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Galaxy Publication

An Up-and-Down Sequential Allocation Trial to Determine the EC50 and EC95 of Remifentanil for Suppression of Bronchoscopic Responses in Elderly Patients Undergoing Fiberoptic Bronchoscopy with Ciprofol Sedation

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ABSTRACT

Opioid agents are commonly administered to control cough during fiberoptic bronchoscopy (FOB). Nevertheless, data defining the optimal remifentanil dosing when FOB is performed under ciprofol sedation remains insufficient. The present study was designed to determine the effective concentrations (EC) of remifentanil needed to attenuate bronchoscopy-related responses in elderly patients undergoing FOB with ciprofol sedation. Patients between 60 and 90 years of age with an American Society of Anesthesiologists (ASA) classification of I–III who were scheduled for fiberoptic bronchoscopy were recruited for this study. Participants were categorized into two groups based on sex (male and female). Remifentanil was given intravenously before the administration of ciprofol. The primary observations included reactions during the procedure, specifically vocal cord activity, coughing episodes, and patient movement. The median effective concentration (EC50) and the 95% effective concentration (EC95) of remifentanil needed to suppress these responses were estimated for each sex using Dixon's up-and-down sequential design. In addition, a dose–response curve was established through Probit analysis. A total of 39 participants were included in the study, comprising 19 men and 20 women. The median effective plasma concentration (EC50) of remifentanil needed to attenuate responses during FOB with ciprofol sedation was 3.25 (2.75–3.26) ng/mL in males and 2.25 (1.75–2.25) ng/mL in females, showing a statistically significant difference (P = 0.0023). According to Probit modeling, the estimated EC50 values were 3.102 ng/mL (95% CI: 2.694–3.749) for males and 2.052 ng/mL (95% CI: 1.345–2.750) for females. The corresponding EC95 values required to suppress bronchoscopic responses were 3.741 ng/mL (95% CI: 3.366–7.699) in males and 2.943 ng/mL (95% CI: 2.456–9.533) in females. The data suggest a clear difference between male and female patients in the remifentanil concentrations (EC50 and EC95) needed to control bronchoscopic responses during FOB with ciprofol sedation, while still allowing preservation of spontaneous breathing in the elderly population.

Keywords: Ciprofol, Remifentanil, Anesthesia, Bronchoscopy, Effective concentration

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Introduction

The swift pace of worldwide demographic aging is placing a heavy burden on healthcare systems [1]. The frequency of lung disorders, in particular, is climbing quickly and mainly affects the older population. In clinical settings, fiberoptic bronchoscopy (FOB) represents a leading modality for detecting and treating such ailments. Present-day protocols endorse performing this examination with sedation to limit coughing spells and operative stress [2, 3]. Propofol is a standard sedative choice. However, it has several disadvantages, including discomfort at the injection site and hemodynamic and ventilatory suppression, underscoring the need for alternative options

[4]. Ciprofol is a novel intravenous general anesthetic agent. By binding to gamma-aminobutyric acid-A receptors (GABAARs), ciprofol produces reliable sedation with rapid induction and emergence, without local pain upon administration [5-7]. This drug likewise shields the heart by attenuating oxidative stress in murine models [8]. Ciprofol has already found effective application in general anesthesia [6, 9-11]. and for calming patients in critical care environments [7].

Opioid agents like alfentanil and remifentanil are routinely administered to blunt coughing during FOB [12, 13]. The ciprofol-remifentanil combination has proven effective in younger subjects undergoing FOB [14].Yet, evidence is scarce concerning the ideal remifentanil dosing to block bronchoscopic reflexes during deep sedation with ciprofol in the geriatric population. This investigation aimed to determine the EC_{50} and EC_{95} values of remifentanil required to abolish FOB reactions via the laryngeal mask (LMA) during ciprofloxacin-induced sedation, with spontaneous respiration maintained, in older patients. We hypothesize that sex-based differences exist in the EC_{50} and EC_{95} values of remifentanil for suppressing FOB-triggered responses in elderly individuals.

Materials and Methods

The research protocol was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (approval No. 2023-E606-01). Registration of the clinical trial was completed in advance on chictr.org.cn (ChiCTR2300077720; registered on 17 November 2023). This investigation was conducted in accordance with internationally accepted ethical standards, including the Declaration of Helsinki, and followed the TREND Statement for reporting. Before participation, all individuals were informed in detail about the study and voluntarily signed written informed consent forms.

Patients

Between 17 November 2023 and 30 December 2023, patients undergoing diagnostic bronchoscopy at the First Affiliated Hospital of Guangxi Medical University were recruited consecutively. Inclusion criteria required participants to be 60–90 years old and to have an ASA physical status of I–III.

Several conditions led to exclusion from the study. These included any contraindication to bronchoscopy, anticipated difficult airway management, marked airway narrowing, or acute infection. Patients were also excluded if they had a known allergy to opioids, uncontrolled hypertension (systolic ≥ 180 mmHg or diastolic ≥ 110 mmHg), or clinically significant arrhythmias such as sinus bradycardia with a heart rate below 50 beats per minute, second-degree or higher atrioventricular or ventricular block, or rhythm disturbances with a high risk of sinus arrest, including sick sinus syndrome.

Other exclusion criteria were severe cardiac dysfunction (NYHA class III or above), abnormal liver function tests indicating hepatic impairment, inability to accurately assess preoperative mental status, a documented history of psychotropic medication use, or any additional condition that investigators considered unsuitable for participation.

Study design

This trial employed an up-and-down sequential allocation approach, with separate stratification for male and female participants.

The EC50 of remifentanil for attenuating FOB-induced responses was derived through a modified Dixon sequential design. Following the accumulation of 7 crossover points, the median effective concentration was calculated as the mean of the midpoint doses from successive patient pairs, with supplementary estimation performed using Probit analysis [15, 16].

Based on preliminary testing, the initial target plasma concentration was set at 2 ng/mL. Thereafter, dosing was titrated in 0.5 ng/mL steps, either increased or decreased depending on the individual response during bronchoscopy. Enrollment was concluded once seven inflection points had been reached.

Sedation and bronchoscopy

Participants were instructed to fast for < 8 hours before anesthesia, and no premedication was administered. Continuous intraoperative monitoring included electrocardiography, non-invasive blood pressure (NIBP), peripheral oxygen saturation (SpO_2), respiratory rate (RR), end-tidal CO_2 ($ETCO_2$), and bispectral index (BIS). Before induction, all patients received preoxygenation via face mask at 6 L/min for 3 minutes.

Remifentanil was delivered via a target-controlled infusion (TCI) system, with adjustments made in 0.5 ng/mL increments based on the preceding patient's response during bronchoscopy. After stabilization of the target effect-site concentration, ciprofol was administered intravenously as a bolus dose of 0.4 mg/kg, followed by a continuous infusion of 0.2–1.0 mg/kg/h [17-19].

Once BIS decreased to ≤ 60, a laryngeal mask airway (LMA) was inserted manually, and correct placement was confirmed using auscultation and capnography. During maintenance anesthesia, BIS was kept between 50 and 60. Fiberoptic bronchoscopy was performed through the LMA by two experienced operators, with bronchoscope selection based on clinical judgment.

During the procedure, topical airway anesthesia was provided using lidocaine (20 mg/mL). The total dose was administered to specific airway regions, including the vocal cords (40 mg), trachea (100 mg), carina (40 mg), right main bronchus (40 mg), and left main bronchus (40 mg).

Assessment of bronchoscopy responses

Bronchoscopy responses were evaluated using a structured scoring system. This system comprised three components: vocal cord activity, cough response, and limb movement. Each component was graded on a four-level scale.

Vocal cord status was classified as: 1) complete relaxation; 2) inward movement during inspiration; 3) outward movement during inspiration; and 4) complete closure of the vocal cords.

Cough response was scored as: 1) no cough; 2) one to two coughs in succession; 3) three to four coughs in succession; and 4) more than five consecutive coughs.

Limb movement was assessed as: 1) no movement of the upper limbs, lower limbs, or trunk; 2) a single movement in any of these regions; 3) two movements; and 4) multiple movements involving all regions.

All assessments were performed during the first insertion of the fiberoptic bronchoscope through the laryngeal mask airway. The total bronchoscopy score ranged from 3 (best response) to 12 (worst response).

Study endpoints

The primary endpoint of the study was the occurrence of a bronchoscopy reaction, which was defined as a total bronchoscopy score greater than 6.

Secondary outcomes included hemodynamic and respiratory parameters recorded at predefined time points: 5 minutes before induction (baseline), loss of consciousness (LOC), BIS ≤ 60, completion of LMA insertion, initiation of FOB, completion of FOB, and time of eye opening. Additional secondary measures included total anesthetic consumption, anesthesia and bronchoscopy duration, and the lowest spontaneous respiratory rate and oxygen saturation (SpO_2).

Safety outcomes focused on adverse events, including the need for assisted ventilation and respiratory depression, defined by at least one of the following: respiratory rate ≤ 8 breaths/min, apnea, or SpO_2 ≤ 90% lasting ≥ 15 seconds. Other complications recorded were hypotension (≥ 20% reduction in mean arterial pressure from baseline), hypertension (≥ 20% increase in mean arterial pressure), sinus tachycardia (> 100 beats/min), sinus bradycardia (< 50 beats/min), injection site pain, delirium, hiccups, postoperative nausea and vomiting, and intraoperative awareness.

Statistical analysis

GraphPad Prism 9.0 (GraphPad, La Jolla, CA, USA) and SPSS version 25.0 (IBM, Chicago, IL, USA) were used for all statistical calculations. For continuous variables that followed a normal distribution (assessed via the Kolmogorov–Smirnov test), results are shown as mean ± SD. Comparisons for normally distributed measures such as MBP, heart rate (HR), and respiratory rate (RR) were carried out using repeated-measures ANOVA. An unpaired t-test was used to compare continuous variables with normal distributions. Non-normally distributed data were expressed as median with interquartile range and analyzed using the Mann–Whitney U test. Categorical variables are reported as counts and percentages, with group differences evaluated by Fisher's exact test. A p-value below 0.05 was considered statistically significant.

Results and Discussion

Patients

A total of 46 elderly patients were initially screened between 17 November 2023 and 30 December 2023. Of these, 39 patients (19 men and 20 women) consented to participate and were included in the final analysis, with no exclusions after enrollment. Baseline demographic data are summarized in **Table 1.**

There were no significant differences between groups in age, body mass index (BMI), or ASA physical status. In contrast, statistically significant differences were observed in both body weight (P = 0.0012) and height (P < 0.0001). The clinical indications for fiberoptic bronchoscopy and related diagnostic procedures were comparable between male and female participants **(Table 2).**

Table 1. Demographic characteristics of patients.

Characteristic	P-value	Female (n = 20)	Male (n = 19)	Overall (n = 39)
Age (years)	0.8783	68.65 ± 6.063	68.95 ± 5.977	68.79 ± 5.944
Weight (kg)	0.0012	49.75 ± 12.97	62.47 ± 9.137	55.95 ± 12.85
Height (cm)	< 0.0001	152.7 ± 5.244	165.1 ± 6.900	158.7 ± 8.703
BMI (kg/m$^{2)}$	0.3964	22.09 ± 3.212	22.94 ± 2.971	22.50 ± 3.128
ASA physical status(n)	0.4971			
II		4	3	7
III		16	16	32

Note: #Results are shown as either mean ± SD or patient count (n). Abbreviations: BMI = body mass index; ASA = American Society of Anesthesiologists.

Table 2. Reasons for performing fiberoptic bronchoscopy and associated diagnostic interventions (tabular format).

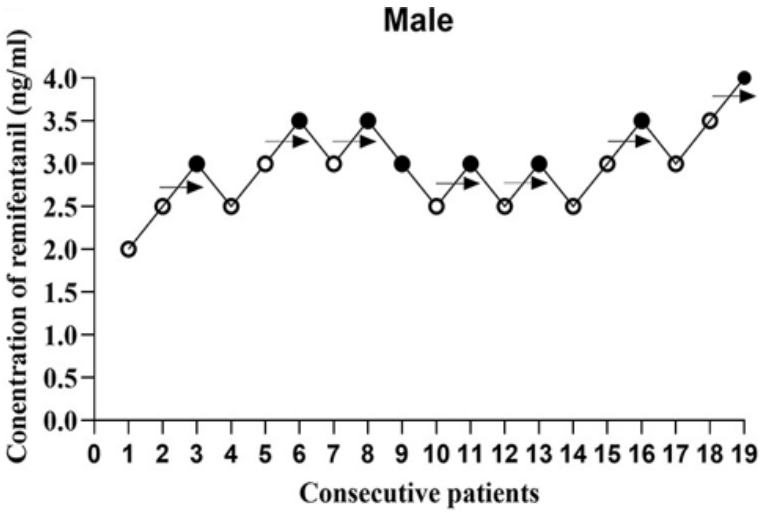
Characteristic	P-value	Female (n = 20)	Male (n = 19)
Indication for FOB	0.810		
Pneumonia		3 (15.0%)	2 (10.53%)
Chronic cough		0 (0%)	1 (5.26%)
EI + BBi		1 (5.0%)	1 (5.26%)
Cancer		5 (25.0%)	4 (21.05%)
COPD		0 (0%)	2 (10.53%)
Suspicion of malignancy		8 (40.0%)	8 (42.11%)
Hemoptysis		1 (5.0%)	1 (5.26%)
Bronchiectasis		2 (10%)	0 (0%)
Fever		1 (5.0%)	1 (5.26%)
Diagnostic procedures	0.780		
BBi+BBr+BAL		0 (0%)	1 (5.26%)
BAL		2 (10.0%)	0 (0%)
BBr+ BAL		4 (20.0%)	6 (31.58%)
EI + BAL + BB+ TBLB		11 (55.0%)	10 (52.63%)
Photodynamics therapy		2 (10.0%)	1 (5.26%)

Note: This table reports values as patient counts with percentages, written as n (%).

The following abbreviations are applied throughout: BAL refers to bronchoalveolar lavage; BBi denotes bronchoscopic biopsy; BBr indicates bronchial brushings; COPD stands for chronic obstructive pulmonary disease; EI represents endobronchial inspection; and TBLB corresponds to transbronchial lung biopsy.

EC_{50} and EC_{95}

Figure 1 illustrates the seven observed crossover (inflection) points. Under ciprofol sedation, the estimated EC50 of remifentanil required to attenuate FOB-related responses was 3.25 (2.75–3.26) ng/mL in male patients and 2.25 (1.75–2.25) ng/mL in female patients, with a statistically significant difference between groups (P = 0.0023).



a)

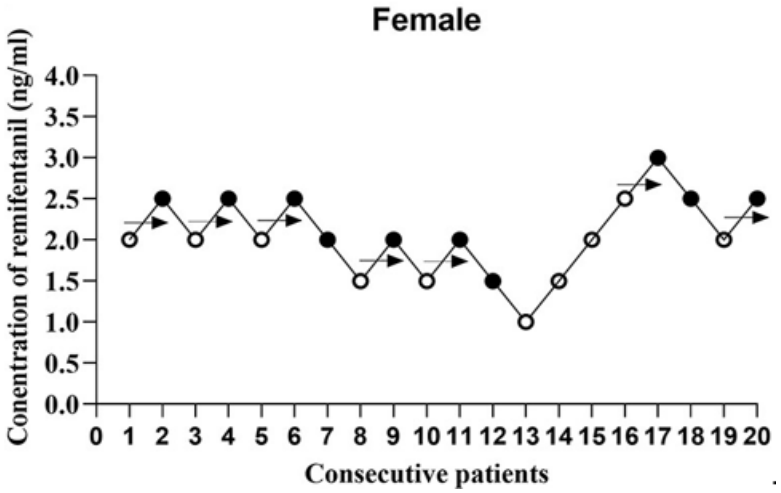


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Figure 1. Remifentanil dose adjustments across consecutive male (a) and female (b) patients undergoing fiberoptic bronchoscopy. Patient responses are depicted as filled black circles for negative reactions and open white circles for positive reactions. Transition points from positive to negative response are indicated by arrows. Seven crossover (inflection) points were achieved in each group.

A dose-response curve derived from the probit analysis illustrating the relationship between remifentanil dosage and the likelihood of no bronchoscopy reaction is presented in **Figure 2.** The EC50 values of remifentanil were compared between the male and female cohorts. Probit analysis revealed that the EC50 of remifentanil necessary to inhibit responses to FOB during deep sedation with ciprofol was 3.102 [95% confidence interval (CI): 2.694 to 3.749] ng/mL in males and 2.052 [95% CI: 1.345 to 2.750] ng/mL in females. The EC95 of remifentanil required to inhibit responses to FOB during deep sedation with ciprofol was 3.741 [95% CI: 3.366 to 7.699] ng/mL in males and 2.943 [95% CI: 2.456 to 9.533] ng/mL in females.

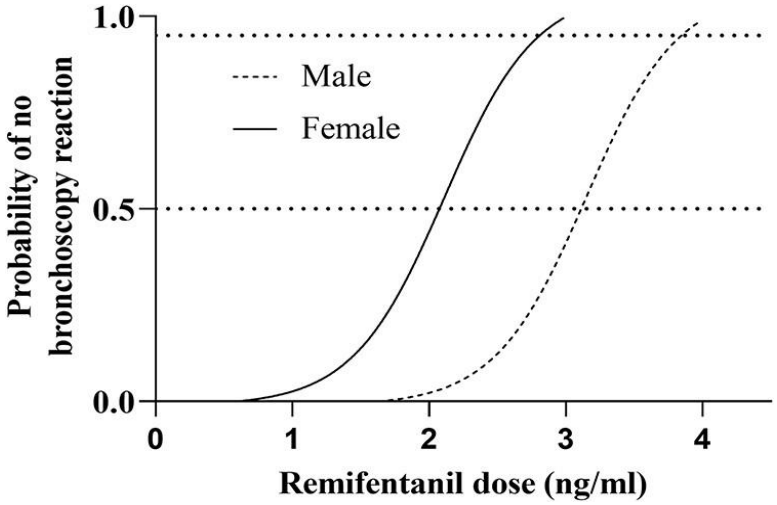

Figure 2. Probit analysis was used to model the association between remifentanil concentration and the likelihood of absence of bronchoscopy response. The figure also illustrates the comparison of EC50 estimates between male and female patients.

Medication

Table 3 summarizes the administered medications. The use of ciprofol and remifentanil did not differ between groups. In addition, the amount of endotracheal lidocaine administered was comparable across groups. No significant differences were observed in the duration of fiberoptic bronchoscopy, anesthesia time, or recovery time.

Table 3. Medication use and respiratory characteristics during fiberoptic bronchoscopy.

Characteristics	P- value	Female (n = 20)	Male (n = 19)
Administration of ciprofol (mg)	0.3088	33.20 (28.68 to 43.68)	39.30 (32.60 to 46.26)
Administration of remifentanil (ug)	0.2010	188.5 (115.6 to 242.1)	216.0 (170.0 to 280.0)
Dosage of Endotracheal lidocaine (mg)	> 0.9999	260.0 (260.0 to 260.0)	260.0 (260.0 to 260.0)
Duration of FOB (min)	0.8817	27.60 ± 15.48	26.85 ± 15.80
Duration of anesthesia (min)	0.6612	32.00 (24.50 to 37.75)	32.00 (19.62 to 37.00)
Duration of recovery (min)	0.7579	8.700 ± 4.044	9.081 ± 3.581
Minimum breathing rate (breaths/min)	0.5668	8.0 (6.25 to 9.75)	8.0 (6.0 to 8.0)
Minimum SpO_2 (%)	0.6195	99 (94 to 100)	99 (96 to 100)

Note: Data are shown as mean ± standard deviation or median with interquartile range, as appropriate. Abbreviations: FOB = fiberoptic bronchoscopy, SpO_2 = peripheral oxygen saturation.

Vital signs during bronchoscopy

Figure 3 and Table 3 present the trends in vital signs. When BIS dropped to 60 or below, male subjects showed notably elevated mean arterial pressure (MAP) ($P < 0.05$) and heart rate (HR) ($P < 0.001$) relative to female subjects. At all other measured time points around the surgery, no meaningful differences between the sexes emerged. Additionally, the lowest observed respiratory rates and minimum oxygen saturation levels did not differ significantly between the two groups.

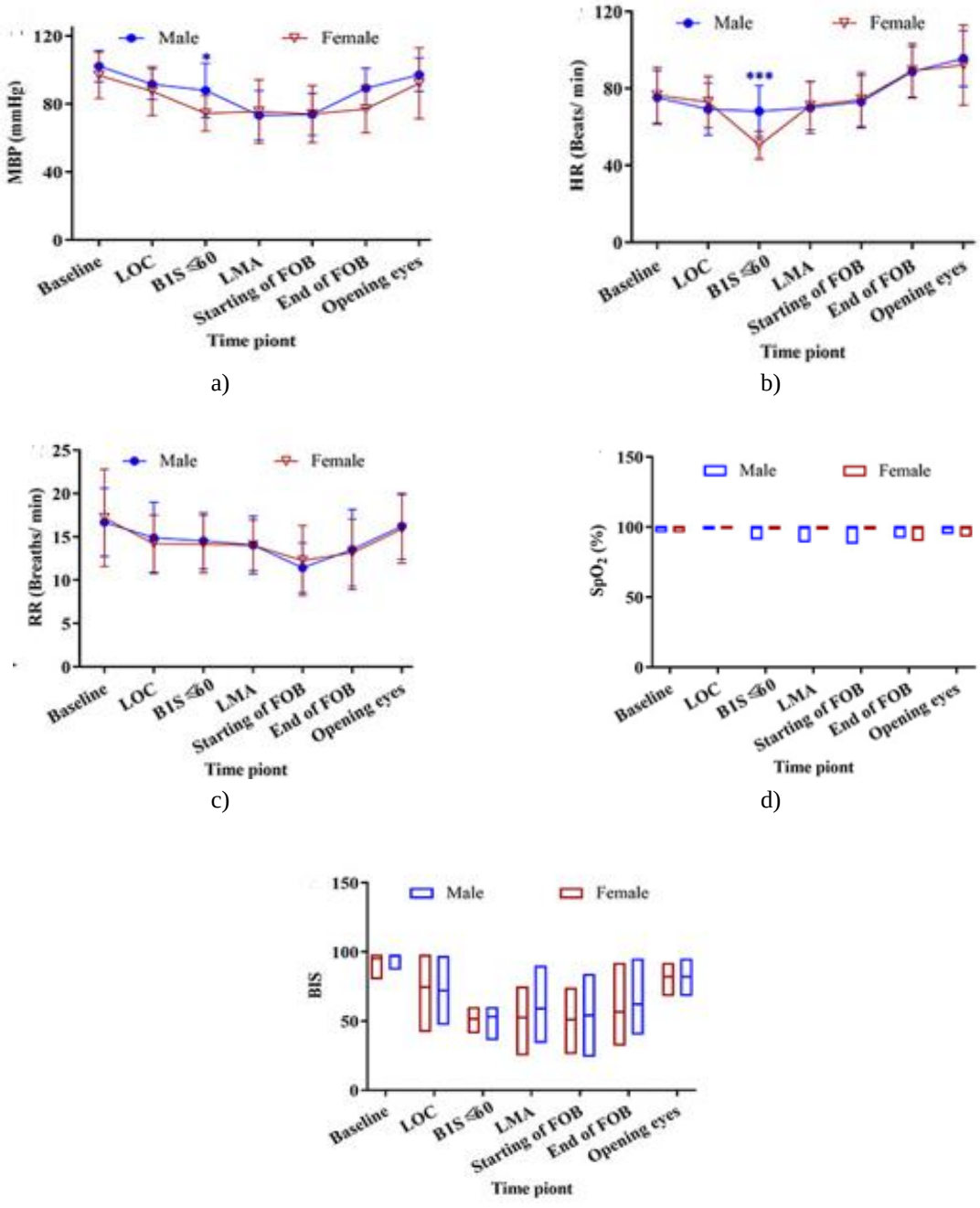

Figure 3. Patient vital sign trajectories. Data are shown as mean ± SD for panels a–c and as median (IQR) for panels d and e. Significance levels: *P < 0.05, ***P < 0.001. (A) Drug effect: F(1,259) = 9.908, P = 0.0018; time effect: F(6,259) = 18.74, P < 0.0001; interaction: F(6,259) = 1.643, P = 0.1357. (b) Drug: F(1,259) =1.333, P = 0.2493; time: F(6,259) = 27.45, P < 0.0001; interaction: F(6,259) = 2.599, P = 0.0183. (c) Drug: F(1,259) = 0.02038, P = 0.8886; time: F(6,259) = 7.480, P < 0.0001; interaction: F(6,259) = 0.1959, P = 0.9778. (d) Drug: F(1,259) = 0.9756, P = 0.3242; time: F(6,259)=2.431, P = 0.0265; interaction: F(6,259) = 0.8971, P = 0.4975. (e) Drug: F(1,259) = 2.475, P = 0.1169; time: F(6,259) = 92.08, P < 0.0001; interaction: F(6,259) = 0.6991, P = 0.6506. Abbreviations: MBP = mean arterial pressure; RR = respiratory rate; HR = heart rate; SpO_2 = oxygen saturation by pulse oximetry; LOC = loss of consciousness; BIS = bispectral index; LMA = laryngeal mask airway; FOB = fiberoptic bronchoscopy..

Adverse events

Table 4 summarizes the adverse event data. The percentage of patients experiencing at least one adverse event did not differ significantly between males (17/17 [89.47%]) and females (15/20 [75.0%]) (P = 0.4075). The most

frequently observed events were respiratory depression (males: 15/19 [78.95%] vs. females: 14/20 [70.0%]; P > 0.7164) and hypotension (males: 14/19 [73.68%] vs. females: 14/20 [70.0%]; P > 0.9999), with no intergroup differences. Assisted ventilation was required for three male patients and two female patients (P = 0.6614). Sinus tachycardia occurred exclusively in the female group (6/20, 30.0%) compared to none in males (P = 0.0202). No significant differences were observed between sexes for hypertension, sinus bradycardia, or hiccups. Additionally, no patient in either group experienced injection pain, delirium, postoperative nausea and vomiting (PONV), or intraprocedural awareness during fiberoptic bronchoscopy.

Table 4. Adverse events occurring during fiberoptic bronchoscopy (tabular display).

Characteristic	P-value	Female (n = 20)	Male (n = 19)
Respiratory depression	0.7164	14 (70.0%)	15 (78.95%)
RR ≤ 8 (breathing/ min)	0.7164	14 (70.0%)	15 (78.95%)
Apnea	> 0.9999	1 (5%)	1 (5.26%)
SpO_2 ≤ 90% (≥ 15s)	> 0.9999	2 (10.0%)	2 (10.53%)
Assisted ventilation	0.6614	2 (10.0%)	3 (15.79%)
Hypertension	> 0.9999	1 (5.0%)	1 (5.26%)
Hypotension	> 0.9999	14 (70.0%)	14 (73.67%)
Sinus tachycardia	0.0202	6 (30%)	0 (0%)
Sinus bradycardia	0.4075	2 (10.0%)	4 (21.05%)
Injection pain	> 0.9999	0 (0%)	0 (0%)
Delirium	> 0.9999	0 (0%)	0 (0%)
Hiccup	0.4872	1 (5.0%)	0 (0%)
PONV	> 0.9999	0 (0%)	0 (0%)
Awareness	> 0.9999	0 (0%)	0 (0%)

Note: Values are shown as the number of cases along with corresponding percentages (%). Abbreviations: SpO_2 = peripheral oxygen saturation; RR = respiratory rate; PONV = postoperative nausea and vomiting.

The present investigation focused on determining the remifentanil exposure needed to adequately suppress fiberoptic bronchoscopy (FOB) responses delivered via a laryngeal mask airway under ciprofol-based deep sedation. The analysis demonstrated a clear sex-dependent difference in both EC50 and EC95, suggesting that elderly male and female patients require distinct remifentanil concentrations to achieve comparable suppression of airway reflexes while spontaneous ventilation is maintained [14, 15]. Remifentanil is a short-acting opioid frequently applied in anesthetic practice for attenuation of nociceptive and sympathetic responses. Prior studies under propofol anesthesia have reported variable EC50 values depending on the stimulus. For example, inhibition of CO_2 pneumoperitoneum responses required approximately 4.17 ng/mL in women and 5.00 ng/mL in men [20]. Likewise, suppression of responses to tracheal intubation and skin incision has been reported at around 5 ng/mL and 2 ng/mL, respectively [21]. Patient-specific conditions may further modify opioid requirements. In Parkinson's disease populations, lower EC50 values have been observed compared with non-Parkinson's patients for both tracheal intubation (1.86 vs 3.20 ng/mL) and skin incision (2.17 vs 3.09 ng/mL), indicating altered sensitivity to remifentanil [22]. To the best of our knowledge, this study is the first to quantify both EC50 and EC95 of remifentanil specifically for suppression of FOB-induced responses via LMA under ciprofol sedation in elderly individuals while preserving spontaneous breathing. The estimated EC50 values were 3.25 ng/mL in males and 2.25 ng/mL in females. These findings reinforce that opioid requirements differ according to both anesthetic regimen and type of stimulus [23, 24]. Opioid response is not uniform between sexes, and clinical evidence consistently shows that men often require greater doses than women to achieve equivalent pharmacodynamic effects [23, 25]. This pattern has been demonstrated in several anesthetic contexts; for example, higher remifentanil requirements have been reported in males during laryngeal mask airway (LMA) insertion under propofol anesthesia [26]. Likewise, studies on CO_2 pneumoperitoneum stimulation have shown a higher EC50 of remifentanil in males compared with females under propofol-based anesthesia [20]. Similar sex-dependent differences have also been observed in the prevention of emergence cough, where male patients required higher opioid exposure [27]. In line with these findings, the present study demonstrated that both EC50 and EC95 of remifentanil for suppression of fiberoptic bronchoscopy (FOB) responses via LMA under ciprofol sedation were lower in females than in males. At the same time, spontaneous respiration was preserved in elderly patients. This

reinforces the notion that sex is a key determinant of interindividual variability in opioid requirements [14, 25]. The underlying causes of this disparity are likely multifactorial. Differences in body composition between males and females may alter pharmacokinetics, as females typically exhibit a higher fat-to-water ratio, which can influence drug distribution. Hormonal influences may also play a role, since estrogen and progesterone have been linked to modulation of μ-opioid receptor (MOR) sensitivity [28-30]. The most frequently observed complications were respiratory depression and hypotension, although their incidence did not differ significantly between male and female groups [31-33]. Respiratory depression associated with opioids remains a key perioperative safety concern [33]. This effect is primarily mediated through μ-opioid receptor (MOR) activation within central respiratory networks [34-36].

This study has several limitations. First, plasma concentrations of remifentanil were not measured directly; instead, effect-site concentrations were estimated using the Minto pharmacokinetic model [37]. Second, the use of the Dixon up-and-down sequential allocation design may limit precision [38]. Finally, all participants were recruited from a single geographic region, which may restrict external validity [39].

Conclusion

The findings indicated that EC50 and EC95 values of remifentanil required to suppress fiberoptic bronchoscopy (FOB) responses via laryngeal mask airway under deep ciprofol sedation differed between male and female elderly patients, while spontaneous respiration was maintained.

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Conflict of Interest: None

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Ethics Statement: None

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