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Safety of remimazolam in deep sedation during flexible fiberoptic bronchoscopy: a prospective, randomized controlled trial

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Abstract

Background Remimazolam is a novel ultrashort-acting sedative and anesthetic drug. Numerous recent studies have demonstrated its sedative effect, however, research has yet to be conducted to explore the safety of remimazolam in deep sedation flexible fiberoptic bronchoscopy (FFB) in elderly patients.

Methods Sixty-six elderly patients who underwent FFB were randomly assigned to either the remimazolam (Group R) or propofol (Group P) group. Initially, both groups received an intravenous injection of 10 μg/kg alfentanil. Subsequently, both groups were administered experimental drugs intravenously: (1) Group R received 0.2 mg/kg remimazolam, and (2) Group P received 1.5 mg/kg propofol. Throughout the FFB, patients were maintained in a state of deep sedation (modified observer's assessment of alertness/sedation score ≤ 1) by titrating the experimental drugs as needed. The primary outcome measured was the incidence of hypoxemia during the FFB. Secondary outcomes included other safety outcomes, effectiveness outcomes, and procedural characteristics.

Results Group R had a lower incidence of hypoxemia compared to Group P (9.1% vs. 45.5%) (RR, 0.20 [95% CI, 0.06–0.63], $P=0.001$). The Minimum SpO_2 and minimum MAP in Group R was higher than in Group P (93.1 ± 3.8 vs. 89.0 ± 6.7, $P=0.004$) (82.8 ± 12.4 vs. 72.8 ± 14.1, $P=0.003$); ΔMAP and ΔHR in Group R was lower than in Group P (15.9 ± 5.2 vs. 28.8 ± 12.4, $P<0.001$), (14.9 ± 3.2 vs. 17.8 ± 4.2, $P=0.003$); the incidence of hypotension in Group R was lower than in Group P (9.1% vs. 30.3%, $P=0.030$); the incidence of injection pain in Group R was lower than in Group P (0% vs. 27.3%, $P=0.001$).

Conclusions During the maintenance of elderly patients under deep sedation with FFB, remimazolam exhibited superior safety than propofol, particularly in terms of respiratory depression and cardiovascular inhibition.

Trial registration The trial was registered, before patient enrollment, in the Chinese Clinical Trial Registry (www.chictr.org.cn) (clinical trial number: ChiCTR2400083383; Principal Investigator: Gongchen Duan; date of registration: 23 April 2024).

Keywords Remimazolam, Flexible fiberoptic bronchoscopy, Deep sedation, Elderly patients

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Introduction

Flexible fiberoptic bronchoscopy (FFB) is an important minimally invasive diagnostic and treatment method for lung cancer and respiratory system diseases. FFB can be conducted under local anesthesia, with preoperative nebulization inhalation or surface infiltration anesthesia commonly used. Its advantages include the simplicity of the procedure and the preservation of the patient's spontaneous breathing [1]. However, individual local anesthesia for FFB has several drawbacks, including difficulty breathing, coughing, pain, fear, anxiety, and airway spasms. Consequently, the British Thoracic Society recommends that all patients undergoing FFB should be sedated, unless contraindicated [2]. Moderate sedation is the preferred depth for FFB, allowing patients to purposefully respond to verbal commands while maintaining a functional airway. However, patients may still need to endure repeated or painful stimuli, as well as potential aggravation of airway damage and ventilation disorders [3]. Studies have shown that patients undergoing FFB under deep sedation do not experience an increased incidence of respiratory depression and hypoxemia [4]. Recent study have also confirmed that compared with traditional methods, when deep sedation by balance propofol sedation is used in bronchoscopy, the satisfaction of patients and operators is relatively high, and does not increase the intraoperative or postoperative adverse events [5]. Elderly patients, with their poor cardiopulmonary reserve, are more sensitive to sedatives and are more likely to experience respiratory depression and hypotension during deep sedation treatment [6]. Therefore, the scheme of deep sedation that is more suitable for FFB in elderly patients needs further research to explore.

Remimazolam is a novel benzodiazepine for intravenous use in procedural sedation. Some studies have confirmed that remimazolam could be safely and effectively used for gastrointestinal endoscopy in elderly patients, with hypoxemia and respiratory depression being less common compared to propofol [7, 8]. Thus, employing remimazolam to sustain deep sedation in elderly patients with FFB may be an appropriate sedation therapy. We designed a randomized, single-blind study using propofol as the control drug to investigate the safety and efficacy of remimazolam in maintaining deep sedation in elderly patients with FFB.

Methods

Ethics and registration

This single-center, single-blind randomized clinical trial was approved by the Clinical Trials Ethics Committee of Lishui People's Hospital (approval no. 2023 – 190) by Chairperson Prof Zhichao Shi on 11 April 2024. This trial was performed in accordance with the Declaration of Helsinki and all enrolled patients provided written informed consent. This study adhered to the CONSORT guidelines.

Patient inclusion and exclusion criteria

This study involved 66 elderly patients who were admitted to Lishui People's Hospital for flexible fiberoptic bronchoscopy from April 2024 to June 2024.

The inclusion criteria were: (1) age between 65 and 80 years, (2) an American Society of Anesthesiologists (ASA) physical status of II or III, and (3) a body mass index between 18.5 and 27.9 kg/m^2. The exclusion criteria included: (1) mental disorders, cognitive dysfunction, or communication difficulties, (2) a diagnosis of respiratory failure ($PaO_2 < 60$ mmHg), (3) New York Heart Association (NYHA) cardiac function class III or IV, (4) patients with suspected difficult airway, (5) a history of allergy to benzodiazepines or propofol, or those who have taken sedative drugs for an extended period, and (6) severe arrhythmias, such as second or third-degree atrioventricular block or significant bradycardia (heart rate < 50 beats per minute).

Randomization and masking

Subjects were randomly assigned into 2 groups of 33 subjects each according to the computer generated random numbers (Group R and Group P). We discreetly placed the randomization results in envelopes until the end of the study. All subjects would wear opaque eye masks after lying flat, and then researchers began to prepare drugs. Therefore, subjects were blinded to their group allocation. Due to the obvious color difference between the two study drugs, it is difficult to blind researchers. The anesthesiologists responsible for the intervention and the personnel recording intraoperative data made clear the grouping status. In addition, the other investigator responsible for postoperative follow-up was blinded to the grouping. The postoperative follow-up was before the subjects were about to leave PACU, and the content was to ask whether there was intraoperative awareness.

Interventions

All patients fasted for 8 h and were deprived of water for 4 h. Upon arrival at the bronchial examination room, patients were premedicated with 5 mL of 2% lidocaine, induced by nebulized inhalation for 15 min prior to flexible fiberoptic bronchoscopy (FFB). Then, the patient was placed in a supine position and underwent routine monitoring, including electrocardiogram, non-invasive blood pressure, respiratory rate, pulse oxygen saturation. A nasal catheter was used to administer humidified oxygen for 3 min at a flow rate of 4 L/min. Moreover, nasal cannula oxygen inhalation at a flow rate of 4 L/min was continued throughout the operation until the end of the operation.

Initially, all patients received an intravenous injection of 10 μg/kg alfentanil (Yichang Humanwell Pharmaceutical Co., Ltd., Yichang, Hubei, China), administered over 30 s. Subsequently, both groups were given their respective experimental drugs intravenously: (1) Group R received 0.2 mg/kg remimazolam (Yichang Humanwell Pharmaceutical Co., Ltd., Yichang, Hubei, China); (2) Group P received 1.5 mg/kg propofol (Beijing Fresenius Kabi Pharmaceutical Co., Ltd., Beijing, China). Throughout the FFB procedure, patients were required to maintain deep sedation. Successful sedation was defined as a Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score of ≤1 (Supplement 1) [4]. If the MOAA/S score was >1, patients would undergo remedial sedation, with 0.05 mg/kg remimazolam administered intravenously in Group R, and 0.5 mg/kg propofol in Group P. One minute after remedial sedation, investigators reassessed the MOAA/S score. If the patient's MOAA/S score was ≤1, the inspection would proceed. When the MOAA/S score remained above 1 after the administration of two additional doses, it was defined as failed sedation, and propofol would be used as a remedial sedation method. Following successful sedation, an experienced bronchoscopist would perform the FFB through the nasal route. If the patient's MOAA/S score recovered to 1 or above during the FFB, additional sedative drugs would be administered until the inspection was completed. The additional dose administered to Group R was 0.05 mg/kg of remimazolam, while Group P received 0.5 mg/kg of propofol. Following the inspection, patients were transferred to the post-anesthesia care unit (PACU), where the MOAA/S score was assessed every minute to confirm sedation recovery (MOAA/S score = 5). During the FFB, if hypotension, bradycardia, hypertension, or tachycardia persisted for more than 30 s, patients were treated with the following vasoactive drugs: ephedrine, atropine, urapidil, and esmolol.

If hypoxemia occured during FFB, the following treatment measures would be applied in sequence: verbal and tactile stimulation; increase oxygen delivery to 10 L/min and raise the jaw; cease inspection and perform mask ventilation; if these measures are ineffective, tracheal intubation would be performed to ensure airway patency.

Outcome measurements

Primary outcome

The primary outcome was the incidence of hypoxemia during the FFB. Hypoxemia was defined as SpO_2 between 75% and 90% for less than 60 s, and severe hypoxemia was defined as SpO_2 less than 75% at any time or less than 90% for more than 60 s [9].

Secondary outcomes

1. Other safety outcomes: During the FFB, the incidence of severe hypoxemia, the minimum SpO2, and the grade of cough (0 = severe, ≥ 5 coughs; 1 = moderate, 3–4 coughs; 2 = minimal, 1–2 coughs; and 3 = no coughing), △MAP (maximum difference in mean arterial pressure), and △HR (maximum difference in heart rate) were recorded. Adverse events were defined as hypotension (mean arterial pressure of ≤70% of baseline and/or <65 mmHg), hypertension (mean arterial pressure of >120% of baseline), bradycardia (heart rate of ≤45 beats/min), tachycardia (heart rate of >120% of baseline), and the frequency of vasoactive drugs. Subjects were asked to describe the intensity of the pain (0 to10 points indicated "no pain" to "unbearable pain"). Injection pain was defined when the numeric rating scale value ≥3.
2. Effectiveness outcomes: The success rate of sedation at a single induced dose was defined as the percentage of successful sedation cases after the induced dose in each group. The success rate of sedation was defined as the percentage of successful sedation cases in each group. Additionally, the number of remedial sedations and the number of additional sedations were considered.
3. Patient baseline characteristics and procedural characteristics include age, height, weight, sex, ASA classification, level of education, total inspection time, sedation recovery time (MOAA/S = 5), and the length of PACU stay.

Sample size and statistical analysis

Twenty patients were included in the pre-experiment, as 10 subjects per group. The number of hypoxemia cases was 4 and 1 in Group P and Group R, respectively. Based on the results of the pre-experiment, the incidence of hypoxemia during FFB was 40% in Group P and 10% in Group R. The sample size was estimated using PASS 15.0 software (PASS, Kaysville, UT). A sample size of 58 patients was required to achieve a power of 0.8 and a significance level of 0.05. Accounting for a 10% attrition rate, we recruited 66 patients for the study (33 patients in each group).

Data processing and analyses were conducted using SPSS 20.0 statistical software (IBM Corp., Armonk, NY, USA). All data are presented as mean ± standard deviation, number (percentage), or median (Q1, Q3), as appropriate. The measurement data were tested for normality using the Shapiro–Wilk test. Normally distributed data were compared between groups using an independent-samples t-test, while non-normally distributed data were compared using the Mann–Whitney U test. The

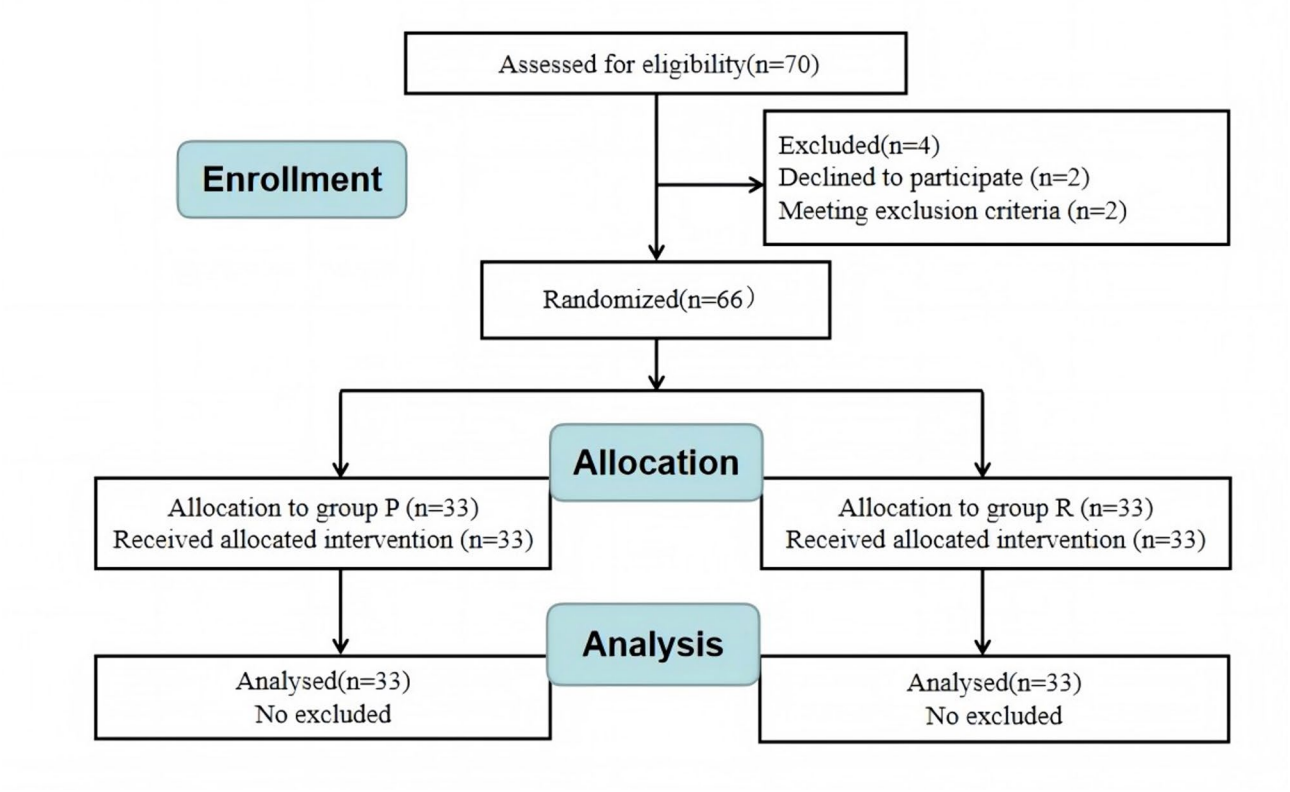

Fig. 1 Flow chart of this study

Table 1 Patient baseline characteristics and procedural characteristics ($n = 33$)

	Group *R*	Group *P*	*P*
Age (years)	71.3 ± 4.0	71.5 ± 3.7	0.825
Height (cm)	165.3 ± 4.7	164.2 ± 4.5	0.353
Weight (kg)	68.6 ± 6.8	67.9 ± 7.8	0.674
Sex, *n* (%)			0.629
Male	24 (72.7)	21 (63.6)	
Female	9 (27.3)	12 (36.4)	
ASA classification, *n* (%)			0.492
II	29 (87.9)	27 (84.8)	
III	4 (12.1)	6 (15.2)	
Level of education, *n* (%)			0.873
< Elementary school	4 (12.1)	5 (15.2)	
Elementary school	11 (33.4)	12 (36.4)	
≥Secondary school	18 (54.5)	16 (48.4)	
Procedure, *n* (%)			0.487
BAL	5 (15.2)	7 (21.2)	
BAL + BBi	18 (54.5)	20 (60.6)	
BAL + BBi + BBr	10 (30.3)	6 (18.2)	
Total inspection time, (min)	8.5 ± 1.9	8.4 ± 2.7	0.958
Sedation recovery time, (min)	8.3 ± 1.5	7.9 ± 1.7	0.407
Length of PACU stay, (min)	15.7 ± 1.9	15.4 ± 3.6	0.699

Notes: Data were presented as mean ± standard deviation or number (percentage)

Abbreviations: ASA, American Society of Anesthesiologists; PACU, post anesthesia care unit; BAL, bronchoalveolar lavage; BBi, Bronchial biopsy; BBr, Bronchial brushing; FFB, flexible fiberoptic bronchoscopy

chi-square test or Fisher's exact test was employed for comparing enumeration data between groups. The significance level for this analysis was set at $\alpha = 0.05$.

Results

In total, 70 patients were initially screened for eligibility, and 4 were excluded. One of them had a history of mental disorders, and three had long-term benzodiazepine use. Finally, data for 33 patients in Group R and 33 patients in Group P were analyzed (Fig. 1).

Patient baseline characteristics and procedural characteristics

The patient characteristics and procedural details were statistically similar between the two groups ($P > 0.05$) (Table 1).

Primary outcome

During the FFB, Group R had a lower incidence of hypoxemia compared to Group P (9.1% vs. 45.5%) (RR, 0.20 [95% CI, 0.06–0.63], $P = 0.001$) (Table 2).

Secondary safety outcomes

During the FFB, the incidence of severe hypoxemia in Group R was also lower than in Group P (3.0% vs. 21.2%, $P = 0.027$); the minimum SpO_2 was higher in Group R than in Group P (93.1 ± 3.8 vs. 89.0 ± 6.7, $P = 0.004$); the

Table 2 Safety outcomes ($n=33$)

	Group *R*	Group *P*	*P*	Effect size (95% CI)
Hypoxemia, *n* (%)	3 (9.1) *	15 (45.5)	0.001	0.20 (0.06,0.63)[a]
Severe hypoxemia, *n* (%)	1 (3.0) *	7 (21.2)	0.027	0.14 (0.02,1.10)[a]
Hypotension, *n* (%)	3 (9.1) *	10 (30.3)	0.030	0.30 (0.09,0.99)[a]
Hypertension, *n* (%)	5 (15.2)	4 (12.1)	0.500	1.25 (0.37,4.25)[a]
Bradycardia, *n* (%)	1 (3.0)	3 (9.1)	0.307	0.33 (0.04,3.04)[a]
Tachycardia, *n* (%)	6 (18.2)	3 (9.1)	0.238	0.20 (0.55,7.33)[a]
Injection pain, *n* (%)	0 (0)*	9 (27.3)	0.001	-
Minimum SpO_2, (%)	93.1 ± 3.8 *	89.0 ± 6.7	0.004	-0.40 (-0.64,-0.16)[b]
Grade of cough	2 (1, 2)	2 (1, 2)	0.224	-0.15 (-0.39,0.09)[b]
ΔMAP, (mmHg)	15.9 ± 5.2 *	28.8 ± 12.4	< 0.001	-1.36 (-1.91,-0.81)[c]
Maximum MAP, (mmHg)	98.6 ± 10.8	101.6 ± 9.0	0.234	-0.30 (-0.79,0.20)[c]
Minimum MAP, (mmHg)	82.8 ± 12.4 *	72.8 ± 14.1	0.003	0.75 (0.24,1.26)[c]
ΔHR, (beats/min)	14.9 ± 3.2 *	17.8 ± 4.2	0.003	-0.77 (-1.28,0.26)[c]
Maximum HR, (beats/min)	79.3 ± 9.6	81.8 ± 9.5	0.307	-0.25 (-0.74,0.24)[c]
Minimum HR, (beats/min)	64.8 ± 9.4	64.0 ± 10.4	0.729	0.09 (-0.40,0.58)[c]
Intraoperative awareness, *n* (%)	0 (0)	0 (0)	-	-
Frequency of vasoactive drugs used, *n* (%)				
Ephedrine	1 (3.0)	6 (18.2)	0.052	0.17 (0.02,1.31)[a]
Atropine	0 (0)	0 (0)	-	-
Urapidil	0 (0)	0 (0)	-	-
Esmolol	0 (0)	0 (0)	-	-
Treating hypoxemia, *n* (%)				
Verbal and tactile stimulation	1 (3.0)	2 (6.1)	0.556	0.5 (-1.95,2.95)[a]
Increase oxygen delivery and jaw thrust	2 (6.1) *	10 (30.3)	0.011	0.2 (-1.41,1.81)[a]
Mask ventilation	0 (0)	3 (9.1)	0.076	-
Tracheal intubation	0 (0)	0 (0)	-	-

Note: Data were presented as mean ± standard deviation, median (Q1, Q3) or number (percentage) as appropriate. Effect size (ES) was calculated as follows: a: Relative Risk was used for categorical outcomes (e.g., Hypoxemia, Severe hypoxemia), as these represent the relative occurrence of an event between the two groups. b: Pearson's r was used for outcomes assessing the effect size based on mean differences (e.g., Minimum SpO_2, Grade of Cough), where the correlation between groups is of primary interest. c: Cohen's d was used for continuous outcomes (e.g., ΔMAP, Maximum MAP, Minimum MAP), which compares the magnitude of mean differences between groups, with larger values indicating greater effect size. *$p < 0.05$, compared with group P

Abbreviations: MAP, mean arterial pressure; HR, heart rate; SpO_2, saturation of peripheral oxygen; CI, Confidence Interval

Table 3 Effectiveness outcomes ($n=33$)

	Group *R*	Group *P*	*P*	RR(95% CI)
Successfully sedation at a induced dose, *n* (%)	31 (93.9)	32 (97.0)	0.500	0.97 (0.87,1.01)
Successfully sedation, *n* (%)	33 (100)	33 (100)	-	-
Number of remedial sedation	0 (0, 1)	0 (0, 1)	0.708	-
Number of additions sedation	1 (0, 1)	1 (0, 1)	0.551	-

Note: Data were presented as number (percentage) or median (Q1, Q3) as appropriate

Abbreviations: RR, Risk ration; CI, Confidence Interval

minimum MAP was higher in Group R than in Group P (82.8 ± 12.4 vs. 72.8 ± 14.1, $P=0.003$); the ΔMAP and ΔHR in Group R was lower than in Group P (15.9 ± 5.2 vs. 28.8 ± 12.4, $P<0.001$), (14.9 ± 3.2 vs. 17.8 ± 4.2, $P=0.003$); the incidence of hypotension and injection pain in Group R was lower than in Group P (9.1% vs. 30.3%, $P=0.030$), (0% vs. 27.3%, $P=0.001$); the incidence of treating hypoxemia by increasing oxygen delivery and jaw thrust in Group R was lower than in Group P (6.1% vs. 30.3%, $P=0.030$) (Table 2).

Secondary efficacy outcomes

There were no significant differences in the success rate of sedation at a single induced dose, the success rate of sedation, the number of remedial sedations, and additional sedations between the two groups (Table 3).

Discussion

The results of this study showed that the incidence of hypoxemia and severe hypoxemia in the Group R were lower than Group P (9.1% vs. 45.5%; 3.0% vs. 21.2%). In addition, compared with propofol remimazolam can also maintain a higher minimum SpO_2 and providing stable

hemodynamics. In terms of patient comfort, remimazolam also had less injection pain. And the success rate of sedation between remimazolam and propofol was similar.

Remimazolam is a new ultrashort-acting benzodiazepine characterized by rapid onset, quick recovery, and minimal side effects, such as hypotension and respiratory depression, making it an ideal sedative [10]. The outcomes indicated that the incidence of hypoxemia and severe hypoxemia was lower in Group R compared to Group P (9.1% vs. 45.5%; 3.0% vs. 21.2%, respectively), and the minimum SpO_2 in Group R was higher than that in Group P. This suggests that, in comparison to propofol, remimazolam induces a milder degree of respiratory depression. Although the research conclusion of Zhang et al. also supports this point, but showing that the incidence of hypoxemia was lower than in our study, which may be related to the older age of our participants [11]. Additionally, this study revealed that the hemodynamics of Group R were more stable than those of Group P, whether in terms of ΔMAP (15.9 ± 5.2 vs. 28.8 ± 12.4) and ΔHR (14.9 ± 3.2 vs. 17.8 ± 4.2), or the incidence of hypotension (9.1% vs. 30.3%). This aligns with the findings of Guo et al. [12]. The risk of injection pain associated with intravenous propofol alone is approximately 60% [13]. In our results, the incidence of propofol injection pain was 27.3%, which may be attributed to the early administration of alfentanil. Intravenous remimazolam typically does not cause injection pain, as Chen et al. study also indicated [14]. The results also indicated that none of the patients experienced intraoperative awareness during postoperative follow-up, which is crucial for patient satisfaction. Intraoperative awareness can lead to significant psychological harm, including post-traumatic stress disorder, and may result in patients refusing subsequent similar examinations [15.

In this prospective randomized controlled trial, the results indicated that deep sedation with non-intubation and preserved spontaneous breathing was utilized for elderly FFB patients, and the effectiveness outcomes of remimazolam were comparable to that of propofol. Previous studies have shown that the success rate of 0.135 mg/kg remimazolam combined with alfentanil in sedating elderly patients undergoing FFB was 65.2% [16]. Thus, a dose of 0.135 mg/kg of remimazolam proved inadequate. In this study, the success rate of sedation with an initial dose of 0.2 mg/kg of remimazolam was 93.9%, and only two patients required an additional dose to achieve deep sedation. It is suggested that a dose of 0.2 mg/kg of remimazolam is more appropriate for achieving deep sedation in elderly patients undergoing FFB.

During the FFB, the shared airway between the surgeon and anesthesiologist, as well as the high risk of nonoperating room anesthesia, present significant challenges to anesthesia management. Selecting an appropriate anesthesia protocol to reduce the incidence of adverse events, particularly hypoxemia, is the core issue of anesthesia management during the FFB. Although most guidelines and expert consensus recommend maintaining mild or moderate sedation during FFB to avoid severe respiratory and circulatory depression, particularly in elderly patients, deep sedation should be prevented [2, 3, 17]. However, for elderly patients, insufficient sedation may lead to severe coughing and cardiovascular adverse events. Some studies have indicated that deep sedation can be safely administered during FFB, resulting in greater patient comfort [18, 19]. Therefore, the challenge lies in how to safely, effectively, and comfortably enable elderly patients to undergo FFB. The results of this study can provide an important theoretical basis for future research.

This study has several limitations. Firstly, the majority of elderly patients involved had an ASA II classification. Whether these findings are applicable to elderly patients with ASA III or IV remains to be investigated further. Secondly, the sedation depth was assessed using a subjective scale (MOAA/S), lacking objective monitoring methods such as the bispectral index, which could impact the timely monitoring of sedation depth in the study. Thirdly, there is no consensus on the optimal dose of remimazolam for FFB, and further research is anticipated to identify a more effective and suitable dosage. Fourth, Due to the obvious difference in the color of the two drugs, it is difficult to blind the intervention administrator and assessor. This may have a impact on the results. Lastly, this study was conducted at a single center with a small sample size. These preliminary results need to be confirmed by a prospective, multicenter study involving a larger sample.

Conclusions

Elderly patients who received FFB under deep sedation, the anesthesia protocol consisting of 0.2 mg/kg remimazolam showed milder respiratory depression and cardiovascular inhibition than the protocol of 1.5 mg/kg propofol. In addition, in this study, the results of the sedation success rate of remimazolam and propofol were similar, suggesting that the effectiveness of remimazolam may be similar to propofol, which needs further research to demonstrate. To sum up, remimazolam in deep sedation could be a more favorable clinical choice for elderly patients undergoing FFB.

Abbreviations

FFB	Flexible fiberoptic bronchoscopy
SpO_2	Pulse Oxygen Saturation
BIS	Bispectral index
ASA	American Society of Anesthesiologists
NYHA	New York Heart Association
MOAA/S	Modified Observer's Assessment of Alertness/Sedation

PACU	Post-anesthesia care unit
MAP	Mean arterial pressure
HR	Heart rate

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-025-03117-8.

Supplementary Material 1

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Author contributions
Dr. Duan had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Luo and Dr. Wu are co-first authors and contributed equally to the article. Concept and design: Duan, Lan, Xu. Acquisition, analysis, or interpretation of data: Duan, Luo. Drafting of the manuscript: Duan, Luo, Wu. Critical revision of the manuscript for important intellectual content: Duan, Luo. Statistical analysis: Lan. Administrative, technical, or material support: Wu, Xu. Supervision: Duan, Luo.

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Data availability
The original data analyzed in this study are included in the article; further inquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate
This trial was conducted in accordance with the Declaration of Helsinki and the Chinese Clinical Trial Specifications. It was approved by the Medical Ethics Committee of Lishui People's Hospital (approval No. 2023 – 190) and registered in the Chinese Clinical Trial Registry (www.chictr.org.cn; registration number: ChiCTR2400083383). Written informed consent was obtained from all participants. This study adhered to the CONSORT guidelines.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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