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Effectiveness of remimazolam besylate combined with alfentanil for fiberoptic bronchoscopy with preserved spontaneous breathing: a prospective, randomized, controlled clinical trial

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Abstract. – OBJECTIVE: The novel short-acting benzodiazepine remimazolam besylate acts rapidly and is used to induce easily controlled sedation. The aim of this study was to investigate the effects of remimazolam besylate combined with alfentanil in patients undergoing fiberoptic bronchoscopy with preserved spontaneous breathing.

PATIENTS AND METHODS: 192 patients undergoing painless fiberoptic bronchoscopy were randomly assigned to either propofol (P group) or remimazolam besylate (R group); both groups also received alfentanil 10 μg/kg. The respiratory rate was recorded during the inspection. Mean arterial pressure (MAP), heart rate (HR), oxygen saturation (SpO_2), Narcotrend values and Modified Observer's Assessment of Alertness and Sedation (MOAA/S) scores were recorded after entry to the operating room (T0), 1 min (T1), 2 min (T2) and 3 min (T3) after anesthesia, immediately after the bronchoscope entered the vocal cords (T4), when the bronchoscope reached the carina (T5), the patient's eyes opened (T6), and 30 min postoperatively (T7). Secondary outcomes included intraoperative hypotension and body movement grading, etc.

RESULTS: There was less respiratory depression during the inspection in the R group than in the P group ($p < 0.01$). The rate of hypotension during the examination was higher in the P group than in the R group ($p < 0.01$). Narcotrend values in the P group were less for the R group at the T1-T5 time points ($p < 0.01$). No difference in the number of body movements ≥ grade 3 was found between the two groups ($p > 0.05$).

CONCLUSIONS: Remimazolam besylate combined with alfentanil for painless fiberoptic bronchoscopy can better preserve the patient's spontaneous breathing and reduce the incidence of respiratory depression during the inspection than propofol.

Key Words:
Alfentanil, Painless fiberoptic bronchoscopy, Propofol, Remimazolam besylate, Sedation.

Abbreviations

ASA, American Society of Anesthesiologists; BP, blood pressure; GABAA, gamma-aminobutyric acid type A receptor agonist; HFNC, high flows nasal cannula; HR, heart rate; MAP, mean arterial pressure; MOAA/S, Modified Observer's Assessment of Alertness and Sedation; PACU, post-anesthesia care unit; RR, respiratory rate; SpO_2, oxygen saturation; T0, entry to the operating room; T1, 1 min after anesthesia; T2, 2 min after anesthesia; T3, 3 min after anesthesia; T4, instantly after the bronchoscope entered the vocal cords; T5, when the bronchoscope reached the carina; T6, eyes opened instantly; T7, 30 min postoperatively.

Introduction

Fiberoptic bronchoscopy plays a particularly important role in the early diagnosis and treatment of pulmonary bronchial diseases[1]. Routine bronchoscopy, however, is a source of both physiological and psychological stress to the patient. The entry of the bronchoscope into the airway will cause partial obstruction and increase airway resistance. As the innervation of the nose, pharynx, and larynx is extensive, the inspection can cause a strong stress response in the body leading to sympathetic excitation, causing an increase in blood concentrations of catecholamines, cortisol, and other hormones, resulting in an increased heart rate (HR) and blood pressure (BP), discomfort in the throat, which may produce violent coughing, nausea and vomiting, and even agitation, which can induce serious complications such as hemoptysis and arrhythmia[2].

Painless sedation fiberoptic bronchoscopy involves the intravenous use of certain specific anesthetics to achieve analgesia, sedation, and amnesia for the successful completion of the procedure[3]. The patient awakens quickly and cognitively recovers rapidly after the examination, which helps to improve the inspection quality and review rate.

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Midazolam and propofol are commonly used clinically for fiberoptic bronchoscopy. Sedation induced by small doses of midazolam rarely causes respiratory and circulatory depression during endoscopy, but its sedative effect remains for a longer period of time, and the patient takes a long time to recover their cognitive abilities[4]. Propofol has the advantages of a short duration of action and rapid and stable recovery, and although it has no analgesic effect and has certain inhibitory actions on cardiovascular functions, it is currently the most widely used anesthetic for bronchoscopy[4-7]. Alfentanil is a μ-opioid receptor agonist, with the advantages of a fast onset of action, short duration of action with rapid recovery, high safety, and eliciting few adverse reactions. Studies[8-12] have shown that alfentanil can inhibit the cough caused by intubation in patients undergoing fiberoptic bronchoscopy and can also inhibit the recovery period induced by inhalation anesthesia in patients undergoing oral surgery. In general, a combination of anesthetics is preferred[13].

Remimazolam besylate is γ-aminobutyric acid type A receptor agonist (GABAA), which has a rapid onset of action, produces a sedative effect comparable to propofol and has a short half-life. It is metabolized *in vivo* by tissue esterases to an inactive metabolite, produces a low incidence of respiratory/circulatory depression[14-16] and has a high safety profile in clinical use. A US study[17,18] in 2018 of patients undergoing bronchoscopy reported that "remimazolam besylate could be safely and effectively used for bronchoscopy and had a faster onset of action and faster recovery of neuropsychiatric functions compared to midazolam".

The objectives of the present research were to evaluate the clinical effects of remimazolam besylate combined with alfentanil in patients undergoing bronchoscopy with preserved spontaneous breathing and to establish an optimized sedation/anesthesia scheme for clinical painless bronchoscopy.

Patients and Methods

Study protocols were approved by the Ethics Committee of Wuhan No. 1 Hospital (No. W202231) and registered before patient enrollment at Chinese Clinical Trials Registry. gov (registration number: ChiCTR2200063975, principal investigator: Li Zhang, date of registration: 22/09/2022, registry URL: http://www.chictr.org.cn/edit.aspx?pid=143285&htm=4). The clinical trial adhered to the principles of the Declaration of Helsinki, and relevant clinical trial specifications and regulations in China. All included patients signed informed consent forms. A total of 192 patients scheduled to undergo fiberoptic bronchoscopy with preserved spontaneous breathing were enrolled (Figure 1).

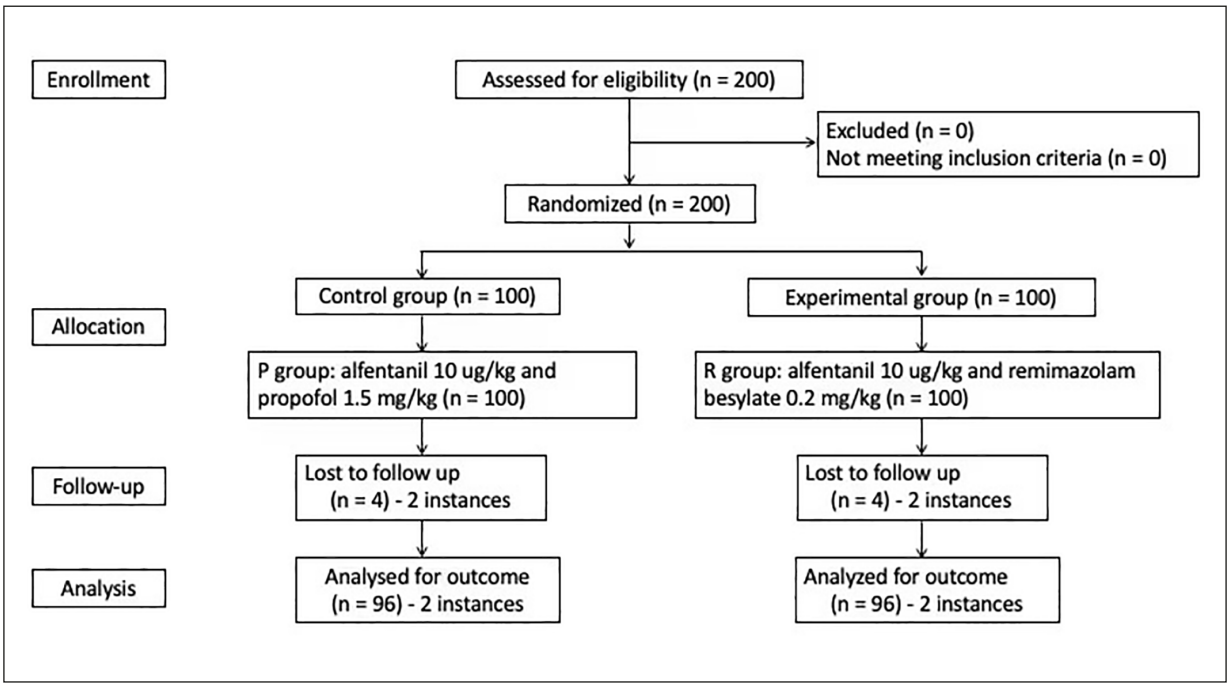

Figure 1. CONSORT flow chart for the participants.

The inclusion criteria were: age 18-65 years, male or female, BMI between 18.5 and 30 kg/m^2, and American Society of Anesthesiologists (ASA) grades I-III. The exclusion criteria were: refusal to participate in the study or individuals who planned to undergo bronchoscopy therapy, a history of severe cardiac, cerebral, pulmonary, hepatic, renal, or metabolic diseases, a history of previous recovery from abnormal surgical anesthesia, ECG recording indicating HR < 50 beats/min, a history of acute respiratory inflammation that had not been cured within 2 weeks, preoperative hypertensive with systolic BP > 180 mmHg and/or diastolic BP > 110 mmHg, or hypotensive patients with BP < 90/60 mmHg, patients with neuromuscular or psychiatric disorders, individuals with esophageal reflux disease, those suspected of narcotic analgesics or sedatives abuse; predicted to have possible or had previous difficult airways, known to be allergic to fat emulsions, benzodiazepines and opioids, had participated in other drug trials within three months, or were unable to communicate effectively or were uncooperative.

Sample Size Estimation

The incidence of respiratory depression was the main evaluation index for the calculation of the sample size. According to the results of preliminary pretests, the incidence of respiratory depression was about 21% for alfentanil combined with remimazolam besylate in patients undergoing bronchoscopy, and about 50% for propofol combined with sufentanil or nalbuphine. Assuming $\alpha = 0.025$ and $\beta = 0.1$, a superiority threshold of 5% was taken to establish the required sample size of 76 cases per group. Considering a 20% shedding rate, 192 cases with 96 in each group were proposed for the study to meet statistical significance.

Patients were entered randomly into the P or R groups sequentially, according to the order of enrollment and group randomization numbers generated by professional statistical software, without skipping numbers or choosing anesthetics independently. After determining the group of patients to be enrolled, drugs were administered by 2 anesthesiologists according to the protocol. Randomized, double-blind controlled groups were as follows: for the R group, alfentanil 10 μg/kg (Yichang Humanwell Pharmaceutical Co., Ltd., Yichang, Hubei, China) was given, followed by remimazolam besylate 0.2 mg/kg intravenously (Yichang Humanwell Pharmaceutical Co., Ltd., Yichang, Hubei, China)[19,20]; intraoperatively depending on the patient's response to stimulation; additional remimazolam besylate 0.05 mg/kg could be administered until the patient was comfortable. For the P group, alfentanil 10 μg/kg followed by propofol 1.5 mg/kg was administered intravenously (Sichuan Kelun Pharmaceutical Co., Ltd., Chengdu, Sichuan, China). Additional propofol doses at 0.5-1.0 mg/kg were administered intraoperatively depending on the patient's response to stimulation until the patient was comfortable. Patients routinely abstained from drinking and eating before bronchoscopy. High flow nasal cannula (HFNC) 10-15 L/min was utilized during the inspection. BP, HR, and oxygen saturation (SpO_2) were routinely monitored.

The anesthetics were administered according to the randomized groups. After the eyelash reflex disappeared, the inspection started. 2% lidocaine 40 mg (2 mL) was routinely applied (sprayed) by the bronchoscopy operator before entering the acoustic portal. During the inspection, the Narcotrend monitoring value remained at 45-70. After the inspection, the patient was moved to the post-anesthesia care unit (PACU) and monitored until fully awake.

Observed Indicators

General indicators

General indicators were age, height, sex, weight, BP and HR before examination, electrocardiogram, past history, anesthesia history and diagnosis.

Main evaluation indicators

Incidence of respiratory depression: defined as the occurrence of SpO_2 < 95% or a respiratory rate (RR) < 10 breaths/min during the period between the start of anesthetic administration and the patient being fully awake.

Secondary evaluation indexes

The indexes were BP, the incidence of hypotension, HR, SpO_2, RR, Narcotrend value, time from the start of anesthesia to the start of the inspection, total inspection time, awakening time, and time from the patient being fully awake to leaving the inspection room, anesthetic effect, Modified Observer's Assessment of Alertness and Sedation (MOAA/S) score, somatic movement grading, patient response scoring when fiberoptic bronchoscope entered

the vocal cords, the vocal cord movement score when the fiberoptic bronchoscope entered and left the nasal cavity (or mouth), etc.

Statistical Analysis

SPSS ver. 26.0 (IBM Corp., Armonk, NY, USA) software was employed for all analyses of data. Data are given as the mean ± standard deviation (x ± s). A *t*-test was employed for comparisons of normally distributed measurements between the 2 groups. ANOVA, with repeated measures design, was employed to make comparisons within groups, and the χ^2 test was used to compare count data. The test level $\alpha = 0.05$, and a difference was deemed to be significant at a *p*-value < 0.05.

Results

In terms of general information statistics, such as the sex ratio, age, or BMI scores ($p > 0.05$) (Table I), no differences were found between the two groups.

The dose of anesthetic administered was greater in the P group than in the R group [1.7 (1.6-2.0) *vs.* 0.25 (0.2- 0.3), $p < 0.001$]; no difference was found in the dosage of alfentanil administered to the 2 groups ($p > 0.05$); the mean number of additional intraoperative medications administered was lower in the P group [1 (0-1) *vs.* 1 (1-2), $p < 0.01$]; respiratory depression during the inspection in the P group was significantly higher than in the R group [38 (39.6%) *vs.* 13 (13.5%), $p < 0.001$]; the number of patients given mandibular support was greater in the P group [37 (38.5%) *vs.* 8 (8.3%), $p < 0.001$]; a higher rate of hypotension occurred during the inspection in the P group *vs.* the R group (8, 8.3% *vs.* 1 (1.0%), $p < 0.05$); the number of cases requiring ephedrine or methoxamine administration was higher in the P group *vs.* the R group [4 (4.2) *vs.* 0, $p < 0.05$]; the number of cases of bradycardia or atropine administration was identical in the two groups (Table II).

No differences were detected at any time point in mean arterial pressure (MAP) ($p > 0.05$), but HR was significantly higher in the R group at time points T1, T4, T5, T6, and T7 ($p < 0.001$), but SPO_2 exhibited no differences at any time point measured ($p > 0.05$) (Figure 2). Narcotrend values exhibited no differences at T0, T6, and T7 in the two groups ($p > 0.05$), but at T1, T2, T3, T4, and T5 time points were higher in the R group *vs.* the P group ($p < 0.001$). MOAA/S scores did not differ at T0, T3, T6, and T7 time points ($p > 0.05$) but were higher in the R group *vs.* the P group at T1, T2, T4 and T5 time points ($p < 0.001$) (Figure 3).

The time from the start of anesthesia to the start of inspection (min) was longer in the R group *vs.* the P group (1.85 ± 0.56 *vs.* 1.44 ±

Table I. Comparison of general information between the 2 groups of patients (n = 192).

Indicators	P group (n = 96)	R group (n = 96)	*p*-value
Sex (male/female)	44/52	48/48	0.563
Age (years)	65.11 ± 13.46	63.57 ± 13.32	0.487
Height (cm)	163.07 ± 7.45	161.72 ± 18.82	0.760
Weight (cm)	58.72 ± 11.31	56.72 ± 12.37	0.277
BMI (kg/m^2)	21.81 ± 3.70	21.26 ± 3.81	0.336

BMI: body mass index.

Table II. Comparison of drug doses, respiratory depression, and cardiovascular events in the two groups (n = 192).

Indicators	P group (n = 96)	R group (n = 96)	*p*-value
Sedative dose (mg/kg)	1.7 (1.6-2.0)	0.25 (0.2-0.3)	< 0.001
Alfentanil (μg/kg)	14.3 (13.4-14.9)	12.7 (9.3-16.7)	0.979
Number of additions	1 (0-1)	1 (1-2)	0.006
Respiratory depression	38 (39.6%)	13 (13.5%)	< 0.001
Number of patients given mandibular support	37 (38.5%)	8 (8.3%)	< 0.001
Hypotension	8 (8.3%)	1 (1.0%)	0.017
Number of ephedrine or methoxamine use cases	4 (4.2)	0	0.043
Bradycardia	2 (2.1%)	0	0.155
Atropine use cases	2 (2.1%)	0	0.155

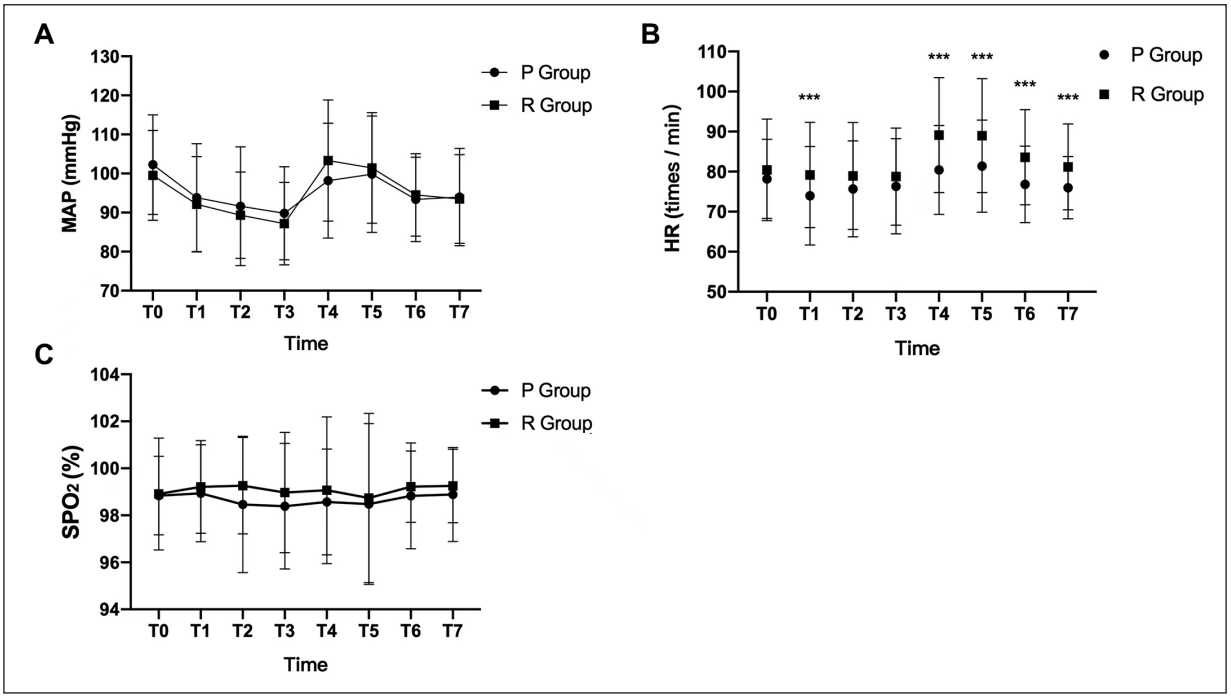

Figure 2. Comparison of (**A**) MAP, (**B**) HR and (**C**) SpO_2 between the two groups of patients at each time point. HR, heart rate; MAP, mean arterial pressure; SpO_2, oxygen saturation.

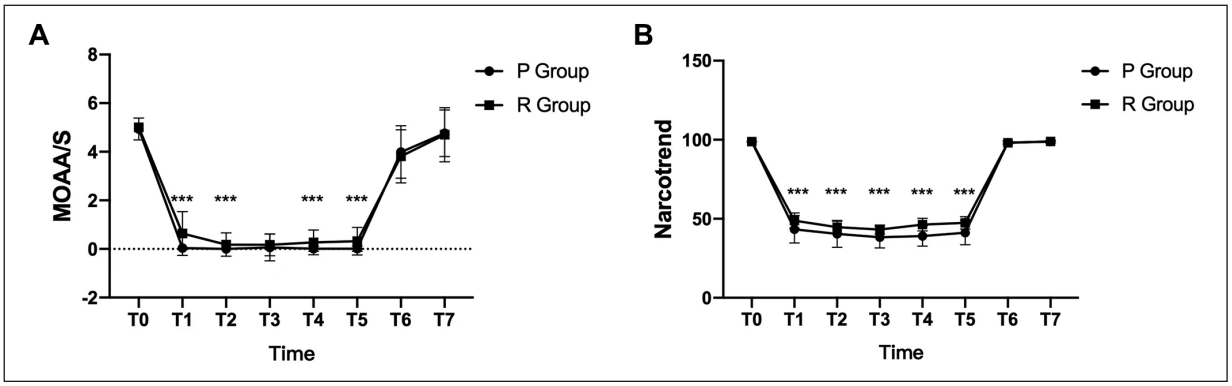

Figure 3. **A**, Narcotrend values and (**B**) MOAA/S scores of patients in both groups at each time point. MOAA/S, Modified Observer's Assessment of Alertness and Sedation.

0.77, $p < 0.001$); the total inspection time was no different between the 2 groups ($p > 0.05$). Awakening time was shorter in the R group *vs.* the P group (5.60 ± 2.47 *vs.* 6.85 ± 5.57, $p < 0.05$). The time from being fully awake to leaving the inspection room was the same for the 2 groups ($p > 0.05$) (Table III).

Somatic movement grading: the number of cases of grades 0 to 4 was different in the 2 groups ($p < 0.001$); the mean score was greater in the R group *vs.* the P group ($p < 0.05$), but the number of cases of somatic movement occurring at ≥ grade 3 was not different ($p > 0.05$). The number of cases of each grade of coughing during the induction period was less in the R group *vs.* the P group ($p < 0.001$), with moderate to severe coughing during the induction period being less in the R group ($p < 0.05$). No difference was detected with regard to coughing during the inspection between the 2 groups ($p > 0.05$) or the number of cases of operator discomfort score grading ($p > 0.05$). Patient scoring when the fiberoptic bronchoscope entered the vocal cords was the same in the 2 groups ($p > 0.05$). The vocal cord movement score when it

Table III. Comparison of the time from the start of anesthesia to the start of the examination, total examination time, time to awaken and time to leave the room in both groups (n = 192).

Indicators	P group (n = 96)	R group (n = 96)	*p*-value
Time from the start of anesthesia to the start of the examination (min)	1.44 ± 0.77	1.85 ± 0.56	< 0.001
Total inspection time (min)	11.21 ± 6.81	10.42 ± 5.41	0.239
Wake up time (min)	6.85 ± 5.57	5.60 ± 2.47	0.046
Time away from room (min)	12.68 ± 4.46	12.16 ± 2.09	0.318

Table IV. Comparison of body movement grading, degree of choking, and vocal motility in the two groups of patients examined (n = 192).

Indicators	P group (n = 96)	R group (n = 96)	*p*-value
Body movement classification (0/1/2/3/4)	9/39/27/11/9	0/22/58/13/2	< 0.001
Body movement grading score	1.71 ± 1.10	1.95 ± 0.67	0.010
Number of cases of grade 3 or higher somatic movements	20 (20.8%)	15 (15.6%)	0.455
Degree of choking during the induction period (none/light/moderate/severe)	19/63/10/2	4/90/2/0	< 0.001
Moderate to severe choking during the induction period	12 (12.5%)	2 (2.1%)	0.013
Coughing during operation (none/ mild/moderate/severe)	2/37/14/5	0/13/10/2	0.425
Operator discomfort score (0/1/2/3/4)	62/26/4/1/1	60/29/4/0/1	0.879
Scoring when entering the vocal cords	2.83 ± 1.28	3.34 ± 1.72	0.154
Vocal cord movement score during entry into the nasal cavity	3.32 ± 0.93	3.17 ± 0.82	0.015
Vocal cord movement score when leaving the nasal cavity	3.11 ± 0.90	3.08 ± 0.53	0.184

entered the nasal cavity was higher in the P group *vs.* the R group ($p < 0.05$), and the vocal cord movement score when it left the nasal cavity was not different in the 2 groups ($p > 0.05$) (Table IV).

Adverse effects 24 h after bronchoscopy and the number of cases of drowsiness were the same for both patient groups ($p > 0.05$). The number of vertigo cases was significantly lower in the R group compared to the P group [20 (20.8%) *vs.* 41 (42.7%), $p < 0.01$]; the number of cases of abdominal distension was significantly lower in the R group [9 (9.4%) *vs.* 26 (27.1%), $p < 0.01$].

Satisfaction scores: patient, anesthesiologist and endoscopist satisfaction scores were virtually identical in the 2 groups ($p > 0.05$) (Table V).

Discussion

This research was a prospective, randomized, double-blind, parallel, positive-controlled study. The main aim was to evaluate the safety and efficacy of remimazolam combined with alfentanil for painless bronchoscopy with preserved spontaneous breathing compared to propofol combined with alfentanil. The main findings were: (1) the incidence of respiratory depression during the examination of remimazolam combined with alfentanil was lower, which could better preserve the patient's spontaneous breathing; (2) the depth of sedation of remimazolam combined with alfentanil was shallower than that of propofol, but

Table V. Comparison of postoperative-related complications and satisfaction scores between the two groups (n = 192).

Indicators	P group (n = 96)	R group (n = 96)	*p*-value
Drowsiness	16 (8.3%)	16 (8.3%)	1.000
Giddiness	41 (42.7%)	20 (20.8%)	0.002
Nausea and vomiting	0	1 (1.0%)	1.000
Bloating	26 (27.1%)	9 (9.4%)	0.003
Patient satisfaction score	9.58 ± 0.69	9.44 ± 0.65	0.132
Anesthesiologist satisfaction	9.33 ± 0.89	9.28 ± 0.59	0.634
Endoscopist satisfaction	9.36 ± 1.19	9.21 ± 0.70	0.268

could meet the requirements of painless bronchoscopy; (3) the incidence of hypotension during the examination of remimazolam combined with alfentanil was smaller than that of propofol; (4) the incidence of coughing during the examination when remimazolam combined with alfentanil was used was smaller than for propofol, and the somatomotor response was comparable to that of propofol.

In the present study, the incidence of respiratory depression in patients in the R group was less than in the P group. Accordingly, the number of patients requiring mandibular oxygenation was less in the R group, with the above indicators showing that the rate of occurrence of respiratory depression in patients in the R group was low, findings consistent with the results of previously published research[21-23]. In a multicenter prospective randomized study that looked at the incidence of respiratory depression in elderly patients after the use of remimazolam during gastroscopy, it was shown that the incidence of respiratory depression was significantly lower with remimazolam than with propofol, findings consistent with the results of the present study[24].

The number of patients who had hypotension between the induction of anesthesia and the end of the examination was greater in the P group *vs.* the R group and mainly occurred during the period after intravenous injection and before the entry of the bronchoscope into the vocal cords. It has been shown that hypotension common occurs during propofol sedation for colonoscopy, and its degree and duration are related to patient injury[25]. In our study, however, only 1 patient in the R group experienced hypotension out of 96 patients. This result strongly suggests that remimazolam besylate produces a milder depression of the circulation, consistent with previous findings[26,27], likely due to its ability to maintain a normal cardiac output[28]. However, the MAP of the total sample size statistics was the same in the 2 groups at all time points investigated. The HR was greater in the R group vs. the P group at T1, T4, T5, T6, and T7; findings possibly related to the weaker sedation depth produced by remimazolam *vs.* propofol. The Narcotrend value was significantly higher in the R group than in the P group during the period from T1 to T5, and similarly, the MOAA/S scores were significantly higher in the R group compared to the P group at T1, T2, T4, and T5. This finding shows that the depth of sedation was weaker with remimazolam than propofol, however, none of the tested patients experienced intraoperative awareness. This finding is consistent with Xin's study, which used 3 doses of remazolam (0.1 mg/kg, 0.15 mg/kg, and 0.2 mg/kg) all of which met the criteria for successful sedation[21].

The time between the onset of anesthesia and the start of bronchoscopy was longer for the R group *vs.* the P group, and the interval from intravenous administration to the disappearance of the eyelash reflex was found to be essentially consistent with previously published data[23]. The time from the end of the operation to the patient's awakening was faster for the R group *vs.* the P group. Remimazolam besylate is metabolized *in vivo* by tissue lipase and rapidly hydrolyzed to zolpidem propionic acid. The affinity of this metabolite to the GABAA receptor is only 1/400th that of remimazolam, and it has almost no sedation activity, which greatly shortens the time of waking up, because it is not metabolized by the liver and kidneys, a characteristic that in patients with liver and kidney dysfunction is beneficial, making patient wake up times shorter. The time to leave the operating room was similar for both groups, in good agreement with the findings of a previous study[29], in which patients sedated with remimazolam besylate were discharged from the hospital after colonoscopy with no inferiority to propofol.

In terms of coughing, the induction coughing grade and the number of moderate-to-severe coughing cases in the R group were less than in the P group. This result shows that the coughing response of remimazolam besylate combined with alfentanil during induction was less severe than that of propofol combined with alfentanil. In addition to the mechanism of alfentanil itself in inhibiting the coughing response, it may be related to the factors of the bronchoscopy operator and patients themselves, which needs further clinical observations. From the fact that operator discomfort scores did not differ between the 2 groups, it is evident that neither somatic movements nor the coughing response of the two administration methods during the inspection affected the operator's experience. The vocal cord movement score at the time of entering the nasal cavity was higher in the P group *vs.* the R group, but no difference was found in the vocal cord movement score at the time of nasal cavity leaving between the 2 groups, and overall the vocal cord movement score was > 3 in both groups. This suggests that the vocal cord was in a state of movement, indicating that both groups of patients had the same preservation of spontaneous breathing during the inspection.

In terms of associated complications, cases of vertigo were higher in the P group *vs.* the R group,

probably due to the low affinity of the metabolite of remimazolam besylate, zolonepropionic acid, for GABAA receptors. Nausea and vomiting rates were the same in the 2 groups postoperatively, but the number of patients with postoperative bloating was significantly higher in the P group *vs.* the R group. This finding may be related to the higher coughing response of patients in the P group, thus causing a high flow of oxygen to enter the stomach through the esophagus.

Limitations

There were a number of limitations to the study. First, it was conducted at a single center, with a small cohort size, and therefore the results may not be generally representative. Second, the remimazolam besylate dosage administered was based on reports in the published literature, and no sequential dose was employed, so whether we used the optimal dose will be the subject of follow-up research. Finally, the physician who operated the bronchoscope was not always the same, so there may have been inadvertent biases in the operating time and proficiency operating experience, which will be the subject of further observation in subsequent studies.

Conclusions

Remimazolam besylate combined with alfentanil for painless bronchoscopy better preserved spontaneous breathing and reduced respiratory depression during an examination compared with propofol plus alfentanil anesthesia. There was less intraoperative hypotension, less coughing, comparable somatomotor response to propofol, a faster awakening time than for propofol, and in an incidence of postoperative vertigo and bloating. Remimazolam besylate combined with alfentanil can be safely used for painless bronchoscopy with preserved spontaneous breathing.

Trial Registration

Chinese Clinical Trial Registry (ChiCTR2200063975).

Conflict of Interest

The authors declare that they have no conflict of interest.

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Ethics Approval

The study was approved by the Ethics Committee of Wuhan No. 1 Hospital (No. W202231). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent

The study was conducted after obtaining informed written consent from the patients.

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Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' Contributions

Conceptualization: L. Zhang, Z.-J. Chen; Formal analysis: L. Zhang; Funding acquisition: L. Zhang, Z.-J. Chen; Investigation: L. Zhang, L. Yu, L. Xu, J.-F. Wang, J.-Y. Li; Project administration: Z.-J. Chen; Visualization: All author; Writing-original draft: L. Zhang; Writing- review & editing: All authors.

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