

Effects of Fentanyl-Reduced Regimen with Esketamine and Remimazolam on Bronchoscopy in Elderly Patients

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Objective: This randomized controlled study aimed to explore the safety and efficacy of a fentanyl-reduced regimen combining esketamine and remimazolam for bronchoscopy in elderly patients.

Methods: A total of 274 elderly patients (aged 65–85 years, ASA I–III) underwent bronchoscopy in our hospital from September 2024 to May 2025 were randomly divided into two groups: the study group (remimazolam 0.2 mg/kg + esketamine 0.3 mg/kg + fentanyl 0.5 ug/kg) and the control group (remimazolam 0.2 mg/kg + fentanyl 1.5 ug/kg). Remimazolam 0.05 mg/kg was added as needed to maintain sufficient sedation in both groups. The primary outcome was the incidence of procedure-related hypoxemia ($SpO_2 < 90\%$). Secondary outcomes included the procedural success rate, recovery metrics (time to awakening, time to discharge, and quality of recovery score), satisfaction levels (patient and endoscopist scores), and adverse events (incidences of hypotension and hypertension, degree of salivation, and body movements like coughing or limb swings).

Results: The study group had a lower incidence of hypoxemia (2.19% vs 9.49%, $p = 0.010$) and shorter awakening time (17.47 ± 3.10 vs 19.33 ± 3.78 , $p < 0.001$), as well as a higher QoR-15 score (138.95 ± 2.41 vs 137.38 ± 2.70 , $p < 0.001$) compared to the control group. The incidence of hypotension was significantly lower in the study group (0.73% vs 18.25%, $p < 0.001$). Although the study group exhibited a significantly higher degree of salivation ($p < 0.001$), no aspiration occurred. There were no significant differences in sedation success rate, discharge time, patient/endoscopist satisfaction, or incidence of agitation between the two groups.

Conclusion: The fentanyl-reduced regimen ensures sedation efficacy, and reduces adverse events like respiratory depression and hypotension, despite increasing salivation. It provides a safer anesthetic option for bronchoscopy in elderly patients.

Keywords: esketamine, remimazolam, fentanyl, hypoxemia, bronchoscopy, elderly patients

Introduction

Bronchoscopy is a crucial diagnostic and therapeutic tool for respiratory diseases. As an invasive procedure, it may trigger severe coughing, laryngospasm, arrhythmia, and other risks,^{1–3} often requiring deep sedation or general anesthesia. Elderly patients face higher risks of cardiopulmonary complications during bronchoscopy due to reduced respiratory and circulatory reserve and comorbidities, making it challenging to seek balance among sedation, analgesia and cardiopulmonary protection.

Current consensus guidelines for bronchoscopy anesthesia recommend lidocaine topical anesthesia combined with sedatives (eg, propofol or benzodiazepines) and opioid analgesics.^{4,5} However, opioids like fentanyl may increase the risk of respiratory depression.⁶ Traditionally, most sedation regimens use propofol combined with opioids for sedation and analgesia. However, propofol can aggravate the respiratory depression and hypotension of fentanyl.^{7,8}

Remimazolam, a new short-acting benzodiazepine, has shown lower incidences of hypotension and injection pain than propofol for bronchoscopy sedation, with good safety in elderly patients.⁹ Nevertheless, the combination of remimazolam and

fentanyl for sedation in elderly patients still has a respiratory inhibitory effect of about 8%.^{10–12} These studies indicate the necessity of reducing opioids.

Esketamine, a dextrorotatory isomer of ketamine, acts as a non-competitive NMDA receptor antagonist, providing potent analgesia and sedation with minimal respiratory and circulatory depression, thus reducing opioid requirements.^{7,13} Studies have shown that esketamine combined with propofol is more effective than traditional opioid-based regimens for adult bronchoscopy.^{14,15} However, the use of medium and large doses (≥ 1.0 mg/kg) of ketamine alone can lead to a large number of complications such as cardiovascular and cerebrovascular accidents,¹⁶ delirium, and slow resuscitation.¹⁷ For elderly patients, this possibility increases significantly, while small doses, such as 0.3 mg/kg, are insufficient to suppress the pharyngeal reflex during bronchoscopy.¹⁸ Subanesthetic dose of esketamine adjunct to propofol-remifentanyl anesthesia reduces cough scores in pediatric bronchoscopy.¹⁹ However, the potential of a remimazolam-esketamine combination to facilitate an opioid-reducing strategy in elderly patients undergoing bronchoscopy has yet to be evaluated. Therefore, we hypothesized that a fentanyl-reduced regimen with esketamine and remimazolam could reduce adverse events while maintaining sufficient sedation/analgesia in elderly patients undergoing bronchoscopy.

Methods

Study Design

This is a single-center, randomized, controlled, prospective trial designed following the SPIRIT 2013 statement. It was approved by the Ethics Committee of Deyang People's Hospital (Approval No.: 2023-03-011-K02) and registered on the Chinese Clinical Trial Registry (ChiCTR2400084672). Written informed consents were obtained from all participants. The study complies with the Declaration of Helsinki.

Study Population

Inclusion Criteria

Aged 65–85 years; American Society of Anesthesiologists (ASA) grade I–III; body mass index (BMI) 18–28 kg/m²; scheduled for elective sedation-assisted bronchoscopy; able to understand the study protocol and provide written consent.

Exclusion Criteria

Severe cardiovascular diseases (eg, uncontrolled hypertension, coronary heart disease, cardiopulmonary failure); difficult airway (assessed by the LEMON criteria) or hypoxemia (SpO₂ < 90 inhaling air); head trauma or central nervous/psychiatric disorders; substance abuse; allergies to study drugs; glaucoma or increased intraocular pressure; severe hematological disorders; significantly abnormal liver/kidney function.

Randomization and Blinding

A random number table generated by SPSS 23.0 was used to allocate patients to the study or control group with a ratio of 1:1. The numbers were sealed in opaque envelopes. Anesthesiologists opened the envelopes in sequence to determine group assignment. Patients, data recorders, and analysts were blinded; only anesthesiologists knew the grouping, but did not participate in data collection or analysis. After sedation induction, the data recorder entered the examination room, collected related data and supervised the procedure. Unblinding was allowed for severe complications, anesthesia accidents, or incomplete procedures.

Intervention

All patients underwent a standard pre-anesthesia preparation. Upon arrival, an upper limb intravenous line was established. Noninvasive blood pressure, electrocardiograph (ECG), and saturation of peripheral oxygen (SpO₂) were monitored. Pre-oxygenation with 100% oxygen via a dedicated mask was performed at a flow of 6 L/min. Anesthetic induction protocols were as follows:

- **Control group:** Intravenous injection of remimazolam 0.2 mg/kg 3 minutes before the procedure, followed by fentanyl 1.5 ug/kg 1 minute later.

- **Study group:** Intravenous injection of remimazolam 0.2 mg/kg 3 minutes before the procedure, followed by esketamine 0.3 mg/kg + fentanyl 0.5 ug/kg 1 minute later.

Bronchoscopy began when the eyelash reflex disappeared and no body movement was observed. A bolus of 0.05 mg/kg remimazolam was additionally used for cases who underwent unsuccessful sedation induction. About 2% lidocaine 5 mL (100 mg) was sprayed through the biopsy channel at the glottis, carina, and left/right main bronchi. Sedation depth was monitored using the Modified Observer's Alertness/Sedation (MOAA/S) scale every 3 minutes or emergence of slight alterations in facial expression, with 0.05 mg/kg remimazolam administered intraoperatively for inadequate sedation (MOAA/S score > 2) or emergence of body movement, coughing, or swallowing. Chin-lift maneuver was immediately performed when SpO₂ <90%. Manual ventilation was initiated when chin-lift maneuver did not work. The bronchoscope was withdrawn until SpO₂ stabilized above 95%. Vascular active drugs were used to maintain blood pressure within 20% of baseline. The oral secretions are suctioned by the endoscopic physician to prevent them from entering the lower airway.

After the procedure, the satisfaction scores were obtained from the endoscopists. Patients were transferred to the Post-Anesthesia Care Unit (PACU) for standard resuscitation and were allowed to discharge when the Steward score >4. The quality of recovery-15 (QoR-15) scores and satisfaction ratings from the patients were collected via telephone on the next day.

Outcomes

Primary Endpoint

Incidence of hypoxemia (SpO₂ < 90%) during the procedure. Hypoxemia was further defined as mild (75 ≤ SpO₂ < 90% for <60s) and severe (SpO₂ < 75% or SpO₂ < 90% for >60s).²⁰

Secondary Endpoints

- The times of jaw thrust maneuver and manual ventilation.
- Successful sedation: Defined as no rescue sedation and maintained the MOAA/S score ≤1 during endoscopy.
- Successful examination: Defined as not requiring termination of the procedure due to inadequate sedation.
- Awakening time: Time from last drug administration to responsive eye opening.
- Discharge time: Time from awakening to meeting discharge criteria (Steward score > 4).
- Recovery quality: QOR-15 score on the 1st post-procedure day.
- Satisfaction ratings: Patient and operator assessments on a 0–10 scale (0 = extremely dissatisfied, 10 = extremely satisfied).
- Adverse events: Incidences of hypotension/hypertension (blood pressure change >20% of baseline), body movement reactions (coughing, limb movements, etc.) and the degree of salivation: (1) Grade 0: The oral mucosa is dry and no saliva can be seen; (2) Grade 1: The mucosa is slightly moist and there is no accumulation of saliva; (3) Level 2: Obvious saliva accumulation, requiring intermittent aspiration (1–3 times); (4) Level 3: A large amount of saliva gushes out and requires frequent suction (>3 times).

Sample Size Calculation

Sample size calculation was based on the intraoperative hypoxemia incidence observed in the pilot study (30% for the control group vs 15% for the study group). Assuming a two-sided α of 0.05, 85% power, a 1:1 allocation ratio, 133 participants per group were required. Considering 10% dropout rate, we planned to recruit 148 participants per group.

Statistical Analysis

Statistical analyses were performed using SPSS 23.0. Parameters were categorized as quantitative or qualitative. Continuous (quantitative) variables were assessed for normality using the Kolmogorov–Smirnov test. Normally distributed data were presented as mean ± standard deviation and compared with Student's *t*-test; non-normal data were expressed as median (25th–75th percentile) and analyzed using the Wilcoxon rank-sum test. Categorical (qualitative) variables, presented as n (%), will be compared using the chi-square or Fisher's exact test. Statistical significance is defined as $p < 0.05$.

Result

From September 2024 to May 2025, 298 elderly patients underwent general anesthesia for bronchoscopy in our hospital were assessed for eligibility. A total of 24 patients were excluded, including 6 with severe arrhythmia, 1 with severe asthma and 17 declining to participate. Therefore, 274 of them were enrolled and analyzed. The study flowchart was shown in Figure 1. Baseline and demographic data are summarized in Table 1.

Respiratory Outcomes

The overall incidence of hypoxemia was 3 cases (2.2%) in the study group, while there were 13 cases (9.5%) in the control group. The difference is significant ($P = 0.010$). The incidence of mild hypoxemia was 3 cases (2.2%) in the study group versus 9 cases (6.6%) in the control group ($P = 0.077$). No severe hypoxemia occurred in the study group (0%), while 4 cases (2.9%) were observed in the control group ($P = 0.122$). The results are shown in Table 2.

Two cases (1.46%) underwent jaw thrust maneuver and manual ventilation in the study group, significantly less than 11 cases (9.5%) in the control group ($P = 0.011$, Table 2).

Efficiency of Sedation

As shown in Table 2, there was no statistically significant difference in the success rate of sedation between the study group and the control group (86.13% vs 84.67%, $P = 0.732$). All patients in both groups completed bronchoscopy.

Recovery Outcomes

The awakening time of the study group was significantly shorter than that of the control group (17.47 ± 3.10 min vs 19.33 ± 3.78 min, $p < 0.001$, Table 2), but there was no statistically significant difference in discharge time between the

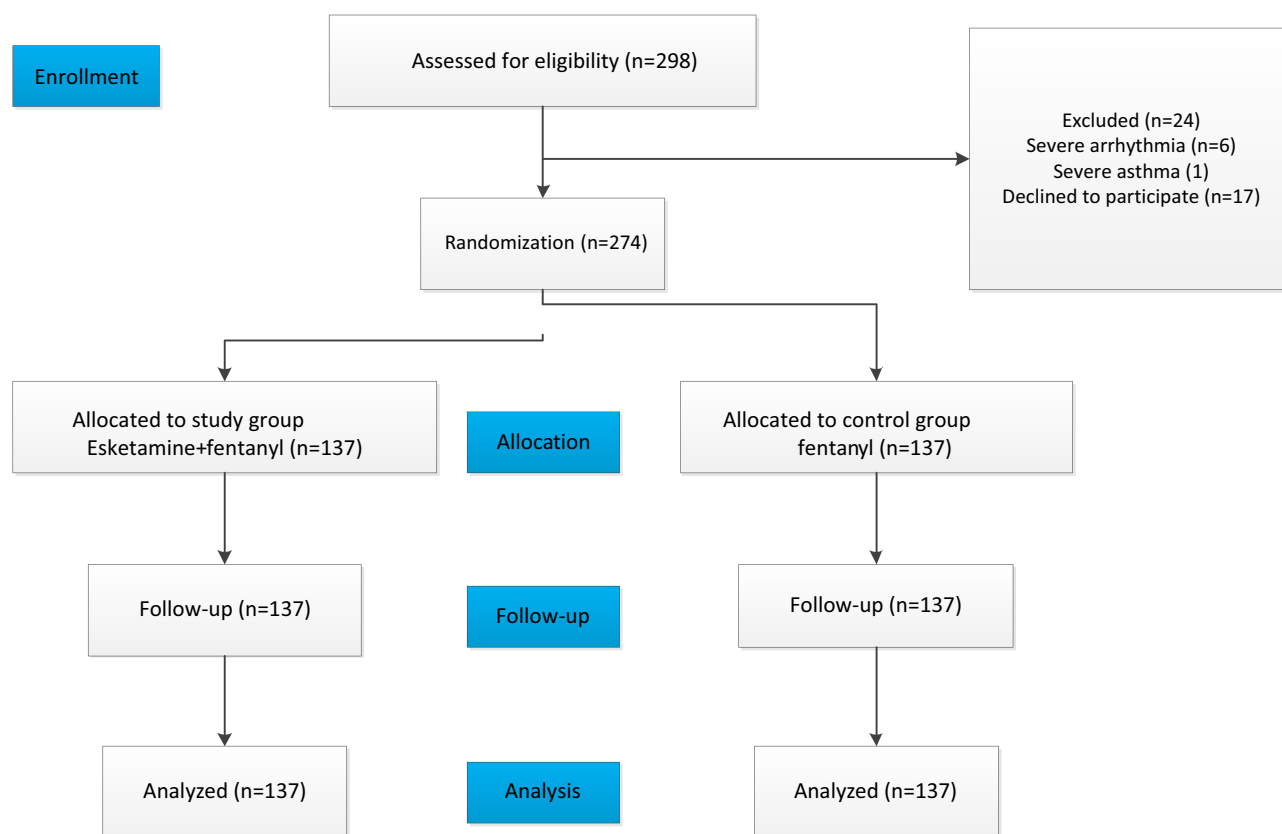


Figure 1 Flowchart of this study.

Table 1 Baseline and Demographic Data of the Enrolled Patients

	Study Group, n = 137	Control Group, n = 137	p
Age (years)	75.15 ± 5.15	75.09 ± 5.27	0.917
Sex (female, %)	54, 39.42%	60, 43.80%	0.463
Weight (kg)	59.80 ± 4.76	60.03 ± 4.58	0.689
Length (cm)	160.41 ± 4.55	160.16 ± 4.62	0.665
BMI (kg/m ²)	23.23 ± 1.40	23.42 ± 1.84	0.319
Cardiovascular disease (n, %)	78, 56.93%	69, 50.36%	0.253
Pulmonary disease	37, 27.01%	45, 32.85%	0.281
Diabetes (n, %)	34, 24.82%	30, 21.90%	0.587
Alcohol use (n, %)	16, 11.68%	15, 10.95%	0.851
Smoker (n, %)	31, 22.63%	33, 24.09%	0.765
Primary diagnosis (n, %)			0.163
Tumor	68, 49.63%	77, 56.20%	
Infection	33, 24.09%	39, 28.47%	
Tuberculosis	12, 8.76%	8, 5.84%	
Other	24, 17.52%	13, 9.49%	
Baseline measurements			
SBP, mmHg	125.36 ± 13.76	124.34 ± 15.84	0.572
DBP, mmHg	69.79 ± 10.23	70.00 ± 9.95	0.862
Heart rate, beats/min	71.16 ± 11.63	71.76 ± 11.61	0.670
SpO ₂ , %	96.05 ± 7.81	95.99 ± 7.78	0.951

Notes: Alcohol use: Having alcohol daily. Smoker: Having smoked at least 100 cigarettes in a lifetime and still smoking at the time of the survey (daily or intermittently).

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; SpO₂, saturation of peripheral oxygen.

Table 2 The Main Outcomes of the Two Groups

	Study Group, n = 137	Control Group, n = 137	P
Hypoxia (n, %)	3, 2.19%	13, 9.49%	0.010
Mild oxygen desaturation (n, %)	3, 2.19%	9, 6.57%	0.077
Severe oxygen desaturation (n, %)	0, 0	4, 2.92%	0.122
Airway maneuver required (n, %)	2, 1.46%	11, 8.03%	0.011
Rate of successful sedation (%)	86.13	84.67	0.732
Rate of successful examination (%)	100	100	1
Total dose of remimazolam (mg)	12.45 ± 1.10	12.51 ± 1.06	0.646
Operation time (min)	9.56 ± 2.15	9.34 ± 2.54	0.121
Awakening time (min)	17.47 ± 3.10	19.33 ± 3.78	<0.001
Discharge time (min)	27.12 ± 4.10	27.39 ± 3.66	0.557
QoR-15	138.95 ± 2.41	137.38 ± 2.70	<0.001
Satisfactory score of patients	8.85 ± 1.29	8.81 ± 1.45	0.826
Satisfactory score of endoscopist	8.84 ± 1.06	8.82 ± 1.37	0.883

Abbreviation: QoR-15, Quality of Recovery-15 questionnaire.

two groups (27.12 ± 4.10 min vs 27.39 ± 3.66 min, $p = 0.557$, Table 2). The scores of QoR-15 in the study group were higher than that of the control group (138.95 ± 2.41 vs 137.38 ± 2.70, $p < 0.001$) (Table 2).

Adverse Events

The incidence of hypotension in the study group was significantly lower than that in the control group (0.73% vs 18.25%, $p < 0.001$, Table 3). Only 2 cases (14.60%) of hypertension occurred in the study group. There was no statistical

Table 3 Adverse Reactions During the Study Process

	Study Group, n = 137	Control Group, n = 137	P
Hypertension (n, %)	2, 1.46%	0, 0	0.498
Hypotension (n, %)	1, 0.73%	25, 18.25%	<0.001
Body movement (n, %)	19, 13.87%	21, 15.33%	0.732
Agitation (n, %)	6, 4.38%	4, 2.92%	0.519
Nausea and vomiting (n, %)	7, 5.11%	9, 6.57%	0.606
Delayed emergence (n, %)	0, 0	0, 0	1
Degree of salivation			<0.001
Grade 0 (n, %)	2, 1.46%	19, 13.87%	
Grade 1 (n, %)	21, 15.33%	103, 75.18%	
Grade 2 (n, %)	107, 78.10%	13, 9.49%	
Grade 3 (n, %)	7, 5.11%	2, 1.46%	

Notes: The degree of salivation: (1) Grade 0: The oral mucosa is dry and no saliva can be seen; (2) Grade 1: The mucosa is slightly moist and there is no accumulation of saliva; (3) Level 2: Obvious saliva accumulation, requiring intermittent aspiration (1–3 times); (4) Level 3: A large amount of saliva gushes out and requires frequent suction (>3 times).

difference in body movement response between the two groups (13.87% vs 15.33%, $p = 0.732$, Table 3). There were no statistically significant differences in the other measured adverse reactions such as the incidence of agitation during the recovery period (4.38% vs 2.92%, $P = 0.519$), nausea and vomiting (5.11% vs 6.57%, $P = 0.606$), and delayed emergence (0 vs 0, $P = 1$) between the two groups (Table 3).

The degree of saliva secretion in the study group was significantly higher than that in the control group ($p < 0.001$, Table 3).

Satisfactory Scores of Patients and the Endoscopist

There was no statistically significant difference in the satisfaction of patients (8.85 ± 1.29 vs 8.81 ± 1.45 , $p = 0.826$) or the endoscopist (8.84 ± 1.06 vs 8.82 ± 1.37 , $p = 0.883$) between the two groups (Table 2).

Discussion

This study evaluated the safety and efficacy of a fentanyl-reduced regimen compared with a conventional fentanyl regimen for bronchoscopy in elderly patients. The main findings demonstrated that the fentanyl-reduced strategy significantly reduced the incidence of procedure-related hypoxemia and hypotension. Additionally, it shortened awakening time and improved the quality of recovery. Notably, there were no significant differences in sedation success rate, procedural completion rate, discharge time, or patient/operator satisfaction between the two groups, confirming that the fentanyl-reduced regimen maintains efficacy while enhancing safety.

The choice of a “fentanyl-reduced” rather than “opioid-free” strategy was driven by the specific demands of bronchoscopy. Bronchoscopy involves strong stimulations (eg, glottis and bronchial mucosal irritation), which can trigger body movements, coughing, or swallowing if analgesia is insufficient—potentially disrupting the procedure or increasing complications.⁴ Previous evidence indicates that complete elimination of opioids may exacerbate these stimulatory responses in invasive procedures like bronchoscopy, as opioids play a key role in blunting visceral and somatic pain signals.⁶ By contrast, a “reduced” strategy retains a low dose of fentanyl (0.5 ug/kg) to provide basic analgesia, while esketamine (0.3 mg/kg) compensates for the reduced opioid dose with its potent analgesic effect via NMDA receptor antagonism. This approach aligns with the British Thoracic Society guidelines, which emphasize balancing analgesia and safety in bronchoscopy, ensuring patients tolerate intense stimuli without excessive opioid-related adverse effects.⁵ Our results support this opioid-reduced strategy for bronchoscopy.

The selection of remimazolam and esketamine in this regimen is rooted in their unique advantages for painless diagnosis and treatment, especially in elderly patients. Remimazolam, a short-acting benzodiazepine, acts on GABA receptors to induce rapid sedation with quick recovery and minimal hepatorenal metabolism—critical for elderly patients

with reduced organ reserve.^{9,21} Compared with propofol, remimazolam is associated with lower incidences of hypotension and injection pain, reducing circulatory risks in older adults.²² Esketamine, by antagonizing NMDA receptors, provides potent analgesia, reduces opioid requirements, and causes minimal respiratory depression.^{13,23} Unlike high-dose ketamine (≥ 1.0 mg/kg), which may induce cardiovascular events or delirium in the elderly, the low dose (0.3 mg/kg) used here avoids such risks while enhancing hemodynamic stability via mild sympathomimetic effects—effectively counteracting the hypotensive tendency of remimazolam and fentanyl.^{16,24,25} This combination outperforms traditional regimens (eg, propofol + fentanyl) by reducing respiratory depression and hypotension, consistent with studies showing esketamine-based regimens improve safety in invasive procedures.¹⁵

Other notable findings include the higher degree of salivation in the study group, which is likely related to the cholinergic effects of esketamine. Although esketamine significantly increased salivary secretions, this was effectively managed by standard suctioning and did not impact the procedural success rate or endoscopist satisfaction, demonstrating its clinical insignificance,¹⁹ demonstrating its clinical insignificance. Additionally, patient satisfaction was comparable between the groups, possibly due to effective analgesia, the blunted short-term emotional perception post-anesthesia^{26,27} and the anterograde amnesia induced by remimazolam,²⁸ which may have reduced recall of procedural discomfort. For operators, the benefits of fewer respiratory interruptions likely offset the minor inconvenience of increased salivation.²⁹

Considering the advantages of remimazolam and esketamine, their combinations have been widely used. Sub-anesthetic doses of remimazolam plus esketamine provided sufficient sedation but less respiratory and circulatory fluctuation for painless procedures,^{30,31} which promotes the application to vulnerable populations. For old patients underwent colonoscopy, 0.15 mg/kg remimazolam + 0.3 mg/kg esketamine induced a 100% sedation rate with fewer cardiopulmonary side effects and faster recovery compared with 1.5 mg/kg propofol + 0.3 mg/kg esketamine.³² The present study evidences that subanesthetic remimazolam-esketamine can provide a feasible opioid-reduced effects for bronchoscopy, a procedure with more difficult management for anesthesiologists.

This study has several limitations. First, it is a single-center trial, which may limit the generalizability of results to diverse populations. Second, the sample size, while calculated to detect differences in hypoxemia, may be insufficient to assess rare adverse events (eg, laryngospasm).³³ Third, we did not quantify sputum volume or long-term recovery outcomes (eg, delirium beyond 24 hours), which could provide deeper insights into the effects of esketamine.⁷ In addition, although the vital signs were routinely monitored, we did not pre-specify hemodynamic changes as an outcome for systematic analysis; future studies would benefit from a more detailed investigation of heart rate variability and arrhythmias to fully assess the cardiovascular response to this regimen. Finally, the blinded design was limited to patients, data recorders, and analysts—anesthesiologists were unblinded, introducing potential bias in intraoperative drug adjustments. We required and trained the anesthesiologists to strictly follow the research protocol, which minimizes this bias to the greatest extent.

Conclusion

The fentanyl-reduced regimen with esketamine and remimazolam ensures sedation efficacy and reduces hypotension during bronchoscopy in elderly patients, offering a safer anesthetic option. These findings provide important evidence for clinical practice and hold promising value for promotion in anesthesia for bronchoscopy in elderly patients.

Data Sharing Statement

The data generated during the current study are available from the corresponding author on reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is 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 to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

All authors declare no conflicts of interest in this work.

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