

# Comparison of the Safety and Efficacy of Remimazolam Besylate versus Dexmedetomidine for Patients Undergoing Fiberoptic Bronchoscopy: A Prospective, Randomized Controlled Trial

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**Objective:** Remimazolam besylate is a novel ultra-short-acting benzodiazepine that is rapidly hydrolyzed to zolpidem propionic acid by tissue lipases. We designed this study to compare the safety and efficacy of remimazolam besylate alfentanil versus dexmedetomidine–alfentanil for fiberoptic bronchoscopy (FB).

**Methods:** One hundred and twenty patients undergoing FB into this prospective randomized controlled trial were divided into two groups. The anesthesia induction consisted of 6 mg/kg/h of remimazolam besylate in the RA group and 0.5 µg/kg of dexmedetomidine in the DA group. 1–2 mg/kg/h of remimazolam besylate or 0.2–0.7 µg/kg/h of dexmedetomidine were administered to maintain during FB. The lowest oxygen saturation, success rate of FB, hemodynamics, time metrics, bronchoscopy feasibility, drug dose requirements, patient and bronchoscopist satisfaction scores, occurrence of intraoperative awareness, number of patients willing to repeat FB with the same sedation regimen, and occurrence and severity of adverse events.

**Results:** The lowest oxygen saturation during the FB was significantly higher in the RA group ( $P = 0.001$ ). Compared with the variables in the DA group, peripheral oxygen saturation, systolic blood pressure, and diastolic blood pressure were significantly lower at T2 and T3 in the RA group ( $P < 0.05$ ). Heart rates were significantly higher from T2 to T4 in the DA group ( $P < 0.05$ ). More patients experienced bradycardia in the DA group ( $P = 0.041$ ). Compared with time metrics in the DA group, the induction time, fully-alert time, and recovery room-leaving time were all significantly shorter in the RA group ( $P < 0.05$ ). The bronchoscopy feasibility scores in the RA group were significantly lower at T2, whereas they were lower at T3 in the DA group ( $P < 0.05$ ).

**Conclusion:** Remimazolam besylate is superior to dexmedetomidine when combined with alfentanil during FB, promoting faster patients' recovery, better operative conditions and respiratory stability with similar rates of occurrence and severity of adverse events.

**Keywords:** remimazolam besylate, dexmedetomidine, fiberoptic bronchoscopy, alfentanil, propofol

## Introduction

Fiberoptic bronchoscopy (FB) is an essential procedure for diagnosing and treating respiratory diseases.<sup>1</sup> The FB frequency and quality have increased over the past decades, and sedation is recommended by most guidelines for a comfortable procedure in patients without contraindications.<sup>2,3</sup> An ideal anesthesia method provides rapid onset and recovery, stable hemodynamics, and early mobilization, achieving high patient turnover, shortening off-work times, and reducing postoperative complication rates.<sup>4,5</sup> However, the optimal sedation/analgesia regimen for comfortable FB procedures remains unclear because the line between moderate sedation (conscious sedation) and deep sedation is blurry.<sup>6</sup>

Drug combinations are more beneficial than single-drug regimens in bronchoscopy sedation because combinations enhance each drug's therapeutic action while minimizing their adverse effects.<sup>7</sup> Benzodiazepines have been the most frequently used sedative agent during bronchoscopies. Combinations of midazolam and opiates may induce

hypoventilation, particularly in patients with pre-existing respiratory disease.<sup>8–10</sup> Remimazolam besylate is a novel ultra-short-acting benzodiazepine. It is metabolized by tissue lipases and rapidly hydrolyzed to zolpidem propionic acid, an agent with almost no sedation activity. Moreover, remimazolam besylate can be administered to patients with liver and kidney dysfunction because its metabolism is not liver- or kidney-dependent.<sup>11</sup> In a study, remimazolam besylate was superior to propofol at preserving the patient's spontaneous breathing and reducing the incidence of respiratory depression.<sup>12</sup> Dexmedetomidine (used for painless endoscopies) is a highly selective  $\alpha_2$  adrenergic agonist with sedative and analgesic properties that does not cause respiratory depression. However, it may cause bradycardia and hypotension, and it has a slow onset when used as a single sedative.<sup>13,14</sup>

Alfentanil has favorable pharmacological advantages for bronchoscopy, such as fast effects and recovery, providing good analgesia, minor cardiovascular effects, minimal respiratory depression, and low incidence of cough, postoperative nausea, and vomiting.<sup>15</sup> All these characteristics of alfentanil minimize the postprocedural workload. In addition, all of alfentanil's actions can be immediately reversed by administering naloxone. As a result, alfentanil is a great choice for patients undergoing daytime surgical procedures.<sup>16</sup> The combination of alfentanil and remimazolam besylate can result in fast onset and quick recovery, and should be ideal for FB sedation. Thus, we designed this prospective, randomized controlled trial to compare the safety and efficacy of remimazolam besylate–alfentanil versus dexmedetomidine–alfentanil for FBs.

## Materials and Methods

### Patients

We conducted this prospective, randomized controlled trial in a tertiary center after obtaining the approval of its protocol by the Medical Ethics Committee of Liaocheng People's Hospital (#2023045). We also registered the clinical trial in the Chinese site of clinical trial.org (ChiCTR2300070361). This trial adhered to the Helsinki Declaration and the CONSORT guidelines were also followed.

We obtained verbal and written informed consents for this trial from each patient before enrollment. Between April and September 2023, we recruited 120 Patients who were undergoing FB. The inclusion criteria comprised individuals with ages between 50 and 70 years, American Society of Anesthesiologists (ASA) grades between I and II, and oxygen saturation (SpO<sub>2</sub>) measurements > 90% (room air). We excluded individuals with asthma; severe sleep apnea syndrome (apnea–hypopnea index > 40); drugs or alcohol abuse; difficult airways;<sup>17</sup> severe cardiac, hepatic, and/or renal dysfunction; communication barriers; Amsterdam Preoperative Anxiety and Information Scale (APAIS) scores >10; history of psychiatric disorders; and those participating in other clinical trials in the preceding 3 months.

### Randomization and Blinding

We randomly assigned 120 patients to one of the two groups using sealed sequentially numbered envelopes to form an RA group (remimazolam besylate combined with alfentanil) and a DA group (dexmedetomidine combined with alfentanil). A staff nurse responsible for the preparation of investigational drugs was the only person with access to the random list. The patients, anesthesiologist, and bronchoscopist were all blinded to the allocations of the trial until the end of the study.

### Anesthesia

All patients fasted for 8 h for solids and 2 h for clear fluids without any pre-medication before their FB. After gaining peripheral venous access with a 20-G needle, 5 mL/kg of 0.9% sodium chloride solution was infused before sedation, and then adjusted to 5 mL/kg/h. The patients' peripheral oxygen saturation (SpO<sub>2</sub>), electrocardiogram, noninvasive blood pressure measured at 3-minute intervals, end-tidal carbon dioxide (PetCO<sub>2</sub>), and respiratory rate (RR) were constantly monitored during the FB. Supplemental oxygen flow was administered through a nasal cannula at 3 L/min after the airway nebulization with lidocaine.<sup>18</sup>

Each patient was administered 10  $\mu$ g/kg of intravenous (IV) alfentanil 5 minutes before Anesthesia induction and 0.5–2  $\mu$ g/kg/min during the procedure. We induced anesthesia with 6 mg/kg/h of remimazolam besylate in the RA group

and 0.5 µg/kg of dexmedetomidine in the DA group for 10 minutes. Anesthesia was maintained using either remimazolam besylate at a dose of 1–2 mg/kg/h in the RA group or dexmedetomidine at a dose of 0.2–0.7 µg/kg/h in the DA group. The anesthesiologist adjusted the infusion rate of the aforementioned drugs to maintain a Modified Observer's Assessment of Alert (MOAA/S) score <3. Propofol was the only permitted alternative sedative in this trial. All procedures were performed by the same bronchoscopist who had performed more than 800 endoscopies before participating in the trial, according to the international guidelines.<sup>19</sup> During the procedure, the bronchoscopist administered local anesthesia with 6 mL of 2% lidocaine (1 mL to the vocal cords, 2 mL to the bronchus, 1 mL to the tracheal carina, 1 mL to the right main bronchus, and 1 mL to the left main bronchus) to all patients in a spray-as-you-go fashion. Remedial lidocaine was given at the discretion of the bronchoscopist if cough interfered with the procedure, but the total dose never exceeded 5 mg/kg according to the recommendations in a previous study.<sup>20</sup> All patients were routinely transferred to the recovery room after the procedure and returned to the ward if the modified Aldrete score became  $\geq 9$ .

## Outcomes

The primary outcome was the lowest oxygen saturation. We also recorded the successful FB rates, demographic characteristics, hemodynamics (recorded at the following time points: T0, patient's arrival at bronchoscopy room; T1, immediately before FB start; T2, immediately after passing the bronchoscope next to the glottis; T3, 5 min after passing next to the glottis; T4, 10 min after passing next to the glottis; T5, end of FB; T6, 5 min after FB; T7, just before the patient left the recovery room), time metrics (induction time, procedure time, fully alert time, and recovery room-leaving time), bronchoscopy feasibility (extent of coughing, vocal cords movements, and limb movements; scored 3 to 12 with 3 representing the optimal score and 12 the worst one),<sup>21</sup> study drug dose requirements, numbers of drugs used, patient and bronchoscopist satisfaction scores (5-point scales: 1, dissatisfied; 5, satisfied), instances of intraoperative awareness, number of patients willing to repeat FB with the same sedation regimen, instances and severity of adverse events (evaluated on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events 4.0).<sup>22</sup>

We defined hypoxemia as an SpO<sub>2</sub> <90% for >30 s, and we treated it with oxygen supplementation at 10 L/min, verbal, and tactile stimulation, chin lifts, jaw thrust, face mask, temporary manual ventilation, or even tracheal intubation. Bradycardia was defined as a HR < 50 beats/min lasting >30s; and, we treated it with 0.2–0.4 mg of atropine. Hypotension was defined as a mean blood pressure (MBP) decrease >20% compared with the baseline value lasting >30s, we treated it with 8 µg of noradrenaline. Hypertension was defined as an MBP increase >20% compared with the baseline value and lasting >30s; we treated it with 10–15 mg of urapidil.

## Statistical Analysis

The mean and standard deviations of the lowest oxygen saturation in the DA and RA groups were 84.52±8.43% and 89.17±8.55%, respectively, according to our pilot study results. A power calculation with  $\beta = 0.8$  and  $\alpha = 0.05$  revealed a required sample size of 54 patients in each group. Considering a 10% dropout rate for our trial, we recruited 120 patients.

We conducted statistical analyses using GraphPad Prism 9.0 and SPSS 23.0 (SPSS, Chicago, IL, USA). We confirmed the normalcy of the data using a Shapiro–Wilk test. In addition, we assessed the homogeneity of variances using Levene's test. Continuous Outcomes were presented as means ± standard deviations or medians and interquartile ranges, and we analyzed them by performing the Student's *t* or Mann–Whitney *U*-tests. We used repeated-measures analysis of variance to assess the feasibilities of hemodynamics and bronchoscopy. Qualitative data are presented as numbers and frequencies, and we analyzed them using  $\chi^2$  or Fisher's exact tests. We considered  $P < 0.05$  as indicative of statistical significance.

## Results

### Patient Demographic Characteristics

Between April and September 2023, we recruited 189 patients who underwent FB. We excluded 69 patients who presented the following criteria: asthma ( $n = 11$ ); severe sleep apnea syndrome (apnea–hypopnea index >40) ( $n = 7$ );

drugs or alcohol abuse ( $n = 18$ ); difficult airway ( $n = 5$ ); severe cardiac, hepatic, and/or renal dysfunction ( $n = 12$ ); communication barriers ( $n = 3$ ); Amsterdam Preoperative Anxiety and Information Scale (APAIS) scores  $>10$  ( $n = 8$ ); history of psychiatric disorders ( $n = 3$ ); and participation in other clinical trials in the preceding 3 months ( $n = 2$ ). As a result, we randomized 120 patients and divided them into the RA and DA groups ( $n = 60$ , each; Figure 1). We found similar patient demographic characteristics and FB indications ( $P > 0.05$ ; Table 1).

## Safety Outcomes

The lowest oxygen saturation during the FB procedure was significantly better in the RA group ( $89.2 \pm 2.5\%$ ) than in the DA group ( $84.9 \pm 2.6\%$ ,  $P = 0.001$ ; Table 2). Compared with patients in the DA group, the  $\text{SpO}_2$ , systolic blood pressure (SBP), and diastolic blood pressure (DBP) values were significantly lower at T2 and T3 in the RA group ( $P < 0.05$ ; Figure 2). Similarly, the HRs were significantly higher from T2 to T4 in the DA group ( $P < 0.05$ ; Figure 2). However, the respiratory rates (RR) were similar in both groups ( $P > 0.05$ ; Figure 2).

The incidences of hypotension, hypertension, tachycardia, and intraoperative awareness were also similar between the groups ( $P > 0.05$ ; Table 2). However, more patients experienced bradycardia in the DA group than in the RA group ( $P = 0.041$ ; Table 2). Ten patients in the RA group and 16 in the DA group experienced hypoxia and required increased oxygen delivery; among them, 4 patients in the RA group and 7 patients in the DA group also required verbal and tactile stimulation. However, we did not have to pause the procedure for any patient during this trial. No patients were recorded

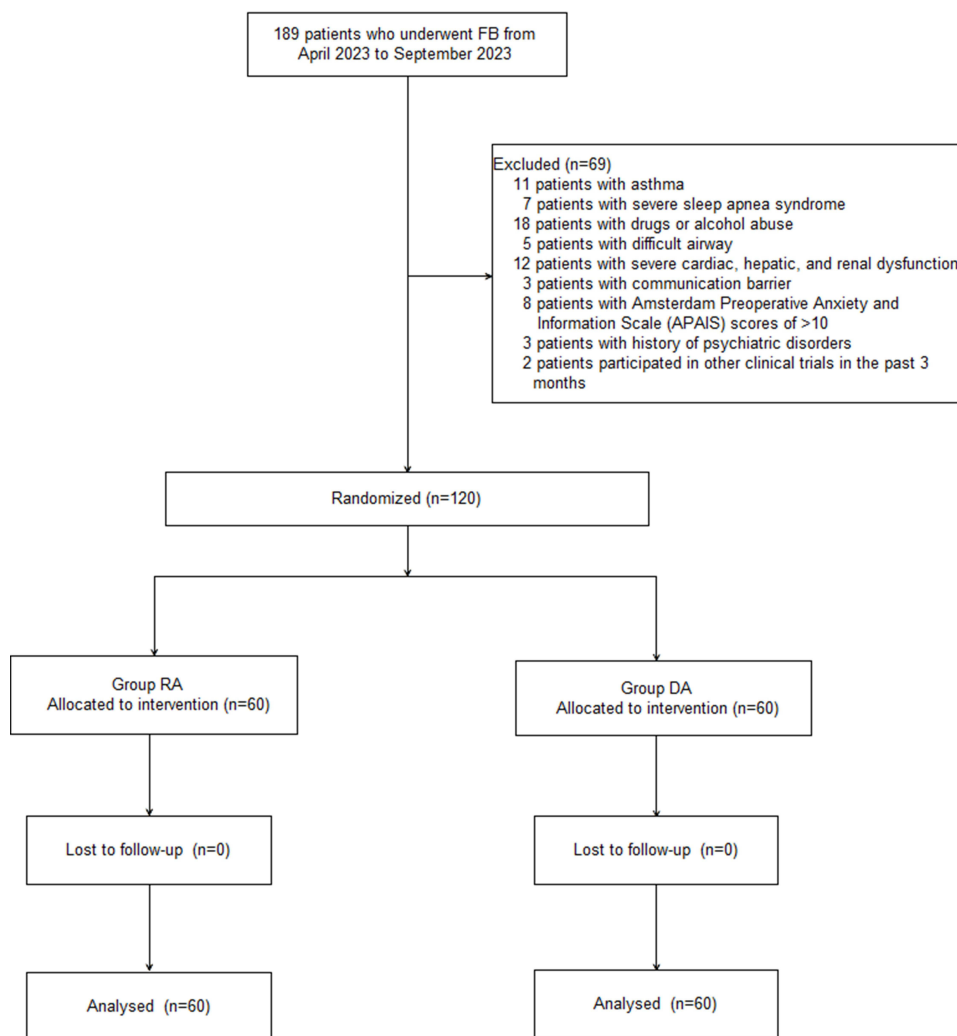


Figure 1 Patient flowchart with CONSORT guidelines.

**Table 1** Demographic Characteristics and Indication of FB Between the Two Groups

Variable	Group RA (n=60)	Group DA (n=60)	P-value
Age (years)	60.7±4.3	60.9±4.2	0.782
Sex (male/female)	40/20	41/19	0.845
History of smoking, n (%)	33 (55.0%)	38 (63.3%)	0.353
FEV1/FVC (%)	91.2±2.4	91.5±2.1	0.388
Height (cm)	166.9±4.7	166.1±4.7	0.373
Body weight (kg)	67.2±6.2	67.6±7.4	0.729
BMI (kg/m <sup>2</sup> )	24.1±1.9	24.5±2.3	0.342
ASA I/II (n)	22/38	23/37	0.850
Comorbidity, n (%)			0.939
Hypertension	14 (23.3%)	15 (25.0%)	
Diabetes	9 (15.0%)	11 (18.3%)	
Coronary heart disease	10 (16.7%)	13 (21.7%)	
Indication, n (%)			0.460
Lung cancer	22 (36.7%)	15 (25.0%)	
Pneumonia	23 (38.3%)	31 (51.7%)	
Pulmonary tuberculosis	7 (11.7%)	6 (10.0%)	
Others	8 (13.3%)	8 (13.3%)	
Procedure, n (%)			0.741
Endobronchial inspection	17 (28.3%)	16 (26.7%)	
Bronchoscopic biopsy	25 (41.7%)	29 (48.3%)	
Bronchoalveolar lavage	18 (30.0%)	15 (25.0%)	

**Note:** Variables presented as mean ±SD or number of patients n (%).

**Abbreviations:** RA, remimazolam besylate combined with alfentanil; DA, dexmedetomidine combined with alfentanil; FEV1, Forced Expiratory Volume in the first second; FVC, Forced Vital Capacity; BMI, Body Mass Index; ASA, American Society of Anesthesiology.

**Table 2** The Safety Outcomes Between the Two Groups

Variable, n (%)	Group RA (n=60)	Group DA (n=60)	P-value
Lowest oxygen saturation	89.2±2.5	84.9±2.6*	0.001
Incidence of intraoperative awareness	6 (41.3%)	8 (37.0%)	0.570
Hypotension	13 (10.9%)	6 (26.1%)	0.080
Hypertension	3 (8.7%)	2 (8.7%)	1.000
Bradycardia	5 (6.5%)	13 (10.9%)*	0.041
Hypoxia	10 (19.6%)	16 (26.1%)	0.184
Tachycardia	6 (8.7%)	3 (10.9%)	0.491

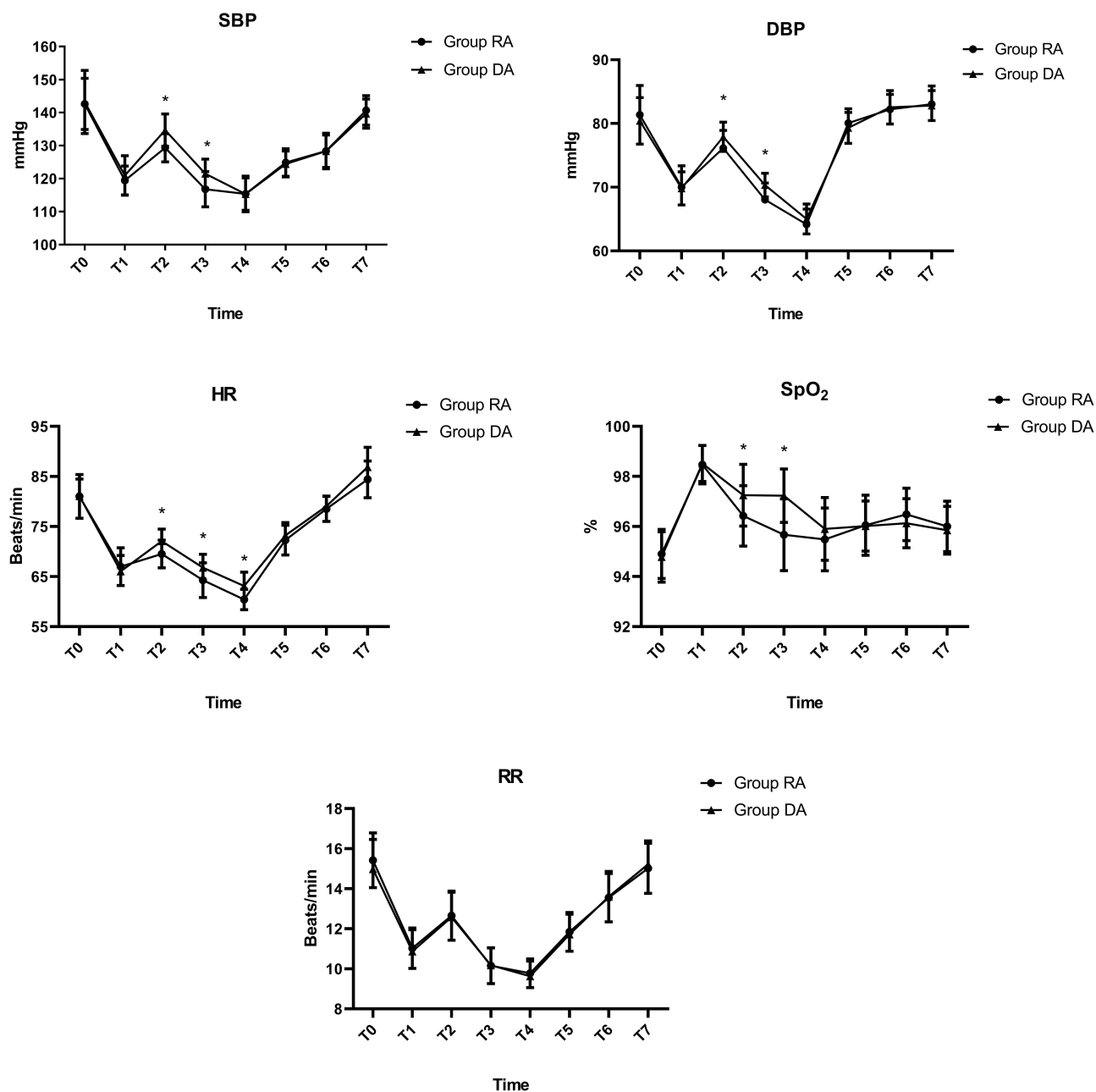
**Notes:** Variables presented as mean ±SD or number of patients n (%). \**P* < 0.05 vs Group RA.

**Abbreviations:** RA, remimazolam besylate combined with alfentanil; DA, dexmedetomidine combined with alfentanil.

injection pain and postoperative cognitive impairment in this trial. Both groups presented a grade-1 severity of adverse events.

## Efficacy Outcomes

Both groups presented similar rates of successful FBs, numbers of drugs used, patient and bronchoscopist satisfaction scores, and numbers of patients willing to repeat the procedure with the same sedation regimen (*P* > 0.05; Table 3). Compared with patients in the DA group, those in the RA group had significantly shorter induction times (6.6±2.0 min vs 9.0±1.2 min), times to fully alert (4.4±1.3 min vs 7.0±1.5 min), and recovery room-leaving times (11.8±1.6 min vs 16.6±2.3 min; all *P*s < 0.05; Table 3). However, the procedure times were similar for both groups (22.0±3.1 min vs 22.3±3.5 min; *P* = 0.619; Table 3).



**Figure 2** Hemodynamic measurements. Compared with patients in the DA group, SpO<sub>2</sub>, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly decreased at T2 and T3 in the RA group. Similarly, heart rate (HR) was significantly increased from T2 to T4 in the DA group. Time points are as follows: T0: arrival at bronchoscopy room, T1: immediately before start of FB, T2: immediately after entering the glottis, T3: 5 min after entering the glottis, T4: 10 min after entering the glottis, T5: end of FB, T6: 5 min after FB, T7: leaving the recovery room. \**P* < 0.05 vs RA group. **Abbreviations:** RA, remimazolam besylate combined with alfentanil; DA, dexmedetomidine combined with alfentanil.

Compared with the bronchoscopy feasibility scores in the DA group, those in the RA group were significantly lower at T2 (*P* < 0.05; Table 3). However, the T3 scores were similar in both groups (*P* > 0.05; Table 3).

## Discussion

According to our Results, the RA group had a higher lowest oxygen saturation mean during FBs and shorter mean induction, fully alert, and recovery room-leaving times than the DA group. However, the procedure times were similar in both groups. Compared with patients in the DA group, the scores of bronchoscopy feasibility were significantly lower at T2 (but not at T3) in the RA group.

**Table 3** The Efficacy Outcomes Between the Two Groups

Variable	Group RA (n=60)	Group DA (n=60)	P-value
Procedure success, n (%)	55 (91.7%)	52 (86.7%)	0.378
Time metrics			
Induction time (min)	6.6±1.9	9.0±1.2*	0.001
Procedure time (min)	22.0±3.1	22.3±3.5	0.619
Time to fully alert (min)	4.4±1.3	7.0±1.5*	0.001
Time to leaving the recovery room (min)	11.8±1.6	16.6±2.3*	0.001
Scores of bronchoscopy feasibility			
T2	5.0 (5.0–6.0)	7.0 (6.0–8.0)*	0.001
T3	5.0 (4.0–6.0)	5.0 (4.3–6.0)	0.369
Consumption of alfentanil (µg)	671.7±62.7	676.0±73.7	0.729
Consumption of remimazolam besylate (mg)	69.2±14.1	–	
Consumption of dexmedetomidine (µg)	–	45.0±6.5	
Number of remedies, n (%)	9 (15.0%)	13 (21.7%)	0.345
Patient satisfaction scores	5.0 (4.0–5.0)	4.0 (4.0–5.0)	0.111
Bronchoscopist satisfaction scores	4.0 (4.0–5.0)	4.0 (4.0–5.0)	0.628
Willing to the repeat FB, n (%)	53 (88.3%)	51 (85.0%)	0.591

**Notes:** Variables presented as mean ±SD, median (interquartile range), or number of patients n (%). T2: immediately after entering the glottis, T3: 5 min after entering the glottis. \*P < 0.05 vs Group RA.

**Abbreviations:** RA, remimazolam besylate combined with alfentanil; DA, dexmedetomidine combined with alfentanil; FB, flexible bronchoscopy.

FBs are widely used for diagnosing and treating pulmonary diseases, but the patients' intolerance throughout the process poses iatrogenic risks. Thus, both the British Thoracic Society guideline of 2013 and Interventional pulmonology group of the Chinese Thoracic Society guideline of 2019 have suggested that drugs providing appropriate levels of sedation and stabilizing cardiovascular and respiratory markers be given in combination during FBs to reduce patients' pain and anxiety and minimize adverse effects, especially for procedures expected to be long and complex.<sup>2,3</sup> All patients presented to the procedural room without any pre-medication because a previous study demonstrated no benefit from either routine glycopyrrolate or atropine premedication.<sup>23</sup>

The advantages of preserving spontaneous breathing (with sedation) during FBs include obstruction occurrence prevention and stable hemodynamics promotion, especially for patients with a narrowed airway tract.<sup>24</sup> The amnesic and anxiolytic properties of benzodiazepines may be more beneficial for patients than the antitussive and analgesic properties of opioids.<sup>25,26</sup> The addition of opioids to dexmedetomidine or benzodiazepines is also beneficial as the combinations reduce the amount of sedative and analgesic drugs needed, minimize anxiety, decrease the injection pain of sedative drugs, reduce induction times, and decrease the occurrence of nausea and vomiting. Moreover, these combinations may improve the sedation levels during bronchoscopy.<sup>27</sup> Thus, we used remimazolam besylate or dexmedetomidine–alfentanil combinations in our trial.

A propofol–fentanyl combination has been shown to be superior to a propofol–alfentanil combination for sedation–analgesia during colonoscopies. This may be due to the longer acting time of fentanyl, which improves the operation conditions.<sup>28</sup> However, the contrasting results of another study remind us to be vigilant to the respiratory depression caused by fentanyl.<sup>29</sup> Moreover, alfentanil may bind with more affinity to opioid receptors, it has a shorter effect, a small distribution volume, and displays a more rapid effect onset than fentanyl.<sup>30</sup> Due to its low incidence of respiratory obstruction, postoperative nausea, and vomiting, and its minimal impact on the respiratory and circulatory systems, alfentanil is an ideal choice over equipotent doses of fentanyl or sufentanil for spontaneous breathing during general anesthesia.<sup>31</sup> Alfentanil and remifentanyl have similar effect onset times, but bolus injections of remifentanyl can easily cause more serious adverse reactions such as bradycardia, hypotension, respiratory depression, nausea, bucking, and muscle rigidity, which has also been reported in our previous study.<sup>32,33</sup> Moreover, alfentanil combined with propofol has been shown to achieve a satisfactory degree of sedation during bidirectional endoscopies.<sup>34</sup> We chose to use alfentanil for this trial on the basis of all of these considerations.

The incidence of respiratory depression is relatively high when alfentanil is used alone, whereas fewer instances of respiratory depression occur when propofol is used with alfentanil.<sup>35</sup> However, alfentanil (5 µg/kg) cannot be administered immediately before a propofol infusion due to hypoxemia induction risks.<sup>36</sup> Immediate injections of 5–10 µg/kg of alfentanil before the infusion of propofol or midazolam caused significant hypoxemia in another study, but the incidence of respiratory depression was significantly reduced after a 5 min interval. In addition, the study recommended using relatively high doses of sedative drugs and low doses of alfentanil for adult patients undergoing bronchoscopy.<sup>37,38</sup> We used 10 µg/kg of intravenous (IV) alfentanil 5 minutes before anesthesia induction on the basis of those numbers.

Remimazolam besylate has been suggested to be suitable for application in anesthesia induction to reduce unfavorable hemodynamic responses during intubation.<sup>39</sup> We recorded SpO<sub>2</sub>, HR, SBP, and DBP values and found them all to be significantly lower at T2 and T3 in the RA group than in the DA group. Continuous infusions of remimazolam besylate have become more frequent to induce and maintain anesthesia because these infusions prevent the hemodynamic and anesthesia depth instabilities that were often recorded after intermittent boluses. Moreover, the total administered dose and the patient recovery times tend to be lower and shorter after the continuous infusion than after a bolus of remimazolam besylate.<sup>40</sup> Thus, we administered a loading dose (6 mg/kg/h of remimazolam besylate for 10 minutes) during anesthesia induction and a maintenance dose (1–2 mg/kg/h) to the patients in the group RA. The combination of remimazolam besylate with alfentanil has been shown to better preserve the patient's spontaneous breathing and reduce the incidence of respiratory depression than propofol during FBs.<sup>41</sup> However, to the best of our knowledge, the safety and efficacy of remimazolam besylate–alfentanil versus dexmedetomidine–alfentanil had not been compared before this trial.

The combination of dexmedetomidine and alfentanil was shown to result in more instances of respiratory depression than dexmedetomidine alone, but the quality of sedation and the extent of coughing were similar between both regimens.<sup>42</sup> In patients undergoing endoscopy, single-use alfentanil causes less damage to postoperative cognitive function, less risk of hypotension, and shorter discharge time than dexmedetomidine.<sup>25</sup> A previous study reported a lower lowest oxygen saturation in the RA group compared to the value in the DA group, albeit with a non-statistically significant difference. This may be due to the effects of alfentanil on the respiratory center of the brainstem, especially when opioids are associated with benzodiazepines.<sup>43</sup> By contrast, our results showed that the lowest oxygen saturation during the FB (usually during anesthesia induction) was significantly higher in the RA group than in the DA group. However, we did not record significant differences between the two groups regarding RRs. This may be due to differences in monitoring methods, drug combinations, ventilation modes (manually ventilated via laryngeal mask vs spontaneous ventilation with nasal cannula), and discrimination criteria.<sup>44</sup>

In a finding similar to those of others, more patients experienced bradycardia in the DA group than in the RA group in our trial. According to the British Thoracic Society guidelines, P<sub>ET</sub>-CO<sub>2</sub> monitoring is most useful for patients with high risk of CO<sub>2</sub> retention; however, we found no patients with respiratory depression. Hypertension and tachycardia are common during bronchoscopy and may lead to cardiac ischemia. The prophylactic addition of a β adrenergic antagonist may prevent this response. However, we did not adopt this strategy because the incidences of these two adverse reactions in our initial trial were significantly lower than those in a published study,<sup>45</sup> probably due to sedation protocol differences.

According to the results of previous research, we did not find patients reporting injection pain in the RA group, probably due to the water-soluble characteristics of remimazolam besylate and off-target interactions with transient receptor potential receptors on sensory neurons.<sup>46</sup> Consistent with the research results of previous study, Our findings on the induction, fully alert, and recovery room-leaving times were consistent with those of others showing all significantly shorter times in the RA group than in the DA group. In addition, the bronchoscopy feasibility scores were higher in the DA group than on the RA group. This may be due to the longer onset and half-life of dexmedetomidine compared to those of remimazolam besylate.<sup>47</sup> The rapid recovery of the cognitive function is important for a growing number of people who hope to minimize off-work time immediately after endoscopic procedures. Both remimazolam besylate and dexmedetomidine exert little negative effects on cognitive functions.<sup>14,48</sup> Accordingly, we did not find any patients with postoperative cognitive impairment in this trial. Also, in agreement with others' results, we did not find differences in the number of patients willing to repeat the FB with the same sedation regimen, or in patient satisfaction scores. Patients'



wishes and satisfaction scores may be associated with numerous influencing factors like organization, endoscopy unit facilities, and waiting times.<sup>49</sup>

This trial had the following limitations: First, our patients all came from one hospital; therefore, a large-sample multicenter study is needed to confirm the conclusions of our trial. Second, we included only subjective indicators of the patient sedation level, a choice that may have biased our results. Accurate objective indicators such as the integrated pulmonary index (IPI) may be more accurate for assessing the patient's level of sedation. Third, a ceiling effect on synergistic sedation with midazolam and alfentanil may exist in adult patients.<sup>50</sup> Further research is needed to explore whether the same phenomenon exists with remimazolam besylate and alfentanil. Finally, to reduce statistical bias refer to the age distribution of patients who have received FBs in the past at our center and reduce the statistical bias, we only recruited patients aged 50 to 70 years undergoing short FBs. As a result, we did not record any related complications outside of the respiratory and circulatory systems. These results cannot be extended to elderly patients undergoing lengthy procedures, who may require deeper sedation during bronchoscopy.

In conclusion, remimazolam besylate is superior to dexmedetomidine when combined with alfentanil during FB, promoting faster patients' recovery, better operative conditions, and respiratory stability, while the occurrence and severity of adverse events is similar.

## Data Sharing Statement

The datasets generated during and/or analyzed during the current study are not publicly available due to the privacy policy but are available from the corresponding authors upon reasonable request.

## Ethics Approval and Informed Consent

All procedures performed on the patients were in accordance with the tenets of the 1964 Declaration of Helsinki and its later amendments. The study was approved by the institutional review boards of Liaocheng People's Hospitals.

## 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.

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## Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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