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CLINICAL TRIAL REPORT

Estimation of ED_{50} and ED_{95} of Oliceridine Required to Suppress the Bronchoscopy Response in Patients Undergoing Fiberoptic Bronchoscopy Under Sedation with Cipepofol: An Up-and-Down Sequential Allocation Trial

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Background: Bronchoscopy response is the main challenge during fiberoptic bronchoscopy (FOB) procedure. Opioids are commonly used to suppress bronchoscopy response. This study aimed to estimate the median effective dose (ED_{50}) of oliceridine for suppressing bronchoscopy response during FOB under deep sedation with cipepofol.

Methods: This was an up-and-down sequential allocation trial. Patients were divided into male or female groups. The initial bolus of oliceridine was 40 μg/kg. The next dose of oliceridine was determined based on prior patient's response to FOB with 10 μg/kg step size. After seven inflection points were completed, recruitment was terminated. Following a single bolus of oliceridine, all patients received cipepofol (initial bolus:0.4 mg/kg), with infusion rates subsequently titrated between 0.2 and 1.0 mg/kg/h to maintain bispectral index (BIS) values within the 40–60 range. A laryngeal mask (LMA) was inserted when BIS ≤ 60. The endpoints were bronchoscopy response to FOB. Dixon's up-and-down method was used to calculate the ED_{50} and ED_{95} of oliceridine required to alleviate the bronchoscopy response. A dose-response curve was generated using probit analysis.

Results: A total of 45 patients (23 males, 22 females) were enrolled in the study. The ED_{50} of oliceridine for suppressing the response to FOB under cipepofol sedation did not differ between males (median [interquartile range, IQR] 35.00 [35.00 to 36.00] μg/kg) and females (45.00 [35.00 to 45.00] μg/kg) (P=0.0723). Probit analysis showed the ED_{50} and ED_{95} of oliceridine required to suppress bronchoscopy response to FOB under deep sedation with cipepofol were 30.20 [95% confidence interval (CI):19.98 to 38.78] vs 40.47 [95% CI: 29.49 to 51.40] μg/kg and 46.49 [95% CI: 38.23 to 105.37] vs 57.55 [95% CI: 48.50 to 141.34] μg/kg in males and females respectively.

Conclusion: The ED_{50} and ED_{95} of oliceridine required to suppress bronchoscopy response under cipepofol sedation did not differ between males and females.

Trial Registration: Chictr.org.cn; identifier: ChiCTR2400086635.

Keywords: oliceridine, cipepofol, fiberoptic bronchoscopy, effective dose

Introduction

With the development of technology, bronchoalveolar lavage (BAL), bronchoscopic biopsy (BBi), bronchia brushings (BBr), transbronchial lung biopsy (BLB), bronchoscopic laser treatment, tracheal stent placement, and fiberoptic bronchoscopy (FOB) are commonly used to diagnose and treat respiratory diseases. The insertion of a bronchoscope

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and the treatment procedure can cause strong mechanical stimulation, leading to complications such as arrhythmia, cardiovascular events, airway spasms, coughing, nausea, vomiting, involuntary movement, and even accidental injuries such as tracheal rupture, bleeding, reflux aspiration, and mechanical damage during FOB.

Current guidelines recommend that FOB should be performed under sedation to improve safety and comfort.[1,2] Various anesthetic drugs, such as midazolam, etomidate, propofol, and dexmedetomidine, have been used for sedation during FOB. However, the shortcomings of these drugs constrain their clinical utility, including unpredictable pharmacokinetics (variable onset/recovery times), narrow therapeutic indices requiring careful titration, and adverse effects (respiratory depression, hypotension, arrhythmias, injection pain, and nausea/vomiting).[3] To address these limitations, cipepofol—a structural analogue of propofol—has been developed. Its sedative characteristics mirror propofol's rapid onset/offset but eliminate injection pain,[4–6] with clinical efficacy demonstrated in both general anesthesia induction[5,7–9] and ICU sedation settings.[6]

Opioids are used during FOB to suppress the cough reflex and improve patient's tolerance.[10,11] Conventional opioids, such as fentanyl, remifentanil, and sufentanil, exert their effects by activating both the G-protein and β-arrestin pathways after binding to μ-receptors. However, respiratory depression, itching, chest wall muscle stiffness, nausea, vomiting, and other adverse effects are caused by the β-arrestin pathway. Oliceridine, a novel G-protein-biased opioid, selectively activates the G-protein pathway while minimizing β-arrestin recruitment. This trait preserves analgesic efficacy while reducing opioid-related complications, making it a promising alternative for FOB sedation.[12,13] Thus, it is important to determine the optimal dose of oliceridine in clinical contexts. However, the ED_{50} and ED_{95} of oliceridine for suppressing bronchoscopy response to FOB under cipepofol sedation remain undefined. This study aimed to investigate the ED_{50} and ED_{95} of oliceridine required to suppress the response to FOB under cipepofol sedation.

Materials and Methods

Ethics

Ethical approval for this study (Ethical Committee No. 2024-E485-01) was provided by the Medical Ethics Committee of the First Affiliated Hospital of Guangxi Medical University, Naning, China (Chairperson Prof. Songqing He) on July 3, 2024, and was registered at chictr.org.cn (ChiCTR2400086635, July 8, 2024). The study adhered to the TREND Statement and the Declaration of Helsinki. Written informed consent was obtained from all patients before the trials.

Study Design and Participants

This was an up-and-down, sequential allocation trial. The patients were assigned to the male and female groups based on gender. The inclusion criteria were as follows: age 18–65 years, scheduled for FOB, and ASA physical status I–III. The exclusion criteria were contraindications for FOB, difficult airways, allergy to opioids or cipepofol, severe hypertension (systolic blood pressure ≥180 mmHg, or diastolic blood pressure ≥110 mmHg), severe arrhythmia, New York Heart Association Class III or above with severe heart failure, liver dysfunction, kidney dysfunction, cognitive impairment, history of use of psychotropic drugs, or any other criteria deemed unsuitable by the researchers for inclusion in this study.

ED_{50} and ED_{95} Calculation

The ED_{50} of oliceridine required to suppress responses to FOB was determined by calculating the average midpoint dose of each pair of patients after seven inflection points were obtained. ED_{50} and ED_{95} were also calculated by probit analysis using a modified Dixon`s up-and-down method.[14,15] The initial intravenous bolus of oliceridine was 40 μg/kg based on a pilot study. The next dose of oliceridine was determined based on previous patient responses to FOB. The step size of oliceridine was 10 μg/kg. After seven inflection points were completed, recruitment was terminated.

Intervention

The patients fasted for ≥ 8 h before FOB. No premedication was administered. Monitors included noninvasive blood pressure (NIBP), electrocardiography (ECG), pulse oximetry (SpO_2), respiratory rate (RR), and Bispectral Index (BIS). Oxygen (6 L/min) was supplied through a face-mask for 3 min before anesthesia. After received a single bolus of

oliceridine (Nhwa, Xuzhou, China), all patients received an initial intravenous bolus of 0.4 mg/kg cipepofol (Haisco, Shengyang, China) and adjusted between 0.2 and 1.0 mg/kg/h to maintained BIS within 40–60.[16–18] A laryngeal mask (LMA) was inserted when BIS score ≤60. Two experienced operators performed the FOB through LMA. Endotracheal 2% lidocaine was administered using a syringe to the following target zones: vocal cords (40 mg), trachea (100 mg), the main carina (40 mg), and the double main bronchi (40 mg).

Assessment of Bronchoscopy Response

The bronchoscopy response was assessed using a bronchoscopy score, including vocal cord movement, cough severity, and limb movement as previous report.[15] In brief, each variable was rated on a 4-point scale. The total bronchoscopy score ranges from 3 (best score) to 12 (worst score). All the scores were assessed by an assistor who was blinded to the allocation and did not participate the trial during the first fiberoptic bronchoscopy. Bronchoscopy response was defined as a final bronchoscopy score >6. An additional bolus of oliceridine (10 μg/kg each time) was administered when bronchoscopy score >6.

Outcome Measure

The primary outcome was the incidence of response to bronchoscopy (bronchoscopy score >6 at the first fiberoptic bronchoscopy insertion). The secondary outcomes included vital signs (NIBP, heart rate, RR, SpO_2, and BIS) at the following time points: 5 min before anaesthesia (baseline), loss of consciousness (LOC), BIS ≤60, completion of LMA insertion, start of FOB, end of FOB, and time of eyes opening. The administration of anesthetic and vascular drugs, duration of anesthesia, length of FOB time, length of recovery time, minimum spontaneous breathing rate, and minimum SpO_2 were also recorded. Adverse events included respiratory depression (defined as meeting one of the following conditions: respiratory rate [RR] ≤8 breaths/min; apnea; SpO_2 ≤90% [≥15s]), hypotension (≥30% decrease in the MAP from baseline), tachycardia (>100 beats/min), bradycardia (<50 beats/min), injection pain, delirium, hiccups, nausea and vomiting, and awareness.

Statistical Analysis

GraphPad Prism 9.0 or SPSS 25.0 was used for analysis. Kolmogorov–Smirnov test was used to test the normality distribution of continuous variables. The normally distributed continuous variables are expressed as mean ± standard deviation. Unpaired *t*-test or repeated-measures analysis of variance was used to compared the normal continuous variables between groups. Non-normally distributed variables are expressed as median (interquartile range). Mann–Whitney *U*-test was used to compared non-normally distributed variables. Fisher's test was used to compare categorical variables between groups. A $P < 0.05$ indicated a statistically significant difference.

Results

Patients

Twenty-three male and 22 female patients were enrolled at the First Affiliated Hospital of Guangxi Medical University between July 8, 2024, and September 5, 2024. All patients completed the trial. The demographic characteristics are shown in Table 1. No differences were found in terms of age, weight, body mass index (BMI), ASA, comorbidity, indications, or procedures (P >0.05). However, there were differences in the height, exposure to smoking and alcohol between the groups (P <0.0001).

ED_{50} and ED_{95}

The sequences of the seven inflection points are shown in Figure 1. There was no different between males and females (median [IQR] 35.00 [35.00 to 36.00] vs 45.00 [35.00 to 45.00] μg/kg, P=0.0723) in the ED_{50} of oliceridine required to suppress response to FOB under cipepofol sedation based on Dixon`s up-and-down methods.

The dose-effect curve of the oliceridine dose and the probability of no FOB response are shown in Figure 2. The ED_{50} and ED_{95} were calculated using probit analysis. The ED_{50} of oliceridine required to suppress FOB response under cipepofol sedation were 30.20 [95% confidence interval (CI):19.98 to 38.78] and 40.47 [95% CI: 29.49 to 51.40] μg/kg in

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Table 1 Demographic Characteristics

	Male (n=23)	Female (n=22)	*p* Value
Age (y)	58.00 (45.00 to 63.00)	59.00 (48.00 to 61.00)	0.9686 [a]
Weight (kg)	55.00 (51.50 to 67.00)	53.00 (42.50 to 60.50)	0.0917 [a]
Height (cm)	166.5±5.591	155.2±6.117	< 0.0001 [b]
BMI (kg/m^{-2})	19.62 (18.81 to 23.44)	22.44 (18.40 to 24.11)	0.8542 [a]
ASA physical status II/III (n)	11/12	14/8	0.3726 [c]
Comorbidity			
Hypertension	4 (17.40%)	6 (27.27%)	0.1075 [c]
Diabetes mellitus	5 (21.74%)	2 (9.09%)	0.4140 [c]
Smoking history	20 (86.96%)	0 (0%)	<0.0001[c]
Alcohol abuse	15 (65.22%)	0 (0%)	<0.0001[c]
Indication for FOB			0.8263 [c]
Pneumonia	3 (13.04%)	3 (13.64%)	
Chronic cough	1 (4.35%)	3 (13.64%)	
Suspicion of malignancy	15 (65.21%)	12 (54.54%)	
Cancer	1 (4.35%)	2 (9.09%)	
COPD	1 (4.35%)	0 (0%)	
Bronchiectasis	1 (4.35%)	2 (9.09%)	
Hemoptysis	1 (4.35%)	0 (0%)	
Diagnostic procedures			0.8893 [c]
BBr+BAL	6 (26.09%)	7 (31. 81%)	
TBNA	1 (4.35%)	5 (22.73%)	
BBr+BAL+TBLB	7 (30.43%)	6 (27.27%)	
TBLB+TBNA	0 (0%)	1 (4.55%)	
BBr+BAL+TBNA	6 (26.09%)	2 (9.09%)	
BBr+BAL+TBNA+TBLB	3 (13.04%)	1 (4.55%)	

Notes: Data are expressed as mean ± standard deviation, median (interquartile range), or N (%). [a]Data are analyzed by Mann–Whitney test. [b]Data are analyzed by unpared *t* test. [c]Data are analyzed by Fisher's exact test.

Abbreviations: ASA, American Society of Anaesthesiologists; BMI, body mass index; BAL, Bronchoalveolar lavage, BBr, bronchia brushings; COPD, Chronic obstructive pulmonary disease; FOB, fiberoptic bronchoscopy; TBNA, Bronchial aspirative biopsy; TBLB, Transbronchial lung biopsy.

males and females, respectively. The ED_{95} of oliceridine required to suppress the FOB response under cipepofol sedation was 46.49 [95% CI: 38.23 to 105.37] and 57.55 [95% CI: 48.50 to 141.34] μg/kg in males and females respectively.

Anesthetic and Breath Characteristics

Anesthetic and breath characteristics are summarized in Table 2. The total administration of cipepofol was more in the male group (76.1± 32.00 mg) than that in the female group (51.98±13.64 mg) (P=0.0022). The total administration of oliceridine was higher in the male group (3.987±1.623 mg) than in the female group (3.130±0.9427 mg) (P=0.0369). The duration of FOB procedures (P=0.0051) and anesthesia (P=0.0159) was longer in the male group than in the female group. The minimum breathing rate was lower in the female group than in the male group (P=0.0013). No differences were found in ephedrine administration, duration of recovery, minimum SpO_2, or assisted ventilation characteristics between the groups.

Vital Signs

Vital signs are shown in Figure 3. No differences were found in terms of NIBP, heart rate, respiratory rate, SpO_2, or Bis values between the groups.

Adverse Events

The adverse events are shown in Table 3. The incidence of respiratory depression was higher in females than in males (72.73% vs 21.74%, P=0.0009). The incidences of hypotension, bradycardia, tachycardia, injection pain, hiccups, PONV, delirium, and awareness did not differ between the groups.

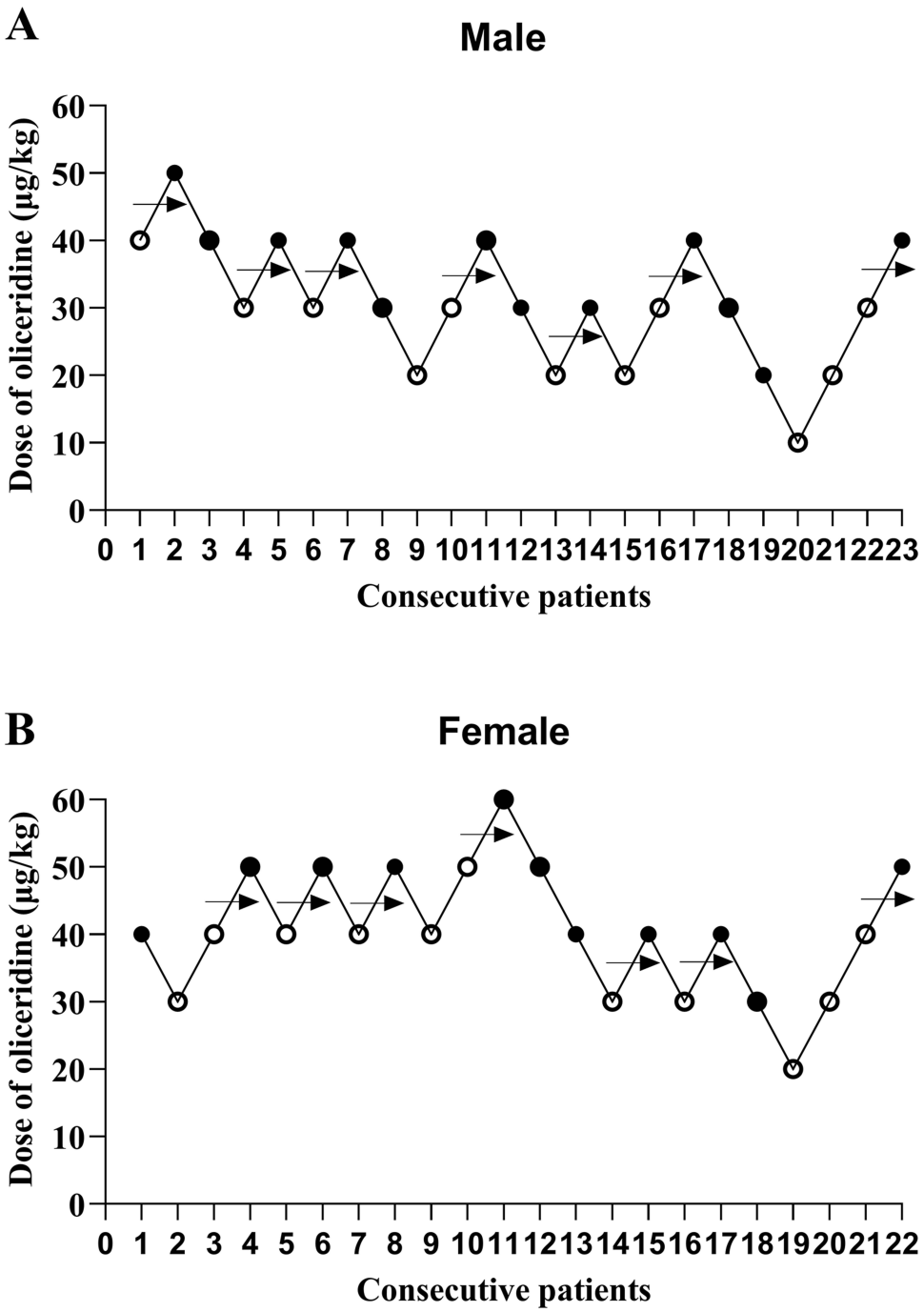

Figure 1 Estimation of negative (black circle) and positive (white circle) bronchoscopy response to FOB under a predetermined dose of oliceridine using Dixon's up-and-down methods in male (**A**) and female (**B**) patients. The arrow represented the inflection point of the bronchoscopy response from positive to negative. The ED_{50} of oliceridine for suppressing response to FOB under deep sedation with cipepofol in male and female groups were 35.00 (35.00 to 36.00) μg/kg and 45.00 (35.00 to 45.00) μg/kg, respectively.

Discussion

Our study reported that the ED_{50} and ED_{95} of oliceridine are required to suppress the FOB response under cipepofol sedation. The current results indicated that there was no statistical difference in the ED_{50} and ED_{95} of oliceridine required to suppress the FOB response under cipepofol sedation between males and females.

Opioid-based drugs are the cornerstone of anesthesia and pain control owing to its effectiveness.[19] Conventional opioids, such as fentanyl, remifentanil, and sufentanil, show analgesic and cough suppressant effects by binding to the μ-

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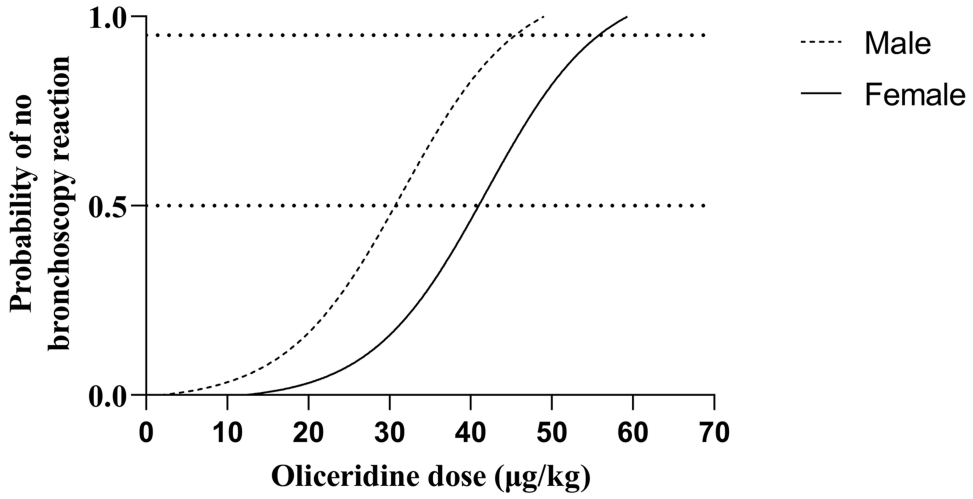

Figure 2 An oliceridine dose and no bronchoscopy response curve from the probit analysis in male (dashed line) and female groups (solid line). Probit analysis showed the ED_{50} of oliceridine required to suppress bronchoscopy response to FOB under deep sedation with cipepofol were 30.20 [95% CI:19.98 to 38.78] μg/kg and 40.47 [95% CI: 29.49 to 51.40] μg/kg in male and female respectively. ED_{95} of oliceridine required to suppress response to FOB under deep sedation with cipepofol were 46.49 [95% CI: 38.23 to 105.37] μg/kg and 57.55 [95% CI: 48.50 to 141.34] μg/kg in male and female respectively.

receptor, especially G-protein. However, these conventional opioids also activate β-arrestin protein, resulting in side effects such as respiratory depression, itching, nausea, and vomiting.[20–23] However, opioid-related side effects may limit its use. Oliceridine, a novel opioid, has been approved as an intravenous treatment for acute pain by activating the G-protein. Oliceridine hardly activates the β-arrestin protein, resulting in a lower incidence of side effects.[12] Oliceridine was well tolerated in Chinese patients at doses between 0.75 and 3.0 mg.[24] The ED_{50} and ED_{95} of oliceridine required to inhibit noxious stimulation, such as intubation, LMA, CO_2 pneumoperitoneum, and skin incision during propofol- or cipepofol-based anesthesia, have not been reported. To our knowledge, our results are the first to investigate the ED_{50} and ED_{95} of oliceridine required to suppress FOB responses through the LMA under cipepofol sedation. Our results showed that the ED_{50} of oliceridine for suppressing FOB response under cipepofol sedation did not differ between male and female (35.00 [35.00, 36.00] vs 45.00 [35.00, 45.00] μg/kg, P=0.0723). The ED_{50} of oliceridine required to inhibit noxious stimulation, such as intubation, LMA, CO_2 pneumoperitoneum, and skin incision, requires further investigation. The probit analysis results of ED_{50} and ED_{95} with wide CIs, suggest variability. The wider the CIs, the more severe the individual differences. We belief the dosage of oliceridine varies greatly among individuals.

Table 2 Anesthetic and Breath Characteristics

	Male (n=23)	Female (n=22)	*p* Value
Administration of cipepofol (mg)	76.1± 32.00	51.98±13.64	0.0022 [a]
Administration of oliceridine (mg)	3.987±1.623	3.130±0.9427	0.0369 [a]
Administration of ephedrine (mg)	0 (0 to 0)	0 (0 to 7.5)	0.2444 [b]
Duration of FOB (min)	33.51±15.51	22.11±9.578	0.0051 [a]
Duration of anesthesia (min)	39.29±16.54	28.64±11.28	0.0159 [a]
Time of LOC (min)	4.387±1.199	4.164±0.9469	0.4931 [a]
Time of BIS≤60 (min)	5.691±2.436	4.959±0.7545	0.1844 [a]
Duration of recovery (min)	12.60±5.534	10.69±6.340	0.2862 [a]
Minimum breathing rate (breaths/min)	11 (9 to 14)	3 (0 to 8.5)	0.0013 [b]
Minimum SpO_2 (%)	99 (98 to 100)	99.5 (95.75 to 100)	0.9853 [b]
Assisted ventilation	4 (17.39%)	9 (40.91%)	0.1075 [c]

Notes: Data are presented as mean ± standard deviation, median (interquartile range), or n (%). [a]Data are analyzed by unpared *t* test. [b]Data are analyzed by Mann–Whitney test. [c]Data are analyzed by Fisher's exact test.

Abbreviations: FOB, fiberoptic bronchoscopy; SpO_2, pulse oxygen saturation.

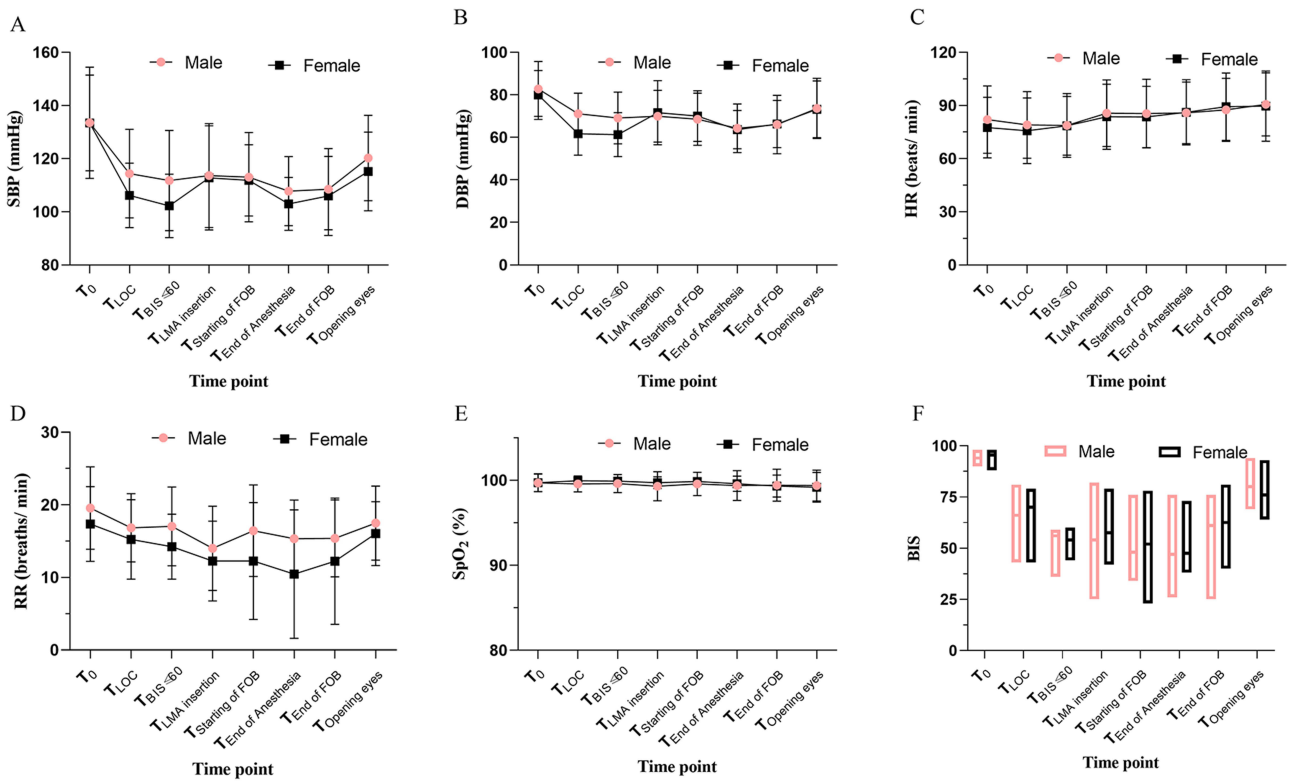

Figure 3 Vital signs of patients. Variables are presented as mean ± standard deviation (**A–E**) or median (interquartile range) (F). (**A**) Group: F (1, 43) = 1.594, P=0.2135; Time: F (4.563, 196.2) = 22.67, P<0.0001; Time × Group: F (7, 301) = 0.8423, P=0.5529; Subject: F (43, 301) = 5.654, P<0.0001; (**B**) Group: F (1, 43) = 0.7153, P=0.4024; Time: F (4.370, 187.9) = 18.67, P<0.0001; Time × Group: F (7, 301) = 2.532, P=0.0152; Subject: F (43, 301) = 7.841, P<0.0001; (**C**) Group: F (1, 43) = 0.07054, P=0.7918; Time: F (3.769, 162.1) = 17.82, P<0.0001; Time × Group: F (7, 301) = 0.8316, P=0.5617; Subject: F (43, 301) = 42.02, P<0.0001; (**D**) Group: F (1, 43) = 4.919, P=0.0319; Time: F (4.644, 199.7) = 7.663, P<0.0001; Time × Group: F (7, 301) = 0.8190, P=0.5721; Subject: F (43, 301) = 6.311, P<0.0001; (**E**) Group: F (1, 43) = 0.3147, P=0.5777; Time: F (3.783, 162.7) = 2.123, P =0.0841; Time × Group: F (7, 301) = 0.8687, P=0.5316; Subject: F (43, 301) = 10.69, P<0.0001; (**F**) Group: F (1, 43) = 0.3147, P=0.5212; Time: F (4.661, 200.4) = 115.3 P<0.0001; Time × Group: F (7, 301) = 0.7090, P=0.6645; Subject: F (43, 301) = 2.412, P<0.0001.

Abbreviations: BIS, bispectral index; DBP, diastolic blood pressure; FOB, fiberoptic bronchoscopy; HR, heart rate; LMA, laryngeal mask; LOC, loss of consciousness; RR, respiratory rate; SBP, systolic blood pressure; SpO_2, pulse oximetry.

Sex differences influence opioid efficacy. Males need more conventional opioids to inhibit harmful stimuli than females, such as inhibiting the response to the insertion of LMA and CO_2 pneumoperitoneum.[25–29] For example, the ED_{50} of remifentanil required to inhibit the cough reflex was higher in males than in females.[30] Our results showed that

Table 3 Adverse Events

	Male (n=23)	Female (n=22)	p Value
Respiratory depression	5 (21.74%)	16 (72.73%)	0.0009
RR ≤ 8 (breathing/min)	5 (21.74%)	16 (72.73%)	
Apnea	2 (8.70%)	11 (50%)	
SpO_2 ≤ 90% (≥ 5s)	0 (0%)	0 (0%)	
Hypotension	12 (52.17%)	12 (54.55%)	>0.9999
Tachycardia (>100 beats/min)	3 (13.04%)	3 (13.64%)	>0.9999
Bradycardia (<50 beats/min)	0 (0%)	0 (0%)	>0.9999
Injection pain	0 (0%)	0 (0%)	>0.9999
Delirium	0 (0%)	0 (0%)	>0.9999
Hiccup	0 (0%)	0 (0%)	>0.9999
PONV	0 (0%)	0 (0%)	>0.9999
Awareness	0 (0%)	0 (0%)	>0.9999

Notes: Data are expressed as n (%). Data are analyzed by Fisher's exact test.

Abbreviations: PONV, postoperative nausea and vomiting; RR, respiratory rate; SpO_2, pulse oxygen saturation.

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the ED_{50} of oliceridine required to suppress the FOB response under cipepofol sedation based on Dixon's up-and-down method was lower in males than in females, but the difference was not statistically significant. Probit analysis showed that the ED_{50} and ED_{95} of oliceridine required to suppress the FOB response under cipepofol sedation were lower in males than in females. Our study confirmed the impact of sex differences on opioid efficacy. It is worth mentioning that males need less oliceridine to suppress the bronchoscopy response to FOB than females, which is in contrast to conventional opioids. This inconsistency can be attributed to several reasons. First, the major reason for this is the different mechanisms of action of oliceridine and the conventional opioids. Oliceridine differs from the other opioids. After activating the μ receptor, oliceridine activates the G protein (related to analgesia) and barely activates the β-arrestin protein (related to adverse effects). In contrast, conventional opioids activate both G-protein and β-arrestin proteins. Second, the combined use of anesthetics differed. The sedative-opioid combination is a common practice for procedural sedation and general anaesthesia to improve efficacy and reduce adverse events.[31–34] Previous reports have often used propofol; however, we used cipepofol in this study. Drug interactions can alter the pharmacological outcomes.[35] We cannot exclude the different interactions between propofol or cipepofol and opioids, which resulted in different demands for oliceridine and conventional opioids in males and females. Third, females have a lower percentage of water and a higher percentage of fat than males. The pharmacodynamic differences may affect drug distribution and efficacy. Forth, more male expose to smoking and alcohol than females, which reducing the airway response.

The combination of sedatives with opioids are commonly used for anesthesia. Drug-drug potential interactions may change the pharmacological effects, including synergism, additivity, or antagonism. The interaction may improve the efficacy, but also exaggerate potential adverse effects of both drugs. The combination of cipepofol and oliceridine used in this study results in suppressing bronchoscopy response, also cardiorespiratory inhibition, especially in females. Drug-drug interactions may relay on the modulation of the action site. It is critical to understand the underlying mechanisms, which need further study.

The main complications were respiratory and circulatory depression. The incidence of respiratory depression during FOB under anaesthesia with remifentanil and cipepofol was 70%-78.95%.[15] In the current study, the incidence of respiratory depression during FOB was 21.74% in males and 72.73% in females. Females are more prone to respiratory depression than males. This inconsistency can be attributed to several reasons. First, the major reason for this may be that the oliceridine dose was higher in the female group than in the male group. Oliceridine activates G-protein and hardly activates β-arrestin. However, the adverse effects appeared dose-dependent.[24] High doses of oliceridine are associated with a high incidence of adverse effects. The second reason may be that the use of cipepofol caused transient respiratory depression. Cipepofol is a structural analog of propofol that achieves sedation by binding to GABAARs.[4–6,36] Compared with propofol, cipepofol reduced the incidence of injection pain, but the inhibition of circulation and respiration did not disappear. Cipepofol causes circulatory depression by inhibiting myocardial contractions and vascular tension. Third, the combination of cipepofol with opioids such as oliceridine would exacerbate the cardiorespiratory inhibition. Forth, different definitions of cardiopulmonary depression led to different results. In our study, respiratory depression was defined as at least one of the following criteria: apnea, respiratory rate ≤8 breaths/min, and SpO_2 ≤90% more than 15s). A decrease of >30% in MAP from baseline was defined as hypotension, which differs from other studies. There were no differences in the incidence of tachycardia, bradycardia, injection pain, hiccups, PONV, delirium, or awareness between the groups.

This study has some limitations. First, the ED_{50} and ED_{95} values of oliceridine were calculated using the Dixon`s up-and-down method. This method has been widely used, with acceptable inaccuracies and biases. But the shortcoming of the "up-and-down" method may affect the accuracy of ED_{50} and ED_{95}. Further studies should examine blood ED. Second, all patients were from a single center, and the race was relatively homogeneous. Therefore, our conclusions cannot be directly extrapolated to other races. Third, the current study only included mildly ill patients (ASA I–III); therefore, our conclusions cannot be directly extended to critically ill patients. Finally, the fixed 10ug/kg step size may impact the accuracy of ED_{50}/ED_{95}. Small step size (such as 5 μg/kg or 2.5 μg/kg) should be study in the future.

Conclusion

The result suggested there was no statistical difference between male and female groups in the ED_{50} and ED_{95} of oliceridine required to suppress bronchoscopy response during FOB under deep sedation with cipepofol, but with higher ED values trends and higher incidence of respiratory inhibition in females, which need further investigation.

Abbreviations

ASA, American Society of Anesthesiologists; BAL, bronchoalveolar lavage; BBi, bronchoscopic biopsy; BBr, bronchial brushings; BIS, bispectral index; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; ED, effective dose; EI, endobronchial inspection; ETCO2, end-tidal carbon dioxide; FOB, fiberoptic bronchoscopy; HR, heart rate; LMA, laryngeal mask; LOC, loss of consciousness; MAP, mean arterial pressure; PONV, postoperative nausea and vomiting; RR, respiratory rate; SBP, systolic blood pressure; SpO_2, pulse oximetry; TBLB, transbronchial lung biopsy; TBNA, transbronchial needle aspiration.

Data Sharing Statement

Data are available from the corresponding author upon request.

Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas, took part in drafting, revising, or critically reviewing the article; gave final approval of the version for publication; agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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