Research Square

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Subanesthetic-Dose Esketamine Combined with Remimazolam in Non-Intubated Sedated Flexible Bronchoscopy: A Single-Center Retrospective Cohort Study

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Research Article

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Abstract

Objective

To compare hemodynamic stability, sedative-analgesic consumption, and peri-procedural adverse events between remimazolam-sufentanil sedation with and without low-dose esketamine in patients undergoing non-intubated sedated flexible bronchoscopy.

Methods

A total of 143 patients undergoing sedated flexible bronchoscopy at Guiyang Second People's Hospital between October and December 2025 were retrospectively enrolled. Based on the anesthetic regimen documented in the anesthesia record, patients were classified into a remimazolam group (Group R) receiving sufentanil 0.1 μg/kg plus remimazolam 0.3 mg/kg, or an esketamine group (Group E) receiving esketamine 0.15 mg/kg followed by the same sufentanil–remimazolam regimen. Thirteen cases were excluded due to additional therapeutic interventions during the procedure, or deviation from the study protocol by the operating physician, resulting in 130 patients finally included in the per-protocol analysis, with 65 patients in each group.Mean arterial pressure (MAP) and heart rate (HR) were recorded at baseline (T_0), completion of induction (T_1), and bronchoscope passage through the glottis (T_2). Recovery time, total drug consumption, and incidence of perioperative adverse events were compared between groups.

Results

At T_0, MAP and HR were comparable between groups ($p > 0.05$); At T_1, MAP and HR in Group R decreased significantly from baseline, whereas Group E demonstrated significantly higher MAP and HR than Group R (both $p < 0.05$). At T_2, Group R exhibited a pronounced sympathetic stress response, with significantly higher MAP and HR compared with Group E (both $p < 0.05$). The incidences of cough/body movement, hypotension, and hypoxemia in Group E were significantly lower than in Group R (all $p < 0.05$). Total consumption of remimazolam and sufentanil in Group E was significantly lower than in Group R (both $p < 0.001$). Recovery time was comparable between groups ($p > 0.05$).

Conclusion

Subanesthetic-dose esketamine added to remimazolam–sufentanil sedation was associated with improved hemodynamic stability, reduced supplemental sedative/analgesic requirements, and fewer cough/body movement and hypotensive events during non-intubated flexible bronchoscopy. These findings should be confirmed in prospective randomized trials.

1. Background

Flexible bronchoscopy plays an indispensable role in the diagnosis and management of pulmonary diseases, including procedures such as bronchoalveolar lavage, endobronchial biopsy, and bronchial brushing [1]. Conventional unsedated bronchoscopy is frequently associated with patient discomfort, anxiety, coughing, and procedural intolerance, which compromise examination quality and operator performance [2]. The growing emphasis on patient-centered comfort care has increased the use of sedated flexible bronchoscopy. Under conscious or deep sedation with spontaneous ventilation preserved, this technique not only improves patient tolerance but also facilitates smoother endoscopic maneuvers [2–3].

Propofol combined with opioids has long been the standard regimen for sedated bronchoscopy [4–5]. However, this combination carries substantial risks, especially for elderly patients with limited cardiopulmonary reserve. Excessive doses may precipitate respiratory depression, hypotension, and hypoxemia, whereas inadequate dosing leads to insufficient sedation, coughing, and patient movement [6]. Maintaining a narrow therapeutic window becomes even more challenging when the bronchoscope traverses the glottis; intense airway stimulation frequently triggers acute hemodynamic fluctuations even under adequate sedation.

Esketamine, the S(+)-enantiomer of racemic ketamine, has attracted increasing interest as an adjunct sedoanalgesic agent. Compared with racemic ketamine, esketamine binds to the N-methyl-D-aspartate (NMDA) receptor with approximately two-fold higher affinity, conferring superior analgesic potency at lower doses [7–9]. Unlike most sedative-hypnotic agents, esketamine produces central sympathomimetic effects that preserve cardiovascular tone. Critically, it maintains airway patency and respiratory drive, offering distinct pharmacological advantages for procedures requiring spontaneous ventilation [8]. At subanesthetic doses (typically 0.1–0.5 mg/kg), esketamine augments opioid analgesia, attenuates opioid-induced respiratory depression by increasing respiratory rate and inspiratory drive, and reduces total anesthetic consumption without delaying emergence [10–14].

Remimazolam is a novel ultra-short-acting benzodiazepine hydrolyzed by non-specific tissue esterases independent of organ function to form a pharmacologically inactive metabolite [15–16]. Its predictable pharmacokinetics, rapid onset, titratable sedation, and reversibility with flumazenil make it well-suited for short outpatient procedures [17]. Importantly, remimazolam exhibits a more favorable hemodynamic and respiratory safety profile than propofol, making it an attractive alternative for high-risk patients [16–18]. Its major limitation is the lack of intrinsic analgesic activity; thus, co-administration with opioids is required to blunt airway stimulation during bronchoscopy, which re-introduces the risk of respiratory depression.

Combining remimazolam with subanesthetic-dose esketamine is therefore pharmacologically rational. The sedative effects of these two agents act through distinct receptor systems (GABA and NMDA receptors, respectively), enabling synergistic sedation at reduced individual doses. Meanwhile, the

sympathomimetic and bronchodilatory properties of esketamine counteract the cardiovascular and respiratory depression induced by benzodiazepines and opioids [19–20]. Although accumulating evidence supports this combination in gastrointestinal endoscopy [19], data for flexible bronchoscopy remain sparse. Accordingly, this retrospective cohort study aimed to evaluate hemodynamic stability, peri-procedural safety, and drug-sparing efficacy of subanesthetic-dose esketamine combined with remimazolam in patients undergoing non-intubated sedated flexible bronchoscopy.

2. Materials and Methods

2.1 Study Design and Patients

This single-center retrospective cohort study was reported following the STROBE statement. Clinical records of patients receiving sedated flexible bronchoscopy were retrospectively screened. Clinical data of patients who underwent routine sedated bronchoscopy between October 2025 and December 2025 were analyzed according to pre-specified inclusion and exclusion criteria. Thirteen patients were excluded; 65 patients were enrolled in the esketamine group, and 65 contemporaneous patients were selected for the remimazolam group (Fig. 1). This retrospective study was approved by the Ethics Committee of Guiyang Second People's Hospital (Approval No. JYYY-2026-WZ-09). The requirement for written informed consent was waived owing to the retrospective nature of the investigation. In Group R, participants were aged 54–88 years (mean ± SD: 68.83 ± 10.57 years; 34 males, 31 females). In Group E, participants were aged 49–88 years (mean ± SD: 68.06 ± 9.85 years; 30 males, 35 females). Baseline demographic and clinical characteristics were comparable between the two groups (all $p > 0.05$).

2.2 Inclusion, Exclusion and Elimination Criteria

Inclusion criteria were: (1) age 18–88 years, weight 40–85 kg; (2) scheduled for bronchial suctioning, lavage, brushing, or biopsy requiring painless flexible bronchoscopy; (3) American Society of Anesthesiologists (ASA) physical status Grade I–III; (4) no communication barriers; and (5) eligible records were screened retrospectively.

Exclusion criteria were: (1) severe hepatic, renal, or cardiac dysfunction; (2) central nervous system disease; (3) psychiatric illness or history of substance dependence; (4) poorly controlled hypertension (resting systolic BP > 180 mmHg or diastolic BP > 110 mmHg); (5) abnormal thyroid function; (6) elevated intraocular pressure or severe intracranial hypertension; (7) severe obesity (BMI > 35 kg/m²) or anticipated difficult airway; and (8) known allergy to study drugs or personal/family history of malignant hyperthermia.

Elimination criteria: (1)Patients who require a prolonged operation and who need propofol for maintenance; (2)Patients with tracheotomy; (3)During the painless bronchoscopy procedure, due to the needs of the diagnosis and treatment, additional operations such as foreign body removal and balloon dilation were performed during the procedure.

2.3 Anesthetic Protocol

All patients fasted for at least 6 h for solid food and 2 h for clear liquids before the procedure. After entering the procedure room, intravenous access was established, and continuous monitoring including MAP, HR, pulse oxygen saturation (SpO_2), and electrocardiography (ECG) was initiated. Pre-oxygenation with 100% oxygen via face mask was performed for 3 min before induction.

In Group E, esketamine (Jiangsu Hengrui Pharmaceutical Co., Ltd.; approval No. H20193336; 50 mg/2 mL) was intravenously administered at 0.15 mg/kg over 30 s. One minute later, sufentanil (Yichang Humanwell Pharmaceutical; 50 μg/mL, diluted to 1 μg/mL) was given at 0.1 μg/kg, immediately followed by intravenous remimazolam 0.3 mg/kg. Assisted ventilation with 100% oxygen via face-mask was provided as clinically indicated.

In Group R, sufentanil 0.1 μg/kg (1 μg/mL) was administered, followed by intravenous remimazolam 0.3 mg/kg. Sedation depth was assessed using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale, with a target MOAA/S score ≤ 2 before bronchoscope insertion. The same bronchoscopist performed transnasal insertion of a lubricated flexible bronchoscope in both groups. Topical 2% lidocaine hydrochloride (5 mL) was applied to the glottis, carina, and tracheal carina bifurcation.

During examination, if patients failed to achieve the target sedation depth (MOAA/S score > 2), or developed severe choking cough or persistent spontaneous body movement, supplemental remimazolam 0.2 mg/kg and sufentanil 0.1 μg/kg were rapidly administered. Vasopressors were administered at the attending anesthesiologist's discretion to correct hemodynamic instability. Whenever SpO_2 decreased below 90% or respiratory rate fell below 8 breaths per minute, assisted or controlled ventilation was initiated. Patients were discharged from the post-procedural recovery area once consciousness had fully returned, cardiorespiratory parameters remained stable, and the Steward score was > 4.

2.4 Outcome Measures

The primary outcomes were intraoperative MAP and HR at three time points: T_0 (baseline, on room entry before any drug administration), T_1 (completion of anesthetic induction), and T_2 (when the flexible bronchoscope passed through the glottis). Secondary outcomes included recovery time (from procedure completion to achievement of Steward score > 4), total intraoperative consumption of remimazolam and sufentanil, and the incidence of perioperative adverse events: hypertension (MAP > 20% above baseline), hypotension (MAP < 20% below baseline or requiring vasopressor support), hypoxemia (SpO_2 < 90% for > 30 seconds), cough/body movement requiring intervention, delayed emergence (> 30 minutes to Steward > 4), nausea/vomiting, and dizziness/delirium. Record the number of successful initial sedation cases in each of the two patient groups (where MOAA/S score ≤ 2 after intravenous administration of the induction dose of remimazolam, and no severe choking or body movement was observed during endoscopic intervention is defined as a successful first attempt at sedation).

2.5 Scoring Scale or Standard

MOAA/S Score: Complete consciousness with normal response to normal name calls scores 5; delayed response to normal surname calls scores 4; response only to loud and/or repeated name calls scores 3; response only to mild pushing or slight body movement scores 2; response only to pain stimulation (trapezius muscle compression) scores 1; no response to pain stimulation (trapezius muscle compression) scores 0.

Steward Awakening Scale: Complete consciousness scores 2; response to stimulation scores 1; no response scores 0. Airway patency scores: able to cough as instructed by the physician scores 2; capable of maintaining airway patency independently scores 1; requiring respiratory support scores 0. Limb mobility scores: conscious limb movement scores 2; no conscious limb movement scores 1; no limb movement scores 0.

2.6 Statistical Analysis

Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation (SD) and were compared between groups using the independent-samples t-test; within-group comparisons across time points were performed using one-way repeated-measures analysis of variance (ANOVA) with Bonferroni correction for multiple comparisons. Categorical variables are expressed as frequencies and percentages and were compared using the chi-square (χ^2) test or Fisher's exact test as appropriate. A two-tailed P-value < 0.05 was considered statistically significant.

3. Results

3.1 Patient characteristics

No statistically significant differences were observed between the two groups in terms of gender composition, ASA classification, age, body mass, or examination timing ($p > 0.05$; Table 1).

3.2 Primary outcomes

The hemodynamic data are presented in Table 2. At T_0, MAP and HR was comparable between Group R and Group E (MAP: 104.39 ± 11.29 vs 103.45 ± 13.16 mmHg, $p = 0.661$; HR: 81.58 ± 13.10 vs 80.94 ± 13.75 beats/min, $p = 0.786$). At T_1 (completion of induction), MAP and HR in Group R decreased significantly from T_0 values, whereas both parameters in Group E were significantly higher than those in Group R (MAP: 100.75 ± 14.79 vs 88.66 ± 11.50 mmHg, $p < 0.001$; HR: 77.75 ± 12.40 vs 73.17 ± 13.43 beats/min, $p = 0.045$). At T_2 (bronchoscope passage through the glottis), Group R exhibited a pronounced pressor and tachycardic response compared with T_1, and MAP and HR in Group R were significantly higher than those in Group E (MAP: 104.61 ± 11.13 vs 100.10 ± 13.62 mmHg, $p = 0.041$; HR: 85.52 ± 12.82 vs 79.94 ± 12.61 beats/min, $p < 0.001$).

3.3 Secondary outcomes

The first sedation successful in Group E were significantly higher than those in Group R ,The incidences of cough/body movement, hypotension, and hypoxemia in Group E were significantly lower than those in Group R (all $p < 0.05$; Table 3). No cases of delayed emergence, dizziness/delirium, or nausea/vomiting were observed in either group. Although two cases of hypertension were observed in Group E (vs. zero in Group R), this difference did not reach statistical significance ($p = 0.154$). Total intraoperative remimazolam consumption was significantly lower in Group E than in Group R (18.04 ± 2. 64 vs 29.80 ± 4.10 mg, $p < 0.001$), as was total sufentanil consumption (6.06 ± 1.03 vs 12.48 ± 1.85 μg, $p < 0.001$; Table 4). Recovery time was comparable between groups (12.94 ± 1.27 vs 13.14 ± 1.46 min, $p = 0.608$).

3.4 Comparison of patient and doctor satisfaction in the two groups

The satisfaction of the bronchoscopist and patients with the anesthesia method was higher in Group E than in Group R, and the difference was statistically significant.(all $p<0.05$; Table 4)

Table 1 Comparison of baseline characteristics and examination timing between the two groups of patients undergoing bronchoscopy

Group	Age(years)	Sex (male/female)	ASA (II/III)	Weight (kg)	Inspection time (min)
Group R (n=65)	68.83 ± 10.57	34 / 31	25/ 40	58.2 ± 10.89	13.82 ± 3.32
Group E (n=65)	68.06 ± 9.85	30 / 35	29 / 36	60.06 ± 10.31	13.45 ± 3.91
P-value	0.200	0.483	0.477	0.490	0.152

Table 2. Hemodynamic parameters at different time points (Mean ± SD)

Time point	Group R MAP (mmHg)	Group R HR (bpm)	Group E MAP (mmHg)	Group E HR (bpm)	t (MAP)	t (HR)	P (MAP)	P (HR)
T0	104.39 ± 11.29	81.58 ± 13.10	103.45 ± 13.16	80.94 ± 13.75	0.440	0.272	0.661	0.786
T1	88.66 ± 11.50	73.17 ± 13.43	100.75 ± 14.79	77.75 ± 12.40	-5.239	-2.022	< 0.001	0.045
T2	104.61 ± 11.13	85.52 ± 12.82	100.10 ± 13.62	79.94 ± 12.61	2.066	2.504	0.041	< 0.001

Note: Between-group comparisons at each time point were performed using independent-samples t-tests. Overall analysis of hemodynamic parameters was performed using two-way repeated measures ANOVA (group as between-subjects factor, time as within-subjects factor); when the interaction effect was significant, simple effects analyses were conducted. Pairwise comparisons within each group across time points were performed using paired-samples t-tests with Bonferroni correction.

Table 3. First sedation successful and incidence of perioperative adverse events [n (%)]

Group	First sedation successful	Hypertension	Hypotension	Hypoxemia	Cough/Body movement	Delayed emergence	Dizziness/Delirium	Nausea/Vomiting
Group R (n=65)	44 (67.7)	0 (0.0)	9 (13.8)	5 (7.7)	11 (16.9)	0 (0.0)	0 (0.0)	0 (0.0)
Group E (n=65)	58 (89.2)	2 (3.1)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
P-value	0.003	0.496*	0.008*	0.058*	0.001*	—	—	—

Note: When zero-cell data or insufficient expected frequencies were present, Fisher's exact test was mandatorily applied. No delayed emergence, dizziness/delirium, or nausea and vomiting occurred in either group, thus no statistical tests were performed for these items.

Table 4. Recovery time and total drug consumption (Mean ± SD)

Group	Recovery time (min)	Total remimazolam (mg)	Total sufentanil (μg)
Group R (n=65)	13.14 ± 1.46	29.80 ± 4.10	12.48 ± 1.85
Group E (n=65)	12.94 ± 1.27	18.04 ± 2. 64	6.06 ± 1.03
t / P	T = 0.516, P = 0.608	T = 12.055, P < 0.014	T = 15.878, P < 0.001

4. Discussion

This retrospective cohort study suggests that adding subanesthetic-dose esketamine(0.15 mg/kg) to remimazolam–sufentanil sedation may be associated with improved hemodynamic stability, lowers the rate of peri-procedural adverse events, and reduces sedative-analgesic consumption during non-intubated sedated flexible bronchoscopy.

The most clinically meaningful hemodynamic finding was the attenuation of the sympathetic stress response at T_2 — the time point of glottic passage, representing the most intense nociceptive stimulus of the entire procedure. In Group R, HR rose sharply from T_1 to T_2, indicating insufficient suppression of laryngeal nociceptive reflexes. In comparison, Group E demonstrated smaller, more stable hemodynamic fluctuations throughout both induction and instrumentation. This hemodynamic buffering can be explained by a dual mechanism: esketamine produces central sympathomimetic effects by stimulating catecholamine release, enhancing myocardial contractility and vasoconstriction, thereby counteracting remimazolam- and sufentanil-induced cardiovascular depression [19]. Meanwhile, its NMDA-receptor antagonism interrupts thalamocortical pain transmission and blunts the afferent limb of autonomic stress responses triggered by airway stimulation [20]. These results are consistent with Xie et al. [21], who reported better hemodynamic stability with an esketamine-containing opioid-sparing regimen in elderly patients undergoing bronchoscopy, as well as Xi et al. [22], who demonstrated hemodynamic benefits when esketamine was combined with remimazolam tosylate in cardiovascular anesthesia settings.

Regarding respiratory outcomes, the incidence of hypoxemia and the need for assisted ventilation were significantly lower in Group E. Esketamine is one of few sedative-analgesic agents that actively stimulates respiration: through NMDA receptor blockade in brainstem respiratory centers, it increases respiratory rate and augments inspiratory drive, counteracting opioid-induced ventilatory depression [13, 14]. In addition, esketamine antagonizes histamine-mediated bronchoconstriction and potentiates catecholamine-driven bronchodilation, lowering airway resistance and improving lung compliance, which may be particularly beneficial for patients with reactive airway disease [22]. Pre-treatment with 0.15 mg/kg esketamine also attenuates sufentanil-induced coughing, likely by relaxing bronchial smooth muscle and reducing reflex bronchoconstriction during bronchoscope insertion [21]. This finding is consistent with the substantially lower incidence of cough and body movement observed in Group E in the present study.

The drug-sparing effects observed in Group E are clinically relevant: total remimazolam consumption decreased by 39. %, and sufentanil consumption decreased by 38. % relative to Group R. Esketamine produces sedation and analgesia via NMDA-receptor antagonism, a pathway completely distinct from the GABA-mediated mechanism of remimazolam, allowing pharmacodynamic synergy at reduced individual drug doses [7, 10, 13]. Our findings support the meta-analysis by Chen et al. [11, 13], showing that subanesthetic-dose esketamine reduces propofol and opioid requirements for non-intubated procedural sedation, as well as the retrospective analysis from Zheng et al. [23], which demonstrated reduced postoperative opioid consumption after spinal surgery when peri-operative subanesthetic esketamine was administered.

Importantly, the marked reduction in drug consumption did not prolong recovery. Emergence times were nearly identical between groups (12.94 vs 13.14 min, p = 0.608). This observation aligns with the pharmacokinetic properties of esketamine (rapid extra-hepatic metabolism, terminal half-life ~ 2–3 h) and remimazolam (hydrolysis by non-specific esterases with context-independent offset) [14]. Our results are consistent with reports from Yang et al. [24] and Mishima et al. [25], both of whom found no delayed awakening when ketamine/esketamine was incorporated into procedural sedation regimens.

Although two patients in Group E developed hypertension versus zero in Group R, this difference was not statistically significant (p = 0.154). This suggests that slow prophylactic bolus administration of 0.15 mg/kg esketamine largely avoids the pronounced cardiovascular excitation seen with higher-dose or rapid bolus injection [5, 14].

Limitations

This study has several inherent limitations. First, it is a single-center investigation with a moderate sample size and a short 3-month enrollment window, which limits external validity and generalizability to broader patient populations and other medical centers. Second, the retrospective observational design inevitably introduces selection bias and residual confounding that cannot be fully eliminated by statistical adjustment. Third, we did not perform dose-response analyses for remimazolam or esketamine; hence, the optimal dosage range and dose-dependent efficacy-safety differences of this combined regimen remain unclear. Fourth, only short-term peri-procedural endpoints were assessed; no long-term follow-up data were available, pre-cluding evaluation of long-term safety, persistent adverse effects, or long-term clinical prognosis.

Future large-sample, multi-center prospective controlled studies are therefore urgently required to address these shortcomings, further optimize clinical dosing protocols, explore precise dose-effect relationships and underlying pharmacological mechanisms, and generate high-quality evidence supporting standardized application of subanesthetic-dose esketamine combined with remimazolam in non-intubated sedated flexible bronchoscopy.

Conclusion

In this retrospective cohort study, adding subanesthetic-dose esketamine (0.15 mg/kg) to remimazolam-based sedation for non-intubated sedated flexible bronchoscopy resulted in significantly improved intra-procedural hemodynamic stability, a substantially lower incidence of hypotension, hypoxemia, and cough/body movement, and reduced total remimazolam and sufentanil consumption, without prolonging recovery time. These findings support the pharmacological rationale for combining NMDA-receptor antagonism with GABA-mediated sedation in airway procedures where spontaneous ventilation and hemodynamic stability are priorities. Prospective, randomized, double-blind multi-center trials with standardized dosing and validated sedation monitoring are warranted to confirm these observations and define the optimal esketamine dose for this clinical setting.

Declarations

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Authors' contributions

Jingjie Wang and Ying Cao designed the study.Jingjiew Wang; Luying Deng and Meiyan Liu[12] interpreted the data and wrote the manuscript. All the authors contributed to the editing, review, and approval of the manuscript. Ying Cao provided critical review and revision to the manuscript. Jingjie Wang revised the manuscript. All authors read and approved the final manuscript.

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Data Availability

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This retrospective study was approved by the Ethics Committee of Guiyang Second People's Hospital (Approval No. JYYY-2026-WZ-09). The requirement for written informed consent was waived owing to the retrospective nature of the investigation.

Consent for publication

Not applicable.

Competing interests

The authors declare that they do not have any conflicts of interest.

Clinical trial number:

Not applicable

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Figures

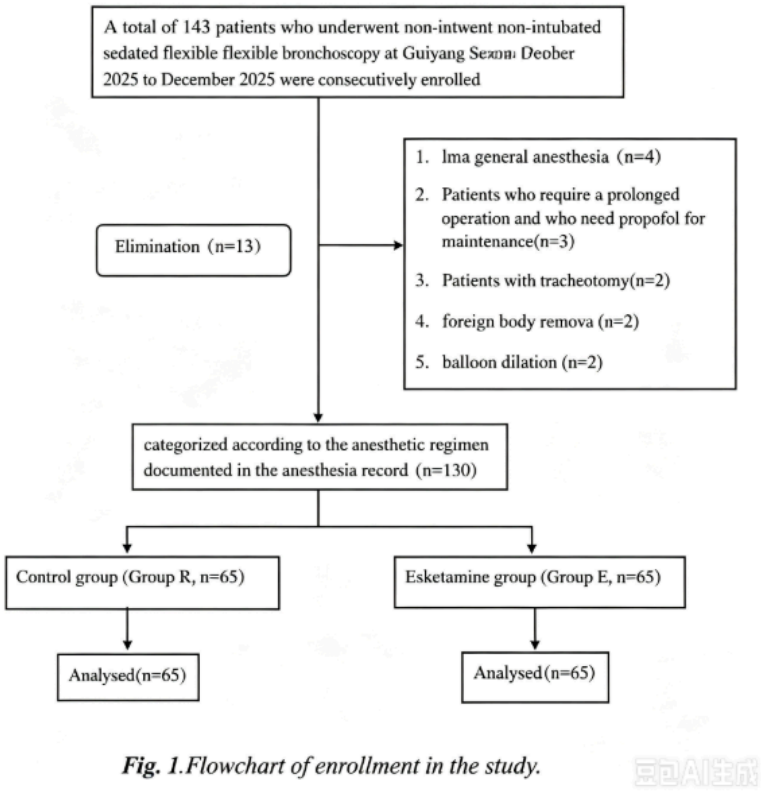


Fig. 1.Flowchart of enrollment in the study.

Figure 1

See image above for figure legend.