory frequency, 12–14 times/min; positive end-expiratory pressure, 5 mmHg; and flow rate, 2.0 L/min. Patient end-tidal carbon dioxide was maintained in the range of 35–55 mmHg. Anesthesia was maintained with sevoflurane at 0.7–1.0 minimum alveolar concentration (MAC), and the BIS value was maintained between 40 and 60. Ropivacaine 0.15% was administered intermittently in the PEA group, and fentanyl and rocuronium were titrated when needed. Proacetamol (2 g) and ketorolac (30 mg) were administered to all patients as part of multimodal analgesia.

Before suturing the skin, the TCI of remifentanil was started at a preset concentration until extubation, and sevoflurane was washed out simultaneously. At the end of suturing, sugammadex sodium (2–4 mg/kg) was administered to reverse the neuromuscular block. The assistant anesthesiologist who waited outside and was blinded to the grouping information was called into the operating room to wake the patients by calling out their name and gently tapping their shoulder every 15 s; all other stimuli were avoided. When the patients could breathe adequately and open their eyes spontaneously or act after a verbal command, the VDLT was removed. Immediately after extubation, the remifentanil infusion was stopped, and 50% oxygen was supplied via a facial mask. After close observation for 3 min, the patient was transferred to the post-anesthesia care unit (PACU).

2.4. BCD-UDM

The BCD-UDM was performed as follows, and the two groups were studied separately. According to the previous study on the inhibition of emergency coughing in patients with an SLT [6,31], the effect-site concentration of remifentanil received in the first patient of the two groups was set at 2.5 ng/ml. For the subsequent patient, the remifentanil concentration was based on the previous patient's response. If a patient experienced smooth emergence before completion of the study, the concentration of remifentanil set for the next patient was randomized with a biased coin, with 11% (b = 0.11) probability of decreasing by one unit (0.5 ng/ml) and 89% (1-b = 0.89) probability of remaining at the same dose [32], with a concentration change set as an increment or decrement of 0.5 ng/ml; the concentration change was determined as a value greater than the standard deviation (SD) in the previous study [6]. If coughing occurred in the previous patient, the concentration of remifentanil was increased by 0.5 ng/ml.

In a dose-finding study using the BCD-UDM, the distribution of data was unknown and not independent. Simulation studies suggested that the stopping rule of enrolling at least 20–40 participants can provide a stable estimate of the target dose for most realistic cases [32,33]. A larger sample size results in increased statistical accuracy, as is evident from the smaller standard errors [34]. Thus, we chose a sample size of 60 to accommodate a potential dropout rate of 5% for each group. A total of 120 patients were recruited, and additional patients were recruited if the number of positive reactions was insufficient until there were 45 patients with a positive response in any of the two groups.

The EC_{90} along with the 95% confidence intervals (CIs) was calculated via the BCD-UDM and isotonic regression method along with the pooled-adjacent-violators algorithm approach (PAVA) using R software, version 3.4.4 (R Foundation of Statistical Computing, Vienna, Austria).

2.5. Data collection

Two practitioners were involved in the emergence phase. Biased-coin allocation was conducted via a series of random responses generated by a computer, and group assignment was concealed in the envelopes. The first anesthesiologist prepared the envelopes and unveiled the group to the subsequent patient. The first anesthesiologist set the TCI of remifentanil according to the given information. The TCI pump was shielded with an opaque covering, and the epidural catheter was covered. The patients and outcome evaluators were blinded to the study settings. The first anesthesiologist also recorded the remifentanil dose, end-tidal sevoflurane concentration, end-tidal carbon dioxide, and other hemodynamic parameters during the procedure and emergence period.

The second anesthesiologist performed extubation, assessed the cough scale score and recorded other complications. The primary outcome was the EC_{90} for smooth emergence in both groups. The secondary outcomes were intraoperative emergence, smooth emergence, recovery, and hemodynamic profiles. Intraoperative fentanyl consumption and the amount of remifentanil infusion during emergencies were recorded. The time interval between the end of the procedure and removal of the VDLT was referred to as the extubation time. The type of surgery, number of incisions, and size of the VDLT were recorded.

The severity of the cough or straining during the emergence period was recorded using a modified 5-point Likert scale based on the Minogue scale [35]: grade 1, no coughing or muscular stiffness; grade 2, single cough response to removal of the tracheal tube that resolved after extubation; grade 3, moderate coughing ($\leq$3 coughs, each lasting for 1–2 s); grade 4, severe cough or muscular stiffness ($\geq$4 coughs, each lasting >2 s); and grade 5, severe restlessness and associated laryngospasm. Herein, grade 1 or 2 was defined as successful smooth emergence. Failure of smooth emergence was defined as the development of grades 3–5. The mean atrial pressure (MAP), HR, BIS, and MAC values were recorded at different time points. From the start of remifentanil infusion, the numbers of patients with bradycardia (HR < 40 beats/min [bpm], treated with intravenous atropine [0.5 mg]), tachycardia (HR > 100 bpm, treated with intravenous esmolol in 10-mg increments), and hypotension (MAP <60 mmHg, treated with vasopressors with intravenous phenylephrine at 0.1-mg increments) were recorded.

Post-anesthetic recovery assessment: After extubation, the numbers of patients with hypoventilation (respiratory rate <8 bpm) and desaturation (SpO_2 <95%) were recorded. Postoperative pain was assessed using the numerical rating scale (NRS) score. Fentanyl (50 μg) was given to patients immediately as a rescue analgesic when the NRS score was $\geq$4. The Ramsay sedation scale score [36], NRS

score, presence of hoarseness or sore throat, and presence of postoperative nausea and vomiting were assessed and recorded 30 min after admission to the PACU.

3. Statistical analysis

Descriptive statistics were used to summarize patients' demographic characteristics and secondary outcomes. Quantitative data are expressed as mean ± SD and were compared using the two-independent sample *t*-test, whereas categorical variables were compared between the groups using the χ^2 test. The Wilcoxon rank-sum test was used to analyze data that were not normally distributed; such data are expressed as median (interquartile range). To explore whether the two groups had similar baseline hemodynamic variables, the Student's t-test was used to compare MAP and HR.

Statistical significance was set at $P < 0.05$. Data were analyzed using the R software (version 4.1.1). A biomedical statistician reviewed the statistical methods and techniques used in this study.

4. Results

4.1. Patient characteristics

The study included 120 patients undergoing elective lung resection surgery (Fig. 1): 60 in the PEA group and 60 in the GA group. None of the patients failed to complete the trial or withdrew from the study. There were no significant differences in demographic and surgical characteristics between the groups. Intraoperative fentanyl consumption was significantly less in the PEA group than in the GA group (178.5 ± 43.6 versus [vs.] 459.8 ± 83.1, $P < 0.001$) (Table 1).

4.2. Primary outcomes

The up-and-down sequences of failed and successful smooth emergence are shown in Fig. 2A and B, which demonstrates the allocation sequence of Ce of remifentanil according to the biased-coin design. According to isotonic regression analysis, the EC_{90} values for smooth emergence were 3.5 ng/ml (95% CI, 3.3–4.4 ng/ml) with a VDLT in the PEA group and 2.7 ng/ml (95% CI, 2.5–3.2 ng/ml) in the GA group. The adjusted success rates from the PAVA are depicted in Fig. 3. The total amount of remifentanil during emergency was significantly larger in the PEA group (164.6 ± 47.9 μg) than in the GA group (127.1 ± 30.4 μg) ($P < 0.001$) (Table 2).

4.3. Secondary outcomes

The emergency profiles are listed in Table 2. The extubation time and the severity of cough were comparable between the groups. Among respiratory complications, 5 patients in the PEA group and 8 patients in the GA group had hypoventilation; however, all patients responded to the encouragement of breathing without desaturation. The MAC value before extubation, the BIS value before and after extubation were also comparable between the groups. None of the patients in either group developed a laryngospasm. The numbers of patients with hypotension during emergency was higher in the in PEA group than in the GA group (46.7% vs. 13.3%, $P < 0.001$). None of the patients in either group experienced bradycardia or tachycardia during emergency.

A hemodynamic comparison of the MAP and HR at each time point is shown in Fig. 4A and B, respectively. The MAP was significantly lower in the PEA group than in the GA group at T_2 (76.6 ± 8.3 mmHg vs. 80.6 ± 11.6 mmHg, $P = 0.035$), T_4 (88.3 ± 11.2

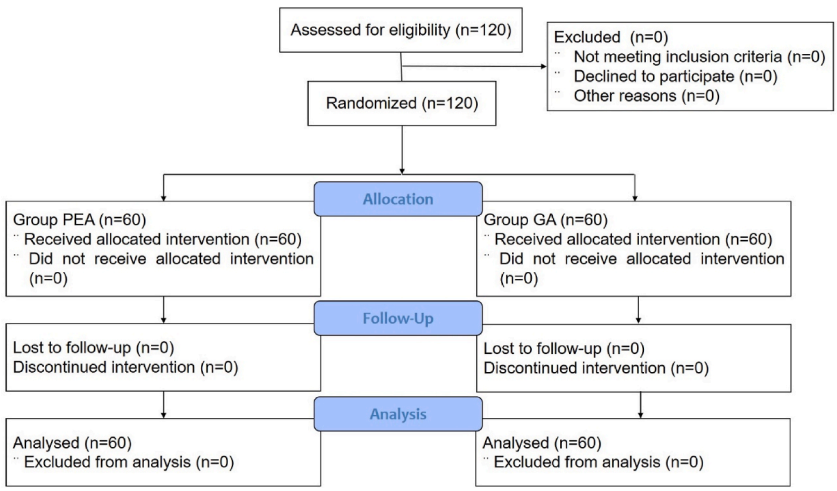

Fig. 1. Flowchart of the study.

Table 1
Demographic and surgical characteristics.

Variables	Group PEA	Group GA	*P*-value
Age (years)	54.1 ± 10.0	52.2 ± 9.6	0.287
Sex			0.085
Male	26 (43.3%)	16 (26.7%)	
Female	34 (56.7%)	44 (73.3%)	
Height (cm)	165.2 ± 6.8	163.6 ± 7.1	0.207
Weight (kg)	65.1 ± 12.4	62.0 ± 9.6	0.127
BMI (kg/m^2)	23.7 ± 3.3	23.1 ± 2.5	0.240
ASA grade			0.465
I	27 (45.0%)	32 (53.3%)	
II	33 (55.0%)	28 (46.7%)	
Mallampati airway			0.570
I	28 (46.7%)	31 (51.7%)	
II	29 (48.3%)	24 (40.0%)	
III	3 (5.0%)	5 (8.3%)	
History of hypertension	15 (25.0%)	8 (13.3%)	1.936
History of diabetes mellitus	5 (8.3%)	3 (5.0%)	0.714
Smoking cessation < 8w	9 (15.0%)	6 (10.0%)	0.581
Duration of surgery (min)	92.0 ± 36.9	80.8 ± 31.2	0.077
Intraoperative fentanyl consumption (μg)	178.5 ± 43.6	459.8 ± 83.1	<0.001
Type of surgery			0.130
lobectomy	33 (55.0%)	22 (36.7%)	
segmentectomy	9 (15.0%)	12 (20.0%)	
wedge resection	18 (30.0%)	26 (43.3%)	
Number of incisions	2.2 ± 0.9	1.9 ± 0.9	0.160
Size of VDLT			0.153
32	34 (56.7%)	42 (70.0%)	
35	11 (18.3%)	11 (18.3%)	
37	15 (25.0%)	7 (11.7%)	

All data are presented as the mean ± SD or the number of patients (percentage). VDLT, video double-Lumen tube.

mmHg vs. 93.4 ± 14.7 mmHg, P = 0.032), and T_5 (94.5 ± 11.5 mmHg vs. 99.9 ± 15.5 mmHg, P = 0.029). The HR of the two groups were comparable at all time points.

Recovery profiles after admission to PACU are listed in Table 3. Ramsay sedation scores were comparable 30 min after admission to the PACU in both groups. Patients in the PEA group had a lower NRS pain score at 30 min after admission to the PACU than those in the GA group (0.2 ± 0.4 vs. 0.80 ± 1.0, P < 0.001). Two patients in the GA group complained of pain with an NRS score >4 in the PACU and were treated with 50 μg of fentanyl each. The incidence of postoperative nausea and vomiting, sore throat and hoarseness were comparable between the groups.

5. Discussion

Although an infusion of remifentanil is an effective method for smooth emergence after general anesthesia [14], the optimal Ce of the TCI of remifentanil in patients with a VDLT has not been systematically investigated, and there is especially a lack of guiding information in the context of general anesthesia or general anesthesia combined with regional anesthesia. Therefore, we conducted this study to elucidate these concerns in patients undergoing elective thoracic surgery.

The primary outcome of this study was the EC_{90} for smooth emergence. For practitioners, a higher percentile (e.g., EC_{90}) is more clinically significant, whereas extrapolation through the Dixon–Mood sequential method to the higher percentile of the lowest effective concentration is unreliable and limits its clinical value, which may impose substantial bias [33]. Sequence-preserving regression analysis is a statistical method commonly used in clinical trials, which is based on the assumption that the probability of efficacy of a drug does not decrease as the dose increases, whereas the BCD-UDM and PAVA algorithms can directly estimate the effect-site concentration (EC) at any quartile [32], which is preferred for the estimation of higher or lower tail quantiles, such as ED_{90} or ED_{10} [34].

The reported EC_{50} values for smooth emergence in patients with an SLT were approximately 1.0–2.5 ng/ml [6,18,31]. The DLT is curved, larger in diameter, higher in rigidity, and inserted deeper into the main bronchus level than an SLT [19,37], and it is reasonable to assume that the EC of remifentanil for smooth emergence with a DLT is higher than that with an SLT. Lee et al. [7] reported that in female patients under general anesthesia maintained by sevoflurane, the EC_{50} and EC_{95} values for suppression of cough during DLT extubation were 1.67 ng/ml and 2.28 ng/ml, respectively. In Kang's study of the DLT, the EC_{50} was 3.76 ng/ml and the EC_{95} was 4.92 ng/ml [20]. In the present study, the EC_{90} for smooth emergence was 3.5 ng/ml in epidural general anesthesia, which was higher than that in general anesthesia (2.7 ng/ml). The first reason for these concentration differences between our study and previous studies is that we only calculated the EC_{90}, not the EC_{50} and EC_{95}. Second, although these two studies also enrolled patients undergoing VATS, only general anesthesia with different protocols was performed. Moreover, the definition of the severity of coughing was inconsistent between the studies. In Lee's study, coughing was defined as a sudden contraction of the abdominal muscle, and there was no clear

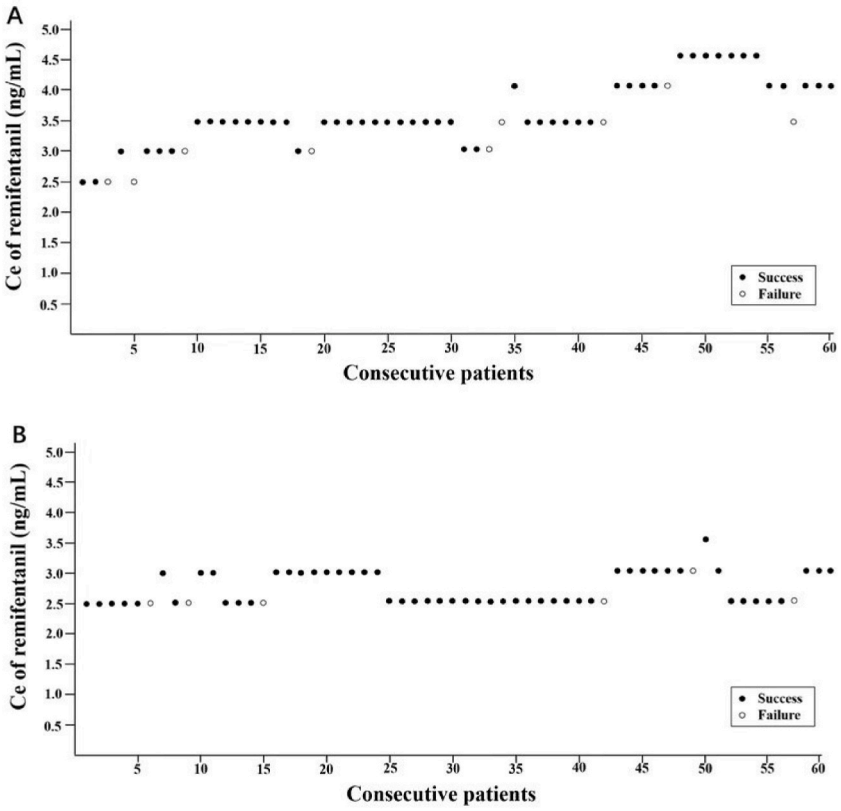

Fig. 2. The biased coin design up-and-down sequence. Graph of successful (solid circle) and failed (hollow circle) with different remifentanil concentrations in PEA group (A) and GA group (B).

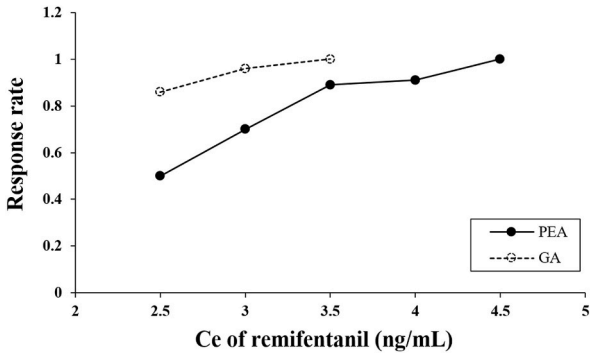

Fig. 3. Pooled adjacent violators algorithm (PAVA) response rates in PEA group (solid circle) and GA group (hollow circle).

description of coughing in Kang's study. In the present study, a modified 5-point Likert scaled based on the Minogue scale [35] was used, and grade 1 or 2 was defined as successful smooth emergence. In other words, the patient can maintain no coughing, muscular stiffness, or a single cough response to the removal of the DLT that resolves after extubation, which is clinically acceptable and more in accordance with the clinical setting. In addition, the traditional DLT was used in previous studies, whereas the VDLT was used in the present study; it has been reported that the outer diameter measured at the proximal edge of the tracheal cuff of the VDLT was larger than that of the DLT [25]. We, therefore, speculated that a larger tube may cause more irritation to the airway and thus change the doses of remifentanil. Finally, the intraoperative fentanyl consumption was significantly higher in the GA group than in the PEA group, and the large doses of fentanyl-induced residual effects may explain why the EC_{90} for smooth emergence was higher in the PEA group than in the GA group. In addition, the extubation time in PEA group (4.7 $\pm$ 3.2min) was slightly longer than that in GA group (3.8 $\pm$ 2.8min), which may also attribute to the higher doses of remifentanil during emergence period in PEA group.

Remifentanil is an ultra-short-acting opioid drug with a short context-sensitive half-time, which guarantees rapid onset and

Table 2
Emergency profiles of two groups.

Variables	Group PEA	Group GA	*P*-value
Extubation time (min)	4.7 ± 3.2	3.8 ± 2.8	0.114
Amount of remifentanil infusion during emergency (μg)	164.6 ± 48.0	127.1 ± 30.4	<0.001
Severity of cough	1.7 ± 1.0	1.6 ± 0.8	0.475
MAC value before extubation	0.04 ± 0.05	0.04 ± 0.05	1
BIS immediately before extubation	41.4 ± 9.0	41.7 ± 7.7	0.862
BIS immediately after extubation	96.8 ± 1.6	96.4 ± 1.5	0.241
Hypoventilation	5 (8.3%)	8 (13.3%)	0.557
Desaturation	0	0	–
Bradycardia/tachycardia	0/0	0/0	–/–
Laryngospasm	0	0	–
Hypotension	28 (46.7%)	8 (13.3%)	<0.001

All data are presented as the mean ± SD or the number of patients (percentage). MAC, minimum alveolar Concentration; BIS, bispectral index.

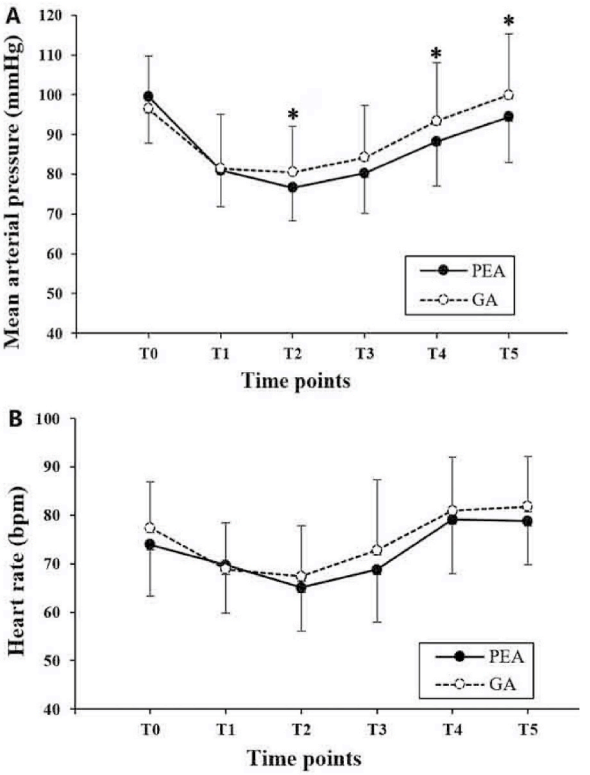

Fig. 4. Hemodynamics of two groups during emergence. T_0, Before induction; T_1, Before remifentanil infusion during emergence; T_2, The end of surgery; T_3, Immediately before extubation; T_4, Immediately after extubation; T_5, 3 min after extubation. *P < 0.05 vs. GA group.

minimal accumulation risk [38]. Even at a target Ce of 6 ng/ml, critical complications such as desaturation, hypotension, and bradycardia were not observed in patients with American Society of Anesthesiologists (ASA) classifications I–II, although chest wall rigidity was suspected in 2.34% of patients, which was described as mild and transient chest discomfort [39]. Simone et al. [40] reported a case series of a TCI of remifentanil for conscious sedation during endobronchial ultrasound-guided transbronchial needle aspiration. During the procedure, the Ce of remifentanil was adjusted between 3 and 4 ng/ml in relation to the clinical response with Ramsey scores of 2–3, and 2 of 20 patients experienced over-sedation (Ramsey score >3) and mild hypoxia; however, patients could breathe on command. Herein, although some patients in both groups experienced hypoventilation, all of them responded to the encouragement of breathing without desaturation. Regarding other safety concerns, more patients needed additional vasopressors during emergency in the PEA group than in the GA group, which may be attributed to a higher dose of remifentanil infusion and epidural anesthesia-induced vasodilation. Moreover, it is reasonable that patients in the PEA group had a lower NRS score of pain 30 min after admission to the PACU than those in the GA group, which indicated the better analgesic effects provided by epidural anesthesia.

BIS monitoring is considered a reliable method for monitoring one's state of consciousness [41]. Ferreira et al. found that under

Table 3
Recovery profiles after admission to PACU.

Variables	Group PEA	Group GA	*P*-value
Ramsay sedation score 30min after admission to PACU			0.559
1	0	0	
2	59 (98.3%)	58 (96.7%)	
3	1 (1.7%)	2 (3.3%)	
NRS score of pain 30min after admission to PACU	0.2 ± 0.4	0.8 ± 1.0	<0.001
Rescue analgesia (NRS≥4)	0	2 (3.3%)	0.362
PONV	0	0	–
Sore throat	13 (21.7%)	6 (10.0%)	0.134
Hoarseness	0	1 (1.7%)	0.315

All data are presented as the mean ± SD or the number of patients (percentage). PACU, post-Anesthesia care unit; PONV, postoperative nausea and vomiting.

total intravenous anesthesia with propofol and remifentanil, a bolus of remifentanil decreases the BIS value, an effect independent of intubation and surgical stimuli [42]. In the present study, with the washout of sevoflurane, remifentanil was the dominant drug affecting the BIS value, which was maintained at approximately 40–50. Additionally, when calling a patient's name or applying a small stimuli such as tapping on the shoulder before extubation, the BIS value suddenly reached 90–100; thus, the "all or none" phenomenon of remifentanil deserves to be further studied.

Our study has several limitations. First, our study investigated the EC_{90} in sevoflurane-maintained anesthesia; however, anesthesia maintenance with propofol or other inhalational agents may also have affected the results [15,43,44]. For example, the use of desflurane for anesthesia maintenance was associated with faster emergence but a higher incidence of coughing [45]. Second, in addition to epidural block, thoracic paravertebral block, intercostal nerve blocks, serratus anterior plane block, and erector spinae plane block are also supplements to general anesthesia [46,47], and we only investigated whether the EC_{90} for smooth emergence was affected by epidural anesthesia. However, the results of the present study revealed a tendency that more intravenous opioids used intraoperatively may be correlated with less remifentanil during emergencies. Third, it is difficult to simulate effect-site fentanyl concentration which is due to its relatively long context-sensitive half-time, and thus fentanyl was titrated when needed and only the total amount of fentanyl was presented. Lastly, the present study recruited only patients with ASA classifications I–II, so it is premature to extrapolate our protocol to the senile and debilitated population.

6. Conclusions

In patients undergoing VATS with epidural general anesthesia and general anesthesia, the EC_{90} values for smooth emergence with a VDLT were 3.5 ng/ml and 2.7 ng/ml, respectively. This practice effectively inhibits coughing and maintains hemodynamic responses, with minor adverse events. We suggest that remifentanil infusion be continued during the emergence period until the DLT is successfully removed.

Authors' contributions statement

Yuxin Li: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper. Siying Li: Contributed reagents, materials, analysis tools or data. Ling Jiang: Conceived and designed the experiments; Performed the experiments; Wrote the paper. Yiming Liu: Conceived and designed the experiments; Analyzed and interpreted the data. Changhong Miao: Conceived and designed the experiments; Performed the experiments. Chao Liang: Conceived and designed the experiments; Performed the experiments.

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Data availability statement

Data will be made available on request.

Additional information

The clinical trial described in this paper was registered at Chinese Clinical Trial Registry under the registration number ChiCTR2100054230.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e18897.

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